NDA 20-272

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NDA 20-272

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Janssen Research Foundation
Attention: Ruth Wasserman
Director, Regulatory Affairs
1125 Trenton-Harbourton Road
Titusville, New Jersey 08560-0200

Dear Ms. Wasserman:

Reference is made to your New Drug Application (NDA) dated April 15, 1992, submitted pursuant to section 505(b) of the Federal Food, Drug, and Cosmetic Act for RISPERDAL® (risperidone) 1 mg, 2 mg, 3 mg, 4 mg, and 5 mg Tablets.

We also acknowledge receipt of your additional communications dated:

May 1, 1992	June 4, 1992	June 22, 1992
June 26, 1992	June 30, 1992	July 7, 1992
July 9, 1992	July 14, 1992	July 16, 1992
September 30, 1992	October 27, 1992	October 28, 1992
October 30, 1992	November 9, 1992	November 20, 1992
November 24,1992	December 7, 1992	December 9, 1992
December 21, 1992	December 22, 1992	December 23, 1992
February 1, 1993	February 2, 1993	February 10(2), 1993
March 5, 1993	March 9, 1993	March 11, 1993
March 15, 1993	March 25(2), 1993	March 29(2), 1993
March 30(2), 1993	March 31, 1993	April 1, 1993
April 2(2), 1993	April 8, 1993	April 13, 1993
May 4(2), 1993	May 12, 1993	May 14, 1993
May 17(2), 1993	May 24, 1993	June 3, 1993
June 18, 1993	July 1, 1993	July 6, 1993
July 9, 1993	August 10, 1993	August 20, 1993
August 23, 1993	August 25, 1993	August 27, 1993
September 24, 1993	October 13, 1993	October 28, 1993

We have completed our review of this application, as amended, and have concluded that adequate information has been presented to demonstrate that the drug product is safe and effective for use as recommended in the final text of labeling attached to this letter. Accordingly, the application, with these labeling revisions, is approved, effective as of the date of this letter.

Labeling

Accompanying this letter (ATTACHMENT 1) is the verbatim text of the labeling under which RISPERDAL® may be marketed.

Biopharmaceutics

Dissolution Specifications

(a) The following "interim" dissolution specification for all strengths of Risperdal® tablets are required:

Method: USP Apparatus II (Paddle) at 50 rpm
Media: 500 mL of 0.1 N HCl
NLT 80% drug released in 45 minutes

(b) Within three months of the date of this approvable action, you are requested to submit dissolution data on 12 individual tablets, for each strength of Risperdal® tablets manufactured at both the sites (Beerse, Belgium and Gurabo, Puerto Rico) according to the dissolution method specified below:

USP apparatus (Paddle method) at rpm in mL of simulated gastric fluid (without pepsin and a pH of 1.2) at 37±0.5°C.

You have apparently conducted some dissolution using this method and based on limited data, it appears that simulated gastric fluid may reduce the variability and accelerate drug release for all the tablet strengths as compared to the current medium which is 0.1 N HCl. This may allow for setting of a more appropriate dissolution specification.

Bio-Waiver

The tablet cores for each of the five dosage strengths proposed for marketing are proportionally identical for all excipients. There are minor differences in the film coating for each of the tablet strengths representing the different color additives. Therefore, a waiver of in vivo bioequivalence study for the 2 mg, 3 mg, and 5 mg strength tablets manufactured at Beerse, Belgium and also in vivo bioequivalence study between the two manufacturing sites (Beerse, Belgium and Gurabo, Puerto Rico) for all the tablet strengths (1, 2, 3, 4, and 5 mg) are granted, based on the linear kinetics of the drug and on in vitro dissolution profiles submitted in this application for this immediate release product.

Post-Marketing Studies

Although you have provided clear evidence of the effectiveness and safety of RISPERDAL®, a number of important questions related to its optimal use remain to be answered. We note your agreement to carry out the following studies after approval:

Clinical

Long-Term Effectiveness Studies:

Although the evidence submitted unequivocally documents the short-term efficacy of RISPERDAL® in the management of the manifestations of psychosis, there is no evidence bearing directly on the effectiveness of this drug in the maintenance treatment of remitted/partially remitted psychotic patients. Because it is likely that Risperdal will be widely used for these purposes, it is critical that appropriate clinical studies be undertaken to evaluate its safety and effectiveness in long-term use.

We note your submitted protocol for a study of relapse prevention and staff of the Division of Neuropharmacological Drug Products expect to discuss this and any other proposals with you.

Pharmacokinetic Interaction Study:

Although in vitro studies suggest that risperidone is not a potent inhibitor of cytochrome P450IID6, only in vivo studies would be capable of confirming whether or not risperidone or its active metabolite have a clinically important effect on the pharmacokinetics of other drugs metabolized by this isozyme. Consequently, an in vivo study is needed to explore the potential for such interaction. It is possible that a detailed submission of literature study N97249, which reported no effect of risperidone 6 mg on the metabolic ratio of dextromethorphan, will be sufficient.

Pharmacology

A lack of understanding of the mechanism underlying the high rate of perinatal mortality observed in rat pups impairs the ability of prescribers to make an informed judgement in the use of this drug product. Studies to clarify this matter are therefore needed.

The segment III reproduction studies and a multigenerational study in rats revealed an increase in pup mortality during the first four days of lactation for pups born to dams receiving risperidone at doses ranging from 0.16 to 5 mg/kg/day. Because it cannot be determined if this effect on survival is related to effects of the drug on the developing fetus in utero or is secondary to maternal neglect, we have labeled risperidone pregnancy category C. We recommend that you conduct a cross-fostering experiment in order to determine whether the deaths occurred as a result of fetal abnormalities or if they occurred because of other problems during lactation. If this experiment clearly establishes that the adverse effect on pup mortality is occurring as a result of maternal neglect rather than an effect of drug on the fetus, the labeling may be changed from pregnancy category C to pregnancy category B.

We suggest a study comparing a control group and the high dose group (5 mg/kg/day) treated from gestation day 15 through postnatal day 21. Each group should contain 20 pregnant dams. Half of the dams in each group should be removed from the cage after giving birth and placed with a litter from the other treatment group for nursing. All groups should continue nursing through day 21 postpartum.

MANUFACTURING AND CONTROLS

The validation of the analytical methods has not been completed for this application. We would appreciate your full cooperation in resolving any problems that may arise.

Promotional Material

Please submit, in triplicate, the advertising copy that you intend to use in your proposed introductory promotional and/or advertising campaign. Please submit one copy to the Division of Neuropharmacological Drug Products and two copies to the Division of Marketing, Advertising and Communications, HFD-240, Room 17B-17. Please submit all proposed materials in draft or mock-up form, not final print. Also, please do not use form FD-2253 for this submission; this form is for routine use, not proposed materials.

At the present time, we would consider any advertisement or promotional labeling for RISPERDAL® false, misleading, or lacking fair balance under sections 502(a) and 502(n) of the Act if there is presentation of data that conveys the impression that risperidone is superior to haloperidol or any other marketed antipsychotic drug product with regard to safety or effectiveness.

Please submit 12 copies of the FPL as soon as it is available. Seven of the copies should be individually mounted on heavy-weight paper or similar material. The submission should be designated for administrative purposes as "FPL for approved NDA 20-272". Approval of the submission by FDA is not required before the labeling may be used. Should additional information relating to the safety and effectiveness of this drug product become available, further revision of the labeling may be required. We remind you that you must comply with the requirements for an approved NDA as set forth under 21 CFR 314.80 and 314.81

Sincerely yours,

Robert Temple, M.D.
Director
Office of Drug Evaluation I
Center for Drug Evaluation and Research

ATTACHMENT

ATTACHMENT 1

FINAL LABELING

RISPERDAL™
(Risperidone tablets)

DESCRIPTION

RISPERDAL™ (risperidone) is an antipsychotic agent belonging to a new chemical class, the benzisoxazole derivatives. The chemical designation is 3-[2-[4-(6-fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]ethyl]-6,7,8,9-tetrahydro-2-methyl-4H-pyrido[1,2-a]pyrimidin-4-one. Its molecular formula is $C_{23}H_{27}FN_4O_2$ and its molecular weight is 410.49. The structural formula is:

[Insert structural formula here.]

Risperidone is a white to slightly beige powder. It is practically insoluble in water, freely soluble in methylene chloride, and soluble in methanol and 0.1 N HCl.

RISPERDAL™ for oral use is available in tablets of 1 mg (white, scored), 2 mg (orange), 3 mg (yellow), 4 mg (green), and 5 mg (peach). Inactive ingredients are colloidal silicon dioxide, hydroxypropyl methylcellulose, lactose, magnesium stearate, microcrystalline cellulose, propylene glycol, sodium lauryl sulfate, and starch (corn). Tablets of 2, 3, 4, and 5 mg also contain talc and titanium dioxide. The 2 mg and 5 mg tablets contain FD&C Yellow No. 6 Aluminum Lake; the 3 mg and 4 mg tablets contain D&C Yellow No. 10; the 4 mg and 5 mg tablets contain FD&C Blue No. 2 Aluminum Lake.

CLINICAL PHARMACOLOGY

Pharmacodynamics

The mechanism of action of RISPERDAL™ (risperidone), as with other antipsychotic drugs, is unknown. However, it has been proposed that this drug's antipsychotic activity is mediated through a combination of dopamine type 2 (D2) and serotonin type 2 (5-HT2) antagonism. Antagonism at receptors other then D_2 and $5HT_2$ may explain some of the other effects of RISPERDAL™.

RISPERDAL™ (risperidone) is a selective monoaminergic antagonist with high affinity (Ki of 0.12 to 7.3 nM) for the serotonin type 2 ($5HT_2$), dopamine type 2 (D_2), α_1 and α_2 adrenergic, and H_1

histaminergic receptors. RISPERDAL™ antagonizes other receptors, but with lower potency. RISPERDAL™ has low to moderate affinity (Ki of 47 to 253 nM) for the serotonin $5HT_{1C}$, $5HT_{1D}$, and $5HT_{1A}$ receptors, weak affinity (Ki of 620 to 800 nM) for the dopamine D_1 and haloperidol-sensitive sigma site, and no affinity (when tested at concentrations $>10^{-5}$ M) for cholinergic muscarinic or β_1 and β_2 adrenergic receptors.

Pharmacokinetics

Risperidone is well absorbed, as illustrated by a mass balance study involving a single 1 mg oral dose of ^{14}C-risperidone as a solution in three healthy male volunteers. Total recovery of radioactivity at one week was 85%, including 70% in the urine and 15% in the feces.

Risperidone is extensively metabolized in the liver by cytochrome $P_{450}IID_6$ to a major active metabolite, 9-hydroxy-risperidone, which is the predominant circulating specie, and appears approximately equi-effective with risperidone with respect to receptor binding activity and some effects in animals. (A second minor pathway is N-dealkylation). Consequently, the clinical effect of the drug likely results from the combined concentrations of risperidone plus 9-hydroxy-risperidone. Plasma concentrations of risperidone, 9-hydroxy-risperidone, and risperidone plus 9-hydroxy-risperidone are dose proportional over the dosing range of 1 to 16 mg daily (0.5 to 8 mg B.I.D.). The relative oral bioavailability of risperidone from a tablet was 94% (CV=10%) when compared to a solution. Food does not affect either the rate or extent of absorption of risperidone. Thus, risperidone can be given with or without meals. The absolute oral bioavailability of risperidone was 70% (CV=25%).

The enzyme catalyzing hydroxylation of risperidone to 9-hydroxy-risperidone is cytochrome $P_{450}IID_6$, also called debrisoquin hydroxylase, the enzyme responsible for metabolism of many neuroleptics, antidepressants, antiarrhythmics, and other drugs. Cytochrome $P_{450}IID_6$ is subject to genetic polymorphism (about 6-8% of caucasians, and a very low percent of Asians have little or no activity and are "poor metabolizers") and to inhibition by a variety of substrates and some non-substrates, notably quinidine. Extensive metabolizers convert risperidone rapidly into 9-hydroxy-risperidone, while poor metabolizers convert it much more slowly. Extensive metabolizers, therefore, have lower risperidone and higher 9-hydroxy-risperidone concentrations than poor metabolizers. Following oral administration of solution or tablet, mean peak plasma concentrations occurred at about 1 hour. Peak 9-hydroxy-risperidone occurred at about 3 hours in extensive metabolizers, and 17 hours in poor metabolizers. The apparent half-life of risperidone was three hours (CV=30%) in extensive metabolizers and 20 hours (CV=40%) in poor metabolizers. The apparent half-life of 9-hydroxy-risperidone was about 21 hours (CV=20%) in extensive metabolizers and 30 hours (CV=25%) in poor metabolizers. Steady

state concentrations of risperidone are reached in 1 day in extensive metabolizers and would be expected to reach steady state in about 5 days in poor metabolizers. Steady state concentrations of 9-hydroxy-risperidone are reached in 5-6 days (measured in extensive metabolizers).

Because risperidone and 9-hydroxy-risperidone are approximately equieffective, the sum of their concentrations is pertinent. The pharmacokinetics of the sum of risperidone and 9-hydroxy-risperidone, after single and multiple doses, were similar in extensive and poor metabolizers, with an overall mean elimination half-life of about 20 hours. In analyses comparing adverse reaction rates in extensive and poor metabolizers in controlled and open studies, no important differences were seen.

Risperidone could be subject to two kinds of drug-drug interactions. First, inhibitors of cytochrome $P_{450}IID_6$ could interfere with conversion of risperidone to 9-hydroxy-risperidone. This in fact occurs with quinidine, giving essentially all recipients a risperidone pharmacokinetic profile typical of poor metabolizers. The favorable and adverse effects of risperidone in patients receiving quinidine have not been evaluated, but observations in a modest number ($n \approx 70$) of poor metabolizers given risperidone do not suggest important differences between poor and extensive metabolizers. It would also be possible for risperidone to interfere with metabolism of other drugs metabolized by cytochrome $P_{450}IID_6$. Relatively weak binding of risperidone to the enzyme suggests this is unlikely (See PRECAUTIONS and DRUG INTERACTIONS).

The plasma protein binding of risperidone was about 90% over the in-vitro concentration range of 0.5 to 200 ng/mL and increased with increasing concentrations of α_1-acid glycoprotein. The plasma binding of 9-hydroxy-risperidone was 77%. Neither the parent nor the metabolite displaced each other from the plasma binding sites. High therapeutic concentrations of sulfamethazine (100 μg/mL), warfarin (10 μg/mL) and carbamazepine (10 μg/mL) caused only a slight increase in the free fraction of risperidone at 10 ng/mL and 9-hydroxy-risperidone at 50 ng/mL, changes of unknown clinical significance.

Special Populations

Renal Impairment

In patients with moderate to severe renal disease, clearance of the sum of risperidone and its active metabolite decreased by 60% compared to young healthy subjects. RISPERDAL™ doses should be reduced in patients with renal disease (See PRECAUTIONS and DOSAGE and ADMINISTRATION).

Hepatic Impairment

While the pharmacokinetics of risperidone in subjects with liver disease were comparable to those in young healthy subjects, the mean free fraction of risperidone in plasma was increased by about 35% because of the diminished concentration of both albumin and α_1-acid glycoprotein. Risperidone doses should be reduced in patients with liver disease (See PRECAUTIONS and DOSAGE and ADMINISTRATION).

Elderly

In healthy elderly subjects renal clearance of both risperidone and 9-hydroxy-risperidone was decreased, and elimination half-lives were prolonged compared to young healthy subjects. Dosing should be modified accordingly in the elderly patients (See DOSAGE and ADMINISTRATION).

Race and Gender Effects

No specific pharmacokinetic study was conducted to investigate race and gender effects, but a population pharmacokinetic analysis did not identify important differences in the disposition of risperidone due to gender (whether corrected for body weight or not) or race.

Clinical Trials

The efficacy of RISPERDAL™ in the management of the manifestations of psychotic disorders was established in 3 short-term (6- to 8-week) controlled trials of psychotic inpatients who met DSM III-R criteria for schizophrenia.

Several instruments were used for assessing psychiatric signs and symptoms in these studies, among them the Brief Psychiatric Rating Scale (BPRS), a multi-item inventory of general psychopathology traditionally used to evaluate the effects of drug treatment in psychosis. The BPRS psychosis cluster (conceptual disorganization, hallucinatory behavior, suspiciousness, and unusual thought content) is considered a particularly useful subset for assessing actively psychotic schizophrenic patients. A second traditional assessment, the Clinical Global Impression (GGI), reflects the impression of a skilled observer, fully familiar with the manifestations of schizophrenia, about the overall clinical state of the patient. In addition, two more recently developed, but less well evaluated scales, were employed; these included the Positive and Negative Symptoms Scale (PANSS) and the Scale for Assessing Negative Symptoms (SANS).

The results of the trials follow:

(1) In a 6-week, placebo controlled trial (n=160) involving titration of RISPERDAL™ in doses up to 10 mg/day (BID schedule), RISPERDAL™ was generally superior to placebo on the BPRS total score, on the BPRS psychosis cluster, and marginally superior to placebo on the SANS.

(2) In an 8-week, placebo controlled trial (n=513) involving 4 fixed doses of RISPERDAL™ (2, 6, 10, and 16 mg/day, on a BID schedule), all 4 RISPERDAL™ dose groups were generally superior to placebo on BPRS total score, BPRS psychosis cluster, and CGI severity score; the 3 highest RISPERDAL™ dose groups were generally superior to placebo on the PANSS negative subscale. The most consistently positive responses on all measures were seen for the 6 mg dose group, and there was no suggestion of increased benefit from larger doses.

(3) In an 8-week, dose comparison trial (n=1356) involving 5 fixed doses of RISPERDAL™ (1, 4, 8, 12, and 16 mg/day, on a BID schedule), the four highest RISPERDAL™ dose groups were generally superior to the 1 mg RISPERDAL™ dose group on BPRS total score, BPRS psychosis cluster, and CGI severity score. None of the dose groups were superior to the 1 mg group on the PANSS negative subscale. The most consistently positive responses were seen for the 4 mg dose group.

INDICATIONS AND USAGE

RISPERDAL™ (risperidone) is indicated for the management of the manifestations of psychotic disorders.

The antipsychotic efficacy of RISPERDAL™ was established in short-term (6 to 8 weeks) controlled trials of schizophrenic inpatients (See CLINICAL PHARMACOLOGY).

The effectiveness of RISPERDAL™ in long-term use, that is, for more than 6 to 8 weeks, has not been systematically evaluated in controlled trials. Therefore, the physician who elects to use RISPERDAL™ for extended periods should periodically re-evaluate the long-term usefulness of the drug for the individual patient (See DOSAGE AND ADMINISTRATION).

CONTRAINDICATIONS

RISPERDAL™ (risperidone) is contraindicated in patients with a known hypersensitivity to the product.

WARNINGS

Neuroleptic Malignant Syndrome (NMS)

A potentially fatal symptom complex sometimes referred to as Neuroleptic Malignant Syndrome (NMS) has been reported in association with antipsychotic drugs. Clinical manifestations of NMS are hyperpyrexia, muscle rigidity, altered mental status and evidence of autonomic instability (irregular pulse or blood pressure, tachycardia, diaphoresis and cardiac dysrhythmia). Additional signs may include elevated creatinine phosphokinase, myoglobinuria (rhabdomyolysis), and acute renal failure.

The diagnostic evaluation of patients with this syndrome is complicated. In arriving at a diagnosis, it is important to identify cases where the clinical presentation includes both serious medical illness (e.g., pneumonia, systemic infection, etc.) and untreated or inadequately treated extrapyramidal signs and symptoms (EPS). Other important considerations in the differential diagnosis include central anticholinergic toxicity, heat stroke, drug fever, and primary central nervous system pathology.

The management of NMS should include: 1) immediate discontinuation of antipsychotic drugs and other drugs not essential to concurrent therapy; 2) intensive symptomatic treatment and medical monitoring; and 3) treatment of any concomitant serious medical problems for which specific treatments are available. There is no general agreement about specific pharmacological treatment regimens for uncomplicated NMS.

If a patient requires antipsychotic drug treatment after recovery from NMS, the potential reintroduction of drug therapy should be carefully considered. The patient should be carefully monitored, since recurrences of NMS have been reported.

Tardive Dyskinesia

A syndrome of potentially irreversible, involuntary, dyskinetic movements may develop in patients treated with antipsychotic drugs. Although the prevalence of the syndrome appears to be highest among the elderly, especially elderly women, it is impossible to rely upon prevalence estimates to predict, at the inception of antipsychotic treatment, which patients are likely to develop the syndrome. Whether antipsychotic drug products differ in their potential to cause tardive dyskinesia is unknown.

The risk of developing tardive dyskinesia and the likelihood that it will become irreversible are believed to increase as the duration of treatment and the total cumulative dose of antipsychotic drugs administered to the patient increase. However, the syndrome can develop, although much less commonly, after relatively brief treatment periods at low doses.

There is no known treatment for established cases of tardive dyskinesia, although the syndrome may remit, partially or completely, if antipsychotic treatment is withdrawn. Antipsychotic treatment, itself, however, may suppress (or partially suppress) the signs and symptoms of the syndrome and thereby may possibly mask the underlying process. The effect that symptomatic suppression has upon the long-term course of the syndrome is unknown.

Given these considerations, RISPERDAL™ should be prescribed in a manner that is most likely to minimize the occurrence of tardive dyskinesia. Chronic antipsychotic treatment should generally be reserved for patients who suffer from a chronic illness that (1) is known to respond to antipsychotic drugs, and (2) for whom alternative, equally effective, but potentially less harmful treatments are not available or appropriate. In patients who do require chronic treatment, the smallest dose and the shortest duration of treatment producing a satisfactory clinical response should be sought. The need for continued treatment should be reassessed periodically.

If signs and symptoms of tardive dyskinesia appear in a patient on RISPERDAL™, drug discontinuation should be considered. However, some patients may require treatment with RISPERDAL™ despite the presence of the syndrome.

Potential for Proarrhythmic Effects

Risperidone and/or 9-hydroxy-risperidone appears to lengthen the QT interval in some patients, although there is no average increase in treated patients, even at 12-16 mg/day, well above the recommended dose. Other drugs that prolong the QT interval have been associated with the occurrence of torsades de pointes, a life-threatening arrhythmia. Bradycardia, electrolyte imbalance, concomitant use with other drugs that prolong QT, or the presence of congenital prolongation in QT can increase the risk for occurrence of this arrhythmia.

PRECAUTIONS

General

Orthostatic Hypotension

RISPERDAL™ may induce orthostatic hypotension associated with dizziness, tachycardia, and in some patients, syncope, especially during the initial dose-titration period, probably reflecting its alpha-adrenergic antagonistic properties. Syncope was reported in 0.2% (6/2607) of RISPERDAL™ treated patients in phase 2-3 studies. The risk of orthostatic hypotension and syncope may be minimized by limiting the initial dose to 1 mg BID in normal adults and 0.5 mg

BID in the elderly and patients with renal or hepatic impairment (See DOSAGE AND ADMINISTRATION). A dose reduction should be considered if hypotension occurs. RISPERDAL™ should be used with particular caution in patients with known cardiovascular disease (history of myocardial infarction or ischemia, heart failure, or conduction abnormalities), cerebrovascular disease, and conditions which would predispose patients to hypotension (dehydration, hypovolemia, and treatment with antihypertensive medications).

Seizures

During premarketing testing, seizures occurred in 0.3% (9/2607) of risperidone treated patients, two in association with hypernatremia. RISPERDAL™ should be used cautiously in patients with a history of seizures.

Hyperprolactinemia

As with other drugs that antagonize dopamine D_2 receptors, risperidone elevates prolactin levels and the elevation persists during chronic administration. Tissue culture experiments indicate that approximately one-third of human breast cancers are prolactin dependent in vitro, a factor of potential importance if the prescription of these drugs is contemplated in a patient with previously detected breast cancer. Although disturbances such as galactorrhea, amenorrhea, gynecomastia, and impotence have been reported with prolactin-elevating compounds, the clinical significance of elevated serum prolactin levels is unknown for most patients. As is common with compounds which increase prolactin release, an increase in pituitary gland, mammary gland, and pancreatic islet cell hyperplasia and/or neoplasia was observed in the risperidone carcinogenicity studies conducted in mice and rats (see CARCINOGENESIS). However, neither clinical studies nor epidemiologic studies conducted to date have shown an association between chronic administration of this class of drugs and tumorigenesis in humans; the available evidence is considered too limited to be conclusive at this time.

Potential for Cognitive and Motor Impairment

Somnolence was a commonly reported adverse event associated with RISPERDAL™ treatment, especially when ascertained by direct questioning of patients. This adverse event is dose related, and in a study utilizing a checklist to detect adverse events, 41% of the high dose patients (RISPERDAL™ 16 mg/day) reported somnolence compared to 16% of placebo patients. Direct questioning is more sensitive for detecting adverse events than spontaneous reporting, by which 8% of RISPERDAL™ 16 mg/day patients and 1% of placebo patients reported somnolence as an adverse event. Since RISPERDAL™ has the potential to impair judgment, thinking, or motor skills, patients should be cautioned about operating hazardous machinery, including automobiles, until they are reasonably certain that

RISPERDAL™ therapy does not affect them adversely.

Priapism

A single case of priapism was reported in a 50 year-old patient receiving RISPERDAL™ in a large, open premarketing experience (approximately 1300 patients). This event occurred after 11 months of treatment with RISPERDAL™ alone, and required surgical intervention. While the relationship of this event to RISPERDAL™ use cannot be established on the basis of a single case, other drugs with alpha-adrenergic blocking effects have been reported to induce priapism, and it is possible that RISPERDAL™ may share this capacity.

Thrombotic Thrombocytopenic Purpura (TTP)

A single case of TTP was reported in a 28 year-old female patient receiving RISPERDAL™ in a large, open premarketing experience (approximately 1300 patients). She experienced jaundice, fever, and bruising, but eventually recovered after receiving plasmapheresis. The relationship to RISPERDAL™ therapy is unknown.

Antiemetic effect

Risperidone has an antiemetic effect in animals; this effect may also occur in humans, and may mask signs and symptoms of overdosage with certain drugs or of conditions such as intestinal obstruction, Reye's syndrome, and brain tumor.

Body Temperature Regulation

Although not reported with risperidone, disruption of body temperature regulation has been attributed to other antipsychotic agents. Caution is advised when prescribing for patients who will be exposed to extreme heat.

Suicide

The possibility of a suicide attempt is inherent in schizophrenia, and close supervision of high risk patients should accompany drug therapy. Prescriptions for RISPERDAL™ should be written for the smallest quantity of tablets consistent with good patient management, in order to reduce the risk of overdose.

Use in Patients with Concomitant Illness

Clinical experience with RISPERDAL™ in patients with certain concomitant systemic illnesses is limited. Caution is advisable in using RISPERDAL™ in patients with diseases or conditions that could affect metabolism or hemodynamic responses.

RISPERDAL™ has not been evaluated or used to any appreciable extent in patients with a recent history of myocardial infarction or unstable heart disease. Patients with these diagnoses were excluded from clinical studies during the product's premarket testing. The electrocardiograms of approximately 380 patients who received RISPERDAL™ and 120 patients who received placebo in two double-blind, placebo-controlled trials were evaluated, and the data revealed one finding of potential concern, i.e., 8 patients taking RISPERDAL™ whose baseline QTc interval was less than 450 msec were observed to have QTc intervals greater than 450 msec during treatment; no such prolongations were seen in the smaller placebo group. There were 3 such episodes in the approximately 125 patients who received haloperidol. Because of the risks of orthostatic hypotension and QT prolongation, caution should be observed in cardiac patients (See PRECAUTIONS and WARNINGS).

Increased plasma concentrations of risperidone and 9-hydroxy-risperidone occur in patients with severe renal impairment (creatinine clearance <30 mL/min/1.73 m^2), and an increase in the free fraction of the risperidone is seen in patients with severe hepatic impairment. A lower starting dose should be used in such patients (See DOSAGE AND ADMINISTRATION).

Information for Patients

Physicians are advised to discuss the following issues with patients for whom they prescribe RISPERDAL™:

Orthostatic Hypotension

Patients should be advised of the risk of orthostatic hypotension, especially during the period of initial dose titration.

Interference With Cognitive and Motor Performance

Since RISPERDAL™ has the potential to impair judgment, thinking, or motor skills, patients should be cautioned about operating hazardous machinery, including automobiles, until they are reasonably certain that RISPERDAL™ therapy does not affect them adversely.

Pregnancy

Patients should be advised to notify their physician if they become pregnant or intend to become pregnant during therapy.

Nursing

Patients should be advised not to breast feed an infant if they are taking RISPERDAL™.

Concomitant Medication

Patients should be advised to inform their physicians if they are taking, or plan to take, any prescription or over-the-counter drugs, since there is a potential for interactions.

Alcohol

Patients should be advised to avoid alcohol while taking RISPERDAL™.

Laboratory Tests

No specific laboratory tests are recommended.

Drug Interactions

The interactions of RISPERDAL™ and other drugs have not been systematically evaluated. Given the primary CNS effects of risperidone, caution should be used when RISPERDAL™ is taken in combination with other centrally acting drugs and alcohol.

Because of its potential for inducing hypotension, RISPERDAL™ may enhance the effects of antihypertensive agents.

RISPERDAL™ may antagonize the effects of levodopa and dopamine agonists.

Chronic administration of carbamazepine with risperidone may increase the clearance of risperidone.

Chronic administration of clozapine with risperidone may decrease the clearance of risperidone.

Drugs that Inhibit Cytochrome $P_{450}IID_6$ and Other P_{450} Isozymes

Risperidone is metabolized to 9-hydroxy-risperidone by cytochrome $P_{450}IID_6$, an enzyme that is polymorphic in the population and that can be inhibitied by a variety of psychotropic and other drugs (See CLINICAL PHARMACOLOGY). Drug interactions that reduce the metabolism of risperidone to 9-hydroxy-risperidone would increase the plasma concentrations of risperidone and lower the concentrations of 9-hydroxy-risperidone. Analysis of clinical studies involving a modest number of poor metabolizers (n≈70) does not suggest that poor and extensive metabolizers have different rates of adverse effects. No comparison of effectiveness in the two groups has been made.

In-vitro studies showed that drugs metabolized by other P450 isozymes, including 1A1, 1A2, IIC9, MP, and IIIA4, are only weak

inhibitors of risperidone metabolism.

Drugs Metabolized by Cytochrome $P_{450}IID_6$

In vitro studies indicate that risperidone is a relatively weak inhibitor of cytochrome $P_{450}IID_6$. Therefore, RISPERDAL™ is not expected to substantially inhibit the clearance of drugs that are metabolized by this enzymatic pathway. However, clinical data to confirm this expectation are not available.

Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis

Carcinogenicity studies were conducted in Swiss albino mice and Wistar rats. RISPERDAL™ was administered in the diet at doses of 0.63, 2.5, and 10 mg/kg for 18 months to mice and for 25 months to rats. These doses are equivalent to 2.4, 9.4, and 37.5 times the maximum human dose (16 mg/day) on a mg/kg basis or 0.2, 0.75 and 3 times the maximum human dose (mice) or 0.4, 1.5 and 6 times the maximum human dose (rats) on a mg/m^2 basis. A maximum tolerated dose was not achieved in male mice. There were statistically significant increases in pituitary gland adenomas, endocrine pancreas adenomas and mammary gland adenocarcinomas. The following table summarizes the multiples of the human dose on a mg/m^2 (mg/kg) basis at which these tumors occurred.

TUMOR TYPE	SPECIES	SEX	MULTIPLE OF MAXIMUM HUMAN DOSE in mg/m^2 (mg/kg)	
			LOWEST EFFECT LEVEL	HIGHEST NO EFFECT LEVEL
Pituitary adenomas	mouse	female	0.75 (9.4)	0.2 (2.4)
Endocrine pancreas adenomas	rat	male	1.5 (9.4)	0.4 (2.4)
Mammary gland adenocarcinomas	mouse	female	0.2 (2.4)	none
	rat	female	0.4 (2.4)	none
	rat	male	6 (37.5)	1.5 (9.4)
Mammary gland neoplasms, Total	rat	male	1.5 (9.4)	0.4 (2.4)

Antipsychotic drugs have been shown to chronically elevate prolactin levels in rodents. Serum prolactin levels were not measured during the RISPERDAL™ carcinogenicity studies; however, measurements during subchronic toxicity studies showed that

RISPERDAL™ elevated serum prolactin levels 5 to 6 fold in mice and rats at the same doses used in the carcinogenicity studies. An increase in mammary, pituitary, and endocrine pancreas neoplasms has been found in rodents after chronic administration of other antipsychotic drugs and is considered to be prolactin mediated. The relevance for human risk of the findings of prolactin mediated endocrine tumors in rodents is unknown (see Hyperprolactinemia under PRECAUTIONS, GENERAL).

Mutagenesis

No evidence of mutagenic potential for RISPERDAL™ was found in the Ames reverse mutation test, mouse lymphoma assay, in vitro rat hepatocyte DNA-repair assay, in vivo micronucleus test in mice, the sex-linked recessive lethal test in Drosophila, or the chromosomal aberration test in human lymphocytes or Chinese hamster cells.

Impairment of Fertility

RISPERDAL™ (0.16 to 5 mg/kg) was shown to impair mating, but not fertility, in Wistar rats in three reproductive studies (two Segment I and a multigenerational study) at doses 0.1 to 3 times the maximum recommended human dose on a mg/m^2 basis. The effect appeared to be in females since impaired mating behavior was not noted in the Segment I study in which males only were treated. In a subchronic study in Beagle dogs in which risperidone was administered at doses of 0.31 to 5 mg/kg, sperm motility and concentration were decreased at doses 0.6 to 10 times the human dose on a mg/m^2 basis. Dose-related decreases were also noted in serum testosterone at the same doses. Serum testosterone and sperm parameters partially recovered but remained decreased after treatment was discontinued. No no-effect doses were noted in either rat or dog.

Pregnancy

Pregnancy category C. The teratogenic potential of RISPERDAL™ was studied in three Segment II studies in Sprague-Dawley and Wistar rats and in one Segment II study in New Zealand rabbits. The incidence of malformations was not increased compared to control in offspring of rats or rabbits given 0.4 to 6 times the human dose on a mg/m^2 basis. In three reproductive studies in rats (two Segment III and a multigenerational study), there was an increase in pup deaths during the first 4 days of lactation at doses 0.1 to 3 times the human dose on a mg/m^2 basis. It is not known whether these deaths were due to a direct effect on the fetuses or pups or to effects on the dams. There was no no-effect dose for increased rat pup mortality. In one Segment III study, there was an increase in stillborn rat pups at a dose 1.5 times higher than the human dose on a mg/m^2 basis.

Placental transfer of risperidone occurs in rat pups. There are no

adequate and well-controlled studies in pregnant women. However, there was one report of a case of agenesis of the corpus callosum in an infant exposed to risperidone in utero. The causal relationship to RISPERDAL™ therapy is unknown.

RISPERDAL™ should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Labor and Delivery

The effect of RISPERDAL™ on labor and delivery in humans is unknown.

Nursing Mothers

It is not known whether or not risperidone is excreted in human milk. In animal studies, risperidone and 9-hydroxy-risperidone were excreted in breast milk. Therefore, women receiving RISPERDAL™ should not breast feed.

Pediatric Use

Safety and effectiveness in children have not been established.

Geriatric Use

Clinical studies of RISPERDAL™ did not include sufficient numbers of patients aged 65 and over to determine whether they respond differently from younger patients. In general, a lower starting dose is recommended for an elderly patient, reflecting a decreased pharmacokinetic clearance in the elderly, as well as a greater frequency of decreased hepatic, renal, or cardiac function, and a greater tendency to postural hypotension (See CLINICAL PHARMACOLOGY and DOSAGE AND ADMINISTRATION).

ADVERSE REACTIONS

Associated with Discontinuation of Treatment

Approximately 9% percent (244/2607) of RISPERDAL™-treated patients in phase 2-3 studies discontinued treatment due to an adverse event, compared with about 7% on placebo and 10% on active control drugs. The more common events (≥ 0.3%) associated with discontinuation and considered to be possibly or probably drug-related included:

Adverse Event	RISPERDAL™	Placebo
Extrapyramidal symptoms	2.1%	0
Dizziness	0.7%	0
Hyperkinesia	0.6	0

Somnolence	0.5%	0
Nausea	0.3%	0

Suicide attempt was associated with discontinuation in 1.2% of RISPERDAL™-treated patients compared to 0.6% of placebo patients, but, given the almost 40-fold greater exposure time in RISPERDAL™ compared to placebo patients, it is unlikely that suicide attempt is a RISPERDAL™ related adverse event (See PRECAUTIONS). Discontinuation for extrapyramidal symptoms was 0% in placebo patients but 3.8% in active-control patients in the phase 2-3 trials.

Incidence in Controlled Trials

Commonly Observed Adverse Events in Controlled Clinical Trials:

In two 6- to 8-week placebo-controlled trials, spontaneously-reported, treatment-emergent adverse events with an incidence of 5% or greater in at least one of the RISPERDAL™ groups and at least twice that of placebo were: anxiety, somnolence, extrapyramidal symptoms, dizziness, constipation, nausea, dyspepsia, rhinitis, rash, and tachycardia.

Adverse events were also elicited in one of these two trials (i.e., in the fixed dose trial comparing RISPERDAL™ at doses of 2, 6, 10, and 16 mg/day with placebo) utilizing a checklist for detecting adverse events, a method that is more sensitive than spontaneous reporting. By this method, the following additional common and drug-related adverse events were present at at least 5% and twice the rate of placebo: increased dream activity, increased duration of sleep, accommodation disturbances, reduced salivation, micturition disturbances, diarrhea, weight gain, menorrhagia, diminished sexual desire, erectile dysfunction, ejaculatory dysfunction, and orgastic dysfunction.

Adverse Events Occurring at an Incidence of 1% or More Among RISPERDAL™ Treated Patients:

The table that follows enumerates adverse events that occurred at an incidence of 1% or more, and were at least as frequent among RISPERDAL™-treated patients treated at doses of $\leq$ 10 mg/day than among placebo-treated patients in the pooled results of two 6- to 8-week controlled trials. Patients received RISPERDAL™ doses of 2, 6, 10, or 16 mg/day in the dose comparison trial, or up to a maximum dose of 10 mg/day in the titration study. This table shows the percentage of patients in each dose group ($\leq$ 10 mg/day or 16 mg/day) who spontaneously reported at least one episode of an event at some time during their treatment. Patients given doses of 2, 6, or 10 mg did not differ materially in these rates. Reported adverse events were classified using the World Health Organization preferred terms.

The prescriber should be aware that these figures cannot be used to predict the incidence of side effects in the course of usual medical practice where patient characteristics and other factors differ from those that prevailed in this clinical trial. Similarly, the cited frequencies cannot be compared with figures obtained from other clinical investigations involving different treatments, uses and investigators. The cited figures, however, do provide the prescribing physician with some basis for estimating the relative contribution of drug and nondrug factors to the side effect incidence rate in the population studied.

Treatment-Emergent Adverse Experience Incidence in 6- to 8-Week Controlled Clinical Trials[1]

Body System/ Preferred Term	RISPERDAL™ ≤ 10 mg/day (N = 324)	RISPERDAL™ 16 mg/day (N = 77)	Placebo (N = 142)
Psychiatric Disorders			
Insomnia	26%	23%	19%
Agitation	22%	26%	20%
Anxiety	12%	20%	9%
Somnolence	3%	8%	1%
Aggressive reaction	1%	3%	1%
Nervous System			
Extrapyramidal symptoms[2]	17%	34%	16%
Headache	14%	12%	12%
Dizziness	4%	7%	1%
Gastrointestinal System			
Constipation	7%	13%	3%
Nausea	6%	4%	3%
Dyspepsia	5%	10%	4%
Vomiting	5%	7%	4%
Abdominal pain	4%	1%	0%
Saliva increased	2%	0%	1%

Toothache	2%	0%	0%
Respiratory System			
Rhinitis	10%	8%	4%
Coughing	3%	3%	1%
Sinusitis	2%	1%	1%
Pharyngitis	2%	3%	0%
Dyspnea	1%	0%	0%
Body as a Whole			
Back pain	2%	0%	1%
Chest pain	2%	3%	1%
Fever	2%	3%	0%
Dermatological			
Rash	2%	5%	1%
Dry skin	2%	4%	0%
Seborrhea	1%	0%	0%
Infections			
Upper respiratory	3%	3%	1%
Visual			
Abnormal vision	2%	1%	1%
Musculo-Skeletal			
Arthralgia	2%	3%	0%
Cardiovascular			
Tachycardia	3%	5%	0%

1 Events reported by at least 1% of patients treated with RISPERDAL™ ≤ 10 mg/day are included, and are rounded to the nearest %. Comparative rates for RISPERDAL™ 16 mg/day and placebo are provided as well. Events for which the RISPERDAL™ incidence (in both dose groups) was equal to or less than placebo are not listed in the table, but included the following: nervousness, injury, and fungal infection.

2 Includes tremor, dystonia, hypokinesia, hypertonia, hyperkinesia, oculogyric crisis, ataxia, abnormal gait, involuntary muscle contractions, hyporeflexia, and extrapyramidal disorders. Although the incidence for 'extrapyramidal disorder' does not appear to differ for the '≤ 10 mg/day' group and placebo, the data for individual dose groups in fixed dose trials do suggest a dose/response relationship (see DOSE DEPENDENCY of ADVERSE EVENTS).

Dose Dependency of Adverse Events

Extrapyramidal Symptoms: Data from two fixed dose trials provided evidence of dose-relatedness for extrapyramidal symptoms associated with risperidone treatment.

Two methods were used to measure extrapyramidal symptoms (EPS) in an 8-week trial comparing four fixed doses of risperidone (2, 6, 10, and 16 mg/day), including (1) a parkinsonism score (mean change from baseline) from the Extrapyramidal Symptoms Rating Scale and (2) incidence of spontaneous complaints of EPS:

Dose Groups	Pbo	Ris 2	Ris 6	Ris 10	Ris 16
Parkinsonism	1.2	0.9	1.8	2.4	2.6
EPS Incidence	13%	13%	16%	20%	31%

Similar methods were used to measure extrapyramidal symptoms (EPS) in an 8-week trial comparing five fixed doses of risperidone (1, 4, 8, 12, and 16 mg/day):

Dose Groups	Ris 1	Ris 4	Ris 8	Ris 12	Ris 16
Parkinsonism	0.6	1.7	2.4	2.9	4.1
EPS Incidence	7%	12%	18%	18%	21%

Other Adverse Events: Adverse event data elicited by a checklist for side effects from a large study comparing 5 fixed doses of RISPERDAL™ (1, 4, 8, 12, and 16 mg/day) were explored for dose-relatedness of adverse events. A Cochran-Armitage Test for trend in these data revealed a positive trend ($p<0.05$) for the following adverse events: sleepiness, increased duration of sleep, accommodation disturbances, orthostatic dizziness, palpitations, weight gain, erectile dysfunction, ejaculatory dysfunction,

orgastic dysfunction, asthenia/lassitude/increased fatiguability, and increased pigmentation.

Vital Sign Changes:

RISPERDAL™ is associated with orthostatic hypotension and tachycardia (See PRECAUTIONS).

Weight Changes:

The proportions of RISPERDAL™ and placebo-treated patients gaining ≥ 7% of body weight were compared in a pool of 6- to 8-week placebo-controlled trials, revealing a statistically significantly greater incidence of weight gain for RISPERDAL™ (18%) compared to placebo (9%).

Laboratory Changes:

A between group comparison for 6- to 8-week placebo-controlled trials revealed no statistically significant RISPERDAL™/placebo differences in the proportions of patients experiencing potentially important changes in routine serum chemistry, hematology, or urinalysis parameters. Similarly, there were no RISPERDAL™/placebo differences in the incidence of discontinuations for changes in serum chemistry, hematology, or urinalysis. However, RISPERDAL™ administration was associated with increases in serum prolactin (See PRECAUTIONS).

ECG Changes:

The electrocardiograms of approximately 380 patients who received RISPERDAL™ and 120 patients who received placebo in two double-blind, placebo-controlled trials were evaluated and revealed one finding of potential concern, i.e., 8 patients taking RISPERDAL™ whose baseline QTc interval was less than 450 msec were observed to have QTc intervals greater than 450 msec during treatment (see Warnings). Changes of this type were not seen among about 120 placebo patients, but were seen in patients receiving haloperidol (3/126).

Other Events Observed During the Pre-Marketing Evaluation of RISPERDAL™

During its premarketing assessment, multiple doses of RISPERDAL™ were administered to 2607 patients in phase 2 and 3 studies. The conditions and duration of exposure to RISPERDAL™ varied greatly, and included (in overlapping categories) open and double-blind studies, uncontrolled and controlled studies, inpatient and outpatient studies, fixed-dose and titration studies, and short-term or longer-term exposure. In most studies, untoward events associated with this exposure were obtained by spontaneous report and recorded by clinical investigators using terminology of their

own choosing. Consequently, it is not possible to provide a meaningful estimate of the proportion of individuals experiencing adverse events without first grouping similar types of untoward events into a smaller number of standardized event categories. In two large studies, adverse events were also elicited utilizing the UKU (direct questioning) side effect rating scale, and these events were not further categorized using standard terminology (Note: These events are marked with an asterisk in the table that follows).

In the listings that follow, spontaneously reported adverse events were classified using World Health Organization (WHO) preferred terms, with minor modifications for clarity. The frequencies presented, therefore, represent the proportion of the 2607 patients exposed to multiple doses of RISPERDAL™ who experienced an event of the type cited on at least one occasion while receiving RISPERDAL™. All reported events are included except those already listed in Table 1, those events for which a drug cause was remote, and those event terms which were so general as to be uninformative. It is important to emphasize that, although the events reported occurred during treatment with RISPERDAL™, they were not necessarily caused by it.

Events are further categorized by body system and listed in order of decreasing frequency according to the following definitions: frequent adverse events are those occurring in at least 1/100 patients (only those not already listed in the tabulated results from placebo controlled trials appear in this listing); infrequent adverse events are those occurring in 1/100 to 1/1000 patients; rare events are those occurring in fewer than 1/1000 patients.

Psychiatric Disorders: Frequent: increased dream activity*, diminished sexual desire*, nervousness. Infrequent: impaired concentration, depression, apathy, catatonic reaction, euphoria, increased libido, amnesia. Rare: emotional lability, nightmares, delirium, withdrawal syndrome, yawning.

Central and Peripheral Nervous System Disorders: Frequent: increased sleep duration* Infrequent: dysarthria, vertigo, stupor, paraesthesia, confusion. Rare: aphasia, cholinergic syndrome, hypoaesthesia, tongue paralysis, leg cramps, torticollis, hypotonia, coma, migraine, hyperreflexia, choreoathetosis.

Gastro-intestinal Disorders: Frequent: anorexia, reduced salivation*. Infrequent: flatulence, diarrhea, increased appetite, stomatitis, melena, dysphagia, hemorrhoids, gastritis. Rare: fecal incontinence, eructation, gastroesophageal reflux, gastroenteritis, esophagitis, tongue discoloration, cholelithiasis, tongue edema, diverticulitis, gingivitis, discolored feces, GI hemorrhage, hematemesis.

Body as a Whole/General Disorders: Frequent: fatigue. Infrequent:

edema, rigors, malaise, influenza-like symptoms. Rare: pallor, enlarged abdomen, allergic reaction, ascites, sarcoidosis, flushing.

Respiratory System Disorders: Infrequent: hyperventilation, bronchospasm, pneumonia, stridor. Rare: asthma, increased sputum, aspiration.

Skin and Appendage Disorders: Frequent: increased pigmentation*, photosensitivity*. Infrequent: increased sweating, acne, decreased sweating, alopecia, hyperkeratosis, pruritis, skin exfoliation. Rare: bullous eruption, skin ulceration, aggravated psoriasis, furunculosis, verruca, dermatitis lichenoid, hypertrichosis, genital pruritus, urticaria.

Cardiovascular Disorders: Infrequent: palpitation, hypertension, hypotension, AV block, myocardial infarction. Rare: ventricular tachycardia, angina pectoris, premature atrial contractions, T wave inversions, ventricular extrasystoles, ST depression, myocarditis.

Vision Disorders: Infrequent: abnormal accommodation, xerophthalmia. Rare: diplopia, eye pain, blepharitis, photopsia, photophobia, abnormal lacrimation.

Metabolic and Nutritional Disorders: Infrequent: hyponatremia, weight increase, creatine phosphokinase increase, thirst, weight decrease, diabetes mellitus. Rare: decreased serum iron, cachexia, dehydration, hypokalemia, hypoproteinemia, hyperphosphatemia, hypertriglyceridemia, hyperuricemia, hypoglycemia.

Urinary System Disorders: Frequent: polyuria/polydipsia*. Infrequent: urinary incontinence, hematuria, dysuria. Rare: urinary retention, cystitis, renal insufficiency.

Musculo-skeletal System Disorders: Infrequent: myalgia. Rare: arthrosis, synostosis, bursitis, arthritis, skeletal pain.

Reproductive Disorders, Female: Frequent: menorrhagia*, orgastic dysfunction*, dry vagina*. Infrequent: nonpuerperal lactation, amenorrhea, female breast pain, menorrhagia, leukorrhea, mastitis, dysmenorrhea, female perineal pain, intermenstrual bleeding, vaginal hemorrhage.

Liver and Biliary System Disorders: Infrequent: increased SGOT, increased SGPT. Rare: hepatic failure, cholestatic hepatitis, cholecystitis, cholelithiasis, hepatitis, hepatocellular damage.

Platelet, Bleeding and Clotting Disorders: Infrequent: epistaxis, purpura. Rare: hemorrhage, superficial phlebitis, thrombophlebitis, thrombocytopenia.

Hearing and Vestibular Disorders: Rare: tinnitus, hyperacusis, decreased hearing.

Red Blood Cell Disorders: Infrequent: anemia, hypochromic anemia. Rare: normocytic anemia.

Reproductive Disorders, Male: Frequent: erectile dysfunction*. Infrequent: ejaculation failure.

White Cell and Resistance Disorders: Rare: leukocytosis, lymphadenopathy, leucopenia, Pelger-Huet anomaly.

Endocrine Disorders: Rare: gynecomastia, male breast pain, antidiuretic hormone disorder.

Special Senses: Rare: bitter taste.

* Incidence based on elicited reports.

DRUG ABUSE AND DEPENDENCE

Controlled Substance Class - RISPERDAL™ is not a controlled substance.

Physical and Psychologic Dependence - RISPERDAL™ has not been systematically studied in animals or humans for its potential for abuse, tolerance or physical dependence. While the clinical trials did not reveal any tendency for any drug-seeking behavior, these observations were not systematic and it is not possible to predict on the basis of this limited experience the extent to which a CNS-active drug will be misused, diverted and/or abused once marketed. Consequently, patients should be evaluated carefully for a history of drug abuse, and such patients should be observed closely for signs of RISPERDAL™ misuse or abuse (e.g., development of tolerance, increases in dose, drug-seeking behavior).

OVERDOSAGE

Human Experience

Experience with RISPERDAL™ in acute overdosage was limited in the premarketing database (8 reports), with estimated doses ranging from 20 to 300 mg and no fatalities. In general, reported signs and symptoms were those resulting from an exaggeration of the drug's known pharmacological effects, i.e., drowsiness and sedation, tachycardia and hypotension, and extrapyramidal symptoms. One case, involving an estimated overdose of 240 mg, was associated with hyponatremia, hypokalemia, prolonged QT, and widened QRS. Another case, involving an estimated overdose of 36 mg, was associated with a seizure.

Management of Overdosage

In case of acute overdosage, establish and maintain an airway and ensure adequate oxygenation and ventilation. Gastric lavage (after intubation, if patient is unconscious) and administration of activated charcoal together with a laxative should be considered. The possibility of obtundation, seizures or dystonic reaction of the head and neck following overdose may create a risk of aspiration with induced emesis. Cardiovascular monitoring should commence immediately and should include continuous electrocardiographic monitoring to detect possible arrhythmias. If antiarrhythmic therapy is administered, disopyramide, procainaimde and quinidine carry a theoretical hazard of QT-prolonging effects that might be additive to those of risperidone. Similarly, it is reasonable to expect that the alpha-blocking properties of bretylium might be additive to those of risperidone, resulting in problematic hypotension.

There is no specific antidote to RISPERDAL™. Therefore appropriate supportive measures should be instituted. The possibility of multiple drug involvement should be considered. Hypotension and circulatory collapse should be treated with appropriate measures such as intravenous fluids and/or sympathomimetic agents (epinephrine and dopamine should not be used, since beta stimulation may worsen hypotension in the setting of risperidone-induced alpha blockade). In cases of severe extrapyramidal symptoms, anticholinergic medication should be administered. Close medical supervision and monitoring should continue until the patient recovers.

DOSAGE AND ADMINISTRATION

Usual Initial Dose

RISPERDAL™ should be administered on a BID schedule, generally beginning with 1 mg BID initially, with increases in increments of 1 mg BID on the second and third day, as tolerated, to a target dose of 3 mg BID by the third day. Further dosage adjustments, if indicated, should generally occur at intervals of not less than 1 week, since steady state for the active metabolite would not be achieved for approximately 1 week in the typical patient. When dosage adjustments are necessary, small dose increments/decrements of 1 mg BID are recommended.

Antipsychotic efficacy was demonstrated in a dose range of 4 to 16 mg/day in the clinical trials supporting effectiveness of RISPERDAL™, however, maximal effect was generally seen in a range of 4 to 6 mg/day. Doses above 6 mg/day were not demonstrated to be more efficacious than lower doses, were associated with more extrapyramidal symptoms and other adverse effects, and are not generally recommended. The safety of doses above 16 mg/day has not

been evaluated in clinical trails.

Dosage in Special Populations

The recommended initial dose is 0.5 mg BID in patients who are elderly or debilitated, patients with severe renal or hepatic impairment, and patients either predisposed to hypotension or for whom hypotension would pose a risk. Dosage increases in these patients should be in increments of 0.5 mg BID. Dosage increases above 1.5 mg BID should generally occur at intervals of not less than 1 week. Elderly or debilitated patients, and patients with renal impairment, may have less ability to eliminate RISPERDAL™ than normal adults. Patients with impaired hepatic function may have increases in the free fraction of the risperidone, possibly resulting in an enhanced effect (See CLINICAL PHARMACOLOGY). Patients with a predisposition to hypotensive reactions or for whom such reactions would pose a particular risk likewise need to be titrated cautiously and carefully monitored (See PRECAUTIONS).

Maintenance Therapy

While there is no body of evidence available to answer the question of how long the patient treated with RISPERDAL™ should remain on it, the effectiveness of maintenance treatment is well established for many other antipsychotic drugs. It is recommended that responding patients be continued on RISPERDAL™, but at the lowest dose needed to maintain remission. Patients should be periodically reassessed to determine the need for maintenance treatment.

Reinitiation of Treatment in Patients Previously Discontinued

Although there are no data to specifically address reinitiation of treatment, it is recommended that when restarting patients who have had an interval off RISPERDAL™, the initial 3-day dose titration schedule should be followed.

Switching from Other Antipsychotics

Although there are no data to specifically address switching from other antipsychotics to risperidone, immediate discontinuation of the previous antipsychotic treatment upon initiation of RISPERDAL™ therapy is recommended when medically appropriate. In all cases, the period of overlapping antipsychotic administration should be minimized. When switching patients from depot antipsychotics, initiate RISPERDAL™ therapy in place of the next scheduled injection. The need for continuing existing EPS medications should be reevaluated periodically.

HOW SUPPLIED

RISPERDAL™ (risperidone) tablets are imprinted "JANSSEN", and "R" and the strength "1," "2," "3," "4," or "5".

1 mg white, scored tablet: bottles of 60 NDC 50458-300-06, bottles of 500 NDC 50458-300-50, and blister pack of 100 NDC 50458-300-01.

2 mg orange tablet: bottles of 60 NDC 50458-320-06, bottles of 500 NDC 50458-320-50, and blister pack of 100 NDC 50458-320-01.

3 mg yellow tablet: bottles of 60 NDC 50458-330-06, bottles of 500 NDC 50458-330-50, and blister pack of 100 NDC 50458-330-01.

4 mg green tablet: bottles of 60 NDC 50458-350-06, bottles of 500 NDC 50458-350-50, and blister pack of 100 NDC 50458-350-01.

5 mg peach tablet: bottles of 60 NDC 50458-360-06, bottles of 500 NDC 50458-360-50, and blister pack of 100 NDC 50458-360-01.

Storage and Handling - RISPERDAL™ should be stored at controlled room temperature 59°-86°F (15°-30°C). RISPERDAL™ should be protected from light and moisture.

END OF LABELING

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AE/AP
action memo

Memorandum **Department of Health and Human Services**
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

DATE: December 21, 1993

FROM: Paul Leber, M.D.
Director,
Division of Neuropharmacological Drug Products
HFD-120

SUBJECT: Approvable and/or Approval Action Memorandum
NDA 20-272: Risperdal™, Janssen brand of risperidone

TO: File NDA 20-272
&
Robert Temple, M. D.
Director,
Office of Drug Evaluation I
HFD-100

Introduction:

The Division review team has concluded that Risperdal™ will be safe in use and effective for use if marketed for the 'management of the manifestations of psychotic disorders' under the conditions of use described and recommended in the professional product labeling drafted by the Division's review team.

For reasons explicated in the body of this memorandum, the Division believes that the issuance of an approvable action letter is unnecessary and recommends that the Office issue the attached approval action letter that grants Janssen permission to market Risperdal™ under the labeling developed by the Division.

Background:

Negotiations on the final form and content of drug product labeling ordinarily do not take place until a sponsor of an NDA has received and responded to an approvable action letter. Although it has advantages, the sequence of approvable action, labeling negotiations, and final approval action can needlessly extend the time to an approval action, especially in

those circumstances where the approvable action step is largely a formality (e.g., as when virtually all substantive issues affecting approval are already resolved at the time the approvable action issues).

Accordingly, believing that Division and Janssen were largely in agreement about the conditions of use under which Risperdal™ would be safe and effective for use, the Division initiated negotiations with the firm on product labeling. It was our expectation that agreement on a final draft of labeling would be reached readily, making it possible to approve the Risperdal™ NDA without having to go through the usual approvable action step.

Despite protracted deliberations with Janssen's representatives, this goal has not been realized. Rather than reaching speedy agreement, the Division and the firm have become embroiled in a dispute over aspects of product labeling that have nothing at all to do with the safe and effective use of Risperdal™.

Janssen insists that labeling for Risperdal™ provide information about the degree of therapeutic response among, and adverse reactions suffered by, patients randomized to the haloperidol control arm that is incorporated in each of the 3 clinical studies that provide substantial evidence of Risperdal's™ effectiveness. The Division has refused to accede to Janssen's demands because it believes that the side by side presentation of data obtained on Risperdal™ and haloperidol assigned subjects invites a comparison that leads to the conclusion that Risperdal™ has been shown to be superior to haloperidol when, in fact, it has not.

In the Division's view, none of the 3 studies that are a source of the data bearing on the two products is by design capable of adducing the kind and quality of evidence necessary to support a robust, externally valid, conclusion about their relative benefits or risks.

The firm, although acknowledging the validity of the Division's critique of the design of their 3 investigations, will not alter its position. Janssen's view is that the haloperidol data, provided they are accompanied by a statement which warns they cannot serve as a basis for a valid comparison of the relative risks and benefits of Risperdal™ and

haloperidol, may be presented without risk of misleading prescribers.

Negotiations, thus, are at an impasse, one that will not be overcome through further discussions.

The result, in my opinion, is perverse. The agency, publicly committed to expedite the approval of safe and effective drug products, finds its approval of a drug product that has evoked considerable interest in the psychiatric community and among psychiatric patients and their families being delayed solely because of a sponsor's desire for labeling that will facilitate the promotion of the product.

Accordingly, the Division, having concluded that Risperdal™ is 'safe in use' and 'effective for use' under the conditions of use recommended in the labeling drafted by the Division recommends that the NDA be approved. If Janssen finds the labeling under which the approval is made unacceptable, it does not have to market the product, but, given such a decision, the firm will be unable to claim that FDA is responsible for the delay in the product's approval.

The Division's recommendation notwithstanding, I are mindful that the Office may wish to proceed in a more traditional manner. Thus, an approvable action letter notifying the sponsor that the Risperdal™ NDA may be approved provided that Risperdal™ is marketed under the labeling developed by the Division has also been prepared. Although the Division believes the issuance of an approvable letter is unnecessary, it would not object if the Office elects to issue it rather than the approval action.

The remaining sections of this memorandum provide a number of observations that I want to offer for the record about the evidence bearing on the Division's recommendation as well as some comments about the kind and quality of evidence that would be required to make a valid comparison of the risks and benefits of two drug products.

Basis for the approval of Risperdal™:

The case for the approval of the Risperdal™ NDA, provided it is marketed under the labeling drafted by agency's review team, is straight forward

and is explicated in comprehensive detail in Dr. Laughren's excellent Approval Action Memorandum of 12/20/93.

The sponsor has provided results from more than one adequate and well controlled clinical investigation (i.e., Studies 201, 204 and 024) that, upon review, have been found to provide 'substantial evidence' that risperidone is 'effective in use' for the management of the manifestations of psychotic disorders. The Psychopharmacological Drugs Advisory Committee [PDAC] has considered the evidence and has endorsed the Division's conclusions.

The conclusion that Risperdal™ is 'safe for use' derives from reviews of reports of clinical experience involving approximately 2600 patients who participated in phase 2 and 3 trials. Although this experience does not show Risperdal™ to be free of risk, it is more than sufficient, given the nature of alternative modes of treatment available, and the natural history of psychotic illness, to support a conclusion that the risks associated with the use of Risperdal™ do not outweigh the benefits associated with that use. The PDAC shares this view.

Accordingly, the other requirements of the FD&C Act being satisfied, Risperdal™ may be approved for use under the conditions of use described in the draft labeling proposed by the Division.

Comments about the clinical studies that provide 'substantial evidence' of risperidone's effectiveness.

Three clinical investigations (Studies 201, 204 and 024) have been identified as sources of substantial evidence of risperidone's short term effectiveness as an antipsychotic agent.

Each of the three studies was conducted at multiple sites, entered actively psychotic, hospitalized, schizophrenic patients and employed a randomized, parallel control design. Two studies (201 and 204), conducted in North America, employed placebo controls; the third study (024) conducted at multiple sites in 15 countries around the world, did not. Two studies (204 and 024) randomized subjects to a fixed dose of drug;

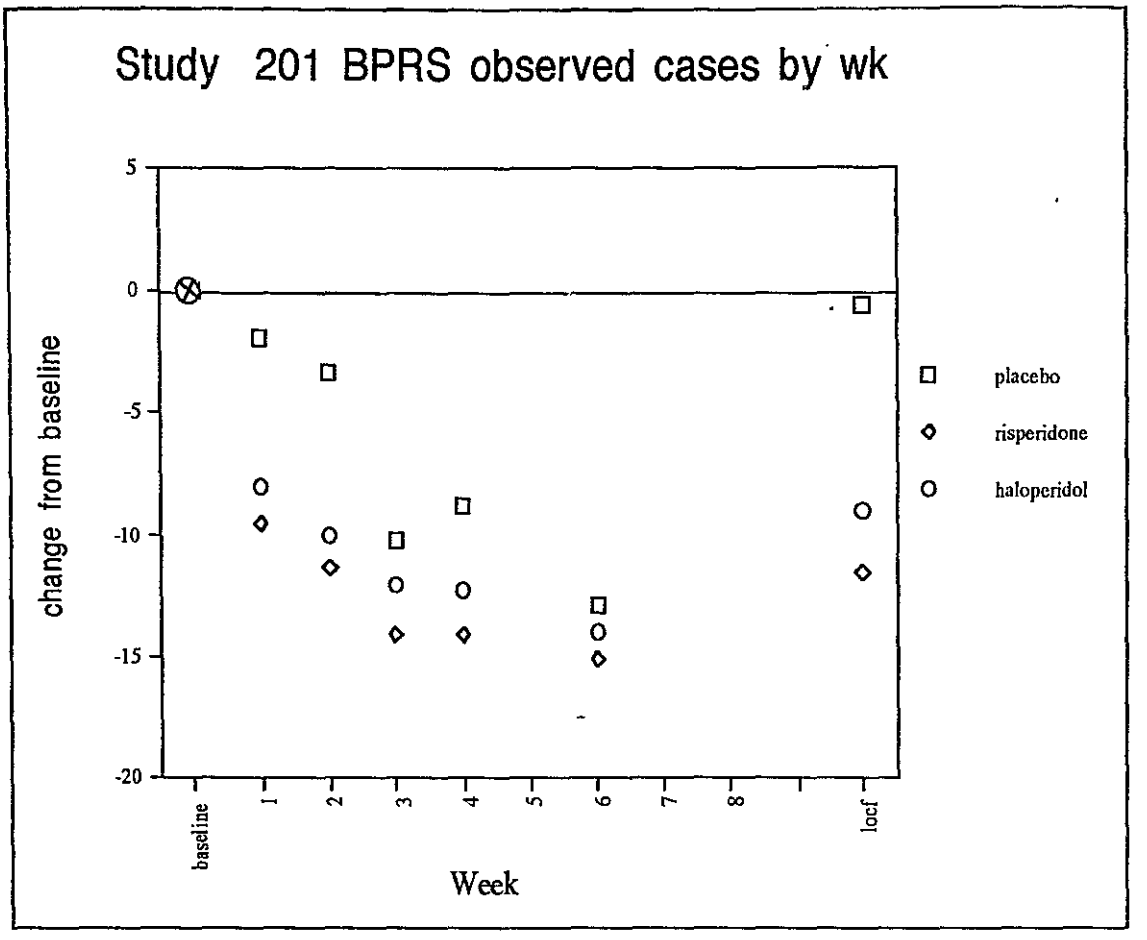
Study (201) allowed flexible titration to a maximum dose. Study 201 was 6 weeks in duration; Studies 204 and 024 were 8 weeks long.

Multiple rating instruments were used in all studies and response to treatment was assessed at multiple time points. Accordingly, there was opportunity for repeated measurement and testing of treatment differences across different measures and at multiple time points.

Although the rating instruments used differed, all studies employed instruments that contained the items found on the Brief Psychiatric Rating Scale, (BPRS), the scale that has been used traditionally to assess the effectiveness of antipsychotic drug products. Accordingly, the outcome of all studies can be compared on items that are, or are equivalent to, the BPRS.

Study 201:

Study 201 provides unequivocal support for the effectiveness of risperidone as an antipsychotic agent. Because of its titration design, it provides little in the way of useful dose response information, however. Importantly, Study 201 is of no value in assessing the comparative efficacy of risperidone and haloperidol because the products are compared under conditions that are entirely arbitrary (e.g., where a 20 mg a day dose of haloperidol fits along its dose response curve relative to 10 mg a day of risperidone is unknown). Accordingly, Study 201 cannot provide a valid basis for the comparison of the two products' comparative adverse event profile which can only be assessed fairly when both products are administered at equi-effective doses. The comparison between Risperdal™ and haloperidol assigned subjects may also be systematically biased in this study, as in others conducted by the sponsor, because only those subjects assigned to haloperidol had the possibility of prior exposure to the treatment to which they were randomized in the study. Finally, the estimates of treatment effect provided by study 201 are analysis dependent, as the following diagram documents.



The discrepancy of the LOCF and OC results observed in the diagram above are a consequence of the high incidence of premature discontinuations that occurred in this study. Only 51% (80/156) of those in the 'intent to treat' sample still remained at the end of the study's 4th week. As a consequence, the observed cases (OC) data set, which contains a disproportionate number of those subjects exhibiting spontaneous improvement, finds no between treatment differences at week 6. The LOCF based analysis, on the other hand, probably overestimates the treatment effect of the two active drugs because it is biased by the scores of placebo assigned subjects who were discontinued earlier and who might have continued to improve had they remained in the study.

Incidentally, there is a belief that the dropout rate observed in Study 201 is at least in part due to its design. Investigators, aware that a patient

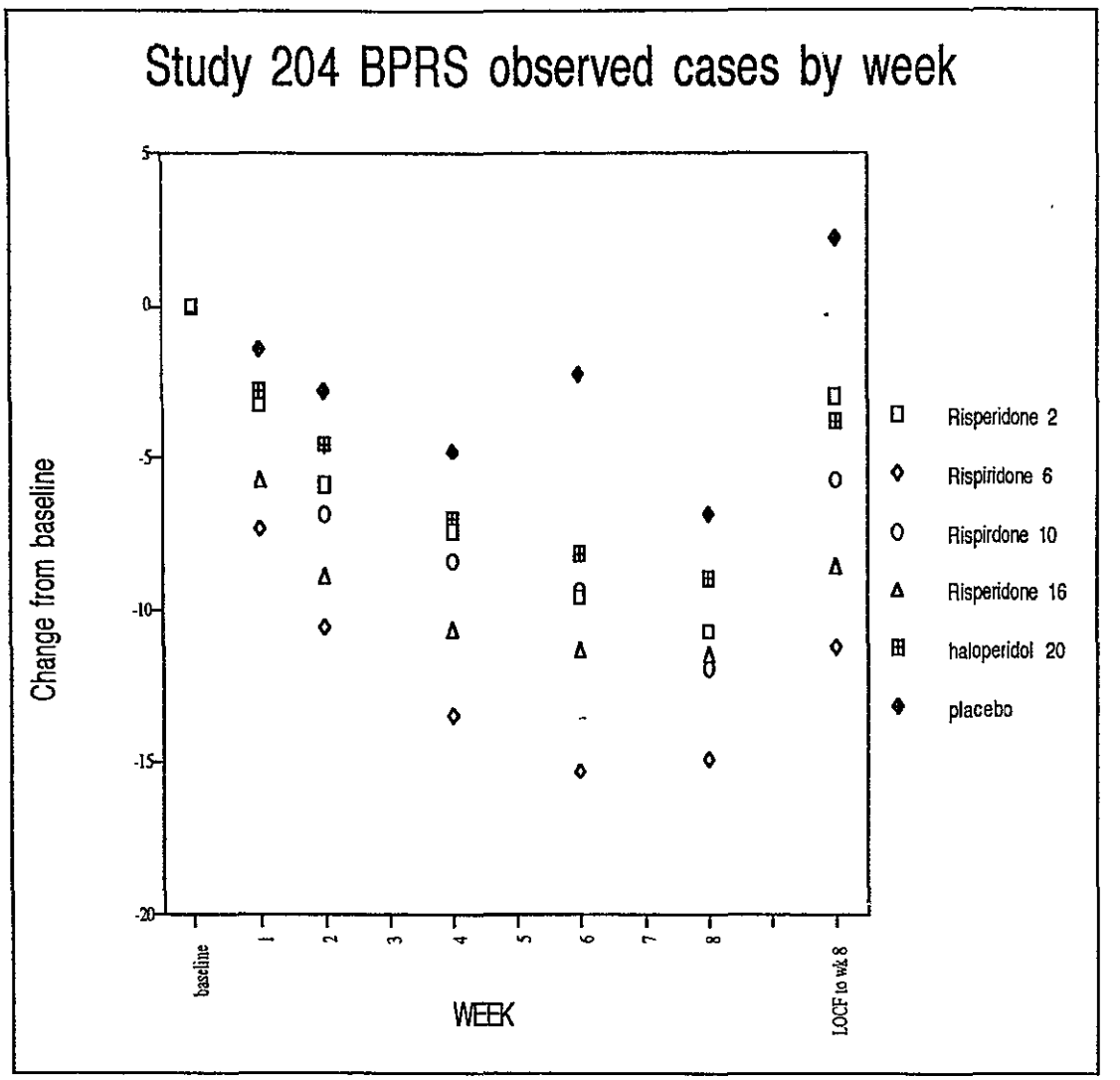
doing less well than expected had as much as one chance in 3 of being on placebo, might well have been inclined to discontinue such patients more readily than in a study where assignment to an inactive treatment was less likely. This speculation is not inconsistent with the fact that the rate of premature discontinuations is lower in Studies 204 (67% [349/515] at week 4) and Study 024 (81%, [1096/1356] at week 4) in which there was respectively, a 1 in 6 and a zero, risk of being assigned to placebo.

Study 204:

Study 204, like Study 201, provides unequivocal support for a conclusion that risperidone is an effective antipsychotic drug. Conducted at 26 US and Canadian based sites, it enrolled 513 acutely psychotic hospitalized patients, randomizing them, in a balanced design, to 4 fixed daily doses of risperidone (2, 6,10 and 16 mg/d), to 20 mg of haloperidol, or to placebo for 8 weeks. The intent of the study was, as recorded in the protocol, "to determine the safety and efficacy of 4 fixed doses of risperidone relative to placebo and haloperidol in the treatment of chronic Schizophrenia.

As the following diagram illustrates, the results of the LOCF and OC analyses differ in the estimates they provide of the size of the treatment effect of the active treatments. Study 204 differs from Study 201 in that analyses of both data sets achieve statistical significance, a consequence probably attributable to the former's larger size.

It is noteworthy that the outcome of the group randomized to 6 mg a day of risperidone (the group with best outcome among all 6 groups) is superior, at a statistically significant level, to the response of the group randomized to treatment with 20 mg of haloperidol. Although this finding has internal validity, it has no reliable interpretation regarding the relative effectiveness of risperidone and haloperidol. That such caution is necessary in interpreting the data is documented by the fact that patients assigned to the 16 mg and 10 mg a day dose of risperidone do not fair as well as those assigned to the 6 mg dose. It is probable that a similar, non-monotonic dose response relationship exists with haloperidol.



There is a possibility, nevertheless, that the sponsor may have intended that Study 204 be used to establish the comparative performance of risperidone and haloperidol. If that were the case, however, it is not clear why only one[1] dose of haloperidol was evaluated nor why a 20 mg

[1] It is generally acknowledged that the relative effectiveness (or potency) of two drugs cannot be validly estimated from a study that evaluates only single doses of one or both of the drugs. At a minimum 3, fixed, relatively widely spaced, doses of a drug are necessary to estimate the shape of its dose response function.

daily dose of haloperidol was used.

(N.B., In a December 14, 1993 letter to Dr. Temple, the firm offers an explanation: basically, that the dose of 20 mg was the one their consultants thought was most representative of haloperidol's use in clinical practice for inpatients of the type being randomized in the trial. This explanation, however, does not answer the basic question as to where along haloperidol's dose response surface, a 20 mg daily dose lies)

In sum, although Study 204 provides compelling support for Risperdal's effectiveness as an antipsychotic, it is incapable by virtue of its design of supporting any externally valid conclusion about the relative performance of haloperidol and Risperdal™. In fact, as noted above, the evidence developed in Study 204 calls attention to the risk of assuming that a higher dose of an antipsychotic drug invariably produces a better therapeutic response than a lower one, a point that must be considered in evaluating the relative low rank order of haloperidol's effect size in this study. For similar reasons, therefore, the incidence of adverse events observed in this study are not valid estimates of relative incidence of adverse events that would be obtained under conditions where haloperidol and Risperdal™ are administered at equi-effective doses.

Study 024

Study 024, conducted at 110 non-domestic sites in 15 countries, enrolled 1557 psychotic patients, randomizing them to 5 fixed doses of risperidone (1,4, 8 ,12, 16 mg/d) or haloperidol 10 mg/day. The study did NOT include

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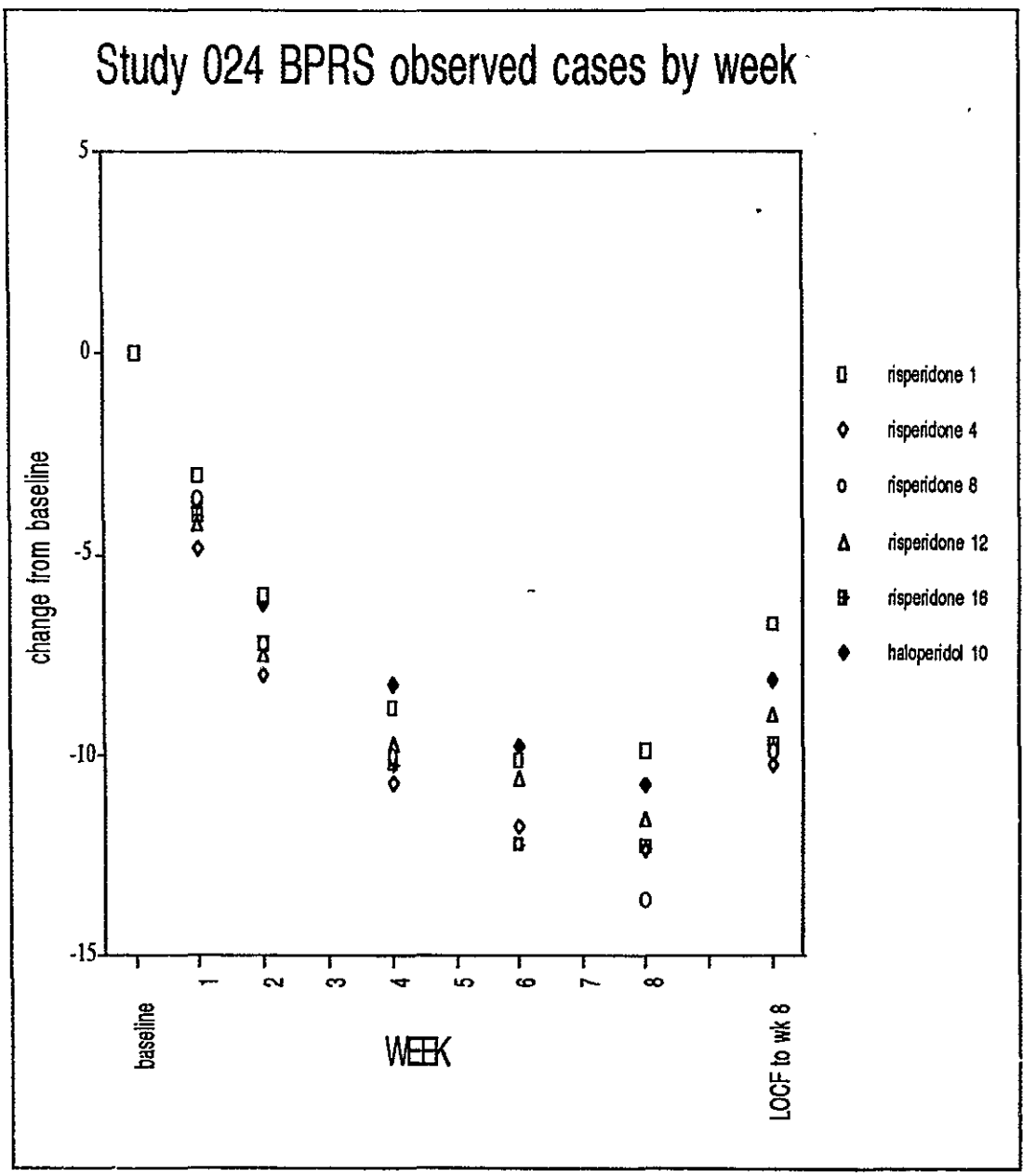
Accordingly, at least 6 active treatment arms are required, 7 if a placebo arm is included in the design, in a study intended to compare the effectiveness and relative safety of two drug products. It should be noted, however, that a control arm employing single doses of an active standard drug is often included in controlled trials to evaluate the sensitivity of the patient sample to drug treatment effects. Such a treatment arm is useful on those occasions where no difference is found between the investigational treatment and a placebo control (e.g., if the active standard treatment cannot be distinguished from placebo, the study is considered 'failed' rather than 'negative.')

a placebo treatment arm.



Because 148 of the patients randomized were at study sites that were subsequently determined to be in violation of GCP, the analysis of the study provided by the sponsor was based on a subset of 1356 of the

patients 1557 actually randomized.

Study 024 provides support for the effectiveness of Risperdal, but it is less robust than that provided by Studies 201 and 204. Pairwise contrasts between the 4 higher doses of risperidone (4 mg, 8 mg, 12 mg and 16 mg) and the 1 mg dose of the drug are all statistically significant in the LOCF analysis at 8 weeks, but the OC analysis is not as consistent. In part this may be due to the fact that the 1 mg risperidone dose may have exerted antipsychotic effects; in the absence of a placebo control, however, there is simply no way to be certain.

Study 024 also provides information about the dose response profile of Risperdal™ that, when taken along with the findings of Study 204, justifies recommending that Risperdal™ be administered in the range of 2 to 6 mg a day.

Once again, however, the study, by design is incapable of providing an externally valid estimate of the relative performance of haloperidol and Risperdal™. To be fair, the results are not inconsistent with a conclusion that Risperdal™ causes less EPS at the doses being recommended than haloperidol does when administered at 10 mg a day under the conditions of use allowed in the study, but this conclusion is not equivalent to concluding that the result is so robust that it should be described in product labeling where it may promote more extensive inferences about the relative performance of haloperidol and risperidone than are warranted.

Evidence that Risperdal™ is 'safe for use:'

The review team has evaluated the reports of adverse experiences and results on tests performed on Risperdal™ exposed patients and has concluded that Risperdal™ is 'safe for use' if administered under the conditions of use recommended in the labeling proposed by the Division. This is not to be construed as a warrant, however, that the use of Risperdal will be unaccompanied by reports of untoward events. To the contrary, some individuals to whom Risperdal™ is administered are virtually certain to suffer grievous events, including suicide and unexpected death. Based on the information available at the present time,

however, the risk of such serious events, even if caused by Risperdal™, would seem reasonably acceptable in a drug product intended to treat a serious, potentially life-threatening, illness like schizophrenia, and, accordingly, the Division and its advisors are able to conclude that the risks of Risperdal are reasonably outweighed by the benefits likely to accrue from its administration under the conditions of use proposed.

It bears emphasis that this risk to benefit assessment turns as much on subjective factors and values as it does on hard evidence. Evaluations intended to assess the contribution a drug's pharmacological effects make to the adverse effects observed in association with its use are highly subjective undertakings.

In the setting of a controlled clinical trial, especially were common adverse events are concerned, it is relatively easy to gain a quantitative estimate of relative risk. Specifically, if an adverse event of interest can be easily ascertained, readily classified, and enumerated unambiguously, it is a simple matter to estimate from a direct comparison of the proportion of subjects suffering the event under the drug and the control treatments, the extent of the risk attributable to the drug's action.

In contrast, when an adverse event occurs under conditions of uncontrolled use, it is virtually impossible to distinguish drug caused events from those bearing only a temporal association to the drug's administration. The distinction is especially difficult if the untoward event occurs spontaneously in the general population and/or is a manifestation of the illness under treatment.

If an untoward event is virtually unheard of in the course of a disease, however, its causal association with drug may seem more probable, but even here, the drug may still not be responsible. To illustrate, consider the single case of TTP reported from among Canadian patients exposed to Risperdal in a compassionate use program. It has been identified in the proposed labeling as a possible result of treatment with Risperdal™, but the decision to include it in labeling is based more on the rarity of TTP than objective evidence that Risperdal™ caused the disorder.

Other especially difficult to evaluate conditions include sudden

unexplained deaths and suicides, each of which are known to occur spontaneously and at higher rates in patients with chronic schizophrenia than in the normal population. Its expected higher incidence notwithstanding, each suicide that is temporally linked to the use of Risperdal™,for example, invariably raises questions about the role Risperdal™ might have played in its genesis. Similarly, if a patient on Risperdal™ were to die unexpectedly, it is always possible that a ventricular arrhythmia was responsible and that it occurred as a result of a quinidine like, pro-arrhythmic, effect of Risperdal™ on cardiac repolarization. Accordingly, although none of the deaths observed among patients on risperidone were attributed to this mechanism, labeling mentions the risks of QT prolongation.

Finally, a comment is in order about the results of life-time in vivo carcinogenicity studies in rodents that, although detecting a drug dependent increased incidence of adenocarcinomas in rats and female mice, have been determined to predict no clear signal of risk to humans. This judgment turns on the belief that the mechanism underlying the pathogenesis of these tumors (i.e., elevated prolactin levels stimulating tumor growth) is not operative in humans. This belief, although not inconsistent with the failure of several epidemiologic investigations to find evidence in humans of a link between elevated prolactin and an increased incidence of tumors, is hardly conclusive. The absence of evidence is not evidence of absence. Accordingly, although CDER's CAC's interpretation of the carcinogenicity studies has been endorsed by the PDAC, both the Division and the PDAC believe their findings should be described in product labeling.

In sum, although the review team and the PDAC AC found nothing unusual for an antipsychotic drug product in the preclinical or clinical data (i.e., adverse events and laboratory findings) reported for Risperdal™, their conclusions cannot be taken as a warrant that the use of Risperdal™ is free of serious risk. At best, the conclusion is a reflection of a judgment that the risks of Risperdal™ are reasonable in light of the benefits likely to be associated with its use.

On the basis of what evidence should comparative claims be allowed to appear in product labeling?

The subject has many facets, some practical, others philosophical. It deserves discussion in this memorandum only because of Janssen's insistence that Risperdal™ labeling provide data on haloperidol.

From a purely philosophical perspective I have an antipathy to comparisons that are unfair or based on incomplete information. Rarely, it seems to me, is evidence on the relative risks and benefits of two or more products so reliable, precise, and comprehensive that it allows a general statement to be made about relative risks and benefits. I am mindful, however, that knowledge of certain differences can be critical to the prudent selection and/or safe and effective use of a drug product. Accordingly, in circumstances where a difference is known to exist and to have potentially important clinical consequences, it would be in the public interest to include information about that difference in product labeling[2].

On the other hand, it does not serve the public interest to clutter product labeling with descriptions of factual, but clinically irrelevant, differences.

Above all else, however, before a comparative claim or statement is included in labeling, it should be firmly and fairly established with data that meets a high standard of evidence.

In my view, a claim of comparative advantage should be allowed in product labeling only if 1) it involves an attribute of clinical importance, and 2) is documented with compelling evidence adduced in more than one clinical study, each of which is designed, prospectively, to evaluate the claimed advantage. If such a condition is not imposed, claims of superiority could be advanced on the basis of a finding that reflects no more than the operation of chance or be the result of one of a multitude of post hoc, data

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[2] Certainly, such information would be included in the labeling of the product asserting the advantage. It is an interesting question whether the agency could compel the sponsor of the 'inferior' product to include the same information in the labeling of its product.

conditioned, analyses.

The design of clinical trials intended to compare the properties of two or more drug products must ensure that the conditions of the comparison allow for an appraisal that is fundamentally fair to each of the products. Subjects enrolled in a comparative study, for example, should be naive to the treatments being compared to reduce the possibility that a systematic bias may arise from subjects having had prior experience with one or more of them. As mentioned in an earlier footnote, at least 3, preferably more, widely spaced, fixed, doses of each drug would have to be studied to allow the shapes of the dose response relationship of each drug to be characterized[3], a critical preliminary step to any valid comparison of their properties. It seems likely, however, given the variability among samples of patients in their response to a given dose of a drug, that it will ordinarily be necessary to have each drug and dose combination of interest evaluated in a single study. This requirement might be relaxed if modeling approaches of the type noted in footnote 3 are validated. In any case, methodological details aside, it is best to approach all comparative claims with caution, if not outright distrust, unless it can be assured that they derive from fair, balanced, and comprehensive evaluations conducted at equi-effective doses.

The principles described applied to Janssen's demands:

Some of the evidence in the Risperdal™ NDA, as noted earlier, is not inconsistent with the possibility that risperidone may be associated with a lesser risk of extrapyramidal side effects when administered at doses of 4 mg to 6 mg a day than is haloperidol when administered at doses (10 to 20 mg/day), doses that enjoy widespread use in current clinical practice.

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[3] These suggestions assume a traditional frequentist statistical approach to the analysis of clinical trial data. A case can be advanced that other approaches, in particular those that mathematically model both individual and population responses and the link between them, might provide an acceptable, perhaps superior, alternative. In any case, the point is not so much the choice of method, but the requirement that there be an accurate characterization of the dose response relationship of each drug involved available before a comparison is undertaken.

The issue of regulatory import is whether or not the data pointing toward this possible advantage ought to be presented in Risperdal™ labeling.

Janssen, it is important to note, did not conduct studies of appropriate design to compare the properties of two drug products. To the contrary, although it cannot be known with certainty, it seems probable that Janssen's 3 studies were intended primarily to document the effectiveness and safety of risperidone, and not to make a comparative claim. A haloperidol treatment arm (standard active control) was included in each study, but, from the Division's perspective, its purpose was to serve as an indicator of the 'sensitivity' of the patient sample entered to respond to the effects of antipsychotic drug treatment.

Had the firm sought the agency's advice about the kind and quality of evidence required to support comparative claims, and to my recollection they did not explore that question with us[4], they would have been informed that there are substantive barriers, both philosophical and technical, to doing so successfully.

In addition to discussing the generic points about comparative studies described above, we would have advised them that there is, to our knowledge, no general agreement in the community of how comparative studies of antipsychotic drugs ought to be carried out. In particular, there is no consensus about which specific attributes of antipsychotic drug product performance ought to be considered in making such a comparison. Furthermore, even if there were some level of general agreement on the attributes of antipsychotic drugs that should be considered, the choice of an assessment instrument suitable for making the comparison would still be uncertain. It would be unfair, for example, to compare the effectiveness of two drugs on a rating instrument which registers the untoward pharmacological effects associated with one of them as evidence of an adverse therapeutic outcome (as might occur on a scale rating improvement, or lack thereof, in so-called 'negative' symptoms).

Returning to the matter currently in dispute, it is important to acknowledge that the Division does not deny that a colorable argument can

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[4] There was no 'end of phase 2' meeting.

be advanced, based on the results of Study 024 , that Risperdal™ given at doses in the range recommended in proposed product labeling (2 to 6 mg a day) is likely to produce fewer extrapyramidal signs and symptoms than haloperidol administered without accompanying anticholinergic drugs at a fixed dose of 10 mg a day. On the hand, a single study, the only one examining a dose of haloperidol administered at doses of less than 20 mg a day, seems an inadequate basis to support an implied advantage, even one that is advanced with a caveat.

Furthermore, there are additional factors worthy of consideration. When used in clinical practice, the regimen under which haloperidol is administered may differ from that which obtained in Study 024. Haloperidol, although widely used, is only one of a large number of marketed antipsychotic drug products. What makes the comparison between it and Risperdal™ so uniquely important among all possible pairwise comparisons that it deserves presentation in labeling? Perhaps, if comparisons are to appear in antipsychotic drug product labeling, they should involve all products, or, at a minimum, a representative panel drawn from the product class (e.g., clozapine, thioridazine, chlorpromazine, perphenazine, haloperidol, molindone, etc.).

The list of issues just enumerated is by no means exhaustive. It is intended only to call attention to the fact that many matters ought to be considered in taking a decision that may be interpreted as a precedent by the regulated industries.

In my view, therefore, there is little to be gained, and potentially much to be lost, if we agree to Janssen's demands at this point in time. Risperdal™ can be marketed and used safely and effectively without its labeling mentioning anything whatsoever about the controlled trials that are the source of the evidence that led to its approval, let along a description of the responses of subjects assigned to a control treatment used in those trials, moreover, one that may promote a misleading inference about the product.

From a technical perspective, furthermore, there is no regulatory requirement that forces us to acquiesce to the firm's demands. 21 CFR 201.56 requires only that the labeling of a prescription drug contain "a

summary of the essential scientific information needed for the safe and effective use of [a] drug," and the labeling developed for Risperdal™ by the Division fully meets that requirement.

Conclusion and Recommendations:

Upon review of the information provided in NDA 20-272, the Division concludes that Risperdal™ has been shown, according to the requirements of the FD&C Act, to be a safe and effective drug, provided it is marketed under the conditions of use recommended in the labeling drafted by the Division.

Accordingly, the Division recommends that the approval action letter be issued.

12/21/93

Paul Leber, M.D.
December 21, 1993
08:45 hours

doc Risperdal™ [2.1]12/21
cc: NDA 20-272
HFD-100:
Temple
HFD-120:
Laughren
Mosholder
Fitzgerald
Hardeman
Blum
HFD-730
Nevius
Hoberman

REVIEW AND EVALUATION OF CLINICAL DATA

Application Information

NDA # 20-272

Sponsor: Janssen Research Foundation

Clock Date: April 15, 1992

Drug Name

Generic Name: Risperidone

Proposed Trade Name: Risperdal

Drug Characterization

Pharmacological Category: Antipsychotic

Proposed Indication: Treatment of the symptoms of psychotic disorders

NDA Classification: 1P

Dosage Forms, Strengths, and Routes of Administration:
Oral Caplets in 1, 2, 3, 4, and 5 milligram strengths

Reviewer Information

Clinical Reviewer: Andrew Mosholder, M.D.

Review Completion Date: May 11, 1993

CONTENTS

1.0 Material Utilized in Review

1.1 Material from NDA

The following is a list of specific items reviewed.

Volume	Submission Date	Material
1.1	April 15, 1992	Summary and proposed labelling
1.102	April 15, 1992	Integrated Summary of Effectivesness
1.102-1.108	April 15, 1992	Integrated Safety Summary
1.108	April 15, 1992	Drug Abuse and Overdose Information; Benefit/Risk Statement
1.38-1.101	April 15, 1992	Study reports for Phase 1, 2 and 3 trials
1.234-1.238, 1.250, 1.256, 1.272-1.275, 1.278, 1.280, 1.285, 1.289, 1.290, 1.294, 1.295, 1.300	April 15, 1992	Case report forms
-	June 22, 1992	Response to request for demographic and exposure data
-	September 23, 1992	10-day Safety Report
-	October 27, 1992 October 28, 1992 November 20, 1992 December 7, 1992	Responses to requests for additional tabulations of safety data
-	December 23, 1992	Premature discontinuation summaries
-	February 1, 1993	Responses to requests for information, premature discontinuation summaries

(continued)	Submission Date	Material
-	February 11, 1993	10-Day Safety Report
	February 12, 1993	Response to request for information on adverse event rates
-	March 9, 1993	Responses to requests for safety and efficacy information
-	March 11, 1993 and April 2, 1993	Draft U.S. and foreign labelling
-	March 15, 1993	List of serious adverse events during clinical trials
-	March 30, 1993	Response to request for safety infromation
-	March 30, 1993	Pharmacokinetics in special populations--Study 0005
	April 2, 1993	Response to requests for efficacy data
-	April 8, 1993	Response to requests for safety data

Safety issues were addressed primarily via the Integrated Safety Summary, supplemented by examination of individual study reports and case report forms.

1.2 Material from IND

The division file for IND Janssen's commercial IND for risperidone, was consulted during the course of this review.

The annual report for IND for the period September 7, 1991 to September 6, 1992 was also consulted.

2.0 Background

2.1 Indication

There are currently more than a dozen neuroleptic drugs approved as antipsychotic medications in the U.S. All but one are potent blockers of dopamine D2 receptors, and this blockade is believed to ameliorate psychotic symptoms. Response rates to the antipsychotic actions of these drugs is said to be 75% (Schatzberg and Cole, 1991), but the so-called "positive" symptoms such as hallucinations and delusions respond more robustly than such "negative" symptoms as withdrawal and lack of motivation. In addition, the dopamine blocking antipsychotics are well known to cause troublesome extra-pyramidal side

effects (EPS) and tardive dyskinesia (TD). The remaining neuroleptic, clozapine, is a weaker D2 blocker and probably has a novel mechanism of action. It is an antagonist of D2, D1, serotonin 5HT2, histamine and alpha adrenergic receptors. Clozapine enjoys a claim to greater efficacy than typical neuroleptics, without causing EPS or TD. However, since it can induce agranulocytosis and seizures, its use is limited solely to refractory patients. Risperidone is both a dopamine D2 and a serotonin 5HT2 antagonist. Its D2 blocking potency is lower than traditional neuroleptics, while it has more potent anti-serotinergic activity than any approved antipsychotic. This combination is intended to convey greater efficacy towards negative symptoms, while reducing the risk of extrapyramidal side effects. This line of reasoning is bolstered by preliminary experiments with ritanserin, a serotonergic antagonist, for treatment of negative schizophrenic symptoms (Gelders 1989).

2.2 Related INDs and NDAs

Janssen's commercial IND for risperidone is

The following are the single investigator, compassionate use INDs for risperidone:

Dr. Kenneth Jobson
Dr. Allen Solomon
Dr. Jonathan Tuerk
Dr. Rachel Hamilton
Dr. Steven Potkin
Dr. Hegyvary
Dr. Siris

2.3 Administrative History

The original IND for risperidone was submitted 8/9/88; the drug had already been used in clinical trials in Europe. On 9/6/88 the division held a 30 day safety review meeting and decided to allow the initial U.S. Phase II trial, study 201, to proceed.

The sponsor submitted an amendment 7/27/89 describing protocols 204 and 205: 204 was a Phase Three comparison of haloperidol, risperidone and placebo, and 205 an open label extension of risperidone. This division delayed the extension study pending preliminary demonstration of efficacy.

As preliminary demonstration of efficacy, the sponsor submitted results from protocol 201 on 5/29/90; on the strength of this data women of child bearing potential were permitted to participate and extension studies were allowed.

On 8/29/91 a pre-NDA meeting between members of this Division and representatives of Janssen took place. At this meeting the firm agreed to provide further data from two carcinogenicity reports after submitting the NDA. The division requested that in addition to use of the PANSS instrument to assess efficacy, the "cluster of four items" from the BPRS be analyzed, i.e. unusual thought content, hallucination, suspiciousness, and conceptual disorganization. The division also requested a dose/plasma concentration response analysis. It was agreed that in Protocol 204 each treatment group would be compared to placebo, and the most significant risperidone treatment would be compared to haloperidol. Regarding the integrated safety database, it was mutually agreed that adverse effects reported during the single dose Phase I studies would be considered separately.

A teleconference between the firm and FDA Biopharmaceutics was held 10/3/91 to discuss studies involving patients with renal or hepatic disease, and the bioequivalence of research and market formulations.

2.4 Directions for Use

In the proposed labeling, the only specified contraindication is hypersensitivity to the drug or its components.

There are two warnings in the proposed labeling. The first deals with neuroleptic malignant syndrome. The second concerns tardive dyskinesia, and suggests that risperidone may be less likely to cause TD than traditional neuroleptics.

Orthostatic hypotension is noted to occur especially during initiation of drug therapy. Caution is urged in patients with known cardiovascular disease.

The prescribing physician is advised to caution patients about orthostasis, and to instruct patients not to breastfeed while on risperidone. The physician is also advised to tell patients taking risperidone that if they are pregnant, could become pregnant, or expect to use alcohol, prescription medication or over the counter drugs, they should inform their physician.

The proposed labeling states there has been no evaluation of drug-drug interactions, and advises caution if risperidone is given with other CNS active drugs.

Due to the drug's prolactin elevating property, care is recommended when there is a history of breast cancer.

The drug is classified as Pregnancy category B.

Regarding special populations, it is stated that saftey and effectiveness in children has not been established. For geriatric use the sponsor recommends lower doses, noting that only a limited number of older patients have taken risperidone.

Experience with human overdoses is described as limited, and general supportive measures are advised with particular attention to the cardiovascular system. Based on the elimination half life, the sponsor advises close monitoring for at least 24 hours.

The recommended initial dosage is one milligram BID for all patients, titrated to 2 mg BID on the second day and 3 mg BID on the third day as needed. Doses above 10 mg/d are described as having no more efficacy than lower doses, while carrying a higher risk of EPS. The sponsor states that the safety of doses above 16 mg/d has not been determined.

2.5 Foreign Marketing

As of March 29, 1993, risperidone had never been marketed in any country.

References for section 2

Schatzberg AF and Cole JO, Manual of Clinical Psychopharmacology, 2nd edition, Washington: American Psychiatric Press, 1991

Gelders YV, Thymosthenic Agents, A Novel Approach in the Treatment of Schizophrenia. British Journal of Psychiatry (1989), 155 (suppl. 5), 33-36.

3.0 Chemistry

The chemistry has been reviewed separately. There are no outstanding chemistry concerns of any clinical relevance.

4.0 Animal Pharmacology

The animal pharmacology is reviewed separately, and only a brief summary is presented here.

Nonclinical pharmacology studies show risperidone to be a central and peripheral 5HT2 antagonist. It also has potent dopamine D2 antagonism, and enhances prolactin release. For central D2 activity it appears to be a less potent antagonist than haloperidol, and requires higher doses to induce catalepsy or to block motor activity. Other properties include antagonism of histamine H1 and alpha adrenergic receptors; it has no appreciable antimuscarinic activity. The primary metabolite, 9-OH-risperidone, possesses activities similar to the parent compound.

Acute toxicity was tested in mice, rats and dogs. The LD50 in mice was 82.1 mg/kg for males and 63.1 mg/kg for females. In rats the LD50 was 113 mg/kg for males and 56.6 mg/kg for females. Signs of acute toxicity were felt to be related to the pharmacological actions of the drug and included prostration, collapse, hypothermia and seizures. Some gastrointestinal disturbance was also observed, and necropsies showed GI erosions and bleeding in rodents. Survivors recovered without sequelae. 9-OH-risperidone reportedly caused a similar profile of acute toxicity in rats.

Multidose toxicity studies included three month administration to rats. Findings included decreased weight gain at high doses, changes in sex organs consistent with increased prolactin levels, and laboratory value changes as follows, all of slight magnitude: increased hematocrit, hemoglobin, red blood cell, and BUN; decreased calcium, total protein, glucose, albumin and triglycerides; in urine, a decrease in specific gravity and creatinine and an increase in pH and volume. When rats were administered the drug for 12 months, decreased weight gain was again noted, as were histological changes consistent with high prolactin levels. Laboratory abnormalities, all considered slight, included decreased potassium, BUN, alanine aminotransferase, WBC, platelets, urine creatinine, and increases in cholinesterase and urine volume.

In dogs, three month administration produced sedation, prolactin mediated endocrine changes, decreased body weight gain and increased red blood cells in the spleen red pulp. Laboratory value changes included moderate increase in haptoglobin, slight decreases in hematocrit, hemoglobin and RBC, decreased serum testosterone, and increases in cholesterol and phospholipids. In male dogs, the prolactin mediated organ changes reversed two months after the drug was discontinued. Twelve month dosing studies in dogs showed effects essentially similar to the three month studies. Laboratory value changes here included mild decrease in hematocrit, hemoglobin, RBC, and potassium, and moderate increases in haptoglobin. cholesterol and phospholipids. Cardiovascular studies in concious dogs showed prlongation of the QTc interval with oral dosing.

Fertility studies showed some pup mortality in rats. Teratogenicity studies were negative, in the sponsor's opinion.

In rodent carcinogenicity studies, the drug produced higher rates of mammary adenocarcinoma, pancreatic endocrine adenoma and pituitary adenoma; these

tumors are thought to result from hyperprolactinemia. Risperidone neither induced nor inhibited drug metabolizing enzymes in rats.

Lactating beagles secreted risperidone and its hydroxy-metabolite in their milk.

5.0 Description of Clinical Data Sources

5.1 Primary Development Program

5.1.1 Study Type and Design/Patient Enumeration

Table 5.1.1 enumerates participants in the various phases of the sponsor's development program for Risperidone. A total of 2322 patients exposed to Risperidone provided data for the integrated Phase 2-3 safety database. Please note that there were an additional 140 risperidone exposed patients from studies not included in the integrated safety database; six studies apparently lacked complete individual data, and the sponsor elected to excluded these from the integrated data set. (The table in section 5.2.1 provides further information on these studies.)

The cutoff date for inclusion of clinical data in the integrated safety data set was May 31, 1991. In addition, all deaths and other serious adverse experiences known to Janssen as of April 15, 1992 were reported in the NDA, and those occurring before the May 31, 1991 cutoff date were included in the integrated safety data base. Of course, the sponsor has continued to report serious adverse experiences from ongoing studies as 10-day safety reports to the agency; these cases have been examined as part of the safety review, although they are not included in the integrated database.

Appendix 5.1.1 lists all the studies in the sponsor's clinical development program, with a brief description of each.

For Phase I studies the patient groups were as follows:

Risperidone	175
Active control	7
Placebo	6

Similarly, for Phase 2-3 the corresponding groups are shown below:

Risperidone	2322
Active control	533
Placebo	176

The integrated database includes data from three ongoing open label risperidone studies; however, only patients who completed, or discontinued prematurely, contributed data. There were 192 such patients. Those patients who were still being treated in ongoing trials were not included in the integrated data set.

5.1.2 Demographics

Table 5.1.2.1 presents the demographic information for patients studied in Phase I trials. These subjects were all male, predominantly white and under age 40.

Table 5.1.2.2 provides the demographic profile for all patients in the integrated Phase 2-3 safety data set. Patients were mainly white men under age

40. Only 60 patients 65 years or older were exposed to risperidone; a total of 785 women received the drug. Risperidone was administered to no patients under 16 years of age. The demographic profiles for the risperidone, active control and placebo groups in the integrated safety data set are similar, as the table illustrates.

5.1.3 Extent of exposure (dose/duration)

Table 5.1.3.1 shows the numbers of patients in Phase I trials according to mean daily risperidone dose and duration of administraion. The majority (90%) received only one dose. Investigators found that psychiatric patients tolerated the drug much better than healthy volunteers; for this reason all 60 subjects given the 4 mg dose were patients.

The mean daily dose and duration of risperidone treatment for patients in Phase II and III trials is shown in Table 5.1.3.2. In terms of the proposed daily dose range of 2-10 mg, some 84% of the patients in the integrated safety data set received mean dosages above 2 mg/day; 27% received mean daily dosages in excess of 10 mg. A substantial majority of the patients (84%) were treated for approximately two months or less. There were 213 patients on risperidone for approximately forty weeks or longer, but no patient received the drug for as long as two years.

The table below shows time of exposure calculated in terms of patient-years, for the various treatment groups.

Treatment	Exposure (Patient-Years)
Risperidone	508
All active controls	61 (includes 51 haloperidol patient years)
Placebo	13

In addition, Janssen officials reported in a recent telephone conversation that approximately 25 patients worldwide have received compassionate use risperidone without enrollment in a formal clinical trial.

TABLE 5.1.1 SUMMARY OF ALL STUDIES			
Pools by Study Design	Enumeration by Treatment Group[1]		
	Risperidone	Active Control	Placebo
PHASE 1 (CLINICAL PHARMACOLOGY)			
Single Dose	158	5	4
Multiple Dose	17	2	2
SUBTOTAL	175	7	6
PHASES 2-3 (ANTIPSYCHOTIC STUDIES)			
Placebo Controlled	436	140	176
Inpt/Fixed Dose	348	87	88
Inpt/Dose Titration	88	53	88
Active Controlled	1301	393	0
Outpt/Fixed Dose	1136	226	0
Outpt/Dose Titration	55	52	0
Inpt/Fixed Dose	39	20	0
Inpt/Dose Titration	71	95	0
Uncontrolled	585 (137)	0	0
Outpt/Short-Term	31	0	0
Outpt/Long-Term	333	0	0
Inpatient/Short-Term	220	0	0
Inpatient/Long-Term	138	0	0
SUBTOTAL	2322	533	176
SINGLE DOSE TOTAL	158	5	4
MULTIPLE DOSE TOTAL	2339	535	178
GRAND TOTAL	2497	540	182

[1]Numbers in parentheses represent patients participating in continuation studies but already counted under previous headings.

Table 5.1.2.1
Demographic Profile for Phase 1 Studies

Parameter	Risperidone (N=175)	Placebo (N=6)	Active Control (N=7)
Age (Years)			
Mean	30	25	27
Range			
Groups (%)			
<40 Years	147 (84%)	6 (100%)	7 (100%)
40-64 Years	28 (16%)	0 (0%)	0 (0%)
Sex			
Male	175 (100%)	6 (100%)	7 (100%)
Race			
White	75 (74%)	--	--
Non-White	26 (26%)	--	--
Missing	74	6	7
Weight (kg)			
Mean	78	76	62
Range			

TABLE 5.1.2.2
Demographic Profile for Phase 2 and 3 Studies

PARAMETER	Risperidone Total (N = 2322)	Placebo (N=176)	Active Control (N=533)
AGE (years)			
N	2203	142	484
Mean	39	38	38
Range			
Groups (%)			
<40 Years	1299 (59%)	87 (61%)	298 (61%)
40-64 Years	844 (38%)	54 (38%)	183 (38%)
>= 65 Years	60 (3%)	1 (1%)	3 (1%)
Missing	119	34	49
SEX			
Male	66%	80%	72%
Female	34%	20%	28%
RACE			
White	80%	63%	75%
Non-white	20%	37%	25%
Missing	676	34	128
MEAN WEIGHT (KG)	72	72	74

TABLE 5.1.3.1

Number (Percent) of all Volunteers Receiving Risperidone According to Mean Daily Dose and Duration in Phase 1 Clinical Pharmacology Studies (N =175)

Duration (Days)	<1 mg	1 mg	2 mg	4 mg	TOTAL	(%)
1	6	43	49	60	158	(90.3)
7	-	6	-	-	6	(3.4)
20	-	11	-	-	11	(6.3)
TOTAL	6	60	49	60	175	(100)
(%)	(4)	(34)	(28)	(34)	(100)	

TABLE 5.1.3.2

Number (Percent) of all Patients Receiving Risperidone According to Mean Daily Dose and Duration of Therapy in Phase 2 and 3 Studies (N =2322)

Duration (Days)	≤2mg	2<mg≤4	4<mg≤6	6<mg≤10	>10mg	TOTAL*	(%)
1 Day	12	6	0	0	1	19	(0.8)
2-10 Days	31	32	11	32	23	129	(5.6)
11-21 Days	26	31	25	47	46	175	(7.5)
22-35 Days	33	202	57	90	65	447	(19.3)
36-49 Days	24	26	10	53	36	149	(6.4)
50-64 Days	198	197	65	218	358	1036	(44.6)
65-122 Days	10	9	8	43	21	91	(3.9)
123-274 Days	5	18	9	16	10	58	(2.5)
275-455 Days	24	37	30	44	52	187	(8.5)
456-640 Days	4	2	2	3	4	15	(0.6)
641-822 Days	0	0	0	0	0	0	(0.0)
Not Specified	0	3	0	1	0	5	(0.2)
TOTAL	367	563	217	547	616	2322	(100)
(%)	(15.8)	(24.2)	(9.3)	(23.6)	(26.5)	(100)	

* Includes patients with no dosage information.

5.2 Secondary sources

5.2.1 Other studies and compassionate use

Although many of the overseas trials were not conducted under the risperidone IND, all worldwide clinical trials with the drug to date have been part of Janssen's development program. There were, however, six studies which the sponsor decided not to include in the integrated safety data base, presumably because individual data were lacking. The following table summarizes the numbers of patients in these studies.

SUMMARY OF ALL PHASE 2-3 STUDIES NOT IN THE INTEGRATED SAFETY DATABASE
Enumeration by Treatment Group

Pools by Study Design	Risperidone	Active Control	Placebo
Placebo Controlled	10	0	10
Inpt/Dose Titration	10	0	10
Active Controlled	18	18	0
Inpt/Dose Titration	18	18	0
Uncontrolled	112	0	0
Inpatient/Short-Term	107	0	0
Inpatient/Long-Term	5	0	0
TOTAL	140	18	10

Additionally, the sponsor submitted on 3/29/93 a report of a single dose pharmacokinetic study with 42 subjects.

As of April 8, 1993 the sponsor reported that 10 patients in the U.S. recieved risperidone under compassionate use INDs. Worlwide, including U.S. patients, a total of 1335 individuals in 14 countries have received risperidone on a compassionate use basis.

5.2.2 Post-marketing experience

As of March 29, 1993, risperidone had not been marketed in any country.

5.2.3 Literature

In a literature search by this reviewer using the FDA Library Medline program, all clinical research publications found pertaining to risperidone were in fact descriptions of studies performed under Janssen's development program and submitted in the NDA. The sponsor confirms that all publications in the world literature at the time of submission were addressed in the NDA.

6.0 Summary of Human Pharmacokinetics

The following is a very brief summary of risperidone pharmacokinetic data, which are reviewed separately.

In humans, risperidone is subject to genetically determined metabolic heterogeneity of the debrisoquine type. The primary metabolite, considered pharmacologically active, is 9-OH-risperidone. Oral absolute bioavailability (relative to intravenous administration) in volunteers was 66 ± 28%; there appears to be some first pass liver metabolism. Time to peak plasma concentration was 30-60 minutes after oral administration. Volume of distribution at steady state was approximately 1-2 l/kg. The times to 9-OH-risperidona peak plasma concentrations were 2-5 hours and 8-48 hours, for extensive and poor metabolizers, respectively. The elimination half life for the sum of risperidone and 9-OH-risperidone concentration was about 20 hours in both poor and extensive metabolizers.

In psychotic patients given 4 mg of the compound, two half lives could be defined (3 hours and 15 hours). The area under the curve for the deep

compartment represented approximately 11% of the total area under the curve. 9-OH-risperidone levels peaked at aproximately 5 hours and showed a half life of about 20 hours.

Data from normal volunteers and patients indicates that concentrations of risperidone and 9-OH-risperidone are linear with dose up to 10 mg/day. In normals, steady state pharmacokinetic parameters do not appear to differ substantively from single dose data.

Risperidone is 90% plasma protein bound, and it binds to both albumin and alpha 1-glycoprotein. The hydroxy metabolite is 77% protein bound. Both compounds are displaced by warfarin, sulfamethazine and carbamazepine.

Excretion after seven days was 70% via urine and 14% via feces.

In experimental animals the drug and metabolites were extensively and rapidly distributed, with affinity for liver, lung, melanin containing regions, kidneys, and glandular tissues.

7.0 Efficacy Findings

7.1 Overview of Studies Pertinent to Efficacy

The risperidone NDA comprises reports of 26 Phase 2 and Phase 3 clinical trials that were intended, for the most part, to explore antipsychotic efficacy. Of these, 10 were controlled trials and 16 uncontrolled (open label or single blind). Of the controlled trials, three are primary in the determination of efficacy: Study 201, a U.S. placebo controlled study; Study 204, a U.S.-Canadian placebo controlled study, and Study 024, an overseas, active controlled study. Although Study 024 lacked a placebo group, it did include a low dose group that was considered likely to be distinguished from the higher dose groups. All three involved schizophrenic patients. These three were the largest studies and are the focus of the efficacy review that follows; Study 201 and Study 204 were the only double blind parallel design studies with placebo control. The remaining seven controlled studies included six studies with schizophrenic patients using active controls, and one crossover study in mentally retarded patients using a placebo control. These studies, which are not critical to the determination of efficacy, will only be described briefly in this review. The 16 uncontrolled studies included a total of 6 long term trials (with one of the 6 being an extension to an acute treatment protocol and therefore not considered a separate study); three of these 6 involved treatment of chronic schizophrenic patients, two involved treatment of unspecified psychotic disorders, and one involved treatment of elderly patients with behavior disturbance. There were also eleven uncontrolled short term trials; eight of these involved schizophrenic patients, two involved patients with nonspecific psychotic illness and one involved elderly patients with behavioral problems. Again, as they are not crucial to the question of efficacy, the uncontrolled trials will be reviewed here in brief detail.

7.2 Summary of Studies Pertinent to Efficacy

7.2.1 Study 201

7.2.1.1 Investigators and Location

Nine U.S. sites participated in this trial. The prinicpal investigators were R. Borison with the Augusta VA Medical Center, C-C Chu at the Memphis VA Medical Center, L. Gosenfeld at the Los Angeles VA Medical Center, D. Dunner at Harborview Medical Center in Seattle, C. O'Brien at the Philadelphia VA Medical Center, J. Kang at the University of Nebraska, W. Ryan at the Universtity of Alabama, G. Tollefson at St. Paul-Ramsey Medical Center in St. Paul MN, and W. Wilson at Duke University.

7.2.1.2 Study Plan

Objectives/Rationale

The objective of this trial was to compare the safety and efficacy of risperidone, haloperidol, and placebo in the treatment of acutely ill schizophrenic patients.

Population

The following summarizes inclusion criteria for the study:
•Age between 18 and 65 years old
•Good physical health
•Literate in English
•Hospitalized at time of entry
•Meeting DSM-III-R criteria for schizophrenia
•Score of at least 30 on the Brief Psychiatric Rating Scale (BPRS), with a minimum score of 4 on at least two of the following: conceptual disorganization, suspiciousness, hallucinatory behavior, and unusual thought content.

Patients were excluded for the following:
•History of head trauma, epilepsy, affective disorder, other major psychiatric disorder, recent substance abuse, or organic mental disorder
•History of poor response to neuroleptics
•Previous treatment with risperidone
•Child bearing potential (females)

Planned Study Conduct/Dosing Plan

This trial was a six week, parallel, double blind study; patients were randomized to receive haloperidol, risperidone or placebo. Patients were required to discontinue oral psychotropic medication three days prior to starting the trial (two weeks prior to starting for depot neuroleptic medication). Patients were randomized in blocks of three, with equal chance of receiving any of the three treatments. Randomization was performed at visit 2 (see below). The randomization code was available to the investigator or to Janssen's medical safety officer only in the event of emergency. Medication consisted of identical white tablets containing either 1 mg risperidone, 2 mg haloperidol or placebo. All patients were administered one tablet of their medication the first day; from then until day 18, dose titration up to a maximum of 5 tablets BID was permitted at the investigator's discretion. Increases in dose could only be made by one tablet per day, and dose could not be increased after day 18 (although it could be reduced at any time for an adverse event). Patients who failed to respond or who experienced intolerable extrapyramidal symptoms (EPS) were to be discontinued from the trial. Patients were also to be discontinued in the case of a serious or life threatening event, and were to undergo a final evaluation at discontinuation. A new subject was to be added to the trial if an existing subject dropped out after less than one week on medication. Concomitant medications were permissable if the dosage had been stable for two weeks prior to the study; permissable prn medications included sedatives, Artane and Cogentin for EPS, and chloral hydrate, sodium amytal or IM lorazepam for agitation. The protocol did not include plasma drug level monitoring or other means of determining compliance, except for the requirement that patients surrender any unused medication. Patients were required to remain in the hospital for at least the first week of the study.

Efficacy/Safety Assessments

The Brief Psychiatric Rating Scale (BPRS), Scale for the Assessment of Negative Symptoms (SANS), and Clinical Global Impression (CGI) consituted the

efficacy measures and were performed at every visit. Seven visits were scheduled; visit 1 was at least three days before randomization and initiation of study medication, visits 2-6 were at weekly intervals and visit 7 was two weeks after visit 6. Visit 2 assessments defined the baseline for outcome measurements. Safety assessments included physical examinations, chest radiographs, electrocardiograms, clinical laboratories, Abnormal Involuntary Movements Scale (AIMS) and Chouinard's extrapyramidal side effects scale (ESRS).

Analysis Plan

The sponsor designated the following a priori efficacy parameters: total BPRS score, percent of patients clinically improved as defined by a 20% decrease in total BPRS from baseline, and overall severity on CGI. Other outcome parameters included total SANS score, change in CGI, and comparison of patient dropouts for lack of efficacy or EPS. Parametric analysis was specified for BPRS and SANS data, and nonparametric tests for the other variables.

This Division requested analysis of "key" BPRS item scores, with conceptual disorganization, hallucinatory behavior, suspiciousness, and unusual thought content as key items. This Division also requested observed cases (OC) and last observation carried forward (LOCF) analyses for data at each visit. Finally, the Division asked for a longitudinal data analysis (using the BMDP 5V program) on change from baseline in total BPRS score.

7.2.1.3 Study Conduct/Outcome

Patient disposition

A total of 160 patients constituted the baseline sample, and these same patients also formed the intent-to-treat sample, i.e. those patients receiving at least one dose of their assigned medication and having at least one efficacy assessment after baseline. This included 54 subjects assigned to placebo, 53 to risperidone and 53 to haloperidol. Thirty one percent of placebo patients, 51% of risperidone patients and 42% of haloperidol patients completed the study; overall, 66 patients (41%) completed. Appendix 7.2.1.3.1 shows the patient completion rates by week for each treatment group. The high dropout rate became a factor early; the second week was the last week having a completion rate of ≥70% for all three treatment groups.

As noted, the highest number of dropouts occurred in the placebo group and the lowest in the risperidone group; about half the risperidone patients completed the trial. Adverse events, insufficient response and lack of cooperation were the major causes for early termination. In respect to the last category, oppositionality may have been a product of the acutely psychotic condition of the patients, and therefore the distinction between lac'. of cooperation and lack of effect may be imprecise. Table 7.2.1.3.1 lists reasons for premature discontinuation by treatment group.

Table 7.2.1.3.1 Number (%) of Patients Prematurely Discontinued From Study

Reason	Placebo	Risperidone	Haloperdol
Adverse Event	7 (13%)	6 (11.3%)	7 (13.2%)
Lack of Response	20 (37%)	8 (15.1%)	6 (11.3%)
Withdrew Consent	2 (3.7%)	2 (3.8%)	5 (9.4%)
Uncooperative	4 (7.4%)	9 (17%)	11 (20.8%)
Lost to Followup	2 (3.7%)	0	2 (3.8%)
Ineligible	1 (1.9%)	0	0
Other	1 (1.9%)	1 (1.9%)	0
Total	37 (68.5%)	26 (49.1%)	31 (58.5%)

Demographic Characteristics

Appendix 7.2.1.3.1 presents the demographic characteristics of the patients enrolled. The vast majority (96.3%) were male, consistent with the exclusion criteria. There were no significant differences between groups with respect to sex, age, or race. There were, however, statistically significant differences between treatment groups in certain baseline characteristics. The percentage of patients with a positive familiy history of mental illness was 39% for placebo, 34% for risperidone and 51% for haloperidol. Also, the mean length of time since initial schizophrenic diagnosis was 15.4 for placebo, 14.1 for risperidone and 10.5 for haloperidol. These two factors differed between groups at a 0.01 level of significance.

Baseline Illness Severity

Baseline symptom scores on the efficacy measures did not differ significantly between treatment groups, with the exception of total BPRS score which was highest in the risperidone group. The mean total BPRS at baseline was 52.7 for placebo patients, 56.6 for risperidone and 53.3 for haloperidol; this was significant at a p=0.02 level. Accordingly, the sponsor performed a supplementary analysis using baseline severity score as a covariate in an analysis of covariance test; the results were consistent with the analysis of variance results.

Dosing Information

Appendix 7.2.1.3.1 shows the mean dosages for risperidone and haloperidol treatment groups. The mode daily dose was 10 mg for risperidone and 20 mg for haloperidol. The mean daily number of tablets at endpoint was 7.6 for placebo, 7.8 for risperidone (7.8 mg) and 7.5 (15 mg) for haloperidol.

Concomitant Medications

Concomitant medication was administered to 89% of placebo patients, 93% of risperidone patients and 93% of haloperidol patients. The most commonly

administered medications were chloral hydrate, benztropine, trihexyphenidyl, lorazepam, and acetaminophen.

In 17 instances patients were treated with concomitant medication proscribed by the protocol. There were two such cases for placebo patients, seven for risperidone and eight for haloperidol.

Efficacy Results

As noted previously, the sponsor focused on the following as key efficacy variables: change in total BPRS score, percent of patients with 20% reduction in total BPRS score, and change in CGI severity score. In addition, this Division requested an analysis of the total on the BPRS four item psychosis cluster (conceptual disorganization, hallucinatory behavior, suspiciousness, and unusual thought content).

Appendix 7.2.1.3.2 present the data for these key efficacy variables with both the observed case and the last observation carried forward analyses.

For the variables measured by change from baseline, namely total BPRS, key BPRS items, CGI (severity), and SANS, the sponsor used a two way analysis of variance with treatment and investigator as factors. For percentage of patients improved, the sponsor used the test stratified by investigator. All tests were two sided. The following is a brief summary of the findings.

Total BPRS

For change from baseline in total BPRS score, with the last observation carried forward (LOCF) procedure, both risperidone and haloperidol were significantly superior to placebo at all time points. With the observed cases method, risperidone and haloperidol were superior to placebo only in the first two weeks.

Key BPRS Psychosis Items

Both active drugs demonstrated statistically significant efficacy relative to placebo on the key BPRS items, at every time point, by LOCF. With the observed case method, this effect diminished towards the later weeks for both drugs.

Percent of patients improved via BPRS

In the study report the sponsor indicated that the following expression was used to calculate percent change from baseline, although this was not included in the protocol:

Percent change=100x(total BPRS-baseline total BPRS)/(baseline total BPRS-18)

Presumably subtracting 18 from the denominator corrects for the fact that 18 is the lowest possible BPRS score; however, the effect of this correction is to reduce the denominator and thus magnify the percent change for a given pair of BPRS scores.

Both active drugs were significantly better than placebo in the percentage of patients improved by total BPRS, when analyzed by LOCF. This was observed at

all weeks for risperidone and at all weeks except week two for haloperidol. An observed cases analysis was omitted for this measure.

CGI (severity)

For the CGI of overall severity of schizophrenia, risperidone was superior to placebo at a p=0.05 level only at week three, by LOCF. Haloperidol was not superior to placebo at this level of significance for any time point. With observed case analysis for CGI severity results, neither active drug surpassed placebo by a statistically significant level, except for haloperidol at week 2.

Total SANS

Total SANS scores did not show a significant superiority for risperidone or haloperidol compared to placebo at the final week, although both drugs were superior to placebo at certain earlier weeks. This was true for both the LOCF and OC analyses.

The table below displays a summary of the statistical comparisons between placebo and both active drugs for the most important outcome variables.

Table 7.2.1.3.2 Summary of Efficacy Variables in Study 201

STUDY 201 Week	Week 1		Week 2		Week 3		Week 4		Week 6	
Variable	Ris	Hal	Ris	Hal	Ris	Hal	Ris	Hal	Ris	Hal
BPRS Total										
LOCF	++	++	++	++	++	++	++	++	++	++
OC	++	+	++	++	ns	ns	ns	ns	ns	ns
% Patients Improved on BPRS (LOCF only)	++	+	+		++	+	++	+	++	+
BPRS Psychosis Items										
LOCF	++	++	++	++	++	++	++	++	++	++
OC	++	++	++	++	ns	+	+	ns	ns	ns
CGI Severity										
LOCF	ns	ns	ns	ns	+	ns	ns	ns	ns	ns
OC	ns	ns	ns	+	ns	ns	ns	ns	ns	ns
SANS Total										
LOCF	ns	ns	+	ns	+	ns	+	+	ns	ns
OC	ns	+	+	+	ns	ns	ns	ns	ns	ns

++ p≤0.01 + p≤0.05 ns p>0.05

Other measures

With the longitudinal data analysis of change in total BPRS scores, both active drugs showed significant effectiveness compared to placebo; the treatment-time interaction was not significant.

For change in CGI, the percentage of patients with a score of 4 or better (i.e., minimally improved to very much improved) showed risperidone superior to placebo by a statistically significant margin at week one and week six, under LOCF analysis.

Finally, the proportion of patients withdrawn from the study for insufficient response was lower in both active drug groups than in the placebo group, and for both this difference was significant at a 0.05 level.

7.2.1.4 Conclusions

This study demonstrates the efficacy of risperidone treatment in actively psychotic schizophrenic patients. On primary efficacy variables, risperidone was superior to placebo on total BPRS, key BPRS item score and percent of patients improved. The only primary outcome variable on which it did not show superiority to placebo was CGI of severity of illness, but for this outcome measure haloperidol did not display efficacy either. Similarly, the therapeutic responses on the total SANS were not as robust for either drug.

As noted above, the method of calculating percent improvement was done in a way that enlarged the difference between baseline and treatment BPRS scores; in my view the rationale for this method is dubious, and weakens the findings.

The dwindling of demonstrable effects of haloperidol as the study progressed was likely due to the small numbers of patients remaining in the study at its conclusion; also, patients responding to placebo were preferentially retained over the course of the study, and in the comparison this may have obscured the effect of active drug.

One limitation of this study was the high number of premature discontinuations, which reduced the power of the observed case analysis, and raises questions about the clinical relevance of a trial in which many patients received medication for only a short period of time. This liability is offset, to a certain degree, by the finding that drug effects were statistically significant as early as the first week. Furthermore, given the difficulties inherent in securing the cooperation of acutely psychotic subjects, a high dropout rate is understandable and perhaps difficult to avoid. Not only the total BPRS scores, but also the key BPRS item scores showed a significant drug effect at week one; this is suggestive of a specific antipsychotic effect ameliorating the symptoms, and not merely a sedative or tranquilizing drug effect.

7.2.2 Study 204 (RIS-INT-3)

7.2.2.1 Investigators/Location

Below is a listing of principal investigators by site.

Joyce Small, M.D. Larue D. Carter Memorial Hospital, Indianapolia IN
Richard Borison, M.D., Ph.D. VA Medical Center, Augusta GA
Dennis Charney, M.D. VA Medical Center, West Haven CT

Alan Green, M.D. Massachusetts Mental Health, Boston MA
Jan Volavka, M.D. Manhattan Psychiatric Center, Orangeburg NY
Daniel Luchins, M.D. Illinois Psychiatric Institute & Clinic, Chicago IL
Robert Baker, M.D. and Nina Scholer, Ph.D. Maryview State Hosp., Pittsburg PA
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Raymond Ancill, M.B. and B. Chir, L.M.C.C. Riverview Hospital, Port Coquitlam, British Columbia
Donald Addington, M.B.B.S. The Foothills Hospital, Calgary, Alberta
Guy Chouinard, M.D. Louis-H Lafontaine Hospital, Montreal, Quebec
Barry Jones, M.D.C.M. Royal Ottowa Hospital, Ottowa, Ontario
Gary Remington, Ph.D. The Clarke Institute, Toronto, Ontario
Neelakanta Nair, M.R.C.Psych. Douglas Research Institute, Verdun, Quebec

7.2.2.2 Study Plan

Objective

The objective of this study was to determine the safety and efficacy of four fixed doses of risperidone in the treatment of actively psychotic chronic schizophrenic patients, in comparison to haloperidol and placebo.

Population

Patients were eligible if they met the following criteira:

- 18 to 65 years old
- DSM-III diagnosis of chronic schizophrenic disorder
- Literate
- In good physical health
- Currently hospitalized
- Score of 60-120 on total Positive and Negative Symptom Rating Scale (PANSS)

Women of child bearing potential using contraception were permitted by an amendment to the original U.S. protocol, and in Canada were permitted from the beginning.

Patients were not enrolled if they had any of the following:
- Neurological disease
- Psychiatric illness other than chronic schizophrenia
- History of recent substance abuse.
- History of previous treatment with risperidone

Planned Study Conduct/Dosing Plan

This double blind, parallel design, nine week trial involved six treatment groups with a planned enrollment of 80 patients in each (60 from the U.S. and 20 from Canada). Dosage groups were risperidone 2, 6, 10, and 16 mg/d; haloperidol 20 mg/d; and placebo. The study began with a one week single blind placebo washout, which could be reduced to three days for acutely ill patients. The dosage was titrated upwards during the second week, and remained fixed after that. (For patients on depot neuroleptics, a four week washout was required.) All subjects were to remain hospitalized until the end of the dose titration at a minimum. Doses were given as a single tablet BID, and the haloperidol, placebo and risperidone tablets appeared identical. Risperidone was supplied in 1, 2, 3, 4, 5, and 6 mg tablets, and haloperidol in 1, 2, 4, 5, 7.5, and 10 mg tablets. To aid compliance, the medication was blister-packed. Patients who completed the study were able to enroll in a one year open label risperidone extension study, providing they had not experienced any significant adverse reactions if they were taking risperidone. Nonresponders who had received at least one week of their assigned medication were permitted to withdraw from the study and enroll in this same open label risperidone extension trial. Patients were discontinued from the study if they had a severe adverse experience, did not respond to treatment, or withdrew consent. To maintain a sufficient total number of subjects, a new subject could be added to the trial if an existing subject failed to complete a full week on the assigned study medication.

At entrance into the study, patients were required to discontinue all psychotropic and antiparkinson medication; other medications were permitted if they had been initiated at least a week before the study. Biperiden, benztropine and procyclidine were permissable for EPS; lorazepam and chloral hydrate were permissable for sedation or sleep.

Efficacy/Safety Assessments

The baseline for outcome measures was determined at the end of the placebo washout peridod; patients were then assessed after 1, 2, 4, 6, and 8 weeks on drug. Efficacy was measured with CGI (both severity and change from baseline), and the Positive and Negative Syndrome Scale (PANSS). The latter instrument, endorsed by this Division at the pre-NDA meeting, is a 30 item instrument that includes all 18 items of the BPRS. It is divided into three subscales: a seven item positive subscale, a seven item negative subscale, and a general psychopathology subscale of 16 items. As with the BPRS, items are appraised on a scale of one to seven. Prior to the study, a representative from Janssen instructed investigators in use of the PANSS, and tested inter-rater reliability using videotapes.

Safety assessments performed during the trial included the Extrapyramidal Symptoms Rating Scale (ESRS), the UKU Side Effect Rating Scale, physical examination, EKG, vital signs, adverse experience monitoring, clinical laboratories, and plasma drug concentrations.

Analysis Plan/Conduct

The sponsor defined two key efficacy measures a priori: the mean total PANSS score change from baseline, and percent of patients improved as indicated by a 20% reduction in total PANSS.

Additionally, the agency requested analysis of the following: (1) total BPRS score derived from the PANSS, (2) the psychosis cluster of four BPRS items (conceptual disorganization, hallucinatory behavior, suspiciousness, and unusual thought content), (3) a longitudinal data analysis with the total PANSS, total BPRS, positive symptom PANSS and negative symptom PANSS scores, and (4) CGI of severity.

A number of secondary outcome variables were selected by the sponsor. These comprised the total PANSS positive subscale, total PANSS negative subscale, total PANSS general psychopathology subscale, global assessment of the study medication compared to previous medication on a seven point scale, and percent of patients withdrawn prematurely for EPS or inadequate response. The protocol also allowed for analysis of individual PANSS items if indicated.

Statistical analysis used the intent-to-treat sample, with two sided p-values for all tests. Change in mean scores from baseline at each time point were analyzed. For the continuous variables, two way analysis of variance was applied, using treatment and investigator as factors. To compare treatment groups, the sponsor used least significant difference test for the continuous variables, and the test for the percentage of patients showing improvement.

The sponsor also made subgroup analyses, according to race and to positive or negative subtype on the PANSS.

In the LOCF analysis, the sponsor chose to carry forward only scores from patients who had actually dropped out of the study. Thus, if a patient missed one visit but came for the next, no data was carried forward for the missing visit.

The sponsor conducted an LOCF analysis for all variables at each week; additionally, to facilitate comparison across studies an observed cases analysis at each week was performed on the derived BPRS, key BPRS psychosis items, CGI severity and negative PANSS scores.

7.2.2.3 Study Conduct/Outcome

Patient Disposition

Five hundred twenty three patients were randomized into the following treatment groups: 88 to placebo, 87 to risperidone 2 mg, 86 to risperidone 6 mg, 87 to risperidone 10 mg, 88 to risperidone 16 mg, and 87 to haloperidol 20 mg. Ten patients refused evaluations after the inital assessment, and so were not included in the analysis (2 were from the placebo group, 1 from risperidone 6 mg, 2 from risperidone 10 mg, 3 from risperidone 16 mg, and 2 from haloperidol).

Two hundred seventy patients (52%) were withdrawn before the end of the study. Principle causes were adverse events, lack of response, lack of cooperation and withdrawal of consent. The placebo group had the highest number of dropouts (61). The following table depicts reasons for premature discontinuation for each of the treatment groups.

PATIENTS PREMATURELY DISCONTINUED FROM STUDY 204

Reason	Placebo n=88	Ris 2 mg n=87	Ris 6 mg n=86	Ris 10 mg n=87	Ris 16 mg n=88	Hal 20 mg n=87
Adverse event	3 (3.4%)	2 (2.3%)	9 (10.5%)	4 (4.6%)	9 (10.2%)	6 (6.9%)
Insufficient Response	51 (58.0%)	41 (47.1%)	12 (14.0%)	25 (28.7%)	18 (20.5%)	36 (41.4%)
Withdrew Consent	3 (3.4%)	5 (5.7%)	4 (4.7%)	3 (3.4%)	2 (2.3%)	2 (2.3%)
Uncooperative	4 (4.5%)	3 (3.4%)	6 (7.0%)	4 (4.6%)	2 (2.3%)	6 (6.9%)
Lost to follow up	0	0	1 (1.2%)	0	1 (1.1%)	1 (1.1%)
Other	0	0	2 (2.3%)	3 (3.4%)	2 (2.3%)	0

Note that the placebo group, as would be expected, had the highest number of dropouts for insufficient response; next highest was in the risperidone 2 mg group.

Appendix 7.2.2.3.1 shows the patient completion rates for each treatment group and time point. As in study 201, the second week of treatment was the latest time when ≥70% of patients remained in all groups

Demographic Characteristics

Patients in the various treatment groups did not differ at a statistically significant level on any of the following characteristics: sex, race, age, diagnostic subtype of schizophrenia, postitive family history of mental illness, weight, height, age of onset of psychosis, age at first hospitalization, number of previous hospitalizations, or duration of current hospitalization. Appendix 7.2.2.3.1 shows selected demographic characteristics by treatment group. The majority of patients were male (83%), and white (71%).

Baseline Illness Severity

Baseline efficacy variables were consistent between groups; there were no statistically significant differences in mean baseline scores for the total PANSS, the PANSS subscales or the CGI.

Concomitant Medications and Protocol Deviations

The vast majority (≥90%) of patients received one or more concomitant medications. Lorazepam was taken by 62% of the total patient group; other frequently used medications included acetaminophen (34%), chloral hydrate (39%), benztropine (20%), milk of magnesia (11%), and procyclidine (10%). As might be expected, the use of EPS medications was lowest in placebo patients (21%) and highest in risperidone 10 mg (35%), risperidone 16 mg (42%) and haloperidol (53%).

There were 122 instances of patients taking disallowed medications, including too recent an injection of depot neuroleptic; disallowed medication use was most frequent in the haloperidol group. Other protocol deviations included enrollment of two patients over 65 years old, enrollment of three patients with

a total PANSS score of ≥120, and starting treatment with less than a three day placebo washout for sixteen patients. From the data listing, the most common protocol violation appeared to be use of EPS medication without completion of the required ESRS instrument; the sponsor did not tabulate the total number of such instances. One patient inadvertently received risperidone 2 mg instead of the intended 16 mg; data from this patient was nonetheless analyzed with the 16 mg group.

Efficacy Results

Appendix 7.2.2.3.2 displays the efficacy results for the main outcome variables; both last observation carried forward and observed case values are shown.

Total PANSS

The greatest change from baseline was seen in the risperidone 6 mg group, which was superior not only to placebo but also to haloperidol at a statistically significant level for all time points. The 2 mg risperidone group surpassed placebo at a 0.05 level of significance at weeks 6 and 8. Risperidone 10 mg reached a statistically significant advantage over placebo for weeks 2, 4, 6 and 8. Risperidone 16 mg was superior to placebo by a statistically significant level at every week.

The haloperidol group was improved by a statisticlly significant margin over placebo at weeks 4, 6 and 8.

For total PANSS, treatment by investigator interaction did not reach significance. Observed cases analysis was not considered for this variable.

Derived BPRS

The total BPRS scores were abstracted from the PANSS, and here again the risperidone 6 mg group had the greatest decrease in scores from baseline at all times. With LOCF, only risperidone 6 mg and 16 mg surpassed the placebo group by a statistically significant level at the first week, but by week 6 and at the final week all active treatment groups were significantly improved relative to placebo.

The observed case analysis showed risperidone 6 mg significantly better than placebo at every time point, but other treatment groups did not demonstrate as consistent an effect; the only time point showing an effect relative to placebo for all the active treatments was week 6.

Again, treatment by investigator interaction was not of significance.

PANSS Positive Subscale

At the final week, risperidone 6, 10 and 16 mg showed significant improvement relative to placebo for the positive PANSS subscale by LOCF analyses; risperidone 2 mg, although superior to placebo on the total PANSS, was not significantly superior to placebo on this subscale. Haloperidol 20 mg also showed significant advantage over placebo for the positive subscores at the final week by LOCF. An observed cases analysis was not considered for this variable.

PANSS Negative Subscale Total

Wtih the exception of the risperidone 2 mg group, the risperidone groups generally showed significant improvement on the PANSS negative subscale relative to the placebo group. This effect tended to be lost towards the end of the trial using the OC analysis. Haloperidol 20 mg was never significantly superior to placebo on the negative subscale scores. (One might suppose that this rather high dose of haloperidol is not optimum to show amelioration of negative symptoms.)

BPRS Psychosis Cluster

On the four BPRS cluster items, at week one only risperidone 6 mg and 16 mg showed a significant degree of improvement over placebo. By week four, however, the three higher dose groups of risperidone all were significantly improved over placebo; this effect persisted until the end of the trial, by either LOCF or OC methods. The risperidone 2 mg group did not have as much response, and reached statistical superiority over the placebo group only for week 6; this was the case under both the OC and the LOCF analyses.

Haloperidol was significantly better than placebo for weeks 4, 6 and 8 by LOCF, and for only week 6 by OC analysis.

There were no significant treatment by investigator interactions.

CGI Severity

All treatment groups scored significantly better than placebo on the CGI Severity measure. This was the case at every week except week one with the LOCF analysis. With observed cases analysis, all drug groups except risperidone 2 mg showed significant superiority to placebo at several time points.

Percentage of Patients Clinically Improved

The percentage of patients clinically improved, as defined by a ≥20% reduction in total PANSS from baseline, was analyzed with the generalized test controlled for investigator. All the active treatment groups significantly improved relative to placebo at the final week by LOCF analysis. The OC method was omitted for this variable.

As in the previous study, the sponsor's percent improvement calculation included a correction for the lowest possible PANSS score of 30:

% change=100x(total PANSS-baseline total PANSS)/(baseline total PANSS-30)

As discussed above, although there is some logic to this correction, it enlarges the percentage change between the two scores.

Other Outcome Measures

With the longitudinal data analysis using the BMDP 5V program, the results for the total PANSS and derived BPRS were statistically significant in favor of all active treatments over placebo. There was a significant treatment by time interaction which the sponsor attributed to the rapid onset of action of risperidone relative to placebo.

Patient discontinuations (for all reasons, and for insufficient reponse) were significantly lower in the risperidone 6, 10 and 16 mg groups compared to placebo.

No examination of treatment effect as a function of plasma drug level was made by the sponsor, although this Division had requested such an analysis at the pre-NDA meeting. The plasma drug level data showed dose proportionality, but with a large variance. In the risperidone 6 mg group, which had the largest treatment effect, the median risperidone level was 3.19 ng/ml and the median risperidone + 9-OH-risperiodone level was 36.50 ng/ml.

The sponsor conducted a subgroup analysis by race for the total PANSS and percent of patients clinically improved. On these measures, none of the active treatments were superior to placebo for nonwhite patients by a statistically significant margin. This is attributable to lower statistical power for this subgroup (roughly half the size of the white patient sample), in combination with a high rate of improvement among the 27 nonwhite placebo patients. No subgroup analyses by age or sex were undertaken, presumably because the sample was disproportionately composed of young males.

The subgroup analysis by positive or negative PANSS subtypes showed a pattern of results similar to the general analysis.

The table that follows presents in summary form the statistical comparisons for selected outcome variables.

Table 7.2.2.3 Summary of Efficacy Variables for Study 204

Week		Total BPRS					PANSS Negative					BPRS Psychosis Cluster					% Patients Improved on PANSS (LOCF only)					Total PANSS (LOCF only)					CGI Severity				
		2	6	10	16	h	2	6	10	16	h	2	6	10	16	h	2	6	10	16	h	2	6	10	16	h	2	6	10	16	h
1	LOCF	-	*	-	*	-	-	*	-	*	-	-	*	-	*	-	-	*	-	*	-	-	*	-	*	-	-	*	*	*	*
	OC	-	*	-	*	-	-	*	-	*	-	-	*	-	*	-											-	*	*	*	*
2	LOCF	-	*	-	*	-	-	*	*	*	-	-	*	-	*	-	-	*	-	-	-	-	*	*	*	-	*	*	*	*	*
	OC	-	*	-	*	-	-	*	-	-	-	-	*	*	*	-											-	*	*	*	*
4	LOCF	-	*	*	*	*	-	*	-	*	-	-	*	*	*	*	*	*	-	*	-	-	*	*	*	*	*	*	*	*	*
	OC	-	*	*	*	-	-	*	-	*	-	-	*	*	*	-											-	*	*	*	-
6	LOCF	*	*	*	*	*	-	*	-	*	-	*	*	*	*	*	*	*	*	*	-	*	*	*	*	*	*	*	*	*	*
	OC	*	*	*	*	*	-	*	-	-	-	*	*	*	*	*											-	*	*	*	*
8	LOCF	*	*	*	*	*	-	*	*	*	-	-	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*
	OC	-	*	-	-	-	-	-	-	-	-	-	*	*	*	-											-	*	*	-	-

* indicates a score superior to placebo at a p≤0.05 level of significance
- indicates p>0.05 in comparison to placebo

2=risperidone 2 mg 6=risperidone 6 mg 10=risperidone 10 mg 16=risperidone 16 mg
h=haloperidol 20 mg

7.2.2.4 Conclusions

The generally less favorable results for active treatment under the observed cases method may be due to a reduction of statistical power with the diminishing number of patients; the other possibility is an obscuring of drug effects towards the end of the trial by the comparison to placebo responders who remained in the study.

This study also supports the efficacy of risperidone in the treatment of actively psychotic schizophrenic patients. With the LOCF method, all active treatment groups showed superiority to placebo on the primary outcome variables. As with study 201, the primary limitation of this study is the high number of premature discontinuations, which weakened the power of the observed case analysis. In this study as well, the first week was the latest time when ≥70% of patients remained in all treatment groups. The risperidone 6 mg group, however, did show significant improvement over placebo as early as the first week. The treatment effect was the most robust for this dose group, which often demonstrated a larger drug effect than the haloperidol 20 mg control group.

7.2.3 Study 024

7.2.3.1 Investigators/Location

This study involved 110 sites from 15 different countries:

Argentina	VF Donnoli, A Duarte, ME Portnoy, NR Stingo, MS Richards
Austria	Ch Geretsegger, GF Hebenstreit, H Hinterhuber, P Konig, T Platz, W Puhringer, W Schony, H Schubert
Belgium	E DeBleeker, J DeWilde, M Dierck, P Kindts, C Mertens, F Mesotten, J Peuskens, G Touquet
Brazil	A Acioli, LP Bechelli, D Caetano, J Mari, R Moreno, M Versani
Denmark	J Andersen, P Kragh-Sorensen
France	A Bourguignon, G Clerc, G Darcourt, G Ferrey, Ch Gaussares, D Ginestet, M Guibert, Th Lemperiere, H Loo, P Moron, R Pagot, JG Pascalis, M Petit, R Ropert, H Sauret, H Scharbach, AP Van Amerongen
Germany	K Diebold, H Dilling, H Hippius, H Lauter, H-J Moller
Italy	E Aguglia, A Bosio, N Ciani, C Faravelli, P Giordano, D Kemali, G Meco, G Muscettola, P Pancheri, V Rapisarda, L Ravizza, A Rizzoli, E Sacchetti, PL Scapicchio
Mexico	G Baquedano-Lopez, M Camelo-Martinez, F Gonzalez Sandoval, SG Gutierrez, G Heinze, C Pavon Salcedo, LE Rivero Almanzor, JF Torres-Plank, JL Vargas Elias

The Netherlands	AJ Boom, TW Bos, L Brok, JA Den Boer, MJ Hoogschagen, J Rijpkema, AJMP Rutgers, HC Staverman
South Africa	W Bodemer, F Daubenton, RA Emsley, CA Gagiano, GAD Hart, WH Wessels
Spain	E Alvarez, JL Ayuso, J Guimon, M Gutierrez, JJ Lopez-Ibor
Sweden	B Andree, S Back, G Eberhard, A Edsbagge, E Eftring, J Eriksson, N Guldberg, C Kollind, J Lachman, KA Larsson, R Lindelius, P Nilsson, R Persson, J Sin, B Smith, M Swartz, L VonKnorring, IM Wieselgren
Switzerland	F Ferrero
United Kingdom	GP Bray, JC Cookson, JMR Damas-Mora, JM Dingwall, C Hyde, P Jauhar, AS Lee, MG Livingston, RG McCreadie, AM Mortimer, M Peet, SC Rastogi, KL Shrestha, S Soni, E Stonehill, SW Turner

7.2.3.2 Study Plan

Objective

The objective of this study was to compare the safety and efficacy of five fixed doses of risperidone and a single fixed dose of haloperidol in the treatment of acutely ill schizophrenic patients.

Population

Patients were eligible if they met the following criteira:

- Age 18-65 years old
- DSM-III-R diagnosis of Chronic Schizophrenia
- Good physical health
- PANSS score between 60-120

Hospitalization for the first three weeks of the study was desirable but not absolutely required. Women of child bearing potential were permitted if they used contraception.

Patients were excluded on the basis of the following criteria:

- Pregnancy or breast feeding
- Substance abuse disorders
- Psychiatric disorders other than chronic schizophrenia
- Treated with another investigational compound less than 4 weeks before enrollment

Physical examinations, neurological examinations, clinical laboratories, and EKGs were included as screening assessments. The goal for enrollment was a total of 1200 patients, 200 for each of the six treatment groups; each individual study

site was required to enroll subjects in multiples of six, with a minimum of twelve per site.

Planned Study Conduct/Dosing Plan

This was a randomized, double blind, parallel group, fixed dose study of nine weeks duration. The treatment groups comprised risperidone 1, 4, 8, 12, and 16 mg/d, and haloperidol 10 mg/d; there was no placebo control group. The sponsor's rationale for the lower dose of haloperidol in this trial was that it reflected European dosing practices; a placebo arm was not included because certain nations discourage the use of placebo if an effective drug is available. The study began with a one week single blind placebo wash out period, which could be shortened to three days for severely ill patients; patients were required to discontinue all psychotropics and EPS medications. Other medications were permissible only if they had been prescribed at least one week before the start of the trial. Subjects on depot neuroleptics began the wash out period on the day their next injection would have been administered. The study medication was titrated over seven days following the wash out period; afterwards patients remained on a fixed dose for seven weeks. All study medication was given BID as identical single tablets; dosage was increased by substituting pills containing higher milligram amounts. Medication was blister-packed to aid compliance, and patients were to return any unused medication. Plasma drug levels were not measured. The protocol provided for breaking the blind if a patient had a severe adverse event; subjects were to be withdrawn if they suffered a severe event, withdrew their consent, or failed espond to treatment. For EPS, patients could be prescribed biperiden or procyclidin, and for sleep or sedation they could receive lorazepam or oxazepam. Following the study, all patients were eligible for open label long term risperidone treatment.

Efficacy/Safety Assessments

Outcome assesments included the PANSS and CGI; baseline evaluations were made at the end of the placebo washout period and were repeated after 1, 2, 4, 6, and 8 weeks on study medication. Additionally, at the final visit the investigator and patient made a global evaluation of the study medication on a seven point scale.

Safety assessments included the following: history and physical examination, clinical laboratories, weight, vital signs, EKG, ESRS, and UKU side effect scale.

Janssen representatives used videotapes to train investigators in the rating scales and to check inter-rater reliability.

Analysis Plan/Conduct

The primary analysis was performed on the intent to treat sample, i.e. all all patients evaluated both at baseline and at least once after receiving any study medication. This Division requested analysis of the following measures at each time point, using both observed cases and last observation carried forward methods: total BPRS score derived from the PANSS, CGI severity, and BPRS psychosis cluster of four items (conceptual disorganization, suspiciousness, hallucinatory behavior, and unusual thought content). The sponsor focused on two primary outcome measures, the percent of patients showing clinical improvement

by a ≥ 20% reduction in total PANSS score from baseline, and the mean total PANSS score change from baseline. Secondary outcome measures included the PANSS positive subscale, PANSS negative subscale, PANSS general psychopathology subscale, individual PANSS items, the BPRS factor scores, CGI measurement of severity, CGI measurement of overall change, number of dropouts for lack of response, number of dropouts for side effects, and global evaluation of the study drug by the subject and investigator. Additionally, the sponsor conducted a subgroup analysis by positive or negative symptomatology on the PANSS.

Two sided p values were used in every calcultion. For the key outcome measures, the primary comparison was between the risperidone 1 mg group and the other five treatment groups. For PANSS derived variables, scores were analyzed with a two way ANOVA, using treatment and country as factors; treatment groups were compared using least significance test (LSD). For the CGI, the test stratified by country was employed, and comparisons between treatments were made using the test. The test was used to analyze percentage of patients showing improvement on the PANSS.

In the LOCF analyses, the sponsor chose to carry forward only scores from patients who had actually dropped out of the study. Thus, if a patient missed one visit but came for the next, no data was carried forward for the missing visit. (This results in some slight variations in the numbers of patients included at various weeks in a given treatment group.)

The sponsor conducted LOCF analyses by week for major outcome variables (total PANSS, PANSS negative subscale, derived BPRS, key BPRS psychosis items, percent of patients improved on PANSS, CGI severity). In addition, to facilitate comparison across studies, observed cases analyses by week were performed on the derived BPRS, PANSS negative subscale, key BPRS psychosis items, and CGI severity scores. The remaining outcome measures were subjected to an LOCF analysis only for week 8 (i.e., endpoint).

7.2.3.3 Study Conduct/Outcome

Patient Disposition

The total number of subjects entering the trial was 1557; of these, 47 withdrew during the first week of single blind placebo and were not counted in the intent to treat sample. Thus, 1510 patients actually received double blind study medication. Six centers failed a quality assurance audit and were deemed invalid, and data from these sites was not included in safety or efficacy results. (The excluded centers were: in Argentina, N.R. Stingo and M. Suarez Richards; in Mexico, M. Camelo-Martinez, C. Pavon-Salcedo, and L.J. Vargas-Elias; and in Italy, A. Bosio.) This excluded a total of 148 patients from the analysis. Of the remaining patients, a total of 1356 had at least one efficacy assessment on study medication, and these patients formed the intent to treat sample. Appendix 7.2.3.3.1 displays the patient completion rates by treatment group. In this study, all treatment groups retained at least 72% of their sample through the end of the study (range %).

A total of 343 patients withdrew prematurely; the primary reasons were adverse experiences and insufficient response. The following is the sponsor's table listing reasons for dropouts by treatment group.

Number of dropouts by treatment group in Study 024

Reason	Ris 1 mg n=229	Ris 4 mg n=227	Ris 8 mg n=230	Ris 12 mg n=226	Ris 16 mg n=224	Hal 10 mg n=226	Total
Adverse experience	18	15	17	22	31	23	126
Death	0	0	0	0	1	0	1
Suicidal	2	1	1	3	0	2	9
Insufficient response	40	16	24	32	20	22	154
Intercurrent disease	2	0	0	1	1	0	4
Intercurrent event	2	0	2	2	2	0	2
Intercurrent treatment	0	0	0	0	1	2	3
Lost to follow up	3	4	4	6	4	5	26
Selection criteria not met	1	0	1	0	0	0	2
Sufficient response	0	1	0	1	0	1	3
Patient's decision	3	7	9	6	7	15	47
Lack of motivation	3	5	5	5	5	5	28
Uncooperative	0	5	4	7	8	5	29
Other	1	2	1	1	3	3	11
Unspecified	0	0	0	0	0	0	1
Total (%)	58 (25%)	45 (20%)	56 (24%)	62 (27%)	59 (26%)	63 (28%)	343 (25%)

Demograhic Characteristics

Appendix 7.2.3.3.1 portrays demographic characteristics for the different treatment grou . Approximately 80% of patients were white, and about one third were female, with a mean age around 38 years. The groups differed little on these characteristics. In addition, the investigators used statistical methods to compare the following aspects of the six groups: sex, age, weight, height, race, subtype of schizophrenia, family history of psychiatric illness, age at onset of illness, age at first hospitalization, number of previous hospitalizations, duration of current hospitalizations, previous treatment with neuroleptics, and concomitant treatment. No statistically significant comparisons emerged.

Baseline Illness Severity

The mean total PANSS scores at baseline were quite similar for the different groups, ranging from a low of 88.8 (haloperidol) to a high of 90.5

(risperidone 12 mg). These differences were not statistically significant (by two way analysis of variance).

Concomitant Medications

According to the sponsor's study report, the most commonly used concomitant medications were benzodiazepines and EPS medications. The report, however, does not appear to have a tabulation of all concomitant medication use; the data provided is for use of HS benzodiazepines and EPS medications. Nighttime benzodiazepines were used by 30-35% of patients in all treatment groups; use of EPS medication was more variable, with the risperidone 1 mg group having the lowest use (6%), and the haloperidol group the highest (28%). Lorazepam and oxazepam were the most commonly used HS benzodiazepines, as provided for in the protocol, but 13 other benzodiazepines were also administered to small numbers of patients during the trial. Biperiden was by far the most often administered EPS medication, with only a few patients receiving the four other EPS medications used. No data is provided on use of benzodiazepines for agitation.

Sixteen patients deviated from the protocol by concomitant use of a neuroleptic during the study.

Efficacy Results

Baseline was designated as the visit coinciding with the start of double blind medication, i.e. the assessment at the end of the placebo lead in period. Although mean baseline total PANSS scores were comparable among the different treatment groups, differences between countries on baseline total PANSS were significant ($p<0.001$), with Austria having the highest mean baseline total PANSS (97.1) and Spain the lowest (81.8). As with the baseline values, country was a statistically significant factor for week 8 mean change versus baseline on the total PANSS; Switzerland had the highest mean decrease (35.0) and The Netherlands the lowest (7.1). No country had data showing a worsening of scores. (Perhaps this variability reflects cross cultural differences in use of the rating scale.)

Efficacy results for the important outcome variables are dispayed in Appendix 7.2.3.3.2.

Total PANSS

The LOCF analysis for change from baseline in total PANSS showed risperidone 4 mg to be superior to risperidone 1 mg at all time points by a significant margin. The only other comparisons to reach $p=0.05$ significance were risperidone 8 mg over 1 mg at week eight, and risperidone 16 mg over 1 mg at week eight.

PANSS Positive Subscale

The PANSS positive subscale scores at week 8 (LOCF) show a statistically significant advantage for all the other treatment groups over the risperidone 1 mg group.

PANSS Negative Subscale

In contrast to the total PANSS and postive subscale scores, at no time was there a significant difference between risperidone 1 mg and any other treatment groups on the negative PANSS subscale score LOCF analysis. In fact, all groups showed a decreased negative subscale score by week 8. With observed cases, there was no significant advantage for any other treatment over risperidone 1 mg.

Clinical Improvement

Clinical improvement was defined as ≥20% reduction in total PANSS; this was calculated using the same formula as was used in study 204, with the same correction factor in the denominator. Thus, the potential objections already raised apply in this case also.

With the week 8 LOCF results, 60.2% of all patients achieved clinical improvement on the PANSS; among treatment groups this percent ranged from % of risperidone 1 mg patients to 65.8% of risperidone 8 mg patients. These differences were not statistically significant overall (p=0.17). Consequently, in the original submission Janssen made no pairwise comparisons between individual treatment groups. In response to the Division's request, Janssen furnished last observation carried forward data for the clinical improvement variable by week. Not unexpectedly considering the result, the LOCF data showed only scattered significant comparisons (between risperidone 4 mg over risperidone 1 mg at week 2 and week 8, and between risperidone 8 mg over 1 mg at week 8).

Total Derived BPRS

For this measure, by LOCF the risperidone 4 mg group was consistently superior to risperidone 1 mg. For the other treatment groups there were only isolated findings of significance in comparison to risperidone 1 mg; the observed cases results were very similar to the LOCF analysis.

CGI Severity

With LOCF, all treatment groups except haloperidol acheived statistically significant superiority over risperidone 1 mg by the later weeks in the trial. Observed cases data was somewhat weaker in favor of risperidone doses above 1 mg, but still demonstrated significance at many time points.

Haloperidol was never superior to risperidone 1 mg on this measure.

Other analyses

On the subgroup analysis by positive or negative symptomatology type, the negative or mixed subtype patients tended to show less response to risperdone 1 mg than to the other treatments; in contrast, this differential response was not as apparent with the positive and neither subtypes. While the above might suggest that negative subtype patients showed more of a dose response relationship, it was in fact the positive subscale on the PANSS and not the negative symptom subscale that showed consistent inferiority of risperdone 1 mg to the other treatments, both for the total patient population and all the subtypes.

Another subgroup analysis was conducted, in this instance with patients grouped by high or low anxiety/depression cluster scores on the BPRS. A more

robust therapeutic effect was generally observed in the high anxiety/depression group.

Patient's global rating of their study medication compared to their past antipsychotics did not show intergroup differences, although the investigator's global ratings favored risperidone 4 mg.

Dropouts for lack of efficacy were most common in the risperidone 1 mg group, and this reached statistical significance in comparison to all other groups except risperidone 12 mg, which had the next highest dropout rate for lack of effect.

A multiple regression model analysis of total BPRS scores for the risperidone 4 and 8 mg doses was conducted to explore whether certain patient characteristics had prognostic significance. This demonstrated a better resonse for patients who stayed longer in the study, had higher baseline BPRS scores, had shorter duration of symptoms and had no past neurolpetic therapy. The following characteristics had no statistically significant prognostic effect: age, race (white versus nonwhite), body mass index, number of previous psychiatric hospitalizations, dose (4 versus 8 mg), country, sex, family history, DSM-III-R diagnosis, baseline total BPRS score, use of benzodiazepines, and PANSS subtype.

When data from 148 patients at sites excluded for poor quality control are added back to the efficacy results, additional statistically significant favorable comparisons are seen on the total PANSS at week 8 for risperidone 12 mg over risperidone 1 mg, and on percent of patients clinically improved for risperidone 4 and 8 mg over risperdone 1 mg.

Miscellaneous

A total of 196 protocol deviations were found, in 178 total patients. The risperidone 1 mg group had the highest number of deviations (37) and risperdone 16 mg the lowest (26). Too brief a time since the last depot neuroleptic accounted for over half the deviations (103 total, range 15-21 per treatment group). Others included disallowed medical problems (37 total, range 6-9 per treatment group); placebo lead in < 3 days (18 total, range 1-5 per treatment group); use of concomitant neuroleptics (16 total, range 0-6 per treatment group); initial PANSS score not between 60 and 120 (7 total, range 0-3 per treatment group); use of investigational drug < 4 weeks before study (6 total, range 0-2 per treatment group); age > 65 years (5 total, range 0-3 per treatment group); and improper dosage schedule (4 total, range 0-2 per treatment group). Overall, occurrences of protocol deviations appeared to be distributed equitably among groups.

The following table displays a summary of the efficacy results for the main outcome measures.

Summary of Efficacy Variables for Study 024

WEEK		Total Derived BPRS					CGI Severity					% Patients Improved on PANSS (LOCF only)					Total PANSS (LOCF only)					BPRS Psychosis Items Cluster					PANSS Negative Subscale				
		4	8	12	16	h	4	8	12	16	h	4	8	12	16	h	4	8	12	16	h	4	8	12	16	h	4	8	12	16	h
Week 1	LOCF	*	-	-	-	-	*	-	*	-	-	-	-	-	-	-	*	-	-	-	-	*	-	-	-	-	-	-	-	-	-
	OC	*	-	-	-	-	*	-	*	-	-											*	-	-	-	-	-	-	-	-	-
Week 2	LOCF	*	-	-	-	-	*	-	*	*	-	*	-	-	-	-	*	-	-	-	-	*	*	*	*	-	-	-	-	-	-
	OC	*	-	-	-	-	*	-	*	*	-											*	*	-	*	-	-	-	-	-	-
Week 4	LOCF	*	-	-	-	-	*	-	*	*	-	-	-	-	-	-	*	-	-	-	-	*	*	*	*	-	-	-	-	-	-
	OC	-	-	-	-	-	*	-	-	-	-											-	-	-	-	-	-	-	-	-	-
Week 6	LOCF	*	-	-	-	-	*	*	*	*	-	-	-	-	-	-	*	-	-	-	-	*	*	*	*	*	-	-	-	-	-
	OC	-	-	-	-	-	-	*	-	*	-											-	*	-	*	-	-	-	-	-	-
Week 8	LOCF	*	*	-	*	-	*	*	*	*	-	*	*	-	-	-	*	*	-	*	-	*	*	*	*	*	-	-	-	-	-
	OC	*	*	-	*	-	*	*	-	*	-											-	*	-	*	*	-	-	-	-	-

* indicates comparisons superior to risperidone 1 mg at a 0.05 level of significance

\- indicates nonsignificant comparisons to risperidone 1 mg

4: risperidone 4 mg 8: risperidone 8 mg 12: risperidone 12 mg 16: risperiodne 16 mg h: haloperidol 10 mg

7.2.3.4 Conclusions

On balance, this study demonstrates therapeutic activity of risperidone for the psychotic symptoms of schizophrenia. Notably, this study had a much higher completion rate than the two previously described trials; it was also remarkable for the high rate of clinical improvement in all treatment groups, which is probably why only a modest dose response relationship was seen. Nonetheless, the lowest dose group (risperidone 1 mg) did not respond as vigorously as the other groups. Treatment effects, however, were not consistently amplified by dosages beyond 4 mg. All treatments, including haloperidol, showed a similar effect on the PANSS negative symptoms scale.

7.2.4 Other Studies

There were seven other double blind controlled trials which are relevant to demonstration of efficacy. As these were not considered by the sponsor to meet the criteria for adequate and well controlled trials, they are not reviewed here in detail. Table 7.2.4.1 presents a brief summary of these studies. In general, patients were seen to improve with risperidone treatment, and these trials may be considered as lending support for risperidone's activity in psychotic disorders. Note that two of the trials involved conditions other than schizophrenia; Study 008 also included schizoaffective disorder patients and Study 015 involved mentally retarded individuals. Thus there is some direct evidence for extrapolating the efficacy of risperidone to conditions other than schizophrenia, albeit only from small studies.

Additionally, there were 17 open studies with risperidone; these are summarized in Table 7.2.4.2. In general, they demonstrated patient improvement over baseline with risperidone treatment. Studies 007, 013, 002, 005, 035, 011, 004, and 009 included patients with diagnoses other than schizophrenia. A pilot study of IM risperidone for acutely agitated patients, Study 009, did not demonstrate an advantage for this route of administration. Some studies were of much longer duration than the primary clinical trials; studies 026, 013, 030, 035, 011, 004, SLT and 033 all involved long term treatment. While long term trials are very relevant to a drug that will be administered to patients chronically, these were all uncontrolled studies that cannot adequately demonstrate prevention of relapse with risperidone treatment.

Table 7.2.4.1 Other Double-blind Controlled Trials

Protocol	No. Patients	Population	Treatments mg/day[1]	Duration	Assessments	Results
006	44	Chronic Schizophrenic	Ris 12 (2-20) Hal 10 (2-20)	12 weeks	PANSS SADS-C NOSIE CGI-C	Both groups improved over baseline by statistically significant level
008	60	Schizophrenic	Ris 9.1 (2-20) Hal 9.4 (2-20)	8 weeks	BPRS NOSIE CGI	Only comparison made was between treatments; no significant differences found. More dropouts for Ris
022	59	Schizophrenic	Ris 4 or 8 Clozapine 400	28 days	BPRS CGI	Only comparison was between treatments; no significant differences
048	107	Chronic Schizophrenic	Ris 8.5 (5-15) Per 28 (16-48)	8 weeks	PANSS CGI	No significant differences between groups
041	62	Chronic Schizophrenic	Ris 9 (4-12) Hal 9 (4-12) Levo 125 (50-150)	4 weeks	PANSS PAS CGI	Ris patients better than Levo or Hal ($p<0.05$) on total PANSS
008	36	Schizophrenic/ schizoaffective	Ris 2-20 Hal 2-20	8 weeks	BPRS, FKP, DVP, Serejski	No significant differences between groups
015	37	Mentally Retarded	Add on of Ris 8.3 (4-12) or Placebo to existing treatment	21 days cross over	ABC CGI VAS	Ris better than placebo on ABC and CGI ($p<0.05$)

1 Shown as group mean at endpoint, with allowed range in parentheses; no range given for fixed dose
PANSS Positive and Negative Syndrome Scale
SADS-C Schedule for Affective Disorders and Schizophrenia, change version
NOSIE Nurses Observation Scale for Inpatient Evaluation
CGI-C Clinical Global Impression, change version
BPRS Brief Psychiatric Rating Scale
CGI Clinical Global Impression
ABC Aberrant Behavior Checklist
VAS Visual Analogue Scale, Severity of Target Symptom
PAS Psychotic Anxiety Scale
FKP Not specified in study report
DVP Not specified in study report
Serejski Not specified in study report

[Ris Risperidone Hal Haloperidol Levo Levomepromazine Per Perphanzine]

Table 7.2.4.2 Uncontrolled Studies

Protocol	No. Pts.	Population	Dose	Duration	Assessments	Efficacy Results
026	31	Schizophrenic with negative symptoms	2-6 mg	4 weeks	BPRS, SANS, CGI	Significant improvement over baseline
same	18	Extension study	2-6 mg	1 yr	same	Significant improvement over baseline
007	50	Geriatric	1-10 mg	4 weeks	PBES, GTI	Significant improvement over baseline
013	9	Geriatric follow up to 007	1-6 mg	13 mos	PBES, GTI	PBES decreased significantly over baseline
030	5	Extension to 006	≤20 mg	6-13 mos	PANSS, CGI, NOISE	3/5 patients maintained improvement
019	12	Schizophrenic	2-4 mg	6 weeks	SANS, CGI, BPRS	Significant improvement from baseline
002	121	Psychotic	2-10 mg	4 weeks	CGI, BPRS	Significant improvement from baseline
005	17	Psychotic	10-25 mg	4 weeks	CGI, BPRS	Significant improvement from baseline
020	13	Schizophrenic	1-10 mg	4 weeks	CGI, BPRS	Significant improvement from baseline on BPRS
021	11	Chronic schizophrenic with negative symptoms	4-12 mg	4 weeks	BPRS, SANS, CGI, NOISE, AMDP	Significant improvements on SANS total and AMDP depressive syndrome from baseline
036	7	Schizophrenic	4-20 mg	4 weeks	PANSS, MSCS, SANS, MADRS	No statistical comparisons made
035,011,004	264	Psychotic	1-32 mg	≤19 mos	BPRS, GTI	Significant improvement over baseline
SLT	38	Schizophrenic	2-25 mg	8.6-40 mos	safety only	-
033	77	Schizophrenic	1-16 mg	290-580 days	PANSS, CGI, BPRS	Significantly lowered scores from baseline
038	10	Schizophrenic	2-6 mg	4 weeks	Ham-D, BPRS, SANS, STAI-X1	Significantly improved on Ham-D and BPRS but not SANS or STAI-X1
045	83	Schizophrenic	1-10 mg	8 weeks	BPRS, GIR	Improvement noted, but not tested with statistical methods
009	17	Psychotic with agitation	≤12 mg IM/day followed by 2-20 mg oral/day	1 week	BPRS, CGI, Behavior Evaluation	11/17 patients either withdrew for lack of efficacy or showed only slight improvement

BPRS Brief Psychiatric Rating Scale
SANS Scale for Assessment of Negative Symptoms
CGI Clinical Global Impression
PBES Psychogeriatric Behavioral Evaluation Scale
GTI Global Therapeutic Impression
AMDP not specified in study report
MADRS Montgomery Asberg Depression Rating Scale
PANSS Positive and Negative Syndrome Scale
NOISE Nurses Observation Scale for Inpatient evaluation
Ham-D Hamilton Depression Rating Scale
STAI-X1 State Trait Anxiety Inventory X1
GIR Global Improvement Rating

7.3 Summary of Data Pertinent to Important Clinical Issues

7.3.1 Predictors of Response

Regarding negative versus positive schizophrenic symptom patterns, Study 204 showed generally similar responses when patients were grouped according to these subtypes on the PANSS. Study 201 did not include such a subgroup analysis. In Study 024, negative subtype patients showed a greater difference in response between risperidone 1 mg and other treatments, although this difference was due largely to reduction in positive rather than negative symptoms.

In studies 201 and 204, age and sex were not examined with respect to prediction of response; presumably this was because the subjects were mostly young males.

In Study 024, as noted above, the sponsor conducted a post hoc multiple regression analysis to explore whether certain patient characteristics had prognostic significance. This analysis was applied to the risperidone 4 and 8 mg dose groups. Influence on the total BPRS score was explored for the following parameters: age, race (white/nonwhite), body mass index relative to height, history of prior neuroleptic therapy, number of past psychiatric hospitalizations, duration in years of psychotic symptoms, dose, country, sex, family antecedents, duration of therapy (days), diagnosis (DSM-III-R), whether or not the country was defined as having adequate regulatory requirements under the U.S. 1986 drug export bill, baseline total BPRS, use of benzodiazepines, and PANSS subtypes under both systems for subtyping (i.e., typing as positive/negative, or positive, negative, neither or mixed). Of these factors, likelihood of response was increased at a statistically significant level by the only the following: longer duration of treatment, higher baseline BPRS, shorter duration of symptoms, and no prior neuroleptic exposure. Other characteristics did not exert a statistically significant effect.

7.3.2 Size of Treatment Effect

Perhaps the best indication of the size of risperidone's treatment effect is the comparison to haloperidol's effect in the three major studies, postulating that haloperidol exerts the standard antipsychotic effect. In study 201, the mean decrease from baseline in total BPRS was 11.6 for risperidone and 9.0 for haloperidol at endpoint. In study 204, at endpoint the mean decrease from baseline in total derived BPRS was 3.8 for haloperidol 20 mg patients, and for the risperidone patient groups it ranged from 2.9 to 11.2. In fact, the latter value, from the risperidone 6 mg group, was significantly better than the haloperidol value. In study 024, with the highest patient retention of the three studies, at endoint the mean decrease in total derived BPRS from baseline was 8.1 for haloperidol 10 mg, and ranged from 6.7 to 10.2 for the risperidone groups.

Judging by the forgoing comparisons, the treatment effect of risperidone in actively psychotic schizophrenic patients seems to be on the same order as that of haloperidol, and in some instances larger than that of haloperidol. Making meaningful comparisons across studies is not straightforward, however, since dosing of haloperidol was different in each of the three trials. In study 204, the dose of haloperidol was rather high (20 mg/d) and may have exceeded the therapeutic "window" for some patients. Perhaps the most fair comparison is in Study 201, which used dose titration for risperidone and haloperidol both. Even so, in Study 201 the mode daily haloperidol dose was also the maximum permitted dose of 20 mg/d.

7.3.3 Choice of Dose

The sponsor recommends a target dose of 6 mg/day, and suggests that there is no additional therapeutic benefit shown above 10 mg/day. This recommendation is based on data from studies 204 and 024. The sponsor observes that increasing the dose beyond 10 mg resulted in little or no therapeutic gain but did lead to more extrapyramidal symptoms. In study 204, 6 mg/day was the most effective dose, and in study 024, doses from 4 mg upward had essentially the same efficacy. In my opinion, the logic behind the sponsor's choice of dose appears sound. The proposed labelling does not necessarily restrict physicians to doses below 10 mg/day, however.

7.3.4 Duration of Treatment

Janssen conducted no long term controlled trials to address the question of prevention of relapse with risperidone. In the five open long term studies, risperidone patients generally maintained their improvement. Absent a relapse prevention study, however, recommendations for long term treatment with risperidone must rest primarily on inductive reasoning from experience with approved antipsychotics, rather than on the strength of these uncontrolled long term studies. The presumption is that a drug showing efficacy in the treatment of acute psychosis will also be effective in preventing a return of psychotic symptoms when administered as maintenence therapy. Such has been the experience with current antipsychotics.

7.4 Conclusions Regarding Efficacy Data

On balance, the data from the studies described above provide support for the effectiveness of risperidone in the treatment of psychosis, when it is administered in the recommended dose range of 2-16 mg/day.

8.0 Safety findings

8.1 Methods

The risperidone NDA integrated safety summary provided the foundation for the safety assessment which follows. Janssen's integrated safety database included data from Phase 2 and Phase 3 studies; the Phase 1 safety findings were considered separately. The Phase 1 Clinical Pharmacology trials involved the following numbers of subjects:

Phase I (Clinical Pharmacology)

Drug	Number of Subjects
Risperidone	217
Active Control	7
Placebo	6

The sponsor's pooled Phase 2-3 safety database incorporates routine clinical data collected until the cutoff date of 5/31/91, on the following numbers of patients:

Phase II-III (Antipsychotic Studies)

Drug	Number of Patients	Patient Years of Exposure
Risperidone	2322	508
Active Control	533	61
Placebo	176	13

In addition, Janssen included in the original NDA submission reports of deaths and other serious adverse events requiring a 10-day safety report to the agency that occurred in patients who were not included in the May 31, 1991 database. Additional 10-day safety reports were received from the sponsor after the NDA was submitted.

Safety issues were evaluated on the basis of this data set, using Janssen's integrated summary of safety, selected narrative case summaries, and case report forms. Additional safety data from Phase 1 studies, from study sites that were disqualified for poor quality control, and from several additional Phase 2-3 studies which were not part of the integrated safety data base were also considered, but safety findings from the integrated safety data base reports will be emphasized here. Uncommon, severe adverse events were assessed using reports of deaths, premature discontinuations from clinical trials, and "serious" adverse events (as defined below), while more common but less grave adverse reactions were identified through routinely collected safety data. Treatment emergent changes in vital signs, clinical laboratory, chest radiographs and electrocardiogram parameters were examined and are described in Section 8.5. A description of reported overdose cases appears in section 8.6. Section 8.7 contains a discussion of those adverse events deemed both significant and potentially drug related.

8.2 Deaths

In the risperidone NDA, eighteen deaths were reported among patients treated with the drug. These eighteen deaths are summarized in Appendix 8.2. Ten deaths were suicides, and one patient died from each of the following causes: myocardial infarction, accidental drowning, myeloma, pneumonia, liver cell carcinoma, renal failure, cardiac arrest, and AIDS. In the opinion of this reviewer, no deaths can be causally related to risperidone treatment. There was no mortality in the placebo treatment group; two patients receiving active controls died. One of these was a 39 year old male with schizophrenia, patient 006 in Protocol 024. He was receiving haloperidol 10 mg/day when he committed suicide by jumping in front of a train. The second patient from the active control group who died was a 31 year old man with schizophrenia (patient 63 from Protocol 040). While being treated with thioridazine, he committed suicide by hanging.

A few additional comments are in order about two of the risperidone deaths. Patient in study BEL-14 was an 81 year old man who died of renal insufficiency five days after discontinuing risperidone because of an upper respiratory infection. Other than the time of onset of his kidney failure there is nothing that would implicate risperidone, but the etiology of his renal insufficiency was not explained. [At the time of this review, the sponsor has not yet furnished a translated case report form for this patient.] The Canadian patient (DC) who died from AIDS while receiving compassionate use risperidone was noted by his attending physician in the hospital to have episodes of diuresis following his risperidone doses; the physician felt this might be drug related. This patient also developed leukopenia, but the treating physician attributed this to pentamidine rather than risperidone.

Overall mortality was determined for each treatment group in the integrated safety database. For this purpose, deaths were counted if the patient was enrolled in a study included in the integrated safety data set, and if the death occurred no more than 30 days after discontinuation of drug. Patients who expired after 5/31/91 (the integrated safety data base cutoff date) were not counted. For risperidone, this method included 10 of the 18 reported deaths, and for active control patients one out of two reported deaths. The following table displays these figures for risperidone, active controls and placebo, and delineates both the crude mortality and the mortality adjusted for time of exposure to drug.

Drug	Number of Patients	Patient years of exposure	Deaths	Crude mortality	Mortality/ 100 Patient Years
Risperidone	2322	508	10	0.0043	2.0
Active Controls	533	61	1	0.0019	1.7
Placebo	176	13	0	0	0

From this, it will be seen that although the overall mortality rate was somewhat higher in the risperidone group than in the active control group, when adjusted for time of exposure to drug the rates are similar. The placebo group had no

deaths, but also had a much shorter time of exposure to drug than the other two groups.

8.3 Assessment of dropouts

8.3.1 Overall pattern of dropouts

Table 8.3.1 summarizes reasons for premature discontinuation among patients included in the pooled Phase 2-3 safety database. Predictably, the placebo group had the highest rate of discontinuation for lack of efficacy and the lowest rate of discontinuation for adverse events. Patient improvement accounted for very few dropouts, as might be expected for a severely mentally ill population. Discontinuations for both adverse experiences and lack of efficacy occurred at similar rates in the active control and risperidone patient groups. Altogether, roughly one third of both the risperidone and active control patients dropped out of clinical trials prematurely.

TABLE 8.3.1 Rates of Dropout by Treatment Group and Reason for Pooled Phase II-III Database

	Percent Dropping Out		
Reason for Dropout	Risperidone (N=2322)	Placebo (N=176)	Active Control (N=533)
Lack of Efficacy	13.6%	40.3%	14.1%
Adverse Experiences	8.4%	6.8%	10.3%
Patient Improvement	0.6%	0.0%	0.2%
Non-Treatment Related	10.7%	9.7%	10.7%
Total Dropouts	33.3%	56.8%	35.3%

Adverse experiences also includes intercurrent illnesses, abnormal lab results, and patient death.
Lack of efficacy includes deterioration of symptoms and inadequate response.
Patient improvement includes asymptomatic/sufficient response
Non-treatment related includes patient moved, chose to discontinue, lost-to-follow-up, uncooperative, ineligible, and other reasons.

8.3.2 Adverse Events Associated with Dropout

Overall, 8.4% of the 2,322 risperidone treated patients in the integrated Phase 2-3 safety database withdrew because of an adverse experience. For comparison, as shown in Table 8.3.1, the percent discontinuing placebo because of an adverse experience was 6.8%; for active controls the corresponding rate was 10.3%.

There were only two adverse events for which more than 1% of risperidone treated patients discontinued: extrapyramidal symptoms (EPS), and suicide attempts. EPS accounted for 1.7% of risperidone patients who dropped out for an adverse experience; this was roughly half the rate of discontinuation for EPS among active control patients (3.8%). (The term EPS combines reports from investigators of the following signs and symptoms: dystonia, ataxia, choreoathetosis, abnormal gait, hyperkinesia, hypertonia, hypokinesia, oculogyric crisis, tongue paralysis, tremor, involuntary muscle contractions, hyporeflexia,

aggravated parkinsonism, and unspecified extrapyramidal disorder.) Suicide attempts are discussed later in this review.

The following table lists all those adverse experiences that were associated with ≥ 0.3% of the 2,322 risperidone patients discontinuing the drug. Placebo rates for the same adverse experiences are shown for comparison. Some data is missing, since the sponsor did not designate a specific adverse event resulting in discontinuation for 19 of 2322 (0.8%) risperidone patients, 2 of 176 (1.1%) placebo patients, and 2 of 533 (0.4%) active control patients. For these cases, this reviewer assigned an adverse event leading to premature discontinuation wherever possible using information available from case report forms or narrative case summaries; 13 risperidone patients (and 2 haloperidol patients) were assigned reasons for premature discontinuation by this method.

	Percentage of patients dropping out	
Reason	Placebo (n=176)	Risperidone (n=2322)
Extrapyramidal symptoms	0.0%	1.7%
Suicide attempt	0.6%	1.2%
Dizziness	0.0%	0.7%
Agitation	0.0%	0.7%
Somnolence	0.0%	0.5%
Aggressive Reaction	0.0%	0.4%
Psychosis	0.0%	0.3%
Hyperkinesia	0.0%	0.4%
Fatigue	0.0%	0.4%
Nervousness	0.0%	0.3%
Asthenia	0.0%	0.3%
Nausea	0.0%	0.3%
Saliva Increased	0.0%	0.3%
Tachycardia	0.0%	0.3%
Delusion	0.0%	0.3%
Insomnia	0.0%	0.3%
Anxiety	0.0%	0.3%
Thinking Abnormal	0.0%	0.3%

Regarding the list above, one should bear in mind that the total exposure time expressed in patient-years was roughly 40 times higher for risperidone compared to placebo, and therefore the risk of experiencing an adverse event and discontinuing treatment was higher for the risperidone patients.

Suicide attempts will be discussed in more detail in section 8.4. For all the remaining adverse events listed the most common (≥0.5%) events resulting in dropout were EPS, dizziness, agitation and somnolence.

While the presence of agitation on the forgoing list might be interpreted as evidence that risperidone induces agitation, in fact the rate of dropping out for agitation was comparable between risperidone and active controls in the integrated safety dataset (16/2322 or 0.7% for risperidone, and 3/533 or 0.6% for active controls). Likewise, dropping out for aggressive reactions occurred in 9/2322 risperidone patients (0.4%) and 1/533 active control patients (0.2%). (Assessment of these adverse experiences is confounded by the fact that agitation and aggressive reactions can be symptoms of acute psychosis.)

8.4 Safety Findings Discovered with Other Specific Search Strategies

8.4.1 Search for Emergence of Suicidality

As evident from Appendix 8.2, the most common cause of death during the risperidone clinical development program was suicide. The danger of suicide in a chronic schizophrenic population is well known; long term follow up studies have shown that up to 10% of schizophrenic patients eventually commit suicide, with many suicides occurring after a psychiatric hospitalization (Roy, 1986).

The occurrence of suicide was compared between treatment groups in the clinical trials. For the purpose of correlating incidence with the available exposure data, suicides from clinical trials contributing to the integrated safety database were considered. Suicides were counted if they occurred prior to the cut-off date for the integrated safety data set, and no more than thirty days after discontinuation of drug if the patient had stopped medication. The following table shows the numbers of such suicides among risperidone, placebo and active control patients. (Appendix 8.2 lists all reported deaths during the clinical development program, including all suicides, even if they occurred outside the parameters of the integrated safety database.)

Drug	Number of patients	Patient years of exposure	Suicides	Crude Rate	Suicides per 100 Patient Years
Risperidone	2322	508	7	0.0030	1.4
Active Controls	533	61	1	0.0019	1.7
Placebo	176	13	0	0	0

From this, it will be seen that although the crude suicide rate was somewhat higher in the risperidone group compared to the active control group, when expressed in terms of patient years the suicide rate was comparable in the two groups. Placebo patients, with the shortest cumulative exposure time, had no suicides during clinical trials. (Of course, when expressing such data in terms of occurrence per unit of time, one assumes that the event rate does not vary with length of time exposed.)

In a similar fashion, the numbers of patients making suicide attempts were determined and compared between groups from the integrated safety data base. Here, reports from clinical trials of all self destructive behaviors were combined into a single category incorporating suicides, suicide attempts, self inflicted injuries, and overdoses. (The term "suicide attempt" was defined broadly by the sponsor to include suicidal attempts, ideation, gestures, thoughts or tendencies; these events are not classified separately in the WHO adverse event terminology). The following table presents these data.

Drug	Number of patients	Patient years of exposure	Patients with Suicide attempts	Crude rate	Incidence per 100 Patient Years
Risperidone	2322	508	36	0.0155	7.1
Active Controls	533	61	4	0.0075	6.6
Placebo	176	13	1	0.0057	7.5

The crude rate of self destructive behavior was higher in the risperidone group than in the active control or placebo groups, but when calculated in terms of patient years of exposure, the rates are comparable.

Reports of mood disturbance that might accompany self destructive acts were also considered. Depression was, in fact, an infrequent adverse event among risperidone patients. In the two major placebo controlled trials no risperidone patient was reported to have depression as an adverse event, and in the total data set depression was reported in 17/2322 risperidone patients (0.7%); the corresponding figures for active control patients were 2/533 (0.4%). No placebo patients had depression recorded as an adverse event. Depression was given as a reason for premature discontinuation in 3/2322 risperidone patients (0.1%); one of these patients eventually committed suicide 3 months after stopping risperidone treatment (patient study HOL-9002). Premature discontinuation for depression occurred in 1/533 active control patients (0.2%).

8.4.2 Search for Serious Events

The Code of Federal Regulations defines serious adverse drug experiences as one that is fatal or life threatening, is permanently disabling, requires inpatient hospitalization, or is a congenital anomaly, cancer, or overdose (21 CFR 314.80). The sponsor conducted a manual search of the available clinical data for such events, using a broad definition of life threatening to refer to events that were immediately life threatening or life threatening if not treated. The sponsor searched not only the integrated safety data base for such events, but also data from the six Phase 2-3 trials that were not included in the safety database, safety reports from the sites disqualified for poor quality control in study 024, and reports included in the NDA from ongoing studies. For risperidone exposed patients, a total of 64 such events were found by the sponsor with this method. Another 20 serious events, chiefly suicide attempts together with a few additional events identified by this reviewer, were added to this tabulation to yield a total of 84 serious events among the risperidone treated patients. Of these, 36 occurred during open label trials and 48 during double blind risperidone treatment. Self destructive behavior accounted for a large proportion of the serious adverse events. In the following, the majority of these events are discussed under specific sections of the review (deaths, overdoses, suicidal behavior, laboratories, vital signs, electrocardiograms and important events considered potentially drug related). The remainder are listed in Appendix 8.8 as events considered unlikely to be drug related; events from the control groups are shown there as well.

8.5 Other Safety Findings

8.5.1 ADR Incidence Tables

Appendix 8.5.1.1 lists adverse experiences observed during the only placebo controlled dose comparison trial, Study 204. This was an 8 week, fixed dose inpatient trial with acutely ill schizophrenic patients. The tabulation in Appendix 8.5.1.1 includes all adverse events having an incidence of ≥2% in at least one of the risperidone dose groups. Investigator reports of adverse events were classified according to the World Health Organization preferred terms. Note that Appendix 8.5.1.1 contains only spontaneously reported adverse events; in

this study, adverse experience reports were also collected from patients with a symptom rating scale, and the events elicited in this manner will be described separately.

Common and Drug Related Adverse Events

From Appendix 8.5.1.1, the following adverse events occurred at a rate ≥ 5% in at least one risperidone dose group, *and* were seen at least twice as frequently in one or more risperidone dose groups as among placebo patients:

Extrapyramidal symptoms (EPS)	Vomiting
Rhinitis	Nausea
Dyspepsia	Coughing
Constipation	Dizziness
Dysmenorrhea*	Mastitis*
Hyperkinesia	Somnolence
Rash	Tachycardia
Vaginitis*	

*incidence calculated for women only

Dose Response for Common Adverse Events

Visual inspection of rates for these adverse events suggested that the following adverse experiences demonstrated a dose dependency: somnolence, extrapyramidal disorder, and tachycardia. Additionally, vaginitis was seen only in the risperidone 16 mg group.

Adverse Event Rates From Symptom Checklist

In addition to spontaneously reported adverse events, in Study 204 symptoms were elicited with the UKU (Udvalg for Klinske Undersglese) scale (Lingjaerde et al., 1987). This method increases the sensitivity of adverse event data collection, especially since acutely psychotic patients may be too disorganized to report symptoms on their own. Appendix 8.5.1.2 lists for each UKU symptom the percentage of patients who experienced a deterioration from baseline in their scores. Placebo patients are included for comparison. From this tabulation, the following adverse events were reported by ≥5% of patients in one or more risperidone treatment groups, and at least twice as often in one or more ripseridone groups as in the placebo group:

Sleepiness/sedation	Increased duration of sleep
Increased dream activity	Accomodation disturbances
Reduced salivation	Nausea/vomiting
Micturation disturbances	Diarrhea
Orthostatic dizziness	Palpitations/tachycardia
Rash (all types)	Diminished sexual desire
Weight gain	Erectile dysfunction*
Ejaculatory dysfunction	Orgastic dysfunction
Menorrhagia*	

*gender specific incidence

Dose Response for Elicited Adverse Events

The UKU symptom scale was also employed in study 024, the large Phase III study that used an active control. As this study included roughly 225 patients in each of the five risperidone dose groups (1, 4, 8, 12 and 16 mg), it provides a more robust sample to evaluate dose-relatedness of elicited adverse events. When dose relatedness of UKU symptom scale items was analyzed with the Test, the following events emerged as dose-dependent: sleepiness, increased duration of sleep, accomodation disturbances, orthostatic dizziness, palpitations/tachycardia, weight gain, erectile dysfunction, ejaculatory dysfunction, asthenia/lassitude/increased fatiguability, increased pigmentation, and orgastic dysfunction.

8.5.1.2 Other Events Observed During the Premarketing Evaluation of Risperidone

In addition to the forgoing tabulations of adverse experiences, the sponsor collected reports of all adverse events observed during clinical trials and combined them. This list, which appears in Appendix 8.5.1.3, comprises reports from a diversity of Phase 2 and 3 studies involving a total of 2322 patients in the integrated safety database. One should bear in mind that the conditions under which patients were exposed to risperidone varied greatly from study to study, and included a wide range of exposure duration.

For the purpose of this listing, the terms frequent, infrequent and rare are defined in the following way. *Frequent* adverse events occurred in at least 1/100 patients on risperidone, *infrequent* adverse events occurred at a rate of between 1/100 and 1/1000 risperidone patients, and *rare* adverse events occurred in less that 1/1000 risperidone patients. However, adverse events already appearing in Appendix 8.5.1.1 are not included in this listing. To compile this list, adverse event reports from all 2322 risperidone patients in the integrated safety data set have been tabulated according to World Health Organization Body Class and Preferred Term. Some of the adverse events listed may have been incidental and not causally related to risperidone treatment. Adverse experiences marked with an asterisk had their incidence determined from elicited reports; as noted above, the UKU side effect rating scale was used in some trials to collect adverse experience reports. Adverse events listed without an asterisk represent the investigator's description of spontaneously reported adverse events, classified according to WHO Preferred Term. When adverse events were both elicited and spontaneously reported, the spontaneous reporting rate has been used in this list. In study 024, some investigators added adverse events to the UKU scale but did not report them separately under adverse experiences on the

case report forms. Such adverse events from study 024 were not counted in the sponsor's integrated safety database, but if not already listed in Appendix 8.5.1.2 have been added by this reviewer.

This tabulation is a modified version of Janssen's submission dated February 10, 1993.

8.5.2 Laboratory Findings

Clinical laboratories were obtained on patients participating in the risperidone development program, and the findings for chemistry, hematology and urinalysis will be described below. Numbers of patients tested varied, depending on the particular laboratory test. As approximations, roughly 1800 risperidone patients in the total Phase 2-3 database had some type of hematology laboratories performed, as did roughly 120 placebo patients and 340 haloperidol patients. Similarly, about 1700 risperidone patients, 120 placebo patients and 340 haloperidol patients had at least some clinical chemistry studies. Urinalyses were obtained on about 1400 risperidone patients, 120 placebo patients and 270 haloperidol patients; however, systematic collection of urinalysis data was often limited to urine pH and specific gravity.

Laboratory results in the two major placebo controlled trials, trials 201 and 204, will be emphasized in this discussion since they provide the most meaningful comparisons between risperidone and placebo.

8.5.2.1 Serum Chemistry

Appendix 8.5.2.1.1 lists the abnormal chemistry values considered to be of potential clinical significance.

Appendix 8.5.2.1.2 displays the proportions of patients meeting those criteria in placebo controlled trials 201 and 204. Patients were counted if they exceeded a laboratory value parameter one or more times during their study, or up to four days after finishing. The denominator in each case is the number of patients with baseline values that did not exceed the criterion. With a two tailed Test, proportions of patients meeting these criteria did not differ significantly between risperidone and placebo groups for any chemistry value ($p > 0.10$). Along with making this statistical comparison across groups, selected individual cases meeting clinically significant criteria were reviewed individually, as described below.

For some chemistry variables, although clinically significant ranges were not defined and no statistical comparisons were made between risperidone and placebo, the sponsor did determine mean changes from baseline on treatment. These data were pooled for U.S. studies and for foreign studies. By simple inspection, such data on serum triglycerides, cholesterol, chloride, globulin, and potassium showed no consistent pattern of change associated with risperidone treatment. For serum iron, mean values decreased by roughly 10-15 μg/dl at various weeks of treatment with risperidone in U.S. patients (studies 201 and 204), but remained within the normal range. (Serum iron was measured only rarely in foreign trials.)

Discontinuations from clinical trials for chemistry abnormalities were examined. From studies in the integrated Phase 2-3 database, 8/2322 risperidone treated patients, 4/533 active control patients and 4/176 placebo patients

withdrew because of abnormal chemistry values. The specific laboratory findings for these cases are outlined below.

Risperidone	5/2322 (0.2%) for ↑liver enzymes
	2/2322 (0.09%) for ↑CPK
	1/2322 (0.04%) for ↓albumin
Active Controls	2/533 (0.4%) for ↑liver enzymes
	2/533 (0.4%) for ↑CPK
Placebo	3/176 (1.7%) for ↑liver enzymes
	1/176 ((0.6%) for ↑CPK

From the integrated safety data set, the rate of discontinuation for hepatic enzyme abnormalities was 0.2%, 1.7% and 0.4% for risperidone, placebo and active control patients respectively. The rate of discontinuation for CPK elevation was 0.09% for risperidone, 0.4% for active controls and 0.6% for placebo.

In study 204, six patients with elevated CPK had isoenzyme fractionation performed; three were on risperidone and three on haloperidol. In all six cases the source was skeletal muscle.

Individual cases in which a risperidone patient discontinued the drug because of liver enzyme abnormalities were examined:

1. Patient in study 024 was a 55 year old male who developed possible liver enlargement and ascites after 11 days on risperidone; a few months later he died of pneumonia. The patient had elevated transaminases at entry into the study; this finding was attributed to his prior treatment with chlorpromazine, and casts doubt on a relationship of his illness to risperidone treatment.

2. The patient withdrawn for hypoalbuminemia from study 024) also had elevated liver enzymes; this patient was subsequently discovered to have a hepatoma, which in retrospect would account for the abnormal laboratory values.

3. In four other cases in study 205, in study 204, in study 205, and in study 024) patients experienced asymptomatic elevations of liver enzymes while on risperidone and were discontinued from their trials; follow up enzyme values were obtained on patients from study 205 and from study 205, and returned to normal in both cases after discontinuation of risperidone. In patient from study 024, alcohol abuse may have contributed to the enzyme elevation.

A more serious case of hepatic enzyme elevation with risperidone was reported under the risperidone commercial IND after the NDA was submitted (10-day safety report dated 9/23/92). The patient was a male treated with risperidone for approximately two months when his liver enzyme values rose significantly; he had been receiving a dose of 12 mg/day. His SGOT peaked at 324 U, SGPT peaked at 200 U and LDH peaked at 749 U. In addition, he was jaundiced and had a maximum bilirubin value of 7.8 mg/dl. Serologies for hepatitis B and HCV were negative. This is the only case in which a patient on risperidone became symptomatic (i.e. jaundiced) from hepatic dysfunction in the absence of known hepatic disease; the liver enzyme values all returned to normal about one month after the drug was discontinued. It should be noted that since this patient was

not included in the integrated Phase 2-3 database for the NDA, this occurrence can not be related to the available risperidone exposure data as was possible for the cases above; the cohort of patients from which this case derived has not yet been enumerated by the sponsor.

Investigators for RIS-JPN-9003, a study not included in the integrated safety data base, reported treatment emergent hepatic enzyme elevations in three out of 83 patients; none of the three had to discontinue treatment prematurely.

While certain cases show a time relationship between risperidone use and liver enzyme abnormalities which might otherwise suggest a cause and effect relationship, in the integrated safety data base risperidone had the lowest rate of patient discontinuations for hepatic enzyme elevations of all three treatment groups. This latter point argues against attributing hepatic enzyme changes to risperidone. The case of the patient who developed jaundice on risperidone, however, is difficult to dismiss as unrelated to drug, given the severity of the hepatic reaction and the fact that no causal factor other than drug treatment was implicated.

Hyponatremia was reported in two risperidone patients who had seizures (described in section 8.7 below), and was reported as a serious adverse event in one other risperidone patient from protocol 024). In the integrated Phase 2-3 safety data base, however, no patients discontinued risperidone because of hyponatremia. (The two patients with seizures had their adverse experiences after the cutoff date for the safety database, and patient from protocol 024 did not discontinue treatment.) As noted above, in the major placebo controlled studies 201 and 204 there was no statistically significant increase in hyponatremia among risperidone patients in comparison to placebo. Tc exlpore this further, data from the entire Phase 2-3 safety database was considered. Proportions of patients meeting the criterion value for clinically significant hyponatremia are listed below.

Treatment	Patients tested	Patients with [Na]≤129 mEq/L
Risperidone	1651	8
Haloperidol	347	6
Placebo	130	1

These figures yield incidences of 2%, 0.5% and 0.8% for haloperidol, risperidone and placebo respectively. The mean clinically significant sodium concentrations for these patients were 126-127 mEq/L in all three treatment groups; the degree of hyponatremia did not appear more pronounced in any one group. Thus, no pattern connecting risperidone to hyponatremia is apparent from the integrated Phase 2-3 safety data base, despite the isolated cases noted above. The occurrence of hyponatremia in a chronic schizophrenic population is well known; see section 8.7 below.

Endocrinological assessments were included in the placebo controlled dose comparison trial, Study 204. The following table displays the results for patients taking risperidone in the recommended dose range, placebo and haloperidol. Patients were counted if their level was normal at baseline but became abnormal during treatment. The abbreviation TSH refers to thyroid stimulating hormone, and GH refers to growth hormone. (Cortisol was also assayed, but the samples were not taken at a consistent time of day; there were no significant differences between treatment groups)

Abnormality	Placebo	Ris 2 mg	Ris 6 mg	Ris 10 mg	Ris 16 mg	Hal 20 mg
High prolactin	1/32 (3.1%)	7/35 (20.0%)	5/31 (16.1%)	14/38 (36.8%)	17/34 (50.0%)	5/35 (14.3%)
High TSH	0/32	0/35	0/31	0/38	2/34 (5.9%)	1/35 (2.9%)
Low T_3	3/32 (9.4%)	3/35 (8.6%)	4/31 (12.9%)	6/38 (15.8%)	6/34 (17.7%)	8/35 (22.9%)
Low Testosterone	0/20	2/17 (11.7%)	0/22	3/26 (11.5%)	1/20 (5.0%)	2/12 (16.7%)
High GH	5/32 (15.6%)	1/35 (2.9%)	0/31	5/37 (13.5%)	7/34 (20.6%)	2/35 (5.7%)

From this, the most consistent finding associated with risperidone was an increased prolactin level, a phenomenon traditionally ascribed to dopamine antagonism. The proportion of patients having elevated prolactin was higher in the risperidone 10 mg and 16 mg groups than in the haloperidol 20 mg group; this parallels observations from clinical pharmacology studies. The sponsor has attributed risperidone's potency in elevating prolactin to the activity of its hydroxy metabolite.

Endocrinologic measurements were made in Study 024 as well, although no placebo group was available for comparison. Prolactin, GH, TSH, T3 and cortisol were sampled at baseline and on treatment; the principle finding was a dose dependent increase in prolactin levels on risperidone.

On balance, clinical chemistry results did not demonstrate any significant abnormalities clearly associated with risperidone treatment, except for prolactin elevation.

8.5.2.2 Hematology

Appendix 8.5.2.2.1 describes parameters for determining potentially clinically significant changes in hematology values. Appendix 8.5.2.2.2 details the proportions of patients meeting these criteria in the major placebo controlled risperidone trials (protocols 201 and 204). Patients were considered meeting criteria if they exceeded a clinically significant value at least once, either while in the trial or within four days after termination. The denominators represent the number of patients who did not exceed the criterion at baseline for the hematology value in question.

When incidences for placebo and risperidone groups were compared with the two tailed Fisher's Exact Test, there were no significant differences for any hematology values ($p \geq 0.10$).

Additionally, the comprehensive Phase 2-3 safety database was screened for patients who discontinued treatment because of abnormal hematology findings, and individual cases were reviewed.

No patients dropped out because of hematology abnormalities from the placebo or active control groups. A total of two patients out of 2322

discontinued ripseridone because of hematology abnormalities; one had anemia and the other developed Pelger-Huet Anomaly. The latter condition can be either a benign congenital abnormality of granulocytes, or it can develop from exposure to certain drugs (Jandl, 1987). In this patient from study 204), a consulting hematologist diagnosed the aquired rather than the congenital form of the abnormality. The patient's bone marrow demonstrated impaired granulopoeisis.

The other case was patient from study 204, a 39 year old female, discontinued from risperidone because of epistaxis, abdominal bloating, anemia and weight gain. Her baseline hemoglobin was 11.5 g/dl but dropped to 10.3 at the time she discontinued; her total iron at that time was slightly low at 32 μg/dL. Of possible significance is the fact that she experienced recurrent epistaxis during the trial.

An additional case of withdrawal for anemia was reported from one of the trials not included int the integrated safety data base. Patient from Japanese trial 9003 developed an anemia (hgb 10.8) associated with decreased ferritin and plasma iron; after risperidone was stopped and iron supplement administered these values began to return to normal.

In summary, although the case of Pelger-Huet Anomaly suggests that the drug may not be completely inert with regard to the hematopoetic system, there appear to be no clinically relevant hematologic changes associated with risperidone use.

8.5.2.3 Urinalysis

Appendix 8.5.2.3.1 lists the urinalysis values that were considered to be potentially clinically significant. In Appendix 8.5.2.3.2, the proportions of patients from placebo controlled trials meeting these criteria are displayed. The rates did not differ significantly between placebo and risperidone patient groups (Fisher's Exact Test, two tailed, $p > 0.10$). Note, however, that microscopic findings (RBCs, WBCs, casts) were reported for very few patients, and so conclusions drawn for this category must be interpreted cautiously. Substantially more data was available on urine chemistry. No patients withdrew from clinical trials because of abnormal urinalysis results, and for this laboratory parameter no individual cases were reviewed.

Thus, from the available data it is not possible to attribute any particular urinalysis abnormality to risperidone, but it must be kept in mind that data were not collected or analyzed as rigorously for urinalyses as they were for other clinical laboratories.

8.5.3 Vital Signs and Weight

In Phase 2-3 clinical trials, pulse and blood pressure data were obtained on approximately 2060 patients and included in the integrated safety data base. Orthostatic pulse and blood pressure were measured in approximately 1500 risperidone treated patients. Weights were obtained on 1684 risperidone treated patients.

Appendix 8.5.3.1 gives the criteria for determining potentially clinically significant changes in vital signs, and Appendix 8.5.3.2 displays the proportions of patients in placebo controlled clinical trials 201 and 204 exceeding these criteria at least once. Here the denominator is the number of patients who did not meet the particular criterion at baseline. When proportions of risperidone and placebo patients meeting criteria for vital sign changes were compared (using a two tailed Test), only one parameter was significantly increased

among risperidone patients at a $p \leq 0.10$ level: standing pulse was elevated in 10.3% of risperidone patients compared to 2.4% of placebo patients ($p = 0.018$). This elevation in standing pulse is indicative of risperidone's propensity to cause postural hypotension, as will be discussed in section 8.7.

Mean changes on risperidone treatment from baseline vital sign measurements were determined in the individual studies. Inspection of these data from the three primary clinical trials revealed modest decreases in mean diastolic and systolic blood pressures of roughly 6 mmHg or less (especially seen in standing pressures), and increases in mean standing pulse of roughly 7 bpm or less, particularly in the early weeks. These patterns also seem consistent with a tendency of risperidone to cause postural hypotension.

A total of 20 out of 2322 patients (0.9%) treated with risperidone had to discontinue the drug because of vital sign changes. The principal vital sign changes implicated were tachycardia, hypotension, hypertension and postural hypotension. In comparison, one out of 176 placebo patients (0.6%) and three out of 533 patients on active controls (0.6%) withdrew because of vital sign abnormalities. The particular vital sign changes associated with premature discontinuation are listed according to the investigator's description below; where the investigator had not specified a particular vital sign change as an adverse event, this reviewer assigned one if it could be discerned from the case summary or case report form. In addition to these cases, patient #496 in study 205 experienced an irregular pulse on risperidone; this was considered a serious adverse event by the sponsor.

Risperidone (n=2322)	Active controls (n=533)	Placebo (n=176)
Tachycardia 8 (0.3%)	Hypotension 1 (0.2%)	Unspecified 1 (0.6%)
Orthostatic hypotension 5 (0.2%)	Bradycardia 1 (0.2%)	
Hypertension 3 (0.1%)		
Hypotension 4 (0.2%)		

In Phase 1 trials, postural hypotension was seen frequently with risperidone, and one risperidone patient in study HOL-9004 experienced bradycardia.

Weight changes, in addition to being reported as adverse events, were assessed by direct measurement. Using a criterion of $\geq 7\%$ body weight change, the following proportions of patients had significant weight increase or decrease during placebo controlled trials 201 and 204, with patients being counted if they met the criterion one or more times during the trial:

Weight gain
Risperidone 65/363 (18%); Haloperidol 6/119 (5%); Placebo 11/119 (9%)

Weight loss
Risperidone 8/363 (2%); Haloperidol 5/119 (4.2%); Placebo 13/119 (11%)

The higher incidence of weight gain was statistically significant for risperidone compared to placebo : Test, p=0.0003).

The entire Phase 2-3 integrated safety database was searched for patients who discontinued treatment prematurely because of weight changes. There were only two such cases.

One risperidone patient, from study 204, discontinued from treatment because of epistaxis, abdominal bloating, anemia and weight gain; this case has been described above under hematology findings. Although weight gain was reported as an adverse event, recorded weights actually showed weight loss of 1 kg.

The other patient to withdraw prematurely because of weight change was patient from protocol 008; this patient lost weight while receiving haloperidol.

From the foregoing, risperidone treatment is associated with significant weight gain to a greater extent than placebo; the fact that more patients did not discontinue treatment because of weight gain may reflect the short duration of most of the clinical trials, since weight gain of a magnitude to require discontinuation would be most likely to develop after an extended time. In longer term use then, weight gain may emerge as a cause for discontinuation of risperidone treatment.

8.5.4 Electrocardiograms

In the comprehensive Phase 2-3 safety database, approximately 1500 risperidone patients had EKGs performed, along with roughly 340 haloperidol and 120 placebo patients. The following criteria for potentially clinically significant EKG changes were established, although not every parameter was measured in each study:

Heart Rate, high	>120 bpm and increase ≥15 bpm
Heart rate, low	<50 bpm and decrease ≥ 15 bpm
PR interval	≥210 msec
QRS duration, high	≥150 msec
QRS duration, low	≤50 msec
QT interval, high	≥500 msec
QT interval, low	≤200 msec
QTc interval, high	≥450 msec
PQ interval, high	≥200 msec
PQ interval, low	≤120 msec

When rates of possibly significant EKG abnormalities (as defined above, except that the PQ interval was not measured) were compared for aproximately 380 risperidone and 120 placebo patients in studies 201 and 204, no statistically significant differences were found between risperidone and placebo patients (two tailed Test, $p \geq 0.20$). The numbers of patients meeting criteria on treatment (and that did not meet them at baseline) are given in the following table.

Numbers (%) of Patients with Potentially Clinically Significant EKG Changes (Studies 201 and 204)

EKG Variable	Risperidone	Placebo
↑ heart rate	2/385 (0.5%)	1/128 (0.8%)
↓ heart rate	0	1/128 (0.8%)
↑ PR interval	0	0
↓ QRS interval	2/385 (0.5%)	1/127 (0.8%)
↑ QRS interval	0	0
↓ QT interval	0	0
↑ QT interval	0	0
↑ QTc interval	8 (2.1%)	0

Using the same criteria, in the integrated Phase 2-3 safety database, the following EKG abnormalities were encountered in ≥ 0.5% of risperidone treated patients. Findings in placebo patients have already been displayed above; for comparison, the incidence for these abnormalities among haloperidol patients in the Phase 2-3 safety database are listed beside the risperidone incidences :

Finding	Risperidone	Haloperidol
↑ QTc	61/1429 patients, 4.3%	9/325 patients, 2.8%
↓ PQ interval	69/945 patients, 7.3%	12/176 patients, 6.8%
↑ PQ interval	24/945 patients, 2.5%	2/176 patients, 1.1%
↓ heart rate	10/1519 patients, 0.7%	0/348 patients

Regarding the comparison to haloperidol, one should bear in mind that haloperidol is associated with tachycardia and QT prolongation (see current labelling for Haldol).

The entire Phase 2-3 safety database was screened for patients dropping out for changes in their EKGs, and individual cases were reviewed. A total of four patients out of 2322 (0.2%) exposed to risperidone discontinued because of EKG abnormalities. In comparison, one out of 176 (0.6%) patients on placebo discontinued for an abnormal EKG (patient from study 201, who had atrial fibrillation). One of 533 patients (0.2%) on active controls discontinued for an abnormal EKG (patient from study 024, who had bradycardia while taking haloperidol).

The four cases requiring discontinuation of risperidone for EKG abnormalities are presented here in summary form.

1. Patient from study 024 was a 49 year old male with a history of treatment with digitalis. His baseline EKG was normal. Approximately three weeks after beginning risperidone 4 mg/d, he developed chest pain and dyspnea;

an EKG at that time showed grade II AV block. Risperidone was discontinued and a repeat EKG one week later was again normal.

2. Patient from study 024, a 32 year old female with no cardiac history, had a heart rate of 113 bpm and a QTc interval of 439 msec at baseline. After one week on risperidone 1 mg/d, her EKG showed tachycardia to 128 bpm and ST depressions; the QTc was 409. She complained of palpitations, nausea, vomiting and diaphoresis and was withdrawn from the study; a repeat EKG two months later was entirely normal.

3. A third patient, from study 205, was a 31 year old male with a right ventricular conduction delay at baseline; he developed tachycardia (115 bpm) and frequent uniform premature ventricular contractions after three doses of risperidone 2 mg.

4. The fourth patient study 024) was a 21 year old male with a normal baseline EKG; after two days on risperidone 8 mg/d he complained of palpitations and was found to be hypertensive, with ventricular extrasystoles on his EKG.

A fifth patient, from study 024, was listed as having prematurely discontinued risperidone because of palpitations, tachycardia, and abnormal EKG. This patient was not counted above because the case report form did not include an EKG on treatment. The tachycardia and palpitations were well documented, however.

Patient from study 210, who discontinued risperidone prematurely because of hypotension, had a change from normal sinus rhythm on his baseline EKG to bradycardia with risperidone treatment.

Electrocardiogram findings from trials that were not included in the integrated safety data base were also reviewed. In study JPN-9003, patient developed sinus tachycardia and ST-T wave changes on risperidone; these findings resolved after it was discontinued. Another patient in the same study (no patient number given), with a right bundle branch block and tachycardia at baseline, developed ventricular and supraventricular extrasystoles on risperidone; these abnormalities did not result in premature withdrawal, but were noted to have resolved on follow up after the trial.

From the foregoing descriptions, it will be seen that there were a variety of EKG abnormalities leading to discontinuation from risperidone treatment, rahter than a specific finding common to all cases. It should be noted, however, that of the three patients with treatment emergent ventricular extrasystoles, two had conduction abnormalities at baseline.

Another method of evaluating EKG data is to consider mean changes in various EKG parameters between baseline and on-treatment findings. The sponsor provided descriptive statistics of EKG variables as part of the safety analysis of studies 201, 204 and 024; this data will be summarized here.

In study 201, among the 50 patients with EKG data who received risperidone, changes from baseline in the following EKG parameters were evaluated at selected times during the trial: ventricular rate, PR interval, QRS duration, QT interval, and QTc interval. Changes in mean values from baseline reached statistical significance at a 0.05 level only for the following parameters and timepoints:

↑ heart rate of 5.6 bpm (week 2)
↓ PR interval of 3.6 msec (week 6)
↓ QT interval of 10.3 msec (week 2)

In the control groups, the following comparisons reached statistical significance:

↓ QRS duration of 6.7 msec (week 2, placebo)
↓ QT interval of 17.8 msec (week 2, placebo)

In this study, no generalizations appear possible from these isolated findings of significant comparisons.

In study 204, roughly 80 patients in each of the four risperidone dose groups had EKGs performed. Heart rate, PR interval, QRS duration, QT interval, QTc interval, and RR interval were determined from EKGs which were recorded at baseline, one week, eight weeks and endpoint. For risperidone, there were statistically significant changes from baseline means in the following cases:

↑ heart rate (for at least one time point in all dose groups)
↓ PR interval (for one time point in the 6 mg, 10 mg and 16 mg dose groups)
↓ QRS duration (for one time point in the 16 mg group)
↓ QT interval (for at least one time in all dose groups)
↑ QTc interval (for the 16 mg group at week 1)
↓ RR interval (for at least one time point in all dose groups)

In the haloperidol and placebo control groups, there were the following statistically significant comparisons to baseline means:

↓QT interval (endpoint, placebo)
↓QTc interval (week 8 and endpoint, placebo)

On balance, in this study most of the treatment emergent EKG changes observed with risperidone appear referrable to an increase in heart rate. Additionally, a cardiologist reviewed EKGs in this study for changes in conduction, wave forms and dysrhythmias and concluded there were no clinically significant abnormalities attributable to risperidone.

In study 024, baseline and endpoint EKGs were obtained on 885 risperidone patients and 170 haloperidol patients. The following parameters were analyzed: heart rate, PQ, QRS, QT, QTc, and QTm. Mean changes from baseline reached statistical significance for these parameters and treatment groups:

↓ heart rate (risperidone 4 mg and 16 mg groups)
↓ QRS duration of 1.3 msec in the risperidone 16 mg group
↓ QTc (risperidone 16 mg group and haloperidol 10 mg group)
↓ QTm of 4.0 msec in the haloperidol 10 mg group

No specific constellation of treatment emergent EKG findings seems evident from these comparisons in study 024.

Comparing these change from baseline EKG results across studies shows a lack of consistency in observations; an increase in heart rate was noted in studies 201 and 204 but a decrease was seen in 024. Similarly, QTc findings did not agree in studies 204 and 024. Thus, it does not appear possible to make generalizations about risperidone's effect on EKG parameters from consideration

of mean value changes, as no consistent pattern is evident. Furthermore, with multiple comparisons of this type, the possibility that isolated findings of statistical significance could have emerged by chance must be considered.

In Phase I studies, EKG changes observed included increased heart rate and decreased QT interval. In study FRG-9001, subject 1221-11 collapsed after recieving a single 4 mg dose of risperidone; this subject was hypotensive, and the EKG revealed an AV rhythm with a heart rate of 36 bpm. Twenty-four hour ECG recordings on five volunteers taking risperidone 1 mg/day showed an increase in supraventricular tachycardia and extrasystoles. Two subjects in study GBR-9004 had S-T segment changes on risperidone.

In preclinical studies, oral risperidone at clinically relevant doses administered to unanesthetized dogs resulted in prolongation of the QTc interval.

On balance, descriptive statistical methods do not appear to demonstrate any consistent association of EKG changes with risperidone treatment. From the descriptions above, however, it will be seen that EKG abnormalities did occur with some frequency during risperidone use in clinical trials. Tachycardia, ventricular extrasystoles (chiefly in patients with conduction deficits), prolongation of QTc interval, and impaired conduction have all been observed in risperidone treated patients. In the integrated Phase 2-3 safety database risperidone was more often associated with prolonged QTc than was haloperidol, a drug known to be associated with QT prolongation.

8.5.5 Chest X-rays

Chest x-rays were obtained during one of the three major clinical trials, Study 201. In this trial, chest roentgenograms were obtained on 44 risperidone, 40 haloperidol and 34 placebo patients. Chest x-ray findings on follow-up films that were not noted at baseline are listed below, by treatment group. The three findings in the risperidone group seem unlikely to represent effects of risperidone treatment.

Risperidone (44 patients)
- Increased pulmonary markings (1 patient, 2%)
- Aortic atherosclerosis (1 patient, 2%)
- Hyperinflation (1 patient, 2%)

Haloperidol (40 patients)
- Hyperinflation (1 patient, 3%)
- Tortuous aorta (1 patient, 3%)

Placebo (34 patients)
- Hyperinflation (1 patient, 3%)

8.5.6 Special Studies

Protocol RIS-GBR-9004 was a placebo controlled study of sleep EEG changes following single dose risperidone in fifteen healthy male volunteers. Positive findings included delayed REM onset, decreased REM duration, decreased wakefulness and decreased Stage 1 sleep with risperidone.

Study RIS-BEL-16 was a four week open label trial of risperidone in hospitalized schizophrenic patients which included polysomnography. With risperidone, sleep efficiency improved and sleep latency decreased.

8.5.7 Withdrawal Phenomena/Abuse Potential

The sponsor reports no instances of risperidone abuse or dependence. Withdrawal phenomena were not formally assessed after patients discontinued risperidone. Several patients committed suicide within one month of discontinuing risperidone; however, it does not seem reasonable to attribute this to withdrawal, given the absence of other indications of a risperidone withdrawal syndrome and the fact that schizophrenia is known to be a risk factor for suicide.

8.5.8 Human Reproduction Data

Human reproduction data is lacking; the sponsor is not aware of any pregnancies during risperidone clinical trials.

8.6 Overdose Experience

There have been five documented cases of risperidone overdose, defined by ingestion of ≥3 times the intended dose; all patients recovered with no apparent sequelae.

1. Patient in study 035, a 36 year old female, took 300 mg of risperidone. This produced a peak plasma level of 716 ng/ml. The patient developed somnolence, hypotension, tachycardia, hypokalemia, hyperreflexia and muscle rigidity. She was treated with gastric lavage, plasma expansion and activated charcoal; recovery was uncomplicated.
2. Patient in study 024, a 20 year old female, overdosed on 56 mg of risperidone and propranolol. She was treated with gastric wash out and suffered no sequelae.
3. Patient in study 205, a 28 year old male, was treated for a presumptive overdose of 240 mg of risperidone. Signs and symptoms included lethargy, hyponatremia, hypokalemia, prolonged QTc interval and widened QRS. He received treatment with gastric lavage and activated charcoal; his plasma risperidone + 9-OH-risperidone level was 33.6 ng/ml (not considered elevated). He recovered by the next day.
4. Patient in study 033, a 36 year old female, took a multiple drug overdose of 20 mg risperidone, lormetazepam, 14 mg of biperiden, and roughly 1500 mg of promethazine. She was initially semi-comatose but was successfully treated with gastric lavage.
5. Patient in study 024, a 39 year old female, took an overdose of 20 mg of risperidone and an undetermined amount of clozapine. Following emergency treatment she recovered fully.
6. A sixth patient, in study 205, reportedly overdosed on risperidone on two occasions but was never treated for an overdose and apparently had no sequelae.

For mangement of overdose, the sponsor recommends general supportive measures and cardiovascular monitoring. These recommemdations are outlined in the proposed labelling.

8.7 Summary of Important Adverse Events Considered Possibly or Probably Drug Related

8.7.1 Neuroleptic Malignant Syndrome

Neuroleptic malignant syndrome (NMS) is an uncommon, potentially life threatening reaction to neuroleptic drugs. The incidence is not known precisely but is thought to be on the order of 1% of hospitalized patients on neuroleptics (Schatzberg and Cole, 1991) There has been one report from Canada of neuroleptic malignant syndrome with risperidone therapy; this occurred after the cut off date for the NDA integrated safety database and was reported separately. The patient was a 33 year old male taking risperidone 2 mg/day for three days on a compassionate use basis. His signs and symptoms included fever, rigidity, somnolence, urinary incontinence and elevated creatine kinase; he recovered after treatment with rehydration and dantrolene. Confounding this case is the fact that the patient was receiving concomitant neuroleptic therapy, in addition to risperidone, when he developed NMS.

8.7.2 Tardive Dyskinesia

Tardive dyskinesia (TD) is a movement disorder arising from long term neuroleptic therapy. No new cases of tardive dyskinesia attributable to risperidone occurred during clinical trials. The likelihood of observing TD induced by risperidone was significantly limited, however, by the fact that the majority of patients in clinical trials received risperidone for two months or less, an insufficient length of time to reliably determine the incidence of TD (Seeman, 1992). Of 2322 risperidone patients, there were only 362 on risperidone for a duration of 65 days or more. Furthermore, very few elderly women received the drug; this is a group thought to be at greater risk for TD (Kane, 1989) The fact that risperidone causes extrapyramidal symptoms suggests that it may not be inert with respect to TD.

8.7.3 Postural Hypotension and Syncope

Risperidone has a capacity to induce orthostatic hypotension, which is attributed to its α blocking properties. This is evidenced by the frequency of elevated standing pulse among risperidone patients, and it may play a role in the relatively high rate of dizziness reported by risperidone patients. It may also have contributed to some of the syncopal episodes observed in risperidone patients.

Dizziness resulted in 16/2322 (0.7%), and orthostatic hypotension resulted in 5/2322 (0.2%) of integrated safety data base patients discontinuing risperidone prematurely; none of the 176 placebo or 533 active control patients from the integrated safety data base had to withdraw because of dizziness or postural hypotension. (Precise figures for postural hypotension are difficult to determine, since some cases of postural hypotension were recorded simply as hypotension; the incidence of 5/2322 given above is based on a review of the sponsor's premature discontinuation summaries.)

Syncope, conceivably a phenomenon resulting from postural hypotension, occurred in six out of 2322 risperidone patients (0.3%); two of these discontinued treatment as a result. None of the 533 active control patients or

176 placebo patients suffered syncopal episodes. The premature withdrawals for syncope are described here in brief detail.

1. A 36 year old male patient, in study 204, discontinued risperidone after fainting; he had been on 6 mg/day for about six weeks. He was sitting down (rather than standing) when he fainted, and was noted to have an irregular pulse during the episode; he had a history of an incomplete right bundle branch block but no history of syncope.

2. Patient in study RIS-BEL-11, a 17 year old with Sjorgen-Larsson syndrome, fainted after receiving a single dose of risperidone 4 mg and discontinued from the trial.

(Another risperidone patient (#35 in study 022) withdrew for what was termed circulatory failure; this referred to symptoms of vertigo and weakness which may have been an orthostatic phenomenon. A second patient in the same study suffered circulatory failure as an adverse event after 5 days on risperidone, but did not have to discontinue treatment.)

When the time to onset of syncope is examined for the six risperidone patients who fainted (two of whom dropped out and four of whom continued treatment), the mean time to onset is 24 days. In fact, three of the syncopal episodes occurred on the first day of treatment, while the others occurred after five weeks or more of treatment. Thus, syncope was often experienced with initial dosing but was not limited to the first day on drug. Similarly, for the five patients who discontinued for postural hypotension (patients in study 204, 1774 and 446 in study 024, and 62 in study INT-7), the duration of ripseridone treatment ranged from 2-45 days.

Notably, dizziness, postural hypotension and collapse occurred often during the Phase I studies with normal volunteers. In fact, study FRG-9001 had to be terminated because all five volunteers who received a 4 mg risperidone dose collapsed. In study HOL-9004, two out of 26 volunteers collapsed after a 2 mg dose. It was learned that psychiatric patients tolerated the drug somewhat better than normal volunteers, and subsequent Phase 1 studies employed actual patients. Even so, dizziness and postural hypotension remained common adverse events; in study 002 using a single dose of 4 mg in 36 patients, 13 experienced dizziness, 4 developed postural hypotension, and one subject fainted.

From Phase 2-3 trials not included in the integrated safety database, there was one patient who discontinued risperidone prematurely for postural hypotension (study GBR-9003, no patient number).

8.7.4 Seizure

In the integrated safety data set, convulsions occurred in a total of five risperidone treated patients (out of 2322 total); none of the 533 active control patients or 176 placebo patients experienced seizures. There were two additional patients who developed seizures associated with hyponatremia; these occurred after the cutoff date for the integrated safety data set. Taking the five cases ocurring before the cutoff date, the seizure incidence was 0.2% for all risperidone treated patients, or 0.98 per 100 patient years on drug. The cases involving seizures were reviewed individually.

In one instance (patient in study 204) the convulsion followed a head injury sustained in a fall.

In another case, patient in study 024 had a past history of absence seizures, and experienced a seizure characterized by unresponsiveness and urinary incontinence while on risperidone 1 mg/day.

Two patients from study 024 and from study 035) experienced seizures but did not discontinue from the trial.

The fifth case was patient from study 024, a 38 year old woman taking 16 mg/day of risperidone who developed new onset seizures progressing to status epilepticus; she recovered and was later treated with risperidone 8 mg/day.

If, in fact, risperidone has some propensity to lower the seizure threshold, the drug may have been a contributing factor in the two cases involving hyponatremia.

The first of these was patient in study 205, a 58 year old woman taking 8 mg/day of risperidone. She had a seizure and on evaluation was found to have a sodium concentration of 104; she had not taken risperidone for two days at that time.

The second case was patient in study 205, a 34 year old male on 4 mg/day of risperidone, who chose to withdraw from his study. On the following day he received an injection of Prolixin decanoate (37.5 mg) and developed muscle contractions, for which he sought attention at a local emergency room. He was treated with oral Benadryl and half an hour later had a grand mal seizure; at that time he was found to be hyponatremic with a serum sodium of 118.

In chronic schizophrenic patients, hyponatremia resulting from psychogenic polydipsia is a well known phenomenon and is generally considered a symptom of their illness, although some authors have proposed that neuroleptic treatment exacerbates polydipsia (Lawson et al., 1985; Illowsky and Kirch, 1988).

The seizure-inducing properties of neuroleptics have long been recognized; precise data on the incidence of seizures associated with standard neuroleptic treatment are lacking, but the incidence has been estimated at below 1% (Simpson et al, 1988).

8.7.5 Rash

Three patients (0.13% of 2322 total risperidone patients in the integrated safety data base) discontinued risperidone due to a rash. There were no discontinuations for rash in the other treatment groups.

Patient from study 024 developed an itching rash in the groin area and withdrew from the study.

Another patient, from study 204/205, developed a generalized pruritic eruption diagnosed as an allergic response to risperidone; it resolved after the drug was stopped.

The third patient, from study 204/205, developed a rash, hair loss and thrombocytosis; the rash and hair loss improved ten days after stopping risperidone.

In Study RIS-JPN-9003, which was not included in the integrated safety data base, a 51 year old woman (patient discontinued risperidone treatment because of an upper body rash; she was also taking griseofulvin when the rash developed.

In addition to these cases of rash, Patient from study 204 discontinued risperidone due to pruritus; as the patient had a prior history of eczematoid dermatitis, this was viewed as an exacerbation of this preexisting condition.

8.7.6 Edema

Edema (reported variously as edema, leg edema, peripheral edema, dependent edema, generalized edema, and facial edema) was noted in 9/2322 risperidone patients (0.4%), 2/533 active control patients (0.4%) and 0/176 placebo patients. Three risperidone patients dropped out of clinical trials with edema; no patients from other treatment groups withdrew because of edema.

Patient in study 024, a 45 year old male, developed generalized edema after four weeks on risperidone 4 mg/day. Diagnostic evaluations showed no renal, plasma protein or cardiac basis for edema, and the condition resolved two weeks after risperidone was stopped.

A second patient, in study 205, on risperidone for 13 days, developed leg edema which was initially mistaken for thrombophlebitis.

The third patient from RIS-FRG-9004) withdrew after developing edema of the legs and elevated transaminases while on risperidone 8 mg/day; outcome was uncomplicated.

One can speculate that such an effect is related to risperidone's potent α antagonism. Prazosin, a prototypical α-blocker, has been associated with edema at an incidence of 1-4% (according to the labeling for Minipress).

8.7.7 Prolactin elevation

As discussed above in section 8.5.2, risperidone was clearly associated with prolactin elevations. On theoretical grounds we might expect to see a constellation of adverse reactions consistent with elevated prolactin, i.e. lactation, amenorrhea, hypogonadism, and impotence. In the integrated safety database, lactation, amenorrhea, and impotence are recorded as infrequent adverse experiences (incidence between 1/100 and 1/1000). Symptoms attributable to prolactin elevation are often gradual in onset, however, and may turn out to have a higher incidence when patients are exposed to the drug for longer periods. Elevation of prolactin would be of concern in patients having neoplasms sensitive to hormonal influences, such as breast cancer. Additionally, hyperprolactinemia has been proposed as a risk factor for breast cancer, but the evidence for this is not definitive (see current labeling for Haldol).

8.7.8 Priapism

The sponsor has submitted a 10 day safety report (dated 2/11/93) of priapism associated with risperidone use, which occurred after the NDA was submitted. The patient was a 50 year old male receiving risperidone under compassionate clearance in Canada. The patient developed priapism after 11 months on risperidone and required surgical intervention; the outcome was not known by the sponsor. There do not appear to have been any concomitant medications at the time, and the patient's only medical condition was chronic obstructive pulmonary disease. Since this case arose out of compassionate use, the cohort of patients from which it came is undefined, and an estimate of incidence cannot be made. Although a single case is hardly persuasive, there are

theoretical grounds for attributing this event to risperidone. Drugs that are α antagonists are associated with priapism, and the presumptive mechanism involves blocking of adrenergically mediated detumescence; medications thought to induce priapism in this way include chlorpromazine, trazodone, thioridazine, and prazosin (Thompson et al, 1990). Since risperidone is also an α blocker, it may share this capacity to induce priapism.

8.7.9 Extrapyramidal symptoms

As noted above, EPS associated with risperidone clearly demonstrates a dose response relationship. In the entire Phase 2-3 safety data base, EPS events led to 39/2322 (1.7%) of risperidone patients discontinuing treatment prematurely. In those Phase 2-3 studies which were not included in the integrated safety data base, EPS was also observed, and lead to premature discontinuation of patient from study JPN-9003.

Dyskinesia, which was not one of the events incorporated into the EPS category but is conceivably a related phenomenon, resulted in 5/2322 (0.2%) of risperidone patients, 1/533 (0.2%) of active control patients, and 0/176 placebo patients discontinuing treatment. One particularly severe case of dyskinesia deserves mention: patient 19 from study 002, a 57 year old female who developed truncal dyskinesia on risperidone 4 mg/day, with accompanying respiratory difficulties.

For haloperidol, dropouts for EPS occurred in 16/440 (3.6%) patients from the integrated safety data base, roughly twice the incidence seen among risperidone patients.

The sponsor undertook several comparisons of EPS rates between risperidone and haloperidol treated patients. The comparisons that in this reviewer's opinion are the most objective and clinically relevant will be described briefly.

In the placebo contolled studies 201 and 204, EPS was assessed not only by spontaneous reporting but also in a structured way using Chouinard's Extra Pyramidal Symptom Rating Scale (ESRS). Since study 201 employed dose titration, meaningful comparisons are more difficult to make between drug groups; the results in study 204 for selected ESRS categories are shown below.

Study 204 — Mean change from baseline

ESRS category (Lower scores are better)	Pbo	Ris 2 mg	Ris 6 mg	Ris 10 mg	Ris 16 mg	Halop 20 mg
Parkinsonism (range 0-48, by physician exam)	1.2	0.9[h]	1.8[h]	2.4[h]	2.6[Ph]	5.0[P]
Dystonia (range 0-12, by physician exam)	0.2	0.1	0.2	0.1	0.2	0.3
Dyskinetic movements (range 0-42, by physician exam)	2.0	1.9	1.1	0.6[rh]	0.8[r]	1.7

p placebo score better at statistically significant level
h haloperidol score worse at a statistically significant level
r risperidone score better than placebo at a statistically significant level

Note that the first category, parkinsonism, was the one in which both the high dose risperidone and haloperidol groups showed a significant effect relative to placebo; in this category all risperidone groups had significantly lower scores than haloperidol 20 mg.

In study 024, there was no placebo group for comparison; the haloperidol dose was 10 mg rather than 20 mg, which might be expected to induce fewer extrapyramidal symptoms. For the three ESRS items considered above, the increases from baseline in parkinsonism and dystonia scores were significantly higher in the haloperidol 10 mg group than for all the risperidone dose groups (1, 4, 8, 12, and 16 mg). There were no significant differences among treatment groups on the dyskinesia scores.

On balance, risperidone appears capable of inducing extrapyramidal symptoms, but at a somewhat lower rate than equivalent doses of haloperidol.

During risperidone clinical trials, EPS induced by risperidone was treated with traditional antiparkinson medications.

8.7.10 Sedation

Somnolence accounted for premature discontinuation in 12/2322 risperidone treated patients (0.5%); no placebo patients discontinued because of somnolence. As an elicited adverse experience using the UKU scale, sleepiness/sedation was noted more than twice as often in the risperidone 16 mg group than in the placebo group from study 204 (41% vs 16% of the 88 patients in each treatment group). This side effect is important in terms of driving ability and ability to operate machinery, and is particularly relevant if other sedating drugs (particularly psychotropics) are combined with risperidone.

8.7.11 Tachycardia

In study 204, there appeared to be a dose response effect for the occurrence of tachycardia, with the 16 mg risperidone treatment group having the highest rate (5.7%) while the placebo group had none.

In the integrated Phase 2-3 database, a total of 8/2322 patients (0.3%) discontinued risperidone treatment prematurely because of tachycardia. Two of these cases were severe enough to be deemed serious adverse events by the sponsor (patients in study 024). There were no such premature discontinuations among the 533 patients treated with active controls or the 176 treated with placebo.

Some of the tachycardia occurring among risperidone patients conceivably could have been related to orthostatic hypotentsion.

8.7.12 EKG changes

Treatment emergent EKG changes in patients receiving risperidone have included tachycardia, extrasystoles, prolongation of QTc interval, and impaired conduction. These findings are discussed fully under section 8.5.4. While the available data are only suggestive, the possibility that at least some of these changes are drug related must be considered.

8.7.13 Liver Enzyme Elevation

Treatment emergent hepatic enzyme elevations are outlined in Section 8.5.2.1 above. While a statistical increase in liver enzyme elevations was not evident in risperidone patients relative to other treatment groups, the case of jaundice that developed in one risperidone treated patient does appear potentially related to drug treatment.

8.8 Important Events Considered Not Drug Related

During clinical trials involving large numbers of patients, serious untoward events may occur incidentally. (The definition of serious adverse experience is given above in Section 8.4.2.) Appendix 8.8 displays a listing of such adverse events for risperidone. Please note that fatalities have already been included in Appendix 8.2 and are not repeated in Appendix 8.8. Similarly, other adverse events that have already been discussed are omitted from this appendix, as are events such as psychiatric hospitalizations that represent exacerbations of the patient's underlying illness. In my opinion none of the events in Appendix 8.8 can be attributed to treatment with risperidone.

8.9 Summary of Drug Interactions

8.9.1 Drug-Demographic Interactions

Geriatric experience with risperidone is quite limited; only 60 patients aged 65 or older received the drug in clinical studies. None of these patients discontinued treatment prematurely because of an adverse experience. An additional 12 subjects in this age group were exposed to a single 1 mg dose of risperidone in a pharmacokinetic study (protocol 0005); none suffered a serious adverse drug reaction, but their mean decrease in systolic blood pressure, while comparable to the change seen in younger patients, was sizable at 32.5 mmHg. Pharmacokinetic parameters in these 12 subjects revealed an increased elimination half life for 9-OH-risperidone relative to younger subjects; accordingly, the sponsor recommends reduced doses for the elderly.

No patient under 16 years old has received risperidone.

Because risperidone is subject to genetic metabolic polymorphism of the debrisoquine type, one might expect the same difficulties encountered with existing drugs whose pharmacokinetics involve genetic polymorphism. As the sponsor points out, since the hydroxy metabolite of risperidone is active, an individual's metabolic ratio may not be critical to the drug's effect. Nonetheless, the possibility of risperidone inhibiting cytochrome P450IID6 creates a potential for drug-drug interactions, as is the case for current neuroleptics which inhibit the enzyme (Meyer, 1992). In the pharmacokinetic study 0005, three of the subjects characterized as poor metabolizers of risperidone received concomitant medications which may have inhibited cytochrome P450IID6 activity (metoprolol, amitriptyline, and thiethylperazine).

Effects of age and sex on the incidence of certain common adverse experiences were explored in the following way. Combining data from the two primary placebo controlled trials (201 and 204), relative risks for males and females were calculated for each of the adverse events considered:

RRm= risperidone rate in males/placebo rate in males

RRf= risperidone rate in females/placebo rate in females

The ratio of these relative risks was then calculated: RRf/RRm.

To determine confidence intervals for the relative risk ratios, odds ratios for males and females were determined along with a common odds ratio (Mantel-Haenszel method). Homogeneity of the odds ratios so obtained was assessed with the Breslow-Day test.

Similar methods were applied for age (<55 years old versus ≥ 55 years old. The following adverse events were considered: EPS, constipation, dizziness, vomiting, dyspepsia, rhinitis, somnolence, coughing, nausea, rash, and tachycardia.

Dizziness, rash and tachycardia were more frequent in the younger group; coughing was more frequent among men than women. One should be aware that these findings arose out of multiple comparisons and thus should be interpreted cautiously. Also, with the relatively small numbers of women and older patients in these trials, the power of this method to find differences in adverse event rates is limited.

8.9.2 Drug-Disease Interactions

Study 0005 was a single dose pharmacokinetic study which explored the pharmacokinetics of risperidone in patients with renal or liver disease. Eight patients with liver disease and 14 patients with renal disease received a single 1 mg dose of risperidone. The unbound fraction of risperidone was higher in hepatically impaired individuals, owing to reduced albumin and α-1-acid glyocoprotein. Conversely, renal disease patients had higher α-1-acid glycoprotein levels and thus lower unbound fractions of 9-OH-risperidone. Renal clearance of 9-OH-risperidone was reduced in the patients with renal disease, and the sponsor recommends reduced dosing for such patients. In hepatically impaired patients, pharmacokinetic parameters were essentially unchanged; the sponsor theorizes that a diminished intrinsic hepatic clearance is offset by a higher unbound fraction of drug.

8.9.3 Drug-Drug Interactions

The sponsor has not studied interactions of risperidone with other drugs in humans. In vitro, risperidone and 9-hydroxyrisperidone are displaced from plasma binding sites by sulfamethazine, warfarin and carbamazepine.

Patient in Study 002, a 59 year old female, developed tachycardia when she started risperidone, and was administered propranolol as a symptomatic treatment. Following this she became cyanotic and significantly hypotensive, requiring intravenous fluids. The sponsor attributes this response to combined α blockade by risperidone and ß blockade by propranolol. Another possibility would be a pharmacokinetic interaction involving inhibition of cytochrome P450 IID6, which metabolizes ß blockers and risperidone both.

Section 8 References

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9.0 Conclusions

In my opinion, the sponsor has demonstrated the efficacy of risperidone in short term treatment of the psychotic symptoms of schizophrenia. The sponsor has provided no significant evidence of efficacy in the treatment of other psychotic conditions or in the long term treatment of schizophrenia. It seems reasonable to extrapolate findings to these other clinical situations, however, based on experience with existing antipsychotic drugs.

From the available data, risperidone appears reasonably safe when used as the sponsor recommends. One should bear in mind that this conclusion is derived from a data set that is small compared to the number of patients who can be expected to take risperidone once it is marketed, and a rare adverse drug reaction may not necessarily have been detectable from the existing data. This is especially true given that many patients may take risperidone chronically, whereas most of the exposure to risperidone in clinical trials has been of short duration.

10.0 Recommendations

In my opinion, the New Drug Application for Risperdal is approvable from a clinical standpoint. Ths sponsor should be encouraged to conduct further studies on relapse prevention with risperidone treatment, and on drug-drug interactions.

Andrew Mosholder MD 5/11/93

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NDA 20-272
HFD-120:TLaughren/AMosholder/SHardeman

Appendix 5.1.1 Table of All Studies

Phase 1 Studies

Dose Tolerance Studies

RIS-BEL-1 Protocol 001	Open label, single dose tolerance trial; normal male volunteers (n=9); risperidone dose (0.5-2.0 mg orally)
RIS-FRG-9001 Protocol 017	DB, pbo controlled, ascending single dose trial; normal male volunteers (n=20 risperidone, 4 pbo); risperidone dose (1-4 mg oral, 1 mg IM)
RIS-FRG-9002 Protocol 018	DB, pbo controlled, multidose trial; normal male volunteers (n=13); risperidone dose (2 mg oral X 1 day, 1 mg oral X 20 day)
RIS-JPN-9001 Protocols 042 & 044	Open label, active controlled (haloperidol); normal male volunteers (n=6); risperidone dose (0.25 mg-2 mg single dose, and 1 mg X 7 days)
RIS-GBR-9004 Protocol 037	DB, X-O, pbo controlled, single dose sleep EEG trial; normal male volunteers (n=15); risperidone dose (0.5, 2 mg)
RIS-BEL-2 Protocol 003	X-O, single dose food effect trial; normal male volunteers (n=6); risperidone dose (2 mg solution or tablets)
RIS-BEL-16 Protocol 031	Open label, multidose sleep EEG study; patients with schizophrenia (n=10); risperidone dose 5 mg/day X 2 wks followed by 10 mg/day X 2 weeks

Pharmacokinetics Studies

FRK949	Open label, single dose; normal male volunteers (n=3); risperidone dose (1 mg ^{14}C-risperidone)
RIS-HOL-9005 Protocol 073	Open label, single dose; normal male volunteers (n=12); risperidone dose (1 mg IV, IM and orally)
RIS-HOL-9004 Protocol 068	Open label, X-O, single dose bioequivalence trial for oral solution, tablets and capsules; normal male volunteers (n=24); risperidone dose (2 mg in one of four formulations)
Protocol 0001	Open label, X-O, single dose bioequivalence trial comparing two tablet formulations; male psychiatric patients (n=24); risperidone dose (4 mg)
Protocol 0005 RIS-USA-12	Open label, single dose pharmacokinetic trial; normal subjects, elderly, renal disease patients and hepatic disease patients (n=42 total); risperidone dose (1 mg).
Protocol 0002	Open label, X-O, single dose bioequivalence trial comparing three table formulations; male psychiatric patients (n=36); risperidone dose (4 mg)

Phase 2-3 Studies

Placebo Controlled Trials

Protocol 201 RIS-USA-9001	DB, parallel group, 8-center, 6 week, 3 way dose titration trial (risperidone, pbo, haloperidol); inpatients, schizophrenia (n= approx 50 per each of three treatment groups); risperidone dose range (2-10 mg/day), haloperidol dose range (4-20 mg/day), and placebo, all on BID schedule
Protocol 204 RIS-INT-3	DB, parallel group, 27-center, 8 week, 6 way fixed dose trial (risperidone 2, 6, 10, 16 mg/day, haloperidol 20 mg/day, and pbo); inpatients, schizophrenia (n=approx 87 per each of 6 treatment groups); all dosing BID
Protocol 015 RIS-BEL-11	DB, X-O, 6-center, 3 week, dose titration trial (risperidone or pbo added on to existing psychotropic regimen); inpatients, mentally retarded (n=37); risperidone dose range (4-12), BID dosing

Active Controlled Trials

Protocol 024 RIS-INT-3	DB, parallel group, 110 centers, 8 week, 6 way fixed dose trial (risperidone and haloperidol); inpatients, schizophrenia (n=approx. 225 per each of 6 treatment groups); risperidone 1, 4, 8, 12, 16 mg/d and haloperidol 10 mg/d, all on BID schedule.
Protocol 008 RIS-TCH-9001	DB, parallel group, single center, 8 week, 2 way dose titration trial (risperidone vs. haloperidol); schizophrenia or schizoaffective psychosis (n=18 per each of two treatment groups); risperidone and haloperidol dose range 2-20 mg/d on BID schedule.
Protocol 006 RIS-BEL-5	DB, parallel group, six center, 12 week, two way dose titration trial (risperidone and haloperidol); inpatients, chronic schizophrenia (n=22 per each of two treatment groups); risperidone dose range (1-20 mg/d), haloperidol dose range (1-20 mg/d), both on BID schedule.
Protocol 008 RIS-BEL-7	DB, parallel group, seven center, 8 week, two way dose titration trial (risperidone and haloperidol); inpatients, chronic psychosis (n=approx. 30 per each of two treatment groups); risperidone dose range (2-20 mg/d), haloperidol dose range (2-20 mg/d), both on BID schedule.
Protocol 022 RIS-FRG-9005	DB, parallel group, two center, four week, three way fixed dose trial (risperidone and clozapine); inpatients, schizophrenia (n=approx. 20 per each of three treatment groups); risperidone 4, 8 mg/d, clozapine 400 mg/d, all on QID schedule.

Protocol 041 RIS-FRA-9003	DB, parallel group, four center, four week, three way dose titration trial (risperidone, haloperidol, and levomepromazine); inpatients, chronic schizophrenia (n=approx. 20 per each of three treatment groups); risperidone dose range (2-12 mg/d), haloperidol dose range (2-12 mg/d), levomepromazine dose range (25-150 mg/d), all on BID schedule.
Protocol 048 RIS-INT-7	DB, parallel group, 18 center, eight week, two way dose titration trial (risperidone and perphenazine); chronic schizophrenia (n= approx. 53 per each of two treatmetn groups); risperidone dose range (5-15 mg/d), perphenazine dose range (16-48 mg/d), both on BID schedule.

Uncontrolled Trials

Protocol 026 RIS-ITA-9001	Open label, two center, fixed dose 4 week trial; schizophrenia, outpatients (n=31); risperidone dose 2 mg/d for first week, 4 mg/d for second week and 6 mg/d for weeks 3 and 4. Eighteen patients continued with open label treatment for another 11 months.
Protocol 007 RIS-BEL-6	Open label, five center, dose titration 4 week trial; psychogeriatric inpatients (n=50); risperidone dose range (1-10 mg/d on BID schedule).
Protocol 013 RIS-BEL-9	Open label, 13 month follow up to Protocol 007; n=9
Protocol 030 RIS-BEL-15	Open label, 13 month follow up to RIS-BEL-5; n=5; risperidone dose up to 20 mg/d on BID schedule.
Protocol 019 RIS-FRA-9001	Open label, single center six week trial; schizophrenia, inpatients (n=12); risperidone dose 2-4 mg/d on BID schedule.
Protocol 002 RIS-INT-1	Open label, multicenter 4 week trial; psychosis, inpatients (n=121); risperidone dose range 1-10 mg/d on BID schedule.
Protocol 005 RIS-BEL-4	Open label, 4 week rising dose trial; psychosis, inpatients (n=17); risperidone dose 10 mg/d week 1, 15 mg/d week 2, 20 mg/d week 3 and 25 mg/d week 4, on BID-TID schedule.
Protocol 020 RIS-FRG-9003	Open label, 2 center, dose titration 4 week trial; schizophrenia, inpatients (n=13); risperidone dose 1-10 mg/d.
Protocol 021 RIS-FRG-9004	Open label, single center 4 week rising dose trial; schizophrenia with negative symptoms, inpatients (n=11); risperidone dose 2-12 mg on BID schedule.
Protocol 036 RIS-GBR-9003	Open label, 3 center, dose titration 4 week trial; schizophrenia (n=7); risperidone dose 4-20 mg/d on BID schedule.

Protocols 035, 011 and 004 RIS-BEL-17 RIS-HOL-9002 RIS-INT-8	Open label, 28 center, dose titration 12-13 month trial combining three protocols; psychosis (n=264); risperidone dose range 2-20 mg/d on BID schedule.
Protocol RIS-BEL-SLT	Open label, 4 center, compassionate use trial with duration 1-4 years; psychosis (n=38); risperidone dose 2-25 mg/d.
Protocol 033 RIS-ONT-4	Opne label, ongoing 27 center 12 month dose titration trial; schizophrenia (n=77); risperidone dose 2-16 mg/d on BID schedule; only interim results available.
Protocol 038 RIS-ITA-9002	Single blind, cross over, placebo controlled rising dose 4 week trial; schizophrenia, inpatients (n=10); risperidone dose 2 mg QD X 10 d, then 2 mg BID X 10 d, then 2 mg TID X 10 d.
Protocol 202	Open label, ongoing extension trial for 201; n=1; no study report available yet.
Protocol 205	Open label, ongoing extension trial for 204; n=123; no study report available yet.
Protocol 009 RIs-BEL-8	Open label, single center, dose titration 1 week trial of risperidone given IM; acute psychosis (n=17); risperidone dose 4 mg IM up to 3X per day.
Protocol 045 RIS-JPN-9003	Open label, single center, 8 week, dose titration trial; schizophrenia, inpatients (n=83), risperidone dose 1-10 mg on QD or BID schedule.

Appendices for Section 7.0 Efficacy Findings

7.2.1.3.1 Demographic characteristics, patient completion rates and dosing information for Study 201

7.2.1.3.1 Efficacy Results for Study 201

Total BPRS (LOCF and OC)
CGI Severity (LOCF and OC)
Total SANS (LOCF and OC)
BPRS psychosis cluster (LOCF and OC)
Percent of patients clinically improved on BPRS (LOCF)

7.2.2.3.1 Demographic characteristics and patient completion rates for Study 204

7.2.2.3.2 Efficacy results for Study 204

Total PANSS (LOCF)
Percent of patients improved on PANSS (LOCF)
Total Derived BPRS (LOCF and OC)
CGI Severity (LOCF and OC)
Negative PANSS subsore (LOCF and OC)
BPRS psychosis cluster (LOCF and OC)

7.2.3.3.1 Demographic characteristics and patient completion rates for Study 024

7.2.3.3.2 Efficacy results for Study 024

Total PANSS (LOCF)
Percentage of patients improved by PANSS (LOCF)
Total Derived BPRS (LOCF and OC)
CGI Severity (LOCF and OC)
Negative PANSS subscore (LOCF and OC)
BPRS Psychosis Cluster (LOCF and OC)

Study: 201
Demographic Characteristics

Treatment Groups	n	Age (years)		Sex [n (%)]		Race [n (%)]	
		Mean	Range	Male	Female	White	Non-White
Risperidone	53	39.7		53 (100%)	0 (0%)	29 (55%)	24 (45%)
Haloperidol	53	38.4		50 (94%)	3 (6%)	26 (50%)	27 (51%)
Placebo	54	40.3		51 (94%)	3 (6%)	29 (54%)	25 (46%)

Patient Completion Rates
STUDY: 201

Treatment Groups	Number Randomized	Intent-to-Treat Sample*	Number (%) of Patients Completing**				
			Week 1	Week 2	Week 3	Week 4	Week 6
Risperidone	53	51	49 (96)	36 (71)	40 (78)	33 (65)	28 (55)
Haloperidol	53	52	52 (100)	40 (77)	35 (67)	26 (50)	23 (44)
Placebo	54	53	51 (96)	40 (74)	26 (49)	21 (40)	16 (30)

*Patients who received assigned medication and had one or more efficacy assessments
**Includes patients having efficacy data within three days of the scheduled visit (no upper limit for final visit)

Study: 201
Dosing Information

Treatment Groups	n	Mean Dose (mg) for Completers in Active Drug Groups									
		Week 1		Week 2		Week 3		Week 4		Week 6	
		MEAN	STD	MEAN	STD	MEAN	STD	MEAN	STD	MEAN	STD
Risperidone	27	3.9	0.7	8.2	1.3	9.2	1.4	9.4	1.3	9.4	1.3
Haloperidol	22	7.7	1.5	15.6	3.8	17.4	3.8	17.4	3.9	17.6	4.2

TABLE

STUDY : 0201

MEAN CHANGE FROM BASELINE IN TOTAL SYMPTOM SCORE IN BPRS SCALE

LAST OBSERVATION CARRIED FORWARD ANALYSIS

TREATMENT GROUPS	TREATMENT WEEK											
	BASELINE		WEEK 1		WEEK 2		WEEK 3		WEEK 4		WEEK 6	
	N	MEAN	N	MEAN	N	MEAN	N	MEAN	N	MEAN	N	MEAN
RISPERIDONE	51	56.2	51	-9.2	51	-9.9	51	-11.6	51	-10.9	51	-11.6
HALOPERIDOL	52	53.1	52	-8.0	52	-8.8	52	- 9.7	52	- 9.6	52	- 9.0
PLACEBO	53	52.8	53	-1.7	53	-1.5	53	- 1.5	53	- 1.0	53	- 0.6
2-SIDED P-VALUES FOR PAIRWISE COMPARISONS												
RISPERIDONE VS. PLACEBO	0.023		0.002		0.002		<0.001		<0.001		<0.001	
HALOPERIDOL VS. PLACEBO	0.865		0.009		0.007		0.007		0.004		0.005	
RISPERIDONE VS. HALOPERIDOL	0.035		0.568		0.636		0.431		0.590		0.294	

STUDY : 0201
MEAN CHANGE FROM BASELINE IN TOTAL SYMPTOM SCORE IN BPRS SCALE

OBSERVED CASE ANALYSIS*

TREATMENT GROUPS	TREATMENT WEEK											
	BASELINE		WEEK 1		WEEK 2		WEEK 3		WEEK 4		WEEK 6	
	N	MEAN	N	MEAN	N	MEAN	N	MEAN	N	MEAN	N	MEAN
RISPERIDONE	50	56.0	49	-9.5	36	-11.4	40	-14.1	33	-14.1	28	-15.2
HALOPERIDOL	52	53.1	52	-8.0	40	-10.0	35	-12.1	26	-12.3	23	-14.0
PLACEBO	51	52.5	51	-1.9	40	-3.3	26	-10.3	21	-8.8	16	-12.9
2-SIDED P-VALUES FOR PAIRWISE COMPARISONS												
RISPERIDONE VS. PLACEBO	0.021		0.003		0.004		0.158		0.116		0.273	
HALOPERIDOL VS. PLACEBO	0.833		0.016		0.009		0.224		0.099		0.949	
RISPERIDONE VS. HALOPERIDOL	0.033		0.518		0.713		0.877		0.838		0.233	

*Includes patients having efficacy data within three days of the scheduled visit.

TABLE

STUDY : 0201

MEAN CHANGE FROM BASELINE IN CGI - SEVERITY OF SCHIZOPHRENIA

LAST OBSERVATION CARRIED FORWARD ANALYSIS

	TREATMENT WEEK											
	BASELINE		WEEK 1		WEEK 2		WEEK 3		WEEK 4		WEEK 6	
TREATMENT GROUPS	N	MEAN	N	MEAN	N	MEAN	N	MEAN	N	MEAN	N	MEAN
RISPERIDONE	53	4.1	53	-0.5	53	-0.6	53	-0.7	53	-0.7	53	-0.7
HALOPERIDOL	53	3.9	53	-0.5	53	-0 7	53	-0.6	53	-0.7	53	-0.7
PLACEBO	53	3.9	53	-0.3	53	-0.4	53	-0.3	53	-0.3	53	-0.3
2-SIDED P-VALUES FOR PAIRWISE COMPARISONS												
RISPERIDONE VS. PLACEBO	0.320		0.267		0.224		0.027		0.076		0.067	
HALOPERIDOL VS. PLACEBO	0.604		0.214		0.154		0.078		0.115		0.120	
RISPERIDONE VS. HALOPERIDOL	0.131		0.892		0.831		0.648		0.844		0.781	

STUDY : 0201
MEAN CHANGE FROM BASELINE IN CGI - SEVERITY OF SCHIZOPHRENIA

OBSERVED CASE ANALYSIS*

	TREATMENT WEEK											
	BASELINE		WEEK 1		WEEK 2		WEEK 3		WEEK 4		WEEK 6	
TREATMENT GROUPS	N	MEAN	N	MEAN	N	MEAN	N	MEAN	N	MEAN	N	MEAN
RISPERIDONE	50	4.1	49	-0.5	35	-0.8	40	-0.9	33	-1.1	28	-1.1
HALOPERIDOL	53	3.9	53	-0.5	40	-0.9	35	-0.8	26	-1.0	24	-0.9
PLACEBO	51	3.9	51	-0.3	40	-0.4	25	-0.6	22	-0.8	16	-0.9
2-SIDED P-VALUES FOR PAIRWISE COMPARISONS												
RISPERIDONE VS. PLACEBO	0.311		0.348		0.113		0.199		0.333		0.373	
HALOPERIDOL VS. PLACEBO	0.555		0.285		0.028		0.167		0.341		0.895	
RISPERIDONE VS. HALOPERIDOL	0.107		0.912		0.596		0.853		0.966		0.443	

*Includes patients having efficacy data within three days of the scheduled visit

STUDY : 0201
MEAN CHANGE FROM BASELINE IN TOTAL SANS SCORE

LAST OBSERVATION CARRIED FORWARD ANALYSIS

	TREATMENT WEEK											
	BASELINE		WEEK 1		WEEK 2		WEEK 3		WEEK 4		WEEK 6	
TREATMENT GROUPS	N	MEAN	N	MEAN	N	MEAN	N	MEAN	N	MEAN	N	MEAN
RISPERIDONE	51	50.8	51	-6.0	50	-11.3	51	-11.4	51	-9.9	51	-9.8
HALOPERIDOL	52	43.5	52	-8.2	52	-9.3	52	-10.5	52	-9.7	52	-8.5
PLACEBO	53	47.1	53	-3.2	53	-3.2	53	-3.3	53	-2.4	53	-2.8
2-SIDED P-VALUES FOR PAIRWISE COMPARISONS												
RISPERIDONE VS. PLACEBO		0.229		0.318		0.011		0.024		0.036		0.056
HALOPERIDOL VS. PLACEBO		0.443		0.026		0.061		0.053		0.046		0.150
RISPERIDONE VS. HALOPERIDOL		0.050		0.217		0.477		0.739		0.915		0.630

STUDY : 0201
MEAN CHANGE FROM BASELINE IN TOTAL SANS SCORE

OBSERVED CASE ANALYSIS*

	TREATMENT WEEK											
	BASELINE		WEEK 1		WEEK 2		WEEK 3		WEEK 4		WEEK 6	
TREATMENT GROUPS	N	MEAN	N	MEAN	N	MEAN	N	MEAN	N	MEAN	N	MEAN
RISPERIDONE	50	50.5	49	-7.1	35	-12.1	40	-14.8	33	-8.8	28	-9.8
HALOPERIDOL	52	43.5	52	-9.2	40	-11.0	35	-11.3	26	-10.7	23	-11.0
PLACEBO	51	46.9	51	-3.1	40	-4.4	25	-11.0	21	-10.0	16	-13.9
2-SIDED P-VALUES FOR PAIRWISE COMPARISONS												
RISPERIDONE VS. PLACEBO		0.234		0.237		0.017		0.306		0.804		0.481
HALOPERIDOL VS. PLACEBO		0.425		0.035		0.033		0.676		0.509		0.896
RISPERIDONE VS. HALOPERIDOL		0.047		0.361		0.722		0.522		0.329		0.564

*Includes patients having efficacy data within three days of the scheduled visit.

TABLE Study 201 MEAN CHANGE FROM BASELINE IN TOTAL BPRS PSYCHOSIS SUBSCORE*

LAST OBSERVATION CARRIED FORWARD ANALYSIS

	TREATMENT WEEK											
	BASELINE		WEEK 1		WEEK 2		WEEK 3		WEEK 4		WEEK 6	
TREATMENT GROUPS	N	MEAN	N	MEAN	N	MEAN	N	MEAN	N	MEAN	N	MEAN
RISPERIDONE	51	17.2	51	-3.5	51	-4.4	51	-4.6	51	-4.7	51	-4.8
HALOPERIDOL	52	16.7	52	-3.4	52	-4.6	52	-5.0	52	-5.1	52	-5.0
PLACEBO	53	16.7	53	-0.8	53	-1.1	53	-1.2	53	-1.2	53	-1.2
2-SIDED P-VALUES FOR PAIRWISE COMPARISONS												
RISPERIDONE VS. PLACEBO	0.332		<0.001		<0.001		<0.001		<0.001		<0.001	
HALOPERIDOL VS. PLACEBO	0.965		0.001		<0.001		<0.001		<0.001		<0.001	
RISPERIDONE VS. HALOPERIDOL	0.312		0.885		0.849		0.710		0.703		0.894	

STUDY : 0201 MEAN CHANGE FROM BASELINE IN TOTAL BPRS PSYCHOSIS SUBSCORE*

OBSERVED CASE ANALYSIS**

	TREATMENT WEEK											
	BLN		WEEK 1		WEEK 2		WEEK 3		WEEK 4		WEEK 6	
TREATMENT GROUPS	N	MEAN	N	MEAN	N	MEAN	N	MEAN	N	MEAN	N	MEAN
RISPERIDONE	50	17.2	49	-3.6	36	-5.0	40	-5.4	33	-6.0	28	-6.1
HALOPERIDOL	52	16.7	52	-3.4	40	-5.2	35	-5.7	26	-5.4	23	-5.9
PLACEBO	51	16.6	51	-0.9	40	-1.8	26	-3.6	21	-3.7	16	-4.9
2-SIDED P-VALUES FOR PAIRWISE COMPARISONS												
RISPERIDONE VS. PLACEBO	0.305		0.002		<0.001		0.080		0.032		0.104	
HALOPERIDOL VS. PLACEBO	0.979		0.003		<0.001		0.017		0.055		0.627	
RISPERIDONE VS. HALOPERIDOL	0.287		0.865		0.794		0.414		0.921		0.257	

*Includes conceptual disorganization, suspiciousness, hallucinatory behavior, and unusual thought content. **Includes patients having efficacy data within three days of the scheduled visit.

TABLE

STUDY : 0201

CLINICAL IMPROVEMENT FROM BASELINE VIA TOTAL BPRS

LAST OBSERVATION CARRIED FORWARD ANALYSIS

TREATMENT GROUPS	TREATMENT WEEK									
	WEEK 1		WEEK 2		WEEK 3		WEEK 4		WEEK 6	
	n/N	%	n/N	%	n/N	%	n/N	%	n/N	%
RISPERIDONE	28/51	54.9%	29/51	56.9%	32/51	62.7%	32/51	62.7%	33/51	64.7%
HALOPERIDOL	26/52	50.0%	26/52	50.0%	30/52	57.7%	29/52	55.8%	27/52	51.9%
PLACEBO	15/53	28.3%	18/53	34.0%	17/53	32.1%	17/53	32.1%	16/53	30.2%
2-SIDED P-VALUES FOR PAIRWISE COMPARISONS										
RISPERIDONE VS. PLACEBO	0.007		0.020		0.002		0.002		0.001	
HALOPERIDOL VS. PLACEBO	0.022		0.100		0.012		0.020		0.037	
RISPERIDONE VS. HALOPERIDOL	0.637		0.505		0.596		0.479		0.189	

TABLE
STUDY: 204
Demographic Characteristics

Treatment Groups	n	Age (years)		Sex [n (%)]		Race [n (%)]	
		Mean	Range	Male	Female	White	Non-White
Risperidone 2 mg	87	38.4		72 (83%)	15 (17%)	64 (74%)	23 (26%)
Risperidone 6 mg	86	36.9		71 (83%)	15 (17%)	64 (74%)	22 (26%)
Risperidone 10 mg	87	36.4		75 (86%)	12 (14%)	61 (70%)	26 (30%)
Risperidone 16 mg	88	37.4		70 (80%)	18 (21%)	61 (69%)	27 (31%)
Haloperidol 20 mg	87	37.6		74 (85%)	13 (15%)	60 (69%)	27 (31%)
Placebo	88	37.2		74 (84%)	14 (16%)	61 (69%)	27 (31%)

TABLE
STUDY: 204

Treatment Groups	Number Randomized	Intent-to-Treat Sample*	Number (%) of Patients Completing**				
			Week 1	Week 2	Week 4	Week 6	Week 8
Risperidone 2 mg	87	87	87 (100)	75 (86)	55 (63)	42 (38)	35 (40)
Risperidone 6 mg	86	85	84 (99)	79 (93)	67 (79)	55 (65)	54 (64)
Risperidone 10 mg	87	85	80 (94)	72 (85)	59 (69)	53 (62)	47 (55)
Risperidone 16 mg	88	86	83 (97)	74 (86)	68 (79)	56 (65)	55 (64)
Haloperidol 20 mg	87	85	85 (100)	72 (85)	52 (61)	41 (48)	37 (44)
Placebo	88	87	82 (94)	67 (77)	48 (55)	34 (39)	26(30)

*Patients who had at least one efficacy assessment on study medication
**Patients having efficacy data within three days of scheduled visit; no upper limit for final visit

TABLE

STUDY : 0204

MEAN CHANGE FROM BASELINE IN TOTAL PANSS

LAST OBSERVATION CARRIED FORWARD ANALYSIS

TREATMENT GROUPS	TREATMENT WEEK											
	BASELINE		WEEK 1		WEEK 2		WEEK 4		WEEK 6		WEEK 8	
	N	MEAN	N	MEAN	N	MEAN	N	MEAN	N	MEAN	N	MEAN
RISPERIDONE 2 MG	87	89.2	87	- 4.9	87	- 6.0	87	- 5.3	87	- 4.1	87	- 4.4
RISPERIDONE 6 MG	85	94.9	85	-13.3	85	-17.8	85	-18.1	85	-18.5	85	-18.6
RISPERIDONE 10 MG	85	91.8	85	- 4.9	85	- 8.3	85	- 7.9	85	- 9.2	85	- 9.4
RISPERIDONE 16 MG	85	93.9	85	- 9.4	84	-13.5	85	-15.7	85	-14.9	85	-14.4
HALOPERIDOL 20 MG	85	93.6	85	- 4.5	83	- 6.0	85	- 6.1	85	- 5.8	85	- 5.4
PLACEBO	86	92.6	86	- 1.8	86	- 1.2	86	0.6	86	3.8	86	3.6
2-SIDED P-VALUES FOR PAIRWISE COMPARISONS												
RISPERIDONE 2 VS. PLACEBO		0.198		0.222		0.110		0.074		0.023		0.028
RISPERIDONE 6 VS. PLACEBO		0.412		<0.001		<0.001		<0.001		<0.001		<0.001
RISPERIDONE 10 VS. PLACEBO		0.695		0.247		0.017		0.007		<0.001		<0.001
RISPERIDONE 16 VS. PLACEBO		0.665		0.003		<0.001		<0.001		<0.001		<0.001
HALOPERIDOL 20 VS. PLACEBO		0.843		0.274		0.095		0.021		0.002		0.003
RISPERIDONE 6 VS HALOPERIDOL 20		0.535		<0.001		<0.001		<0.001		<0.001		<0.001

TABLE

STUDY : 0204

CLINICAL IMPROVEMENT FROM BASELINE VIA TOTAL PANSS

LAST OBSERVATION CARRIED FORWARD ANALYSIS

	TREATMENT WEEK									
	WEEK 1		WEEK 2		WEEK 4		WEEK 6		WEEK 8	
TREATMENT GROUPS	n/N	%	n/N	%	n/N	%	n/N	%	n/N	%
RISPERIDONE 2 MG	31/87	35.6%	37/87	42.5%	36/87	41.4%	36/87	41.4%	34/87	39.1%
RISPERIDONE 6 MG	33/85	38.8%	50/85	58.8%	48/85	56.5%	49/85	57.6%	52/85	61.2%
RISPERIDONE 10 MG	22/85	25.9%	34/85	40.0%	30/85	35.3%	36/85	42.4%	33/85	38.8%
RISPERIDONE 16 MG	32/85	37.6%	37/84	44.0%	48/85	56.5%	46/85	54.1%	43/85	50.6%
HALOPERIDOL 20 MG	20/85	23.5%	22/83	26.5%	30/85	35.3%	28/85	32.9%	29/85	34.1%
PLACEBO	19/86	22.1%	26/86	30.2%	21/86	24.4%	18/86	20.9%	17/86	19.8%
2-SIDED P-VALUES FOR PAIRWISE COMPARISONS										
RISPERIDONE 2 VS. PLACEBO	0.061		0.109		0.019		0.004		0.006	
RISPERIDONE 6 VS. PLACEBO	0.017		<0.001		<0.001		<0.001		<0.001	
RISPERIDONE 10 VS. PLACEBO	0.658		0.229		0.116		0.003		0.006	
RISPERIDONE 16 VS. PLACEBO	0.022		0.065		<0.001		<0.001		<0.001	
HALOPERIDOL 20 VS. PLACEBO	0.726		0.608		0.082		0.055		0.031	
RISPERIDONE 6 VS. HALOPERIDOL 20	0.032		<0.001		0.006		0.002		<0.001	

TABLE

STUDY : 0204

MEAN CHANGE FROM BASELINE IN TOTAL DERIVED BPRS

LAST OBSERVATION CARRIED FORWARD ANALYSIS

	TREATMENT WEEK											
	BASELINE		WEEK 1		WEEK 2		WEEK 4		WEEK 6		WEEK 8	
TREATMENT GROUPS	N	MEAN	N	MEAN	N	MEAN	N	MEAN	N	MEAN	N	MEAN
RISPERIDONE 2 MG	87	52.1	87	-3.2	87	-4.0	87	-3.6	87	-2.8	87	-2.9
RISPERIDONE 6 MG	85	55.0	85	-7.2	85	-10.2	85	-11.0	85	-11.9	85	-11.2
RISPERIDONE 10 MG	85	53.2	85	-2.8	85	-4.6	85	-4.7	85	-5.2	85	-5.7
RISPERIDONE 16 MG	85	54.3	85	-5.4	84	-7.9	85	-8.8	85	-8.6	85	-8.5
HALOPERIDOL 20 MG	85	54.9	85	-2.8	83	-3.5	85	-4.1	85	-4.2	85	-3.8
PLACEBO	86	54.2	86	-1.2	86	-1.1	86	0.3	86	2.4	86	2.2
2-SIDED P-VALUES FOR PAIRWISE COMPARISONS												
RISPERIDONE 2 VS. PLACEBO		0.213		0.210		0.136		0.051		0.013		0.022
RISPERIDONE 6 VS. PLACEBO		0.623		<0.001		<0.001		<0.001		<0.001		<0.001
RISPERIDONE 10 VS. PLACEBO		0.483		0.371		0.060		0.011		<0.001		<0.001
RISPERIDONE 16 VS. PLACEBO		0.995		0.008		<0.001		<0.001		<0.001		<0.001
HALOPERIDOL 20 VS. PLACEBO		0.778		0.301		0.175		0.012		<0.001		0.003
RISPERIDONE 6 VS. HALOPERIDOL 20		0.925		0.114		0.039		0.025		0.015		0.015

STUDY : 0204
MEAN CHANGE FROM BASELINE IN TOTAL DERIVED BPRS

OBSERVED CASE ANALYSIS*

	TREATMENT WEEK											
	BASELINE		WEEK 1		WEEK 2		WEEK 4		WEEK 6		WEEK 8	
TREATMENT GROUPS	N	MEAN	N	MEAN	N	MEAN	N	MEAN	N	MEAN	N	MEAN
RISPERIDONE 2 MG	87	52.1	87	-3.2	75	-5.8	55	-7.4	42	-9.5	35	-10.7
RISPERIDONE 6 MG	84	55.1	84	-7.3	79	-10.5	67	-13.4	55	-15.3	54	-14.8
RISPERIDONE 10 MG	82	53.1	80	-3.2	72	-6.8	59	-8.4	53	-9.3	47	-11.9
RISPERIDONE 16 MG	84	54.2	83	-5.7	74	-8.8	68	-10.6	56	-11.3	55	-11.4
HALOPERIDOL 20 MG	85	54.9	85	-2.8	72	-4.5	52	-7.0	41	-8.1	37	-8.9
PLACEBO	83	54.3	82	-1.4	67	-2.8	48	-4.8	34	-2.2	26	-6.8
2-SIDED P-VALUES FOR PAIRWISE COMPARISONS												
RISPERIDONE 2 VS. PLACEBO		0.166		0.281		0.170		0.194		0.008		0.220
RISPERIDONE 6 VS. PLACEBO		0.670		<0.001		<0.001		<0.001		<0.001		0.009
RISPERIDONE 10 VS. PLACEBO		0.377		0.299		0.060		0.042		0.004		0.164
RISPERIDONE 16 VS. PLACEBO		0.892		0.010		0.005		0.010		0.001		0.255
HALOPERIDOL 20 VS. PLACEBO		0.892		0.376		0.409		0.133		0.016		0.509
RISPERIDONE 6 VS. HALOPERIDOL 20		0.770		0.004		0.001		0.007		0.007		0.029

*Includes patients having efficacy data within three days of the scheduled visit.

TABLE

STUDY : 0204

MEAN CHANGE FROM BASELINE IN CGI - SEVERITY OF SCHIZOPHRENIA

LAST OBSERVATION CARRIED FORWARD ANALYSIS

	TREATMENT WEEK											
	BASELINE		WEEK 1		WEEK 2		WEEK 4		WEEK 6		WEEK 8	
TREATMENT GROUPS	N	MEAN	N	MEAN	N	MEAN	N	MEAN	N	MEAN	N	MEAN
RISPERIDONE 2 MG	87	3.8	87	-0.2	87	-0.3	87	-0.3	87	-0.2	87	-0.2
RISPERIDONE 6 MG	85	3.8	85	-0.5	85	-0.7	85	-0.8	85	-0.9	85	-0.9
RISPERIDONE 10 MG	85	3.7	85	-0.3	85	-0.4	85	-0.5	85	-0.6	85	-0.6
RISPERIDONE 16 MG	86	3.7	86	-0.3	86	-0.6	86	-0.7	86	-0.6	86	-0.6
HALOPERIDOL 20 MG	85	3.8	84	-0.3	84	-0.4	85	-0.4	85	-0.4	85	-0.4
PLACEBO	87	3.7	87	0.0	87	0.0	87	0.1	87	0.2	87	0.2
2-SIDED P-VALUES FOR PAIRWISE COMPARISONS												
RISPERIDONE 2 VS. PLACEBO			0.542		0.127		0.029		0.042		0.012	0.011
RISPERIDONE 6 VS. PLACEBO			0.272		<0.001		<0.001		<0 001		<0.001	<0.001
RISPERIDONE 10 VS. PLACEBO			0.615		0.034		0.007		<0.001		<0.001	<0.001
RISPERIDONE 16 VS. PLACEBO			0.541		0.009		<0.001		<0.001		<0.001	<0.001
HALOPERIDOL 20 VS. PLACEBO			0.315		0.035		0.002		0.001		<0.001	<0.001
RISPERIDONE 6 VS. HALOPERIDOL 20			0.835		0.006		<0.001		<0.001		<0.001	0.001

STUDY : 0204
MEAN CHANGE FROM BASELINE IN CGI - SEVERITY OF SCHIZOPHRENIA

OBSERVED CASE ANALYSIS*

	TREATMENT WEEK											
	BASELINE		WEEK 1		WEEK 2		WEEK 4		WEEK 6		WEEK 8	
TREATMENT GROUPS	N	MEAN	N	MEAN	N	MEAN	N	MEAN	N	MEAN	N	MEAN
RISPERIDONE 2 MG	87	3.8	87	-0.2	74	-0.4	55	-0.4	42	-0.6	35	-0.6
RISPERIDONE 6 MG	84	3.8	84	-0.5	79	-0.7	66	-1.0	55	-1.2	54	-1.2
RISPERIDONE 10 MG	82	3.7	80	-0.3	72	-0.5	59	-0.8	53	-0.9	47	-1.1
RISPERIDONE 16 MG	85	3.8	84	-0.3	74	-0.7	68	-0.8	56	-0.9	55	-0.8
HALOPERIDOL 20 MG	85	3.8	84	-0.3	73	-0.5	52	-0.6	41	-0.8	37	-0.8
PLACEBO	84	3.7	83	0.0	67	-0.1	48	-0.3	34	-0.2	26	-0.5
2-SIDED P-VALUES FOR PAIRWISE COMPARISONS												
RISPERIDONE 2 VS. PLACEBO	0.528		0.116		0.075		0.493		0.089		0.517	
RISPERIDONE 6 VS. PLACEBO	0.266		<0.001		<0.001		<0.001		<0.001		0.004	
RISPERIDONE 10 VS. PLACEBO	0.578		0.016		0.018		0.011		0.002		0.047	
RISPERIDONE 16 VS. PLACEBO	0.443		0.007		<0.001		0.007		0.003		0.253	
HALOPERIDOL 20 VS. PLACEBO	0.303		0.032		0.037		0.069		0.018		0.193	
RISPERIDONE 6 VS. HALOPERIDOL 20	0.933		0.098		0.065		0.084		0.092		0.081	

*Includes patients having efficacy data within three days of the scheduled visit.

STUDY : 0204
MEAN CHANGE FROM BASELINE IN TOTAL NEGATIVE PANSS SUBSCALE

LAST OBSERVATION CARRIED FORWARD ANALYSIS

	TREATMENT WEEK											
	BASELINE		WEEK 1		WEEK 2		WEEK 4		WEEK 6		WEEK 8	
TREATMENT GROUPS	N	MEAN	N	MEAN	N	MEAN	N	MEAN	N	MEAN	N	MEAN
RISPERIDONE 2 MG	87	23.8	87	-1.3	87	-1.5	87	-1.2	87	-1.1	87	-1.3
RISPERIDONE 6 MG	85	25.5	85	-3.3	85	-4.2	85	-4.1	85	-4.2	85	-3.9
RISPERIDONE 10 MG	85	24.5	85	-0.7	85	-2.1	85	-2.0	85	-2.0	85	-1.9
RISPERIDONE 16 MG	85	24.7	85	-1.9	84	-3.0	85	-4.1	85	-3.2	85	-3.1
HALOPERIDOL 20 MG	85	24.9	85	-0.8	83	-1.3	85	-1.1	85	-0.9	85	-0.7
PLACEBO	86	24.0	86	0.1	86	-0.2	86	-0.1	86	0.1	86	0.2
2-SIDED P-VALUES FOR PAIRWISE COMPARISONS												
RISPERIDONE 2 VS. PLACEBO		0.882		0.082		0.178		0.269		0.273		0.145
RISPERIDONE 6 VS. PLACEBO		0.154		<0.001		<0.001		<0.001		<0.001		<0.001
RISPERIDONE 10 VS. PLACEBO		0.646		0.371		0.043		0.055		0.052		0.048
RISPERIDONE 16 VS. PLACEBO		0.524		0.017		0.004		<0.001		0.003		0.002
HALOPERIDOL 20 VS. PLACEBO		0.413		0.252		0.255		0.264		0.297		0.301
RISPERIDONE 6 VS. HALOPERIDOL 20		0.543		0.003		0.002		0.003		0.003		0.004

STUDY : 0204
MEAN CHANGE FROM BASELINE IN TOTAL NEGATIVE PANSS SUBSCALE

OBSERVED CASE ANALYSIS*

	TREATMENT WEEK											
	BASELINE		WEEK 1		WEEK 2		WEEK 4		WEEK 6		WEEK 8	
TREATMENT GROUPS	N	MEAN	N	MEAN	N	MEAN	N	MEAN	N	MEAN	N	MEAN
RISPERIDONE 2 MG	87	23.8	87	-1.3	75	-2.2	55	-3.1	42	-4.1	35	-4.7
RISPERIDONE 6 MG	84	25.4	84	-3.4	79	-4.4	67	-4.9	55	-5.3	54	-5.2
RISPERIDONE 10 MG	82	24.2	80	-0.6	72	-2.7	59	-2.7	53	-2.8	47	-3.1
RISPERIDONE 16 MG	84	24.6	83	-2.0	74	-3.4	68	-5.4	56	-4.5	55	-4.4
HALOPERIDOL 20 MG	85	24.9	85	-0.8	72	-1.7	52	-3.0	41	-3.4	37	-3.7
PLACEBO	83	24.2	82	0.0	67	-1.4	48	-2.3	34	-2.5	26	-4.4
2-SIDED P-VALUES FOR PAIRWISE COMPARISONS												
RISPERIDONE 2 VS. PLACEBO		0.702		0.111		0.539		0.454		0.337		0.925
RISPERIDONE 6 VS. PLACEBO		0.242		<0.001		0.005		0.025		0.048		0.726
RISPERIDONE 10 VS. PLACEBO		0.951		0.504		0.251		0.521		0.691		0.326
RISPERIDONE 16 VS. PLACEBO		0.713		0.018		0.080		0.008		0.220		0.686
HALOPERIDOL 20 VS. PLACEBO		0.568		0.316		0.844		0.334		0.439		0.613
RISPERIDONE 6 VS. HALOPERIDOL 20		0.545		0.002		0.008		0.210		0.211		0.314

*Includes patients having efficacy data within three days of the scheduled visit.

TABLE

STUDY : 0204

MEAN CHANGE FROM BASELINE IN TOTAL BPRS PSYCHOSIS SUBSCORE*

LAST OBSERVATION CARRIED FORWARD ANALYSIS

	TREATMENT WEEK											
	BASELINE		WEEK 1		WEEK 2		WEEK 4		WEEK 6		WEEK 8	
TREATMENT GROUPS	N	MEAN	N	MEAN	N	MEAN	N	MEAN	N	MEAN	N	MEAN
RISPERIDONE 2 MG	87	14.9	87	-1.2	87	-1.1	87	-1.1	87	-0.9	87	-0.8
RISPERIDONE 6 MG	85	15.7	85	-1.8	85	-3.0	85	-3.2	85	-3.6	85	-3.5
RISPERIDONE 10 MG	85	15.4	85	-1.2	85	-1.7	85	-1.8	85	-2.1	85	-2.2
RISPERIDONE 16 MG	85	15.4	85	-1.5	84	-2.6	85	-2.8	85	-2.9	85	-2.8
HALOPERIDOL 20 MG	85	15.8	85	-1.3	83	-1.7	85	-1.8	85	-2.0	85	-2.1
PLACEBO	86	15.4	86	-0.5	86	-0.7	86	-0.0	86	0.7	86	0.6
2-SIDED P-VALUES FOR PAIRWISE COMPARISONS												
RISPERIDONE 2 VS. PLACEBO			0.380		0.151		0.471		0.111		0.016	0.052
RISPERIDONE 6 VS. PLACEBO			0.648		0.007		<0.001		<0.001		<0.001	<0.001
RISPERIDONE 10 VS. PLACEBO			0.895		0.197		0.084		0.006		<0.001	<0.001
RISPERIDONE 16 VS. PLACEBO			0.978		0.049		0.001		<0.001		<0.001	<0.001
HALOPERIDOL 20 VS. PLACEBO			0.593		0.111		0.068		0.003		<0.001	<0.001
RISPERIDONE 6 VS. HALOP. 20			0.938		0.276		0.034		0.038		0.024	0.059

* Includes conceptual disorganization, suspiciousness, hallucinatory behavior, and unusual thought content

STUDY : 0204
MEAN CHANGE FROM BASELINE IN TOTAL BPRS PSYCHOSIS SUBSCORE*

OBSERVED CASE ANALYSIS**

	TREATMENT WEEK											
	BASELINE		WEEK 1		WEEK 2		WEEK 4		WEEK 6		WEEK 8	
TREATMENT GROUPS	N	MEAN	N	MEAN	N	MEAN	N	MEAN	N	MEAN	N	MEAN
RISPERIDONE 2 MG	87	14.9	87	-1.2	75	-1.5	55	-1.9	42	-2.5	35	-2.9
RISPERIDONE 6 MG	84	15.7	84	-1.9	79	-3.1	67	-4.1	55	-4.7	54	-4.8
RISPERIDONE 10 MG	82	15.5	80	-1.3	72	-2.5	59	-2.9	53	-3.4	47	-3.8
RISPERIDONE 16 MG	84	15.4	83	-1.6	74	-3.0	68	-3.4	56	-4.0	55	-3.9
HALOPERIDOL 20 MG	85	15.8	85	-1.3	72	-2.1	52	-2.5	41	-2.9	37	-3.6
PLACEBO	83	15.4	82	-0.5	67	-1.1	48	-1.2	34	-0.5	26	-1.7
2-SIDED P-VALUES FOR PAIRWISE COMPARISONS												
RISPERIDONE 2 VS. PLACEBO		0.376		0.185		0.584		0.325		0.018		0.235
RISPERIDONE 6 VS. PLACEBO		0.633		0.008		<0.001		<0.001		<0.001		0.001
RISPERIDONE 10 VS. PLACEBO		0.989		0.146		0.041		0.014		<0.001		0.041
RISPERIDONE 16 VS. PLACEBO		0.973		0.039		0.004		0.005		<0.001		0.030
HALOPERIDOL 20 VS. PLACEBO		0.601		0.134		0.145		0.080		0.005		0.078
RISPERIDONE 6 VS. HALOPERIDOL 20		0.965		0.238		0.052		0.021		0.021		0.108

*Includes conceptual disorganization, suspiciousness, hallucinatory behavior, and unusual thought content.
**Includes patients having efficacy data within three days of the scheduled visit.

TABLE
Study: 024
Demographic Characteristics

Treatment Groups	n	Age (years)		Sex [n (%)]		Race [n (%)]	
		Mean	Range	Male	Female	White	Non-White
Risperidone 1 mg	229	38.4		166 (73%)	63 (28%)	189 (83%)	38 (17%)
Risperidone 4 mg	227	38.1		152 (67%)	75 (33%)	183 (81%)	44 (19%)
Risperidone 8 mg	230	37.6		144 (63%)	86 (37%)	189 (82%)	39 (17%)
Risperidone 12 mg	226	37.9		142 (63%)	83 (37%)	185 (82%)	39 (17%)
Risperidone 16 mg	224	38.5		140 (63%)	84 (38%)	189 (84%)	33 (15%)
Haloperidol 10 mg	226	38.1		150 (66%)	76 (34%)	181 (80%)	44 (20%)

Study: 024

Treatment Groups	Number Randomized	Intent-to-Treat Sample*	Numbers (%) of Patients Completing**				
			Week 1	Week 2	Week 4	Week 6	Week 8
Risperidone 1 mg	263	226	219 (97)	204 (90)	186 (82)	167 (74)	167 (74)
Risperidone 4 mg	255	227	219 (96)	212 (93)	188 (83)	179 (79)	178 (78)
Risperidone 8 mg	261	229	222 (97)	207 (90)	187 (82)	171 (75)	171 (75)
Risperidone 12 mg	256	225	222 (99)	210 (93)	183 (81)	160 (71)	160 (76)
Risperidone 16 mg	259	224	216 (96)	201 (90)	173 (77)	158 (71)	155 (69)
Haloperidol 10 mg	263	225	217 (96)	200 (89)	179 (80)	165 (73)	162 (72)

*Patients who had at least one efficacy assessment on medication, omitting patients from excluded sites.
**Patients having efficacy data within three days of the scheduled visit; no upper limit for final visit.

TABLE

STUDY : 024

MEAN CHANGE FROM BASELINE IN TOTAL PANSS

LAST OBSERVATION CARRIED FORWARD ANALYSIS

TREATMENT GROUPS	TREATMENT WEEK											
	BASELINE		WEEK 1		WEEK 2		WEEK 4		WEEK 6		WEEK 8	
	N	MEAN	N	MEAN	N	MEAN	N	MEAN	N	MEAN	N	MEAN
RISPERIDONE 1 MG	226	89.9	223	-5.4	223	-9.6	223	-12.1	224	-13.1	226	-12.5
RISPERIDONE 4 MG	227	89.6	226	-8.3	226	-13.2	223	-16.6	226	-18.3	227	-18.6
RISPERIDONE 8 MG	228	89.3	227	-5.9	228	-10.9	225	-14.0	224	-16.2	228	-17.9
RISPERIDONE 12 MG	225	90.5	223	-7.2	225	-11.6	224	-14.5	223	-15.7	225	-16.6
RISPERIDONE 16 MG	223	89.8	221	-6.7	218	-11.9	222	-14.5	223	-16.3	223	-17.0
HALOPERIDOL 10 MG	223	89.0	220	-6.7	221	-10.1	221	-12.4	221	-14.3	223	-14.9
2-SIDED P-VALUES FOR PAIRWISE COMPARISONS												
RISPERIDONE 1 VS. RISPERIDONE 4			0.745		0.015		0.019		0.016		0.007	0.003
RISPERIDONE 1 VS. RISPERIDONE 8			0.627		0.716		0.412		0.336		0.129	0.011
RISPERIDONE 1 VS. RISPERIDONE 12			0.778		0.155		0.203		0.199		0.194	0.056
RISPERIDONE 1 VS. RISPERIDONE 16			0.753		0.346		0.191		0.260		0.146	0.048
RISPERIDONE 1 VS. HALOPERIDOL 10			0.476		0.303		0.774		0.941		0.592	0.284

TABLE

STUDY : 024

CLINICAL IMPROVEMENT FROM BASELINE VIA TOTAL PANSS

LAST OBSERVATION CARRIED FORWARD ANALYSIS

TREATMENT GROUPS	TREATMENT WEEK									
	WEEK 1		WEEK 2		WEEK 4		WEEK 6		WEEK 8	
	n/N	%	n/N	%	n/N	%	n/N	%	n/N	%
RISPERIDONE 1 MG	62/223	27.8%	94/223	42.2%	124/223	55.6%	129/224	57.6%	123/226	54.4%
RISPERIDONE 4 MG	74/226	32.7%	120/226	53.1%	127/223	57.0%	143/226	63.3%	145/227	63.8%
RISPERIDONE 8 MG	66/227	29.1%	111/228	48.7%	134/225	59.6%	143/224	63.8%	150/228	65.8%
RISPERIDONE 12 MG	72/223	32.3%	103/225	45.8%	119/224	53.1%	126/223	56.5%	131/225	58.2%
RISPERIDONE 16 MG	68/221	30.8%	100/218	45.9%	125/222	56.3%	134/223	60.1%	135/223	60.5%
HALOPERIDOL 10 MG	71/220	32.3%	103/221	46.6%	120/221	54.3%	124/221	56.1%	131/223	58.7%
2-SIDED P-VALUES FOR PAIRWISE COMPARISONS										
RISPERIDONE 1 VS. RISPERIDONE 4	0.271		0.013		0.750		0.173		0.039	
RISPERIDONE 1 VS. RISPERIDONE 8	0.756		0.154		0.400		0.142		0.011	
RISPERIDONE 1 VS. RISPERIDONE 12	0.310		0.468		0.527		0.805		0.447	
RISPERIDONE 1 VS. RISPERIDONE 16	0.529		0.487		0.921		0.578		0.197	
RISPERIDONE 1 VS. HALOPERIDOL 10	0.300		0.328		0.787		0.786		0.368	

TABLE

STUDY : 024

MEAN CHANGE FROM BASELINE IN TOTAL DERIVED BPRS

LAST OBSERVATION CARRIED FORWARD ANALYSIS

	TREATMENT WEEK											
	BASELINE		WEEK 1		WEEK 2		WEEK 4		WEEK 6		WEEK 8	
TREATMENT GROUPS	N	MEAN	N	MEAN	N	MEAN	N	MEAN	N	MEAN	N	MEAN
RISPERIDONE 1 MG	226	48.8	223	-3.0	223	-5.3	223	-6.8	224	-7.1	226	-6.7
RISPERIDONE 4 MG	227	48.6	226	-4.8	226	-7.5	223	-9.2	226	-10.2	227	-10.2
RISPERIDONE 8 MG	228	48.1	227	-3.5	228	-6.4	225	-7.9	224	-9.0	228	-9.9
RISPERIDONE 12 MG	225	49.1	223	-4.1	225	-6.7	224	-7.9	223	-8.5	225	-9.0
RISPERIDONE 16 MG	223	49.5	221	-4.1	218	-7.1	222	-8.5	223	-9.5	223	-9.7
HALOPERIDOL 10 MG	223	48.2	220	-3.6	221	-5.5	221	-6.7	221	-7.8	223	-8.1
2-SIDED P-VALUES FOR PAIRWISE COMPARISONS												
RISPERIDONE 1 VS. RISPERIDONE 4		0.750		0.013		0.016		0.024		0.006		0.003
RISPERIDONE 1 VS. RISPERIDONE 8		0.416		0.571		0.255		0.329		0.107		0.007
RISPERIDONE 1 VS. RISPERIDONE 12		0.756		0.168		0.144		0.278		0.200		0.052
RISPERIDONE 1 VS. RISPERIDONE 16		0.611		0.161		0.071		0.132		0.053		0.018
RISPERIDONE 1 VS. HALOPERIDOL 10		0.463		0.447		0.921		0.835		0.563		0.289

STUDY : 024 MEAN CHANGE FROM BASELINE IN TOTAL DERIVED BPRS												
OBSERVED CASE ANALYSIS*												
	TREATMENT WEEK											
	BASELINE		WEEK 1		WEEK 2		WEEK 4		WEEK 6		WEEK 8	
TREATMENT GROUPS	N	MEAN	N	MEAN	N	MEAN	N	MEAN	N	MEAN	N	MEAN
RISPERIDONE 1 MG	224	48.7	219	-3.0	204	-6.0	186	-8.8	167	-10.1	167	-9.9
RISPERIDONE 4 MG	225	48.7	219	-4.8	212	-8.0	188	-10.7	179	-11.8	178	-12.4
RISPERIDONE 8 MG	227	48.1	222	-3.6	207	-7.2	187	-10.0	171	-12.2	171	-13.6
RISPERIDONE 12 MG	224	49.2	222	-4.2	210	-7.5	183	-9.7	160	-10.6	160	-11.6
RISPERIDONE 16 MG	219	49.4	216	-4.0	201	-7.2	173	-10.2	158	-12.2	155	-12.3
HALOPERIDOL 10 MG	223	48.2	217	-3.7	200	-6.2	179	-8.2	165	-9.8	162	-10.8
2-SIDED P-VALUES FOR PAIRWISE COMPARISONS												
RISPERIDONE 1 VS. RISPERIDONE 4		0.840		0.014		0.031		0.058		0.163		0.018
RISPERIDONE 1 VS. RISPERIDONE 8		0.438		0.421		0.233		0.267		0.085		0.001
RISPERIDONE 1 VS. RISPERIDONE 12		0.677		0.113		0.100		0.403		0.759		0.206
RISPERIDONE 1 VS. RISPERIDONE 16		0.648		0.171		0.228		0.207		0.098		0.050
RISPERIDONE 1 VS. HALOPERIDOL		0.483		0.343		0.865		0.523		0.830		0.430

*Includes patients having efficacy data within three days of the scheduled visit.

TABLE

STUDY : 024

MEAN CHANGE FROM BASELINE IN CGI - SEVERITY OF SCHIZOPHRENIA

LAST OBSERVATION CARRIED FORWARD ANALYSIS

	TREATMENT WEEK											
	BASELINE		WEEK 1		WEEK 2		WEEK 4		WEEK 6		WEEK 8	
TREATMENT GROUPS	N	MEAN	N	MEAN	N	MEAN	N	MEAN	N	MEAN	N	MEAN
RISPERIDONE 1 MG	226	3.9	223	-0.1	223	-0.2	223	-0.4	224	-0.4	226	-0.4
RISPERIDONE 4 MG	227	3.8	226	-0.3	226	-0.5	224	-0.7	226	-0.8	227	-0.8
RISPERIDONE 8 MG	229	3.8	228	-0.2	229	-0.4	225	-0.5	225	-0.7	229	-0.8
RISPERIDONE 12 MG	225	3.8	223	-0.3	225	-0.5	224	-0.6	223	-0.7	225	-0.7
RISPERIDONE 16 MG	223	3.9	222	-0.3	218	-0.5	222	-0.6	223	-0.7	223	-0.8
HALOPERIDOL 10 MG	225	3.7	221	-0.2	223	-0.3	223	-0.4	222	-0.6	225	-0.6
2-SIDED P-VALUES FOR PAIRWISE COMPARISONS												
RISPERIDONE 1 VS. RISPERIDONE 4		0.430		0.015		0.001		<0.001		<0.001		<0.001
RISPERIDONE 1 VS. RISPERIDONE 8		0.552		0.112		0.061		0.104		0.011		0.001
RISPERIDONE 1 VS. RISPERIDONE 12		0.892		0.033		0.013		0.032		0.022		0.014
RISPERIDONE 1 VS. RISPERIDONE 16		0.963		0.095		0.002		0.020		0.006		<0.001
RISPERIDONE 1 VS. HALOPERIDOL 10		0.078		0.686		0.398		0.658		0.170		0.079

STUDY : 024
MEAN CHANGE FROM BASELINE IN CGI - SEVERITY OF SCHIZOPHRENIA

OBSERVED CASE ANALYSIS*

TREATMENT GROUPS	TREATMENT WEEK											
	BASELINE		WEEK 1		WEEK 2		WEEK 4		WEEK 6		WEEK 8	
	N	MEAN	N	MEAN	N	MEAN	N	MEAN	N	MEAN	N	MEAN
RISPERIDONE 1 MG	224	3.9	219	-0.1	206	-0.3	186	-0.5	168	-0.6	167	-0.6
RISPERIDONE 4 MG	225	3.8	219	-0.3	212	-0.5	190	-0.8	178	-0.9	179	-0.9
RISPERIDONE 8 MG	228	3.8	223	-0.3	209	-0.4	186	-0.7	171	-0.9	171	-1.0
RISPERIDONE 12 MG	224	3.8	222	-0.3	210	-0.5	183	-0.7	160	-0.8	160	-0.9
RISPERIDONE 16 MG	219	3.9	217	-0.2	201	-0.5	173	-0.7	158	-0.9	155	-1.0
HALOPERIDOL 10 MG	224	3.7	217	-0.2	200	-0.4	179	-0.5	164	-0.7	162	-0.8
2-SIDED P-VALUES FOR PAIRWISE COMPARISONS												
RISPERIDONE 1 VS. RISPERIDONE 4			0.460		0.027		0.004		0.006		0.054	0.011
RISPERIDONE 1 VS. RISPERIDONE 8			0.550		0.058		0.059		0.123		0.011	<0.001
RISPERIDONE 1 VS. RISPERIDONE 12			0.892		0.038		0.015		0.104		0.195	0.070
RISPERIDONE 1 VS. RISPERIDONE 16			0.935		0.105		0.004		0.116		0.043	0.005
RISPERIDONE 1 VS. HALOPERIDOL			0.087		0.587		0.387		0.811		0.452	0.156

*Includes patients having efficacy data within three days of the scheduled visit.

STUDY : 024
MEAN CHANGE FROM BASELINE IN TOTAL NEGATIVE PANSS SUBSCALE

LAST OBSERVATION CARRIED FORWARD ANALYSIS

	TREATMENT WEEK											
	BASELINE		WEEK 1		WEEK 2		WEEK 4		WEEK 6		WEEK 8	
TREATMENT GROUPS	N	MEAN	N	MEAN	N	MEAN	N	MEAN	N	MEAN	N	MEAN
RISPERIDONE 1 MG	226	26.6	223	-1.8	223	-3.1	223	-4.0	224	-4.4	226	-4.5
RISPERIDONE 4 MG	227	26.2	226	-2.0	226	-3.4	223	-4.5	226	-5.2	227	-5.5
RISPERIDONE 8 MG	228	26.8	227	-1.6	228	-2.8	225	-4.0	224	-4.5	228	-5.2
RISPERIDONE 12 MG	225	26.6	223	-2.0	225	-3.2	224	-4.1	223	-4.7	225	-5.0
RISPERIDONE 16 MG	223	26.2	221	-1.7	218	-3.4	222	-4.3	223	-4.8	223	-5.2
HALOPERIDOL 10 MG	223	26.5	220	-1.9	221	-3.2	221	-3.9	221	-4.5	223	-4.8
2-SIDED P-VALUES FOR PAIRWISE COMPARISONS												
RISPERIDONE 1 VS. RISPERIDONE 4			0.492		0.534		0.479		0.345		0.201	0.124
RISPERIDONE 1 VS. RISPERIDONE 8			0.810		0.648		0.621		0.909		0.880	0.256
RISPERIDONE 1 VS. RISPERIDONE 12			0.838		0.721		0.851		0.810		0.706	0.472
RISPERIDONE 1 VS. RISPERIDONE 16			0.429		0.850		0.565		0.683		0.637	0.369
RISPERIDONE 1 VS. HALOPERIDOL 10			0.732		0.736		0.835		0.810		0.969	0.706

STUDY : 024
MEAN CHANGE FROM BASELINE IN TOTAL NEGATIVE PANSS SUBSCALE

OBSERVED CASE ANALYSIS*

	TREATMENT WEEK											
	BASELINE		WEEK 1		WEEK 2		WEEK 4		WEEK 6		WEEK 8	
TREATMENT GROUPS	N	MEAN	N	MEAN	N	MEAN	N	MEAN	N	MEAN	N	MEAN
RISPERIDONE 1 MG	224	26.6	219	-1.7	204	-3.4	186	-4.7	167	-5.8	167	-5.9
RISPERIDONE 4 MG	225	26.2	219	-2.0	212	-3.6	188	-5.2	179	-5.8	178	-6.2
RISPERIDONE 8 MG	227	26.8	222	-1.6	207	-3.0	187	-4.9	171	-5.8	171	-7.0
RISPERIDONE 12 MG	224	26.5	222	-2.0	210	-3.5	183	-4.8	160	-5.4	160	-5.9
RISPERIDONE 16 MG	219	26.1	216	-1.7	201	-3.4	173	-4.9	158	-5.9	155	-6.0
HALOPERIDOL 10 MG	223	26.5	217	-1.9	200	-3.5	179	-4.4	165	-5.4	162	-6.1
2-SIDED P-VALUES FOR PAIRWISE COMPARISONS												
RISPERIDONE 1 VS. RISPERIDONE 4		0.492		0.611		0.722		0.443		0.999		0.518
RISPERIDONE 1 VS. RISPERIDONE 8		0.865		0.726		0.427		0.805		0.899		0.098
RISPERIDONE 1 VS. RISPERIDONE 12		0.804		0.731		0.892		0.889		0.532		0.881
RISPERIDONE 1 VS. RISPERIDONE 16		0.348		0.803		0.932		0.824		0.947		0.795
RISPERIDONE 1 VS. HALOPERIDOL		0.719		0.663		0.910		0.547		0.630		0.779

*Includes patients having efficacy data within three days of the scheduled visit.

TABLE

STUDY : 024

MEAN CHANGE FROM BASELINE IN TOTAL BPRS PSYCHOSIS SUBSCORE*

LAST OBSERVATION CARRIED FORWARD ANALYSIS

	TREATMENT WEEK											
	BASELINE		WEEK 1		WEEK 2		WEEK 4		WEEK 6		WEEK 8	
TREATMENT GROUPS	N	MEAN	N	MEAN	N	MEAN	N	MEAN	N	MEAN	N	MEAN
RISPERIDONE 1 MG	226	12.9	223	-0.7	223	-1.2	223	-1.7	224	-1.7	226	-1.7
RISPERIDONE 4 MG	227	12.6	226	-1.2	226	-2.1	223	-2.5	226	-2.7	227	-2.6
RISPERIDONE 8 MG	228	12.6	227	-1.0	228	-2.1	225	-2.4	224	-2.8	228	-3.1
RISPERIDONE 12 MG	225	12.8	223	-1.1	225	-1.9	224	-2.5	223	-2.6	225	-2.8
RISPERIDONE 16 MG	223	12.9	221	-1.0	218	-2.1	222	-2.5	223	-2.9	223	-2.9
HALOPERIDOL 10 MG	223	12.7	220	-1.1	221	-1.7	221	-2.3	221	-2.6	223	-2.7
2-SIDED P-VALUES FOR PAIRWISE COMPARISONS												
RISPERIDONE 1 VS. RISPERIDONE 4	0.433		0.037		0.006		0.031		0.007		0.013	
RISPERIDONE 1 VS. RISPERIDONE 8	0.499		0.204		0.006		0.044		0.004		<.001	
RISPERIDONE 1 VS. RISPERIDONE 12	0.899		0.148		0.040		0.022		0.027		0.008	
RISPERIDONE 1 VS. RISPERIDONE 16	0.939		0.166		0.012		0.037		0.003		0.003	
RISPERIDONE 1 VS. HALOPERIDOL 10	0.594		0.108		0.133		0.130		0.023		0.009	

* Includes conceptual disorganization, suspiciousness, hallucinatory behavior, and unusual thought content

STUDY : 024
MEAN CHANGE FROM BASELINE IN TOTAL BPRS PSYCHOSIS SUBSCORE*

OBSERVED CASE ANALYSIS**

	TREATMENT WEEK											
	BASELINE		WEEK 1		WEEK 2		WEEK 4		WEEK 6		WEEK 8	
TREATMENT GROUPS	N	MEAN	N	MEAN	N	MEAN	N	MEAN	N	MEAN	N	MEAN
RISPERIDONE 1 MG	224	12.9	219	-0.7	204	-1.4	186	-2.3	167	-2.6	167	-2.7
RISPERIDONE 4 MG	225	12.6	219	-1.2	212	-2.2	188	-2.8	179	-3.0	178	-3.1
RISPERIDONE 8 MG	227	12.6	222	-1.0	207	-2.2	187	-3.0	171	-3.6	171	-4.0
RISPERIDONE 12 MG	224	12.9	222	-1.1	210	-2.0	183	-3.0	160	-3.0	160	-3.4
RISPERIDONE 16 MG	219	12.9	216	-1.0	201	-2.1	173	-3.0	158	-3.8	155	-3.8
HALOPERIDOL 10 MG	223	12.7	217	-1.1	200	-1.9	179	-2.7	165	-3.2	162	-3.5
2-SIDED P-VALUES FOR PAIRWISE COMPARISONS												
RISPERIDONE 1 VS. RISPERIDONE 4		0.488		0.03		0.014		0.194		0.399		0.200
RISPERIDONE 1 VS. RISPERIDONE 8		0.506		0.188		0.009		0.062		0.018		0.002
RISPERIDONE 1 VS. RISPERIDONE 12		0.995		0.122		0.052		0.074		0.375		0.138
RISPERIDONE 1 VS. RISPERIDONE 16		0.932		0.220		0.035		0.112		0.010		0.014
RISPERIDONE 1 VS. HALOPERIDOL		0.621		0.085		0.103		0.366		0.190		0.046

*Includes conceptual disorganization, suspiciousness, hallucinatory behavior, and unusual thought content.
**Includes patients having efficacy data within three days of the scheduled visit.

Appendices to Section 8.0 Safety Findings

Appendix 8.2 Summary of Deaths Occurring in Risperidone-treated Patients

Appendix 8.5.1.1 Treatment Emergent Adverse Experience Incidences in Study 204

Appendix 8.5.1.2 UKU Symptom Reports from Study 204

Appendix 8.5.1.3 Other Events Observed During the Premarketing Evaluation of Risperidone

Appendix 8.5.2.1.1 Criteria for Identifying Patients With Potentially Clinically Significant Changes in Clinical Chemistry Variables

Appendix 8.5.2.1.2 Proportions of Patients Having Potentially Clinically Significant Changes in Blood Chemistry Variables in Placebo-Controlled Antipsychotic Studies 201 and 204

Appendix 8.5.2.2.1 Criteria for Identifying Patients with Potentially Clinically Significant Changes in Hematology Variables

Appendix 8.5.2.2.2 Proportions of Patients Having Potentially Clinically Significant Changes in Hematology Variables in Placebo-Controlled Antipsychotic Studies 201 and 204

Appendix 8.5.2.3.1 Criteria for Identifying Patients With Potentially Clinically Significant Changes in Urinalysis Variables

Appendix 8.5.2.3.2 Proportions of Patients Having Potentially Clinically Significant Changes in Urinalysis Variables in Placebo-Controlled Antipsychotic Studies 201 and 204

Appendix 8.5.3.1 Criteria for Identifying Patients with Potentially Clinically Significant Changes in Vital Signs Variables

Appendix 8.5.3.2 Proportion of Patients Having Potentially Clinically Significant Changes in Vital Signs Variables in Placebo-Controlled Antipsychotic Studies 201 and 204

Appendix 8.8.1 Summary of Serious Adverse Events Occurring in Risperidone-Treated Patients and Considered Unlikely to be Drug-Related

Appendix 8.8.2 Summary of Serious Adverse Events Occurring in Control Group Patients and Considered Unlikely to be Treatment Related

Appendix 8.2 Summary of Deaths Occurring in Risperidone-treated Patients					
Study/Pt. No.	Age(yrs)	Sex	Dose (mg/d)	Duration (days)	Cause of Death and Comments
RIS-INT-3	38	M	6	26	Death due self-inflicted burns--considered a suicide
RIS-BEL-7	48	F	8	38	Death due to suicide by drowning
RIS-INT-2	59	M	16	41	Death due to myocardial infarction (MI); had prior history of MI
RIS-INT-4	35	F	6	290	Death due to accidental drowning
RIS-BEL-17	52	F	4	182**	Death due to suicide by hanging
RIS-BEL-17	28	M	12	37**	Death due to suicide by unknown method
RIS-INT-2	32	M	16	71	Death due to suicide by carbon monoxide poisoning
RIS-INT-2	52	F	1	56**	Death due to suicide by jumping out a window
RIS-INT-2	58	M	12	4***	Death due to myeloma
RIS-INT-2	55	M	4	11***	Discontinued from trial with worsening liver disease; later died of pneumonia
RIS-INT-2	59	M	8	16**	Death due to primary liver cell carcinoma with lung and per-pancreatic metastases
RIS-INT-4	22	M	16	105	Death due to suicide by hanging
RIS-HOL-9002	48	M	3	35-	Death due to suicide by unknown method
RIS-HOL-9002	45	F	3	183**	Death due to suicide by unknown method
RIS-BEL-14[a]	81	M	2	33**	Death due to renal insufficiency
Compassionate (Austria) (PP)	36	M	4	77	Death due to suicide by hanging
Compassionate (Belgium) (VDM)	73	F	3	141	Death due to cardiac arrest; patient had history of cardiomyophathy, head injury and heart valve surgery
Compassionate (Canada) (DC)	37	M	12	100	Death due to AIDS

*Patients who died and are included in the integrated Phase 2-3 safety data.
**Died within 30 days after discontinuing treatment.
***Died 3-4 months after discontinuing treatment.
a Ongoing open trial in Alzheimer's disease not reported in the safety database.

Appendix 8.5.1.1 Treatment Emergent Adverse Experiences in Protocol 204 (Reported by at Least 2% of Patients Treated with Risperidone 2, 6, 10, or 16 mg)

BODY SYSTEM	PREFERRED TERM	Placebo (n=88)	Risp 2 MG (n=87)	Risp 6 MG (n=86)	Risp 10 MG (n=87)	Risp 16 MG (n=88)
Psychiatric Disorders						
	Agitation	17.0%	23.0%	22.1%	19.5%	25.0%
	Insomnia	15.9%	28.7%	23.3%	24.1%	22.7%
	Anxiety	11.4%	14.9%	16.3%	9.2%	19.3%
	Nervousness	4.5%	0%	5.8%	1.1%	2.3%
	Aggressive Reaction	2.3%	2.3%	1.2%	1.1%	2.3%
	Personality Disorder	0%	2.3%	1.2%	0%	1.1%
	Somnolence	0%	2.3%	2.3%	2.3%	6.8%
Centr & Periph Nerv System Disorder						
	Headache	9.1%	12.6%	16.3%	12.6%	10.2%
	Extrapyramidal Disorder	5.7%	6.9%	10.5%	16.1%	15.9%
	Hyperkinesia	2.3%	1.1%	3.5%	1.1%	8.0%
	Hypertonia	2.3%	1.1%	1.2%	0%	3.4%
	Dyskinesia	1.1%	4.6%	0%	2.3%	0%
	Dystonia	0%	1.1%	0%	1.1%	4.5%
	Dizziness	0%	2.3%	7.0%	1.1%	8.0%
Gastro-Intestinal Disorders						
	Dyspepsia	3.4%	4.6%	7.0%	4.6%	9.1%
	Constipation	1.1%	4.6%	9.3%	4.6%	11.4%
	Saliva Increased	1.1%	2.3%	1.2%	2.3%	0%
	Vomiting	1.1%	2.3%	7.0%	3.4%	8.0%
	Nausea	1.1%	4.6%	7.0%	6.9%	5.7%
	Gastro-Intestinal Disorder NOS	1.1%	0%	0%	0%	2.3%
	Anorexia	0%	2.3%	1.2%	0%	0%
	Abdominal Pain	0%	3.4%	3.5%	1.1%	3.4%
	Tooth Ache	0%	2.3%	2.3%	1.1%	0%
Body as a Whole - General Disorders						
	Injury	4.5%	4.6%	5.8%	2.3%	4.5%
	Pain	3.4%	2.3%	2.3%	4.6%	2.3%
	Asthenia	1.1%	0%	0%	2.3%	1.1%
	Back pain	1.1%	0%	3.5%	2.3%	0%

Appendix 8.5.1.1 Treatment Emergent Adverse Experiences in Protocol 204 (Reported by at Least 2% of Patients Treated with Risperidone 2, 6, 10, or 16 mg)

BODY SYSTEM	PREFERRED TERM	Placebo (n=88)	Risp 2 MG (n=87)	Risp 6 MG (n=86)	Risp 10 MG (n=87)	Risp 16 MG (n=88)
	Oedema	0%	0%	0%	2.3%	0%
	Chest Pain	0%	1.1%	2.3%	1.1%	3.4%
	Fever	0%	1.1%	4.7%	0%	2.3%
Respiratory System Disorders						
	Rhinitis	4.5%	2.3%	12.8%	10.3%	6.8%
	Bronchitis	2.3%	0%	1.2%	0%	2.3%
	Coughing	1.1%	1.1%	7.0%	2.3%	2.3%
	Sinusitis	1.1%	0%	4.7%	2.3%	1.1%
	Dyspnoea	0%	0%	0%	3.4%	0%
	Pharyngitis	0%	1.1%	3.5%	2.3%	2.3%
Skin and Appendages Disorders						
	Rash, combined (includes rash, eczema, maculo-papular rash, skin exfoliation, dermatitis lichenoid, and uriticaria)	2.3%	2.3%	4.7%	3.4%	6.8%
	Rash	1.1%	1.1%	2.3%	2.3%	4.5%
	Seborrhoea	0%	0%	1.2%	2.3%	1.1%
	Skin Disorder	0%	1.1%	0%	1.1%	2.3%
	Skin Hypertrophy	0%	0%	0%	0%	2.3%
	Skin Dry	0%	2.3%	2.3%	2.3%	3.4%
Cardiovascular Disorders, General						
	Hypertension	2.3%	2.3%	0%	0%	1.1%
	Syncope	1.1%	0%	2.3%	1.1%	1.1%
	Hypotension Postural	0%	1.1%	2.3%	0%	1.1%
	Tachycardia	0%	1.1%	4.7%	4.6%	5.7%
	Arrhythmia	0%	0%	0%	0%	2.3%
	ECG Abnormal Specific	0%	2.3%	1.2%	0%	0%
Infections						
	Infection Fungal	3.4%	3.4%	0%	3.4%	2.3%
	Upper Resp Tract Infection	2.3%	1.1%	3.5%	3.4%	2.3%
	Infection	0%	3.4%	2.3%	0%	2.3%
Vision Disorders						

Appendix 8.5.1.1 Treatment Emergent Adverse Experiences in Protocol 204 (Reported by at Least 2% of Patients Treated with Risperidone 2, 6, 10, or 16 mg)

BODY SYSTEM	PREFERRED TERM	Placebo (n=88)	Risp 2 MG (n=87)	Risp 6 MG (n=86)	Risp 10 MG (n=87)	Risp 16 MG (n=88)
	Vision Abnormal	1.1%	2.3%	1.2%	0%	1.1%
	Conjunctivitis	0%	1.1%	1.2%	0%	2.3%
Laboratory Abnormalities						
	Creatine Phosphokinase Increased	1.1%	1.1%	0%	1.1%	2.3%
	Anaemia	0%	2.3%	0%	1.1%	2.3%
Reproductive Disorders, Male*						
	Ejaculation Disorder*	0%	0%	0%	0%	2.9%
Musculo-Skeletal System Disorders						
	Arthralgia	0%	2.3%	2.3%	3.4%	2.3%
Hearing and Vestibular Disorders						
	Earache	0%	0%	0%	2.3%	0%
	Ear Disorder NOS	0%	0%	0%	0%	2.3%
Platelet, Bleeding & Clotting Disorder						
	Epistaxis	0%	0%	0%	2.3%	1.1%
Urinary System Disorders						
	Urinary Incontinence	0%	0%	0%	0%	2.3%
	Urinary Tract Infection	0%	0%	0%	1.1%	2.3%
Reproductive Disorders, Female*						
	Dysmenorrhoea*	0%	0%	0%	8.3%	0%
	Mastitis*	0%	0%	0%	8.3%	0%
	Vaginitis*	0%	0%	0%	0%	5.6%

* GENDER SPECIFIC ADVERSE EXPERIENCES

Appendix 8.5.1.2 UKU symptom reports from Study 204

UKU symptom	Placebo incidence (n=88, 74M, 14F)	Ris 2 mg/d incidence (n=87, 72M, 15F)	Ris 6 mg/d incidence (n=86, 71M, 15F)	Ris 10 mg/d incidence (n=87, 75M, 12F)	Ris 16 mg/d incidence (n=88, 70M, 18F)
Psychic					
Sleepiness/sedation	15.9%	29.9%	33.7%	25.3%	40.9%
Increased Duration of sleep	8.0%	12.6%	27.9%	14.9%	19.3%
Increased dream activity	6.8%	18.4%	15.1%	13.8%	12.5%
Concentration difficulties	34.1%	25.3%	17.4%	19.5%	31.8%
Fatigue	26.1%	20.7%	31.4%	31.0%	42.0%
Failing memory	21.6%	16.1%	18.6%	16.1%	20.5%
Reduced duration of sleep	33.0%	37.9%	23.3%	31.0%	28.4%
Other	0	0	0	0	1.1%
Neurologic					
Parasthesias	6.8%	4.6%	3.5%	3.4%	10.2%
Other	1.1%	0	1.2%	2.3%	4.5%
Autonomic					
Accomodation disturbances	4.5%	10.3%	10.5%	12.6%	17.0%
Reduced salivation	8.0%	17.2%	9.3%	9.2%	12.5%
Nausea/vomiting	9.1%	18.4%	24.4%	20.7%	18.2%
Micturation disturbances	3.4%	12.6%	2.3%	6.9%	9.1%
Diarrhea	6.8%	5.7%	8.1%	8.0%	13.6%
Constipation	18.2%	16.1%	16.3%	14.9%	18.2%
Polyuria/polydipsia	11.4%	6.9%	12.8%	9.2%	15.9%
Orthostatic dizziness	14.8%	16.1%	24.4%	14.9%	36.4%
Increased sweating	9.1%	11.5%	8.1%	9.2%	10.2%
Palpitations/tachycardia	10.2%	13.8%	14.0%	25.3%	22.7%
Other	1.1%	2.3%	0	3.4%	5.7%

(continued) UKU symptom	Placebo incidence (n=88, 74M, 14F)	Ris 2 mg/d incidence (n=87, 72M, 15F)	Ris 6 mg/d incidence (n=86, 71M, 15F)	Ris 10 mg/d incidence (n=87, 75M, 12F)	Ris 16 mg/d incidence (n=88, 70M, 18F)
Miscellaneous					
Other	2.3%	2.3%	4.7%	5.7%	3.4%
Rash, all types	2.3%	10.3%	5.8%	8.0%	5.7%
Psychic dependence	2.3%	2.3%	2.3%	2.3%	1.1%
Physical dependence	0	0	1.2%	0	1.1%
Headache, all types	20.5%	34.5%	16.3%	24.1%	20.5%
Diminished sexual desire	6.8%	9.2%	9.3%	12.6%	14.8%
Increased sexual desire	12.5%	12.6%	14.0%	6.9%	12.5%
Galactorrhea	0	1.1%	1.2%	0	0
Amenorrhea	7.1%	0	6.7%	0	0
Gynecomastia*	1.4%	1.4%	1.4%	1.3%	0
Pruritus	5.7%	6.9%	8.1%	5.7%	6.8%
Photosensitivity	6.8%	2.3%	9.3%	3.4%	5.7%
Increased pigmentation	1.1%	1.1%	0	0	1.1%
Weight loss	15.9%	13.8%	11.6%	8.0%	5.7%
Weight gain	11.4%	20.7%	27.9%	28.7%	26.1%
Erectile dysfunction*	4.1%	2.8%	16.9%	6.7%	18.6%
Ejaculatory dysfunction*	5.4%	5.4%	18.3%	9.3%	18.6%
Orgastic dysfunction	2.3%	2.3%	8.1%	1.1%	11.4%
Menorrhagia*	0	6.7%	6.7%	8.3%	5.6%

*Gender specific incidence

Appendix 8.5.1.3 Other Events Observed During the Premarketing Evaluation of Risperidone
(Adverse Experiences listed in Appendix 8.5.1.1 are not repeated here.)

Psychiatric Disorders: Frequent: increased dream activity*, suicide attempt. Infrequent: impaired concentration, psychosis, depression, apathy, abnormal thinking, hallucination, delusion, paranoid reaction, decreased libido, euphoria, dreaming abnormal, increased libido, impaired psychomotor development, amnesia, neurosis. Rare: emotional lability, catatonic reaction, paroniria, delerium, withdrawal syndrome.

Central and Peripheral Nervous System Disorders: Frequent: increased sleep duration*, decreased sleep duration. Infrequent: ataxia, vertigo, stupor, speech disorder, paraesthesia, confusion, convulsions. Rare: grand mal seizures, dysphonia, hyporeflexia, aphasia, cholinergic syndrome, coordination abnormal, hypoaesthesia, tongue paralysis, leg cramps.

Gastro-intestinal Disorders: Frequent: reduced salivation*. Infrequent: dry mouth, diarrhea, increased appetite, melena, dysphagia, hemorrhoids. Rare: gastritis, stomatitis, fecal incontinence, eructation, flatulence, gastroesophageal reflux, gastroenteritis, esophagitis, ulcerative stomatitis, tongue discoloration, appendicitis, cholelithiasis, tongue edema, diverticulitis, gingivitis.

Body as a Whole/General Disorders: Frequent: fatigue. Infrequent: rigors, malaise. Rare: condition aggravated, peripheral edema, increased therapeutic response, allergy, influ nza-like symptoms, pallor, dependent edema, generalized edema, facial edema, enlarged abdomen, allergic reaction, ascites, substernal chest pain, therapeutic response decreased, precordial chest pain, leg edema.

Respiratory System Disorders: Infrequent: pneumonia. Rare: hyperventialtion, bronchospasm, respiratory disorder, asthma.

Skin and Appendage Disorders: Frequent: increased pigmentation*, photosensitivity*. Infrequent: diaphoresis, acne, decreased sweating, alopecia, hyperkeratosis. Rare: bullous eruption, pruritis, skin ulceration, psoriasis aggravated, skin exfoliation, nail disorder.

Cardiovascular Disorders: Frequent: orthostasis*. Infrequent: hypotension, palpitation, AV block, ventricular tachycardia. Rare: myocardial infarction, circulatory failure, angina pectoris.

Vision Disorders: Infrequent: abnormal accommodation, eye abnormality. Rare: xerophthalmia, diplopia, eye pain, blepharitis, photopsia.

Resistance Mechanism Disorders: Infrequent: viral infection. Rare: otitis media, bacterial infection, herpes simplex, abscess.

Metabolic and Nutritional Disorders: Infrequent: hyponatremia, weight increase, weight decrease. Rare: hypovitaminosis, decreased serum iron, thirst, cachexia,

dehydration, hypokalemia, hypoproteinemia, hyperphosphatemia, hypertriglyceridemia, diabetes mellitus.

Urinary System Disorders: Frequent: polyuria/polydipsia*. Infrequent: micturation disorder, renal insufficiency, urinary retention, polyuria, hematuria, renal pain, cystitis.

Musculo-skeletal System Disorders: Infrequent: myalgia. Rare: arthrosis, torticollis, synostosis, bursitis.

Reproductive Disorders, Female: Frequent: menorrhagia*, orgastic dysfunction*, dry vagina*. Infrequent: nonpuerperal lactation, amenorrhea. Rare: female breast pain, menorrhagia, leukorrhea.

Liver and Biliary System Disorders: Infrequent: abnormal hepatic function, increased SGPT. Rare: increased SGOT, hepatic failure, cholestatic hepatitis.

Platelet, Bleeding and Clotting Disorders: Rare: purpura, hemorrhage not otherwise specified, superficial phlebitis.

Hearing and Vestibular Disorders: Rare: tinnitus.

Red Blood Cell Disorders: Rare: hypochromic anemia.

Reproductive Disorders, Male: Frequent: erectile dysfunction*. Infrequent: impotence. Rare: prostatic disorder.

White Cell and Resistance Disorders: Rare: leukocytosis, lymphadenopathy, leucopenia, white blood cell abnormality not otherwise specified.

Application Site Disorders: Infrequent: inflammation at injection site, otitis externa, cellulitis.

Autonomic Nervous System Disorders: Frequent: diminished sexual desire*. Rare: flushing.

Endocrine Disorders: Rare: gynecomastia, male breast pain.

Neoplasm: Rare: carcinoma, myeloma.

Special Senses: Rare: taste perversion.

* incidence based on elicited reports; event was spontaneously reported by <2 patients in pooled safety database.

Appendix 8.5.2.1.1

Criteria for Identifying Patients With Potentially Clinically Significant Changes in Clinical Chemistry Variables

Lab Description	Low	High
Albumin (G/DL)	2.5	--
Alkaline Phosphatase (U/L)	--	420
BUN (MG/DL)	--	30
CPK (U/L)	--	3X ULN
Calcium (MG/DL)	7	12
Creatinine (MG/DL)	--	2
GGT (U/L)		
female	--	135
male	--	195
LDH (U/L)	--	1125
Phosphorus (MG/DL)	1.5	5.5
Serum Glucose (MG/DL)	45	250
SGOT (U/L)	--	150
SGPT (U/L)	--	165
Sodium (MEQ/L)	129	160
Total Bilirubin (MG/DL)	--	2
Total Protein (G/DL)	5	--
Uric Acid (MG/DL)		
female	--	8.5
male	--	10.5

Appendix 8.5.2.1.2
Proportions of Patients Having Potentially Clinically Significant Changes in Serum Chemistry Variables in Placebo-Controlled Studies 201 and 204

Blood Chemistry Variables	Risperidone			Placebo			Other Active		
	Total Patients	Abnormal		Total Patients	Abnormal		Total Patients	Abnormal	
		#	%		#	%		#	%
Albumin--Low	377	1	0.3	127	0	0.0	128	0	0.0
Alkaline Phosphatase-High	374	0	0.0	123	0	0.0	123	0	0.0
BUN-High	285	0	0.0	101	0	0.0	99	0	0.0
CPK-High	338	25	7.4	95	9	9.5	94	6	6.4
Calcium--Low	383	0	0.0	128	1	0.8	129	0	0.0
Calcium-High	383	1	0.3	128	0	0.0	129	0	0.0
Creatinine-High	384	0	0.0	130	0	0.0	130	0	0.0
GGT-High	365	2	0.5	118	0	0.0	123	2	1.6
LDH-High	330	0	0.0	118	0	0.0	120	0	0.0
Phosphorus--Low	357	0	0.0	112	0	0.0	114	1	0.9
Phosphorus-High	357	7	2.0	112	1	0.9	114	0	0.0
Serum Glucose--Low	377	2	0.5	128	1	0.8	129	2	1.6
Serum Glucose-High	377	1	0.3	128	1	0.8	129	1	0.8
SGOT-High	384	1	0.3	130	0	0.0	129	0	0.0
SGPT-High	370	4	1.1	124	0	0.0	129	0	0.0
Sodium--Low	383	0	0.0	130	1	0.8	131	1	0.8
Sodium-High	383	0	0.0	130	0	0.0	131	0	0.0
Total Bilirubin-High	380	1	0.3	128	1	0.8	129	1	0.8
Total Protein--Low	383	0	0.0	127	0	0.0	128	0	0.0
Uric Acid-High	349	3	0.9	118	0	0.0	119	0	0.0

Appendix 8.5.2.2.1

Criteria for Identifying Patients with Potentially Clinically Significant Changes in Hematology Variables

	LOW	HIGH
HGB (G/DL)		
Female	9.5	16.5
Male	11.5	18.5
HCT (%)		
Female	32	50
Male	37	55
RBC (million/CUMM)	3	6
White Blood Cells (thousand/CUMM)	2.8	16
Neutrophils (%)	15	--
Eosinophils (%)	--	10
Platelets (M/CUMM)	75	700

Appendix 8.5.2.2.2

Proportions of Patients Having Potentially Clinically Significant Changes in Hematology Variables in Placebo-Controlled Studies 201 and 204

Hematology Variables	Risperidone			Placebo			Other Active		
	Total Patients	Abnormal		Total Patients	Abnormal		Total Patients	Abnormal	
		#	%		#	%		#	%
Hemoglobin-Low	382	3	0.8	129	0	0.0	129	1	0.8
Hematocrit-Low	364	10	2.7	125	1	0.8	123	1	0.8
RBC-Low	382	0	0.0	128	0	0.0	129	0	0.0
Hemoglobin-High	382	2	0.5	129	1	0.8	129	1	0.8
Hematocrit-High	364	2	0.5	125	1	0.8	123	1	0.8
RBC-High	382	2	0.5	128	3	2.3	129	0	0.0
WBC-Low	382	3	0.8	127	0	0.0	129	1	0.8
WBC-High	382	3	0.8	127	1	0.8	129	2	1.5
Neutrophils-Low	335	1	0.3	99	1	1.0	100	0	0.0
Eosinophils-High	309	1	0.3	94	0	0.0	95	2	2.1
Platelet Count-Low	383	1	0.3	126	0	0.0	130	0	0.0
Platelet Count-High	383	0	0.0	126	0	0.0	130	0	0.0

Appendix 8.5.2.3.1
Criteria for Identifying Patients With Potentially Clinically Significant Changes in Urinalysis Variables

	LOW	HIGH
Specific Gravity	1.001	1.035
pH	4.6	8
Protein	--	INCREASE>=2
Ketone	--	INCREASE>=2
Glucose	--	INCREASE>=2
Red Blood Cells		
Female	--	>5
Male	--	>1
White Blood Cells	--	>5
Casts	--	INCREASE>=2

Appendix 8.5.2.3.2
Proportions of Patients Having Potentially Clinically Significant Changes in Urinalysis Variables in Placebo-Controlled Studies 201 and 204

Urinalysis Variables	Risperidone			Placebo			Other Active		
	Total Patients	Abnormal		Total Patients	Abnormal		Total Patients	Abnormal	
		#	%		#	%		#	%
Specific Gravity-Low	367	1	0.3	125	0	0.0	123	1	0.8
Specific Gravity-High	367	0	0.0	125	1	0.8	123	0	0.0
Ph--Low	357	0	0.0	124	0	0.0	121	1	0.8
Ph-High	357	0	0.0	124	0	0.0	121	0	0.0
Protein-High	294	0	0.0	99	0	0.0	101	3	3.0
Ketone-High	295	1	[illegible]	103	2	1.9	102	1	1.0
Glucose-High	316	1	0.3	115	1	0.9	114	2	1.8
RBC-High	53	2	3.8	20	2	10.0	29	2	6.9
WBC-High	94	6	6.4	45	5	11.1	49	4	8.2
Casts-High	12	0	0.0	7	0	0.0	9	0	0.0

Appendix 8.5.3.1 Criteria for Identifying Patients with Potentially Clinically Significant Changes in Vital Signs Variables		
	LOW	HIGH
SUPINE SYSTOLIC BP (mmHg)	<=90 MMHG and DECREASE>=20	>=180 MMHG and INCREASE>=20
STANDING SYSTOLIC BP (mmHg)	<=90 MMHG and DECREASE>=20	>=180 MMHG and INCREASE>=20
SUPINE DIASTOLIC BP (mmHg)	<=50 MMHG and DECREASE>=15	>=105 MMHG and INCREASE>=15
STANDING DIASTOLIC BP (mmHg)	<=50 MMHG and DECREASE>=15	>=105 MMHG and INCREASE>=15
SUPINE PULSE (BPM)	<50 BPM and DECREASE>=15	>120 BPM and INCREASE>=15
STANDING PULSE (BPM)	<50 BPM and DECREASE>=15	>120 BPM and INCREASE>=15
TEMPERATURE (°F)	---	101 F and INCREASE>=2

Appendix 8.5.3.2 Proportion of Patients Having Potentially Clinically Significant Changes in Vital Signs Variables in Placebo-Controlled Studies

Vital Signs Variables	Risperidone			Placebo			Active Control		
	Total Patients	Abnormal		Total Patients	Abnormal		Total Patients	Abnormal	
		#	%		#	%		#	%
Systolic, supine BP mmHg-Low	393	20	5.1	137	5	3.6	137	12	8.8
Systolic, supine BP mmHg-High	393	1	0.3	137	1	0.7	137	1	0.7
Diastolic, supine BP mmHg-Low	393	8	2.0	137	2	1.5	137	5	3.6
Diastolic, supine BP mmHg-High	393	3	0.8	137	2	1.5	137	4	2.9
Pulse, supine Bpm-Low	393	1	0.3	137	1	0.7	137	0	0.0
Pulse, supine Bpm-High	393	8	2.0	137	2	1.5	137	2	1.5
Syst. standing mmHg-Low	339	30	8.8	83	6	7.2	83	3	3.6
Syst. standing mmHg-High	339	4	1.2	83	0	0.0	83	0	0.0
Dias. standing mmHg-Low	339	10	2.9	83	0	0.0	83	2	2.4
Dias. standing mmHg-High	339	3	0.9	83	1	1.2	83	1	1.2
Pulse, standing Bpm-Low	339	0	0.0	83	0	0.0	83	0	0.0
Pulse, standing Bpm-High	339	35	10.3	83	2	2.4	83	3	3.6
Temperature (°F) - High	52	0	0.0	53	0	0.0	53	1	1.9

1 A patient may be classified into more than one category for each variable.

Appendix 8.8.1 Summary of Serious Adverse Events Occurring in Risperidone-Treated Patients and Considered Unlikely to be Drug-Related					
Study/Patient Number	Age (yrs)	Sex	Dose[1] (mg/d)	Duration (days)	Adverse Event
CARDIOVASCULAR EVENTS					
205/#689[2]	62	M	8	154[3]	Myocardial infarction
205/#691[2]	61	M	2	65	Myocardial infarction
GASTROINTESTINAL EVENTS					
RIS-BEL-6/#14	74	F	2	20	Gastric volvulus
205/#315	29	M	16	328	Appendicitis
INT-2/#361	47	M	16	15	Appendicitis
INT-2/#1879	28	M	1	15	Appendicitis
RIS-JPN-9003/#46	43	M	2	49	Gastric ulcer
INT-7/#0064	54	M	3	5	Dehydration
204/#403	31	F	2	1	Cholelithiasis
204/#292	60	M	6	28	Diverticulitis
PULMONARY EVENTS					
INT-2/#184	25	F	16	59	Pneumonia
INT-2/#337	19	M	4	56	Pneumonia
201/#125	36	M	5	6	Asthma attack
MISCELLANEOUS					
201/909	30	M	10	22	Flank pain/possible kidney stone

1 Dose taken at onset of adverse event
2 Not included in integrated safety database since adverse event occurred after the cutoff date
3 Includes days on double blind risperidone

Appendix 8.8.2
Summary of Serious Adverse Events Occurring in Control Group Patients (continued)

Study/patient number	Age (yrs)	Sex	Dose (mg/d)[1]	Duration (days)	Adverse Event
024/#2000	53	F	Hal. 10 mg	unspecified	Pneumonia
204/#207	33	M	Hal. 20 mg	52	Bladder catheterization
201/506	45	M	Placebo	9	Atrial fibrillation
210/#130	62	F	Placebo	6	Suicide attempt

1 Dose taken at onset of adverse event

Hardeman

REVIEW AND EVALUATION OF CLINICAL DATA

NDA 20-272
Sponsor: Janssen
Drug: Risperidone
Drug Category: Antipsychotic
Material Reviewed: NDA Safety Update
Date Submitted: October 28, 1993
Date Received: November 1, 1993

I. Background

Janssen submitted NDA 20-272 for risperidone on April 15, 1992. The clinical review of this application was completed May 11, 1993. The present submission is a safety update report on risperidone, which includes routine clinical data collected from 5/31/91 (the cutoff date for the NDA safety database) to 4/15/93. Janssen has also included deaths of patients on risperidone reported through 9/30/93, and foreign postmarketing data on serious adverse events through 8/31/93.

II. Additional Exposure Data

During the period 5/31/91 to 4/15/93, an additional 285 patients received risperidone in Phase II-III clinical trials. Together with the 2322 patients reported in the database for the NDA, this yields a total of 2607 patients exposed to ripseridone in clinical trials. Added safety data on 278 patients who continued to receive risperidone in open label use since the time of the original NDA database has also been included. In addition, since the original NDA submission 56 additional patients have received risperidone in Phase I clinical pharmacology trials.

The following tables present (by treatment group) the updated exposure in Phase I studies and in studies contributing data to Janssen's integrated safety database (which excludes Phase I data). A total of 101 new risperidone patients were administered risperidone in controlled Phase II-III trials; the remaining 184 new risperidone patients received open label treatment.

Patients in Phase I Clinical Trials

Drug Treatment	Phase I through 5/31/91	Phase I 5/31/91-4/15/93	Total
Risperidone	175	56	231
Active Control	7	0	7
Placebo	6	0	6

Patients in Integrated Database Phase II-III Clinical Trials

Drug Treatment	Through 5/31/91	5/31/91-4/15/93	Total
Risperidone	2322	285	2607
Active Control	533	88	621
Placebo	176	19	195

Patient Exposure Years in Integrated Database Phase II-III Clinical Trials

Drug Treatment	Through 5/31/91	5/31/91-4/15/93	Total
Risperidone	508	350	858
Active Control	61	10	71
Placebo	13	2	15

The following table presents updated demographic information for patients in the integrated safety database of the sponsor. It should be noted that no patients under age 15 have been exposed to risperidone, either in the original NDA trials or the post-NDA studies. Within each category, percentages are based on the total number of patients with data.

Demographic Profile for Phase 2 and 3 Studies Through 4/15/93			
	Risperidone (N=2607)	Placebo (N=195)	Haloperidol (N=459)*
AGE (years)			
N	2486	161	429
Mean	39	43	38
Range			
≤44 Years	72%	67%	ns
45-64 Years	25%	20%	ns
≥65 Years	3%	13%	ns
SEX: Male	66%	74%	71%
Female	34%	26%	29%
RACE: White	78%	63%	75%
Non-white	22%	37%	25%

*The sponsor did not provide updated demographic data for other active controls.

The table below depicts the updated exposure to risperidone in the integrated safety database by dose and duration of treatment, for all patients having dosage information. In comparison to the original NDA database, there is now data on a larger number of patients receiving long term risperidone therapy. This is also reflected in the fact that from 5/31/91 to 4/15/93, patient-years of exposure to risperidone increased from 508 to 858 years, while only 285 additional patients received risperidone for the first time.

Number of Patients Receiving Risperidone According to Mean Daily Dose and Duration of Therapy in Phase 2 and 3 Studies Through 4/15/93 (N =2590)

Duration (Days)	≤2mg	2<mg≤6	6<mg≤10	>10mg	TOTAL	(%)
1-21 Days	67	110	78	70	325	(12)
22-49 Days	62	306	153	113	634	(25)
50-64 Days	160	225	194	288	867	(33)
65-274 Days	14	73	113	82	282	(11)
≥275 Days	29	128	158	167	482	(19)
TOTAL	332	842	696	720	2590	(100)
(%)	(13)	(32)	(27)	(28)	(100)	

In addition to the added exposure in clinical trials outlined above, the sponsor estimates that worldwide some 8000 patients have received risperidone either as marketed drug or on a compassionate use basis.

III. Safety Findings from Safety Update

A. Deaths in clinical trials

The table below presents a summary of deaths among risperidone treated patients in clinical trials subsequent to the original NDA submission. None of the deaths appears to be causally related to risperidone treatment. Two of the deaths were suicides, a topic discussed below.

Summary of Deaths Occurring in Risperidone-treated Patients in Clinical Trials (post-NDA)

Study/Pt. No.	Age(yrs)	Sex	Dose (mg/d)	Duration (days)	Cause of Death and Comments
RIS-USA-08** #405	26	M	?	39	Suicide-self inflicted gun shot wound
RIS-FIN-9001 #117*	22	M	6	7	Acute viral myocarditis one month post treatment
RIS-USA-9005 #1001*	41	M	16	270	Suicide-desipramine intoxication
RIS-INT-2/INT-4 #2166/(52)*	53	M	2-6	78	Cancer of bronchus 3 months post treatment

*Patient included in post-NDA integrated safety database **Ongoing study, blind not yet broken

In addition, two deaths reported in the NDA but not included in the original integrated safety database have now been added to the updated safety database (patient 39 in study 029, and patient in study INT-4).

The mortality by treatment group in the integrated safety database, incorporating the post NDA data, is given in the following table.

Drug	Number of Patients	Patient years of exposure	Deaths	Crude mortality	Mortality/ 100 Patient Years
Risperidone	2607	858	15	0.0058	1.7
Active Controls	621	71	1	0.0016	1.4
Placebo	195	15	0	0	0

It will be seen that although the crude mortality was highest in the risperidone treatment group, when corrected for duration of exposure the mortality in the risperidone and the active control groups are similar. This is consistent with the findings in the original NDA database. Thus risperidone treatment does not appear to be associated with excess mortality in clinical trials.

B. Safety Update Data on Premature Discontinuations

Overall Pattern of Dropouts

The table below presents the updated listing of premature discontinuations from clinical trials by treatment group and reason.

Rates of Dropout by Treatment Group and Reason for Pooled Phase II-III Database
NDA and Post-NDA Data Combined

	Percent Dropping Out		
Reason for Dropout	Risperidone (N=2607)	Placebo (N=195)	Active Control (N=533)
Inadequate Response	15.3%	38.5%	12.6%
Adverse Experiences	9.4%	6.2%	11.4%
Asymptomatic/Sufficient Response	0.6%	0%	0.2%
Non-Treatment Related	12.6%	8.7%	10.2%
Total Dropouts	37.9%	53.4%	34.3%

Adverse experiences also includes intercurrent illnesses, abnormal lab results, and patient death. Non-treatment related includes patient moved, chose to discontinue, lost-to-follow-up, uncooperative, ineligible, and other reasons. Inadequate response also includes deterioration of symptoms. Chose to discontinue also includes patient moved.

As in the original NDA data, the placebo group had the highest rate of discontinuation for inadequate response, while the two drug groups had higher rates of discontinuation for adverse events.

Adverse Events Associated with Dropout: Updated data

The following table lists all those adverse experiences that were associated with ≥ 0.3% of risperidone patients discontinuing the drug, combining NDA and post-NDA data. Placebo rates for the same adverse experiences are shown for comparison. Some data is missing, since the sponsor did not designate the adverse event resulting in discontinuation for 0.8% of risperidone patients or 1.0% of placebo patients. For these cases, this reviewer assigned an adverse event leading to premature discontinuation wherever possible using information available from case report forms or narrative case summaries; 14 risperidone patients were assigned reasons for premature discontinuation by this method.

	Percentage of patients dropping out	
Reason	Placebo (n=195)	Risperidone (n=2607)
Extrapyramidal symptoms	0.0%	2.1%
Suicide attempt	0.5%	1.2%
Dizziness	0.0%	0.7%
Hyperkinesia	0.0%	0.6%
Agitation	0.0%	0.5%
Somnolence	0.0%	0.5%
Aggressive Reaction	0.0%	0.4%
Psychosis	0.0%	0.3%
Fatigue	0.0%	0.3%
Nausea	0.0%	0.3%
Insomnia	0.0%	0.3%
Anxiety	0.0%	0.3%

C. Search for Emergence of Suicidality

Two additional suicides of patients receiving risperidone in clinical trials (patient in study 207, and patient in study 202) have been reported in the safety update. One of these (patient in study 202) has been included in the post NDA integrated safety data base; in addition, another suicide reported in the original NDA as being too recent to be included in the integrated safety database has now been added (patient in INT-4). With these data it is possible to update the incidence of completed suicide among risperidone paitents in the integrated safety database, as shown below.

Drug	Number of patients	Patient years of exposure	Suicides	Crude Rate	Suicides per 100 Patient Years
Risperidone	2607	858	9	0.0035	1.0
Active Controls	621	71	1	0.0019	1.7
Placebo	195	15	0	0	0

Here again, the crude incidence is highest for risperidone patients, but when duration of exposure is accounted for the risperidone rate is comparable to the active control group.

Similarly, the sponsor has provided updated reports of suicide attempts in risperidone clinical trials. Here, suicides and all other kinds of self destructive behaviors are combined in a single category denoted as suicide attempts. Combined post-NDA and original NDA data is shown in the following table. (I have included an additional case from the original NDA, patient 53 in BEL-11, since a review of the newly translated case report form submitted by Janssen indicates that the patient was mutilating himself.)

Drug	Number of patients	Patient years of exposure	Suicide attempts	Crude Incidence	Suicide attempts per 100 Patient Years
Risperidone	2607	858	43	0.016	5.0
Active Controls	621	71	5	0.008	7.0
Placebo	195	15	0	0	0

Again, the crude incidence is highest in the risperidone patient group but when adjusted for length of exposure the rates are similar between risperidone and active controls. The placebo group had a much shorter duration of exposure, and the absence of suicide attempts is therefore not inconsistent. On balance, risperidone treatment dose not appear to be associated with increased self destructive behavior in clinical trials.

Regarding depression, which often occurs in association with self destructive behavior, in the post NDA period an additional four patients discontinued treatment with risperidone due to depression. This yields a total of 7 patients out of 2607 (0.27%) who discontinued risperidone due to depression; for active control patients the corresponding figure is 1/621 (0.16%). If corrected for duration of exposure, the incidence of discontinuation for depression is 0.8% per year for risperidone and 1.4% per year for active controls.

D. Premature discontinuations and serious adverse events

The sponsor provided premature discontinuation summaries and case report forms for patients who withdrew from integrated database clinical trials after the cutoff for the original NDA. Janssen also provided narrative case summaries for patients suffering serious adverse events who either did not discontinue treatment or were never in a clinical trial; however, no case report forms were available for these patients. (No narrative case summaries were provided for four patients who discontinued prematurely and were not in the integrated database; the reasons listed in the sponsor's table of premature discontinuations were exacerbation of psychosis, increased insomnia, and insufficient response (2 patients)).

The above information regarding serious adverse events and adverse events leading to premature discontinuations was reviewed with special attention to (1) adverse events not previously reported in the original NDA, and (2) further data on adverse events listed as important and possibly drug related in the original NDA review.

Premature Discontinuations

In their summary accompanying the safety update, Janssen reported that the only reasons for patients discontinuing risperidone in the post-NDA integrated safety data base that were not previously observed were the folowing: antidiuretic hormone disorder and aspiration (INT-4 patient), GI hemorrhage (INT-4 patient), and thrombocytopenia (INT-4 patient . These cases were reviewed. The patient with GI hemorrhage experienced esophagitis following an overdose of acetylsalicylic acid, and in my view is more properly regarded as a dropout for a suicide attempt. The patient listed with thrombocytopenia was actually described on the case report form as discontinuing due to headace and siallorhea; the patient did have a decreased platelet count of 78 giga/L at the time of discontinuation, but the significance of this is questionable since his baseline platelet count was also low (84 giga/L). The case of antidiuretic hormone disorder and aspiration involved a schizophrenic patient who appears to have become hyponatremic and went into a coma; from the information available it is not clear that psychogenic polydipsia was ruled out, although it is known to be common among schizophrenic patients. This patient recovered.

In addition to these three cases, my review disclosed a patient listed as discontinuing with hearing loss, a previously unreported reason for discontinuation (patient in study 033); this was a subjective complaint noted only at the final study visit, however, and was never documented objectively. Manic reaction was also newly reported as a reason for discontinuation from risperidone; the case was not included in the integrated safety database because the study is still in progress (paitent in study 208). As this is the only known case of mania associated with risperidone, a more likely explanation than drug-induced mania is that the patient's original diagnosis of schizophrenia was in error.

The sponsor also compiled summary tables of adverse events and premature discontinuations from pharmacokinetics trials and from trials reported in the literature that were not part of the integrated safety data base. Although narrative case summaries were not provided for these patients, no previously unknown adverse events appeared in these listings.

The remaining narrative case summaries for premature discontinuations disclosed no significant new safety information. On balance, the adverse events described in the safety update as leading to premature discontinuation from risperidone do not materially affect the original NDA safety assessment.

Serious Adverse Experiences

Janssen supplied case summaries for patients experiencing serious adverse events in association with risperidone treatment. These cases were drawn from clinical trials, compassionate use, and foreign postmarketing reports. For the purpose of this review I will discuss all of these reports here in this section.

There was one report of hypoglycemia resulting in a one day hospitalization (patient in study 205). The patient was not diabetic. Hypoglycemia had not been previously reported with risperidone treatment.

While on compassionate use risperidone, a 28 year old female Canadian patient (IND safety report 9/21/93) developed jaundice, fever, bruising and thrombocytopenia. She was diagnosed with thrombotic thrombocytopenic purpura (TTP), and despite a stormy course eventually recovered after receiving plasmapheresis. To give a sense of the number of patients out of which this arose, this event ocurred in March 1993; as of 4/8/93 Janssen reported that there were a total of 587 compassionate use risperidone patients in Canada. The sponsor believes this may be a drug related adverse experience, as the patient did not have a recent viral illness, lupus, or exposure to other drugs except benztropine. TTP has not been reported with risperidone previously but has been associated with exposure to other drugs (for example, see the package insert for ticlopidine).

A middle cerebral artery infarct was reported in a 44 year old male receiving compassionate use risperidone (IND safety report 9/29/93); no cerebral vascular accidents were reported in the original NDA.

Other events in the sponsor's compilation of serious adverse experiences since the NDA were the following: seizures (7 patients); suicide attempt, increased CPK with dizziness, endometrial carcinoma, cholelithiasis, syncope and postural hypotension in a patient with preexisting cardiac disease, and myocardial infarction (1 patient each).

Overdose

An additional case of overdose on risperidone is described in the safety update. The report comes from Canada, where the patient was receiving marketed drug. The patient, a 38 year old female, took an overdose of 36 mg risperidone and 375 mg chlordiazepoxide and developed seizures. The patient's heart rate elevated to 160 beats per minute during the seizures, although her EKG reportedly remained normal. Follow up information on the patient's outcome is not yet available.

Another postmarketing report of overdose was received from Great Britain; the amount ingested was merely 20 mg of risperidone as a result of a prescribing error. The patient experienced tachycardia and pruritus.

Pregnancy

A congenital defect has been reported in a infant exposed to risperidone prenatally (IND safety report 10/25/93). The infant was born without a corpus callosum; the mother had taken risperidone for six days during her fourth month of pregnancy. Numerous other medications were also administered to the mother during the pregnancy. While the fourth month is roughly the time that the corpus callosum develops in the human fetus, this congenital defect is generally not attributed to prenatal toxin exposure; possible etiologies include maternal rubella, chromosomal abnormalities, and familial predisposition. In rodents the lesion has been produced by trypan blue injections during gestation, irradiation, and maternal riboflavin deficiency (Warkany, Congenital Malformations).

In my view, of the serious adverse experiences described in the safety update, most are either unlikely to be drug related or represent adverse drug reactions already documented in the original NDA. An exception is the case of TTP, which may possibly be drug related. Additionally, seizures following overdose on risperidone have not been described previously.

E. Adverse Drug Reaction Incidence

The post-NDA data base contains data from placebo controlled trials on 101 risperidone patients and 19 placebo patients. In my opinion, consideration of this data would not add any useful information on common adverse events, since the number of patients involved is small compared to the studies already reviewed in the original NDA submission.

F. Laboratory Findings

Additional cases of premature discontinuations or serious adverse events involving clinical laboratory findings reported in the safety updat have been described above. Janssen calculated revised incidences of laboratory abnormalities from the post NDA data; however, the utility of these revised figures is doubtful since they include very little additional placebo controlled data. Laboratory abnormalites of possible clinical significance, ocurring at an incidence of greater than 4% in the post-NDA patients, included low hematocrit, elevated eosinophils, hypokalemia, and elevated CPK. Regarding the latter, elevations of CPK have been associated with acute psychosis (Meltzer, J Psychiat Res 10:43-57, 1973). Lack of a meaningful comparison group makes interpretation of these findings difficult. Please refer to the original NDA review for an examination of clinical laboratory findings from placebo controlled trials, which are more readily interpretable.

G. Vital Signs and Weight

Of the integrated safety database patients who discontinued treatment after the original NDA, only one discontinued for a change in vital signs: patient in study 9001 discontinued with postural hypotension. Janssen provided revised incidences for vital sign abnormalities in clinical trials, but in my opinion this data is not as meaningful as the data from placebo

controlled trials reviewed with the original NDA. The most common findings were changes consistent with postural hypotension, reduction in supine blood pressures, and weight increase.

F. Electrocardiograms

In the post-NDA period, no integrated safety data base patients discontinued risperidone due to an abnormal EKG. Abnormally increased QTc was reported in 22/267 (8.2%) of post-NDA patients, and decreased PQ interval was reported in 31/220 (14.1%) of post NDA patients. Of these, the finding with more potential clinical importance is the increase in QTc, which will be considered further here.

If one pools all double blind treated patients in the integrated database, 35/1271 (2.8%) of risperidone patients developed increased QTc, compared to 0/132 placebo patients. For comparison, the incidence of among haloperidol treated patients in double blind trials was 9/343 (2.6%); the current Haldol labeling does describe QT prolongation under adverse events. It should be recalled that these data come from a pooling of studies and that conditions across treatment groups are not necessarily comparable. The data from individual studies is not consistent regarding this possible EKG effect, as was discussed in the original NDA safety review. Thus, although some of the data suggests that risperidone may prolong the QTc, in my view this cannot be a definitive conclusion.

G. Additional information on important drug related adverse events

The original NDA review discussed several important adverse events that were considered possibly or probably drug related. The safety update was reviewed for additional pertinent information on these adverse events, which will be presented here.

Neuroleptic Malignant Syndrome

No new cases were reported.

Tardive Dyskinesia

No additional relevant information was reported. It is apparently still true that risperidone has never been implicated as the sole cause of any patient's tardive dyskinesia.

Postural Hypotension and Syncope

There were 2 additional premature discontinuations for dizziness (study 9001, patient study BEL-19, patient and one for postural hypotension (study 9001, patient . No additional cases of syncope were reported.

Seizures

In the post NDA integrated safety data, there were 2 additional cases of seizure reported (study 204, patients . With the 5 cases from the original NDA, this gives an incidence of 7/2607 (0.26%). Corrected for

duration of exposure, the incidence is 7/858 patient-years, or 0.82% per year.

Rash

No additional patients had to discontinue risperidone due to rash.

Edema

No additional patients discontinued risperidone due to edema.

Prolactin Elevation

There was no additional information on this finding.

Priapism

No additional cases were reported.

Extrapyramidal Symptoms

An additional 17 risperidone patients were listed by the sponsor as discontinuing for extrapyramidal symptoms. Comparative data to placebo has been discussed in the original NDA review.

Sedation

Two additional patients were listed as dropping out for somnolence.

Tachycardia

There were no additional dropouts for this adverse event.

EKG changes

Please refer to the discussion above.

Liver enzyme elevation

There were no additional reports of premature discontinuations or serious adverse events involving elevated transaminases.

H. World Literature

The sponsor submitted a worldwide clinical bibliography lising all publications on risperidone that were not included in the original NDA. Janssen has been asked to supply copies of these references for review. Dr. David Jackson from Janssen reports that there are no findings in the literature that would adversely affect conclusions regarding the safety of risperidone.

IV. Conclusions and Recommedations

Review of the data in the safety update indicates that risperidone is reasonably safe when used as an antispychotic. Adverse events not previously reported in the NDA include the following: manic reaction, hearing loss, hypoglycemia, thrombotic thrombocytopenic purpura (TTP), cerebral vascular accident, and congenital absence of the corpus callosum. Seizure following risperidone overdose was also reported for the first time. Of these adverse events, in my opinion the one of most significance in terms of both severity and possible relationship to risperidone use is the case of TTP. The apparent high incidence of prolonged QTc in the post NDA patients is of potential concern, although this finding is not borne out consistently by data from the controlled trials.

Andrew Mosholder MD 11/7/93

Andrew Mosholder, MD
Division of Neuropharmacologic Drug Products

Orig. NDA 20-272
HFD-120 Div. File
HFD-120 TLaughren/SHardeman/AMosholder

Hardeman

REVIEW AND EVALUATION OF CLINICAL DATA

NDA 20-272
Sponsor: Janssen
Drug: Risperidone
Drug Category: Antipsychotic
Material Reviewed: NDA Safety Update World Literature Bibliography
Date Submitted: November 16, 1993
Date Received: November 18, 1993

Janssen submitted copies of all the available world literature on clinical use of risperidone. Much of the data from these publications, manuscripts and abstracts has been included in the integrated safety data base for risperidone, which was the subject of the safety update. Some of this literature reports on data from studies submitted with the original NDA. The literature submitted was reviewed for information that would materially affect the safety assessment of risperidone. Briefly stated, there were no unexpected safety findings from the literature reviewed. A similar conclusion was reached by Dr. David Jackson of Janssen, who reviewed the world literature and determined that there were no findings which would adversely affect conclusions regarding the safety of risperidone. Several reports contained new data that are worthy of further description, pertaining to certain adverse drug reactions. They will be briefly presented in this review. Citations are given by the sponsor's numbering system.

Several reports dealt with the safety profile of poor versus extensive metabolizers of risperidone, a typology corresponding to individual variations in CYP2D6 function. In study N98704, pharmacokinetic data from the Phase III trial 204 was examined to identify 212 extensive metabolizers and 9 poor metabolizers were identified. There were no important adverse events unique to the poor metabolizer group. Similarly, in study N98703 the sponsor identified 307 extensive metabolizers and 43 poor metabolizers in trial 024. Again, there were no remarkable differences in adverse events between the two metabolic categories. Study N98705 employed pharmacokinetic data from open long term trials to distinguish 159 extensive metabolizers and 18 poor metabolizers; again, there were no important differences in adverse events. All of these studies are limited, or course, by the relatively small number of poor metabolizers available for comparison. Nonetheless, the sponsor had not previously examined potential safety differences arising from metabolic status.

Study N98702 was a clinical pharmacology trial pertinent to the issue of metabolic differences. In this study, 9 healty males (6 extensive metabolizers and 3 poor metabolizers) were administered single oral doses of risperidone 1 mg, 9-OH-risperidone 1 mg, or placebo. Metabolic status did not appear to materially affect the adverse event profile. Of the two active drugs, 9-OH-risperidone appeared to be the more sedative.

Study N96431 examined the tolerability of risperidone in geriatric paitents. Here, 14 patients aged 68-90 received a single 1 mg dose of risperidone followed by 1 mg/day for 10 days. Decreased blood pressure was the most consistent safety finding. In addition, two patients developed premature supraventricular contractions and one patient developed first degree heart block with premature ventricular contractions.

Two reports dealt with interactions with other drugs via CYP2D6. In N96327, 11 extensive metabolizers were administered risperidone with concomitant quinidine, resulting in prolonged t½ for risperidone and reduced AUC for 9-OH-risperidone. This confirms results from in vitro experiments which predicted a reduction of risperidone metabolism by compounds inhibiting CYP2D6. In study N97249, 24 patients were administered risperidone 6

mg/day for 14 days. This produced no change in the subjects' metabolic ratio for dextromethorphan. This result is in agreement with the results of in vitro studies, which did not predict inhibition of CYP2D6 by risperidone.

Also in this submission is a report on protocol 033, which involved long term open label risperidone treatment of chronic schizophrenia. Many of the subjects had participated in a double blind risperidone trial. A total of 386 patients (253 male and 133 female) were treated for up to 12 months. This study contributed considerable data on long term exposure to risperidone which was incorporated in the safety update. In terms of comparisons to baseline for parameters such as laboratories, EKGs, and vital signs, the data is not of much utility, however; baseline measurements were taken while many patients were already receiving risperidone at the conclusion of their double blind trials, so that drug free baseline measurements were not obtained. There were no alarming findings about these parameters, although it did appear that risperidone use was associated with slight mean increases in serum glucose, CPK, and RBCs in the urine; decreased conjugated bilirubin, platelets, WBCs; and increases in body weight. Changes in vital signs were generally small; however, as noted above, the baseline measurements were often not made in a drug free condition. Overall, these findings are of doubtful significance in my opinion, except for the weight gain which has been noted previously.

In summary, the literature submitted by the sponsor clarified certain safety issues, as noted above. In my opinion, no reports contained in this literature would necessitate revision of the previous safety findings concerning risperidone.

MD 11/30/93

Andrew Mosholder, MD
Division of Neuropharmacologic Drug Products

orig. NDA 20-272
HFD-120 Div. File/TLaughren/SHardeman/AMosholder

12-3-93

Temple

M E M O R A N D U M

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: December 20, 1993

FROM: Thomas P. Laughren, M.D. TPL
Group Leader, Psychiatric Drug Products
Division of Neuropharmacological Drug Products
HFD-120

SUBJECT: Recommendation for Approval Action for Risperdal (risperidone)

TO: File NDA 20-272
[**Note:** This overview should be filed with the 4-15-92 original submission.]

1.0 BACKGROUND

Risperidone is a benzisoxazole derivative proposed for use as an antipsychotic; it is structurally different from marketed antipsychotic drugs. It is also pharmacologically different from marketed antipsychotics with respect to its $5HT_2$ antagonism, with the exception of clozapine. Pharmacologically, it can be characterized primarily as a $5HT_2$ and D_2 antagonist, but it also antagonizes alpha 1, alpha 2, and H_1 receptors. The sponsor believes that risperidone may have advantages over some marketed antipsychotics with regard to (1) extrapyramidal symptoms and (2) negative symptoms of schizophrenia.

IND for risperidone was originally submitted 8-9-88. It should be noted that the sponsor never requested an End-of-Phase 2 meeting. We held a pre-NDA meeting with the sponsor on 8-29-91. The focus of this meeting was on clinical data, particularly on analysis of the efficacy data and on format and content of an integrated safety summary.

The risperidone NDA was originally submitted 4-15-92 and was the subject of a 4-29-93 meeting of the PDAC. The Committee voted unanimously that risperidone is effective for the proposed indication and also reasonably safe. Risperidone was discussed a second time at a 7-20-93 meeting of the PDAC; in particular, there was a discussion of the rodent carcinogenicity data for risperidone. The Committee was satisfied with the Division's approach to addressing these findings in labeling (see Pharmacology comments--#3).

A meeting was held with the sponsor on 12-7-93 to try to reach agreement on labeling prior to approval of this product. While we were able to reach agreement on most issues in labeling, we were unable to agree on the issue of whether or not data on haloperidol, the active control used in the three critical studies, should be included in labeling. Consequently, the labeling we have included with the approval package is labeling that we feel is appropriate for this product and does not have the concurrence of the sponsor with regard to haloperidol data. I will elaborate on this issue under section 10.1 of this memo.

2.0 CHEMISTRY

Proposed Name

The proposed proprietary name, i.e., 'Risperdal,' continues to be unacceptable to the Labeling and Nomenclature Committee, apparently because it contains too much of the generic name. However, the USAN rationale for discouraging brand names that are too similar to the generic name is to prevent problems in adopting appropriate nonproprietary names for closely related drugs. Since it is the suffix rather than the prefix that is likely to be important in this regard, I don't think this is a sufficient argument for objecting to the proposed name. Consequently, I recommend that we accept the proposed name Risperdal.

Establishment Inspection

There is apparently a field report recommending against approval on the basis of certain inspection findings. While it is my impression from our chemistry group that the deficiencies may not be substantial and need not hold up approval, this issue is not yet resolved at this time.

Environmental Assessment

A review of the sponsor's 8-16-93 response to the EA deficiencies has not been completed as of the date of this memo.

3.0 PHARMACOLOGY

The most visible pharm/tox issue that needed resolution prior to issuing an approvable letter was a concern about carcinogenicity findings. Subsequent to the 4-29-93 meeting of the PDAC for risperidone, we became aware of differences between risperidone and several other antipsycotic drugs marketed in the US in the profile of endocrine tumors in rodent bioassays. While it is not unexpected to see an increase in endocrine tumors in these bioassays for antipsychotic drugs, of particular concern was the finding of adenocarcinomas in rats (both sexes) and mice (only

females, but there was a question of dose adequacy for the male mouse study). Since the issue had not been discussed at the April 29th PDAC meeting, we decided to reschedule risperidone for the meeting planned for July 20th. In the meantime, the issue was presented to the full CAC on 6-21-93. This committee, while acknowledging that the pattern of findings differed for risperidone from other antipsychotic drugs marketed in the US (and for which we have data), still considered the tumors to be prolactin related and of unknown significance for human tumor production. Consequently, they concluded unanimously that this concern could be addressed through product labeling by stating the findings for risperidone and indicating that the relevance for human risk is unknown. Since the issue had been largely resolved internally before we brought it back to the PDAC, we presented it more as a point of information, along with our plan for addressing the concern, rather than as an issue requiring a specific vote by the committee. The PDAC discussed the issue at length, but in the end, was satisfied with our plan to address the concern in labeling.

The pharmacology group proposed substantial changes to the pharm/tox sections of labeling and these proposed changes have been incorporated into the final labeling that accompanies the approval letter. We will include a statement in the approval letter indicating what additional data would be needed to obtain a change in the pregnancy category from C to B.

4.0 BIOPHARMACEUTICS

Summary of Risperidone Pharmacokinetics

Risperidone is well absorbed and extensively metabolized in the liver to 9-hydroxy-risperidone, which appears to have similar pharmacological activity to the parent drug. Consequently, the clinical effect of the drug most likely results from the combination of risperidone plus 9-hydroxy-risperidone. The absolute bioavailability of risperidone is approximately 70%. There is no food effect. Protein binding for risperidone is about 90% and for 9-hydroxy-risperidone, about 77%. Risperidone, its metabolite, and the combination of parent and metabolite have linear PK over the 1 to 16 mg dosing range. The elimination half-life of risperidone is about 3 hours in extensive metabolizers and about 20 hours in poor metabolizers. The elimination half-life of 9-hydroxy-risperidone is about 21 hours in extensive metabolizers and about 30 hours in poor metabolizers.

Metabolism of risperidone is by hydroxylation (via P450IID6) to 9-hydroxy-risperidone, and then oxidative N-dealkylation. While poor metabolizer status and inhibition by other drugs may result in altered parent/metabolite ratios, the pharmacological similarity of parent and metabolite probably diminishes the importance of this potential problem. In addition, risperidone is only a weak

inhibitor of IID6, thus, it is unlikely that risperidone will interfere with the metabolism of other drugs metabolized by IID6. Nevertheless, the potential for interaction has not been tested in vivo, and we will ask for at least one in vivo study for confirmation. In fact, the sponsor has done no formal drug interaction studies. Three patients receiving carbamazepine in combination with risperidone were found to have about a 50% increase in the clearance of risperidone. One patient receiving clozapine in combination with risperidone was found to have about a 50% decrease in the clearance of risperidone. Pharmacodynamic interactions that might be predicted include (1) enhancement of the effect of antihypertensives, and (2) antagonism of levodopa and other dopamine agonists.

Clearance of risperidone was decreased by about 60% in patients with renal impairment and about 40% in the healthy elderly. While the PK of risperidone was not altered in hepatically impaired subjects, the mean free fraction was increased by about 35%.

Labeling and Other Issues

We have made substantial changes to the proposed PK statements for labeling. We are granting bio-waivers for the 3 and 5 mg tablets and for the two manufacturing sites. The approval letter will include a recommendation for interim dissolution specs along with a request for additional dissolution data to permit setting of more appropriate specifications. Several other general comments will be included in the approval letter.

5.0 CLINICAL DATA

5.1 Efficacy Data

The efficacy data for risperidone were reviewed by Dr. Andrew Mosholder, the clinical reviewer, and by Dr. David Hoberman, the statistical reviewer. The have both reached the conclusion that risperidone has been demonstrated to be effective in the short-term treatment of schizophrenia, and I agree with that conclusion.

This conclusion was derived from three 6-8 week studies of schizophrenic inpatients . All three were double-blind, randomized, parallel group, multicenter studies. In this brief summary, I have focused on the following efficacy variables: BPRS total score, BPRS psychosis cluster, CGI severity, SANS, and PANSS Negative Symptoms scores. I have not included data on percent improvement since the sponsor's measure is idiosyncratic both in definition and in the method of calculation. To my knowledge, there is no general acceptance of this measure in the psychopharmacology community.

1. Study 201 (n=160) was a 6-week, placebo-controlled dose titration study involving risperidone doses up to 10 mg/day and haloperidol doses up to 20 mg/day (all dosing on BID schedule). In fact, most patients in this trial were dosed at the maximum allowable doses. This trial demonstrated superiority for both active drug groups over placebo on the BPRS total score and on the BPRS psychosis cluster (conceptual disorganization, suspiciousness, hallucinatory behavior, unusual thought content). The results on the SANS (Scale for Negative Symptoms) were more marginal, but tended to suggest superiority for risperidone over placebo; the haloperidol effect size was approximately the same as for risperidone, but just missed statistical significance. . There were no statistically significant differences revealed by pairwise comparisons between risperidone and haloperidol for any of the efficacy measures at any time points for either LOCF or OC analyses.

2. Study 204 (n=513) was an 8-week, placebo-controlled, fixed dose study involving 4 fixed risperidone doses (2, 6, 10, and 16 mg/day) and haloperidol at a fixed 20 mg/day dose (all dosing on BID schedule). This trial generally demonstrated superiority for all risperidone groups and haloperidol over placebo on the BPRS total score, on the BPRS psychosis cluster, and on the CGI. The three highest risperidone groups (but not risperidone 2 mg and not haloperidol 20 mg) were generally superior to placebo on the PANSS (Positive and Negative Symptoms Scale) negative subscale. The maximum effect for all variables was seen for the 6 mg risperidone group, with no apparent enhancement at doses above 6 mg. In addition, Risperidone at 6 mg was also superior to haloperidol 20 mg on all 4 variables.

3. Study 024 (n=1356) was an 8-week, dose comparison trial involving 5 fixed doses of risperidone (1, 4, 8, 12, and 16 mg/day) and haloperidol 10 mg/day (all dosing on BID schedule). This trial generally demonstrated superiority for the 4, 8, 12, and 16 mg risperdone groups over the 1 mg risperidone group on the BPRS psychosis cluster and on the CGI. The 4 mg risperidone group also appeared to beat the 1 mg group on the BPRS total score, but the findings were more marginal for the higher risperidone groups. The 10 mg haloperidol group was clearly superior to risperidone 1 mg only on the BPRS psychosis cluster. Among the risperidone groups, the maximum effect was seen for 4 mg, with no apparent enhancement at higher doses. Neither active drug was superior, for any of the dose groups, to the 1 mg risperidone group on the PANSS negative symptoms subscale. No data were available for comparisons of haloperidol with risperidone dose groups higher than 1 mg, however, an inspection of the effect sizes suggested to me that few significant p-values would emerge from such comparisons.

The sponsor characterized the results of these trials somewhat differently, especially with regard to negative symptoms. They concluded that risperidone was shown to be superior to both placebo and haloperidol with regard to both positive and negative symptoms, and they described the trial outcomes in this manner in their proposed labeling for risperidone. I will elaborate on this issue under section 10.1.

There are several efficacy issues that deserve comment here:

Negative Symptoms

While the sponsor has not sought a specific claim for negative symptoms of schizophrenia in the Indications statement of their proposed labeling, their clinical trials description indirectly makes that claim. Since there is no precedent for such a claim, I think this subject raises at least two sets questions. (1) First, where does the notion of negative symptoms fit in the development of antipsychotic drugs? Is there agreement on what constitute negative symptoms? Should negative symptoms be viewed as part of a typical schizophrenic syndrome, or is there a specific negative symptom subtype of schizophrenia that can be teased out and studied separately? How should claims be handled regarding negative symptoms? Would a separate claim for the treatment of negative symptoms be a legitimate claim, or would this be a pseudospecific claim? In other words, is there reason to believe there is differential responsiveness of negative symptoms to drugs in this general class, or do they all have some efficacy for negative symptoms, albeit somewhat less robust than their effects on positive symptoms? (2) That leads me to the second question, what is a fair comparison in looking at effects on negative symptoms? The risperidone study (204) in which there may appear to be superiority for risperidone over haloperidol for negative symptoms involved a haloperidol dose of 20 mg per day, and this raises the question of the appropriateness of haloperidol at this dose for such a comparative claim.

I raised these issues at the PDAC meeting, and while there was a lot of discussion, there was no clear consensus. There was general agreement that these and other issues pertinent to antipsychotic drug development need to be addressed, since many antipsychotic drugs are currently in development.

My sense of the Committee discussion was that there was concern about the fairness of comparing risperidone at 10 mg with haloperidol at 20 mg, a dose that may be on the descending part of the haloperidol dose/response curve and may actually induce negative symptoms. On the other hand, Committee members were appreciative of the fact that the sponsor had actually measured negative symptoms in these trials. I agree with this sentiment and I am inclined to (1) permit the sponsor to describe superiority of risperidone over placebo with regard to negative symptoms for

studies 201 and 204, but (2) not to permit statements suggesting superiority over haloperidol with regard to negative symptoms for study 204. This may, in a sense, be pseudospecific, but I don't think this can be distorted in advertising when cast in this way and I do think it will encourage other sponsors to at least measure the effects of their drugs on negative symptoms. In the meantime, we are planning a special meeting of the PDAC to address this and other issues pertinent to this class of drugs generally.

Continuation Efficacy and Relapse Prevention

The sponsor's proposed labeling is entirely silent on the issue of how long to use risperidone in patients who appear to have achieved a positive response, and this is consistent with the fact that they have provided evidence pertinent only to short-term efficacy. The difficulty, of course, is that schizophrenia is a chronic illness requiring chronic treatment, and a database that only addresses acute treatment is incomplete. There is at present no specific FDA requirement for data pertinent to longer-term treatment for any of the chronic psychiatric indications we deal with. There is substantial data from adequate and well-controlled studies for many marketed antipsychotics demonstrating maintenance efficacy. The situation is parallel to what we often see with antidepressants, and our usual approach is to approve such a drug without long-term efficacy data and simply acknowledge this deficiency in labeling, along with the fact that continued therapy is probably the prudent course with most responding patients. I think this would be the best approach here as well. I would note that the sponsor has submitted a protocol (11-22-93) for a relapse prevention trial that will be conducted over the next few years. This study will compare risperidone (4-8 mg/day), haloperidol (10-15 mg/day), and risperidone 1 mg/day for 1 year in stable schizophrenic patients. The primary outcome variable will be time to relapse.

Problem of Dropouts in Studies of Antipsychotic Drugs

The problem of dropouts from trials involving antipsychotic drugs is clearly illustrated in the two placebo-controlled trials for risperidone. This substantial, early loss of patients from the placebo group for lack of effect is inevitable in studies of schizophrenia and it creates a dilemma in analyzing the data. It is not clear how best to interpret the results of an LOCF analysis when so many placebo patients are lost very early in the trial, and it is not clear how best to estimate the size of the treatment effect. Dr. Hoberman has addressed these concerns in his review. Regardless of how one approaches these data, the conclusion seems to be the same, i.e., risperidone is active as an antipsychotic.

5.2 Safety Data

5.2.1 Original Submission

The safety data for risperidone, including the original submission and numerous amendments in response to our requests for additional information, were reviewed by Dr. Andrew Mosholder from the Psychopharm Group. I worked closely with Dr. Mosholder during his review of this NDA, and I agree with his conclusion that risperidone has been demonstrated to be acceptably safety for use as an antipsychotic.

The sponsor's integrated database in the original submission included approximately 2500 human subjects exposed to risperidone in the sponsor's development program, including 175 in phase 1 studies and 2322 in phase 2-3 studies as of a 5-31-91 cutoff date. Serious events were provided for additional patients not yet included in the integrated database, up to a cutoff date of 4-15-92. In addition, some reports of serious events were available from an open, compassionate use experience involving approximately 1300 patients exposed to risperidone worldwide (not monitored by sponsor).

Patients in the sponsor's integrated phase 2-3 database were roughly two-thirds male, 80% white, and mostly young to middle-aged. There were only 60 patients over age 65. Patients were dosed in a range of 1 to 16 mg/day, on a BID schedule, and most for relatively short intervals, i.e., 2 months or less. Roughly 200 patients were dosed for greater than 9 months.

The common adverse event profile for risperidone included the following: extrapyramidal symptoms (EPS), hyperkinesia, somnolence, dizziness, tachycardia, dyspepsia, nausea, vomiting, constipation, rhinitis, coughing, rash, dysmenorrhea, vaginitis, mastitis, increased dream activity, accomodation disturbances, reduced salivation, micturition disturbances, diarrhea, weight gain, menorrhagia, diminished sexual desire, erectile dysfunction, ejaculatory dysfunction, and orgastic dysfunction. Not surprisingly, there was a strong suggestion of dose dependency for many of these adverse events. While EPS is clearly a risk for risperidone, even at the recommended target dose of 6 mg/day, it also seems clear that the rates of EPS for risperidone are lower than those for haloperidol at doses the sponsor believes to be therapeutically equivalent (However, this claimed therapeutic equivalence has not been definitively established.) While this likely represents an advantage for risperidone over haloperidol, it remains to be seen how risperidone compares with other antipsychotics on the market with regard to this event. Haloperidol is at the high end of the spectrum with regard to risk of EPS.

A careful look at all the other routinely collected safety variables, including serum chemistry, hematology, urinalysis, vital signs, ECGs, and chest X-rays revealed four findings suggestive of clinically important risperidone-related changes for any of these variables. (1) Risperidone is associated with a prominent

elevation of serum prolactin, an effect shared with most other antipsychotics. (2) Risperidone was associated with tachycardia, an effect that appears to be secondary to orthostatic hypotension associated with initial treatment with risperidone. (3) Risperidone is associated with weight gain, an effect that is also common to this class of drugs. (4) Finally, risperidone appears to have some potential for prolongation of the QT interval.

While there were 18 deaths among risperidone-treated patients overall, when adjusted for duration of exposure, the mortality rate was comparable for risperidone and active-control treatment. Furthermore, the causes of death among risperidone patients were not unusual or unexpected for this population. Ten of the deaths were from suicide, but there is a widely recognized risk of suicide for schizophrenic patients (more about this later).

An examination of adverse dropouts revealed a profile of common events causing dropout for risperidone that closely mimicked the common event profile for risperidone overall. There were no serious adverse events associated with risperidone dropout at unexpected or disproportionate rates.

Two special searches were conducted for risperidone, including: suicidality and serious events (using FDA's definition). Risperidone had no greater risk of suicidality than the active control or placebo groups. While other serious events were also reported among risperidone patients in this large population, neither the types of events nor their numbers were unexpected for the population.

Except for pk studies in subjects with renal or hepatic impairment, there were no systematic attempts to explore for drug/disease interactions. A decreased clearance of the 9-OH metabolite was found for renally impaired patients, and hepatically impaired patients were found to have an increase in the free fraction of the metabolite. Clearance of the metabolite was also found to be decreased in the elderly. The absence of formal drug interaction studies was an important omission for a drug that is metabolized by cytochrome $P_{450}IID_6$ (see Biopharm section).

Although not systematically studied, there was no indication of a withdrawal syndrome and no suggestion of drug-seeking behavior.

There were no pregnant women exposed to risperidone in the original NDA database.

The overdose experience with risperidone consisted of 6 patients, all of whom recovered fully. In general, reported signs and symptoms were those resulting from an exaggeration of the drug's known pharmacological effects, i.e., drowsiness, tachycardia and hypotension, and extrapyramidal symptoms.

The following were the adverse events associated with risperidone use that we felt deserved some special mention in labeling:

Neuroleptic Malignant Syndrome: There was one case reported during compassionate use of risperidone. This is expected with this type of drug and is a standard warning.

Tardive Dyskinesia: Since risperidone is associated with EPS, albeit at a lower rate than seen with haloperidol, it is likely that TD is a risk, and risperidone should have the standard TD warning.

Hypotension: Risperidone is associated with orthostatic hypotension associated with dizziness, tachycardia, and in some patients, syncope, especially during initial titration.

Seizures: Seizures were observed in 0.2% of risperidone-treated patients.

Hyperprolactinemia: As noted, risperidone elevates prolactin, as do most other antipsychotics.

QT Prolongation: The potential for QT prolongation deserves a mention in the Warnings section.

Priapism: There was one reported case of priapism in a compassionate use patient. This potential risk may be related to risperidone's alpha blocking effects.

5.2.2 Safety Update

The sponsor submitted a safety update 10-28-93 that extended the cutoff date for the integrated database from 5-31-91 to 4-15-93, thereby adding 56 subjects to the phase 1 database and 285 patients (approximately 2/3 open label patients) to the phase 2-3 database. Additional safety data were provided on 278 patients already counted in the original database. The expanded database included 231 subjects in phase 1 and 2607 patients in phase 2-3. In addition, the sponsor provided data on deaths reported through 9-30-93 and foreign postmarketing data (serious events only) through 8-31-93. The phase 2-3 risperidone exposure increased from 508 to 858 patient exposure years in the expanded database.

The common events profiles for the controlled trials data did not change to an important degree with this expanded population. There were several additional deaths, but the overall findings continued to suggest no difference in mortality rates for risperidone and the active control group. Similarly, there were no important changes in (1) the profiles of dropouts or adverse events associated with dropout, or (2) the suicidality data.

There were 2 additional seizures, and the seizure estimate will be revised for labeling. There were 2 additional overdoses, and these cases will be added to the labeling statement. There were several serious cases that seemed unlikely related to risperidone use. However, 1 case was of particular interest, i.e., a case of TTP in a 28-year-old female who experienced jaundice, fever, bruising, and thrombocytopenia. She did eventually recover after receiving plasmapheresis. We will add a mention of this case to the Precautions section of labeling.

Finally, there was a case of an infant born without a corpus callosum to a mother who had taken risperidone for a brief period during the 4th month, roughly the time during which this structure develops. We will mention this case in labeling.

Overall, while the safety update provided some new information that will permit further modification of our draft labeling, it did not reveal any new findings that would preclude the approval of this drug.

5.2.3 Conclusions Regarding Safety Data

In conclusion, the safety experience for over 2800 patients exposed to risperidone in the premarketing program revealed no adverse findings that would preclude its approval as an antipsychotic.

5.3 Clinical Sections of Labeling

The clinical sections of the sponsor's proposed labeling for Risperdal were grossly inadequate, and we have essentially completely rewritten the clinical sections of labeling. As noted, we were able to reach agreement with the sponsor on some, but not all, aspects of labeling (see section 10.1).

6.0 WORLD LITERATURE

As part of his original review, Dr. Mosholder conducted a Medline search for clinical publications regarding risperidone and concluded that all of the publications in the literature pertained to studies conducted as part of Janssen's development program and described fully in the NDA. Janssen independently confirmed that this was the case. An literature update was included as part of the safety update. Dr. Mosholder reviewed this material and concluded that it did not alter his overall view regarding the acceptable safety of risperidone; I agree with this conclusion.

7.0 FOREIGN REGULATORY ACTIONS

To my knowledge (10-23-93 update), risperidone is approved in 6 countries: the UK (12-92); and Canada, Mexico, Greece, Chile, and

South Africa (all in 93'). The sponsor warrants that risperidone has not been denied approval in any country on the basis of insufficent data for safety or efficacy. However, it was denied approval in Finland on the basis of pricing.

8.0 PSYCHOPHARMACOLOGICAL DRUGS ADVISORY COMMITTEE (PDAC) MEETING

A meeting of the PDAC was held on 4-29-93 to discuss the safety and efficacy of risperidone. As noted above, the Committee voted unanimously that the sponsor had demonstrated risperidone to be effective for the proposed indication and also acceptably safe for this indication. Risperidone was discussed a second time at a 7-20-93 meeting of the PDAC; in particular, there was a discussion of the rodent carcinogenicity data for risperidone. The Committee was satisfied with the Division's approach to addressing these findings in labeling (see Pharmacology comments--#3).

9.0 DSI INSPECTIONS

Investigators from 2 of the 3 studies upon which the approvable action will be based have been inspected: Dr. Lawrence Gosenfeld from Study 201; Drs. Jan Volavka and Richard Borison from Study 204. Studies 201 and 204 were the US studies, and Study 024 was foreign. Dr. Volavka received a NAI rating. Dr. Gosenfeld and Dr. Borison received VAI-2 ratings, however, for minor violations.

10.0 LABELING, SBA, AND APPROVABLE LETTER

10.1 Final Draft of Labeling Attached to Approvable Package

Our proposed draft of labeling is attached to the approvable letter. We have made substantial changes to the sponsor's draft dated 8-23-93 and also later drafts. As noted, we were unable to reach agreement with the sponsor at our 12-7-93 meeting regarding the inclusion of comparative information regarding risperidone and haloperidol in the labeling. The sponsor argued that, since haloperidol was included as an active control in all three critical trials supporting the efficacy claim for risperidone, they should be permitted to include this comparative information in the clinical trials section and elsewhere in labeling. They feel that such information would be useful to clincians in making decisions about the relative merits of the two drugs and to formulary committees in deciding whether or not to include risperidone on their formularies. While I don't object in principle to providing comparative information in labeling, I think there are several reasons why it would it would not be correct to include such information in this particular case. The CFR does permit comparative information to be included in labeling, provided that such statements are 'supported by adequate and well-controlled

trials.' [21CFR201.57(c)(3)(v)] The issue here is whether or not these data come from trials that are adequate and well-controlled from the standpoint of the risperidone/haloperidol comparison. In my view they are not, consequently I believe the comparative information is misleading.

Of the three critical studies, 2 were dose comparison (204 and 024) and 1 was a titration study (201).

(a) In the titration study (201), patients were pushed to the maximum doses of the 2 active drugs, i.e., 10 mg for risperidone and 20 mg for haloperidol. In my view, 20 mg of haloperidol is an excessive dose of haloperidol, a view that was shared by at least some members of the PDAC at our 4-29-93 meeting. In any case, with regard to efficacy, risperidone did not beat haloperidol in any of the pairwise comparisons between these two active drugs. The sponsor tries to suggest indirectly that risperidone is superior to haloperidol with regard to negative symptoms, however, this is based on comparisons with placebo that are misleading. In fact, numerically there is little difference between risperidone and haloperidol in the effect size for this variable (see earlier discussion).

(b) In study 204, 4 doses of risperidone were compared with 1 excessive dose of haloperidol, indeed a dose that is likely to be associated with adverse effects that might be misinterpreted as negative symptoms. Likely because of its excessive dose, haloperidol beats placebo only for global measures and measures including mostly positive symptome, and not for negative symptoms. It is not surprising that 1 of the risperidone doses (6 mg) can be shown supreior to this dose of haloperidol. However, this study is not adequate in design to compare the dose response curves for these 2 active drugs, which is what one needs to do to support comparative claims.

(c) Study 024 is generally a flawed study that shows no effects for any of the active drug groups on negative symptoms and shows inconsistent effects on other variables.

An important point to note is that none of these 3 trials adequately establishes therapeutically equivalent doses of risperidone and haloperidol. Consequently, it is, in my view, not meaningful to attempt to compare these two drugs with regard to an adverse effect, namely, EPS. Given the data we have, I am inclined to believe that risperidone may have less potential than haloperidol for this particular adverse effect, but I feel the data are not sufficiently well-developed to justify including the comparisons in labeling.

I believe there is an important principle at stake here. While it may be useful for clinicians to have access to comparative data regarding different drugs in a class, it seems to me that it is

incorrect to permit a sponsor to select a comparator on the basis of it being the worst from the standpoint of an adverse effect in question. It would be of much greater use to clinicians to have adequate data on several drugs in the class that cover the spectrum with regard to the adverse effect in question. For example, it would likely be quite easy to demonstrate that risperidone is much worse than a drug like thioridazine with regard to EPS, since thioridazine is at the other end of the spectrum from haloperidol. If we permit sponsors to include in labeling information derived from studies designed and conducted in a manner to demonstrate only advantages for their product, it seems to me such information might generally be considered misleading. I think there needs to be public discussion of how best to compare different products in a class, and in fact, we hope to have such a discussion with regard to antipsychotics later next year in a meeting of the PDAC focusing on the best approaches for developing antipsychotic drugs.

In view of the above discussion, I believe it is correct for the agency to approve risperidone with labeling that we feel is appropriate for this product, despite the fact that the sponsor is not in agreement with certain aspects of labeling.

10.2 Foreign Labeling

As noted, risperidone is approved in 2 countries, i.e., the UK and Canada. We reviewed the foreign labeling for risperidone in preparation for drafting the labeling included with the approval package.

10.3 Draft SBA

We have not drafted an SBA for Risperdal. In my view, the primary reviews are sufficient to serve as an alternative to an SBA. Nevertheless, we have included in the approvbl package the sponsor's draft SBA (not modified by us); this document summarizes the sponsor's case for the approvability of risperidone.

10.4 Approval Letter

The approval letter includes (1) finalized labeling, (2) a request that the sponsor commit to doing an in vivo interaction study with another drug metabolized by IID6, e.g., desipramine); (3) dissolution specifications and some general biopharm comments; and (4) a statement indicating what additional studies the sponsor needs to do to obtain a change in the pregnancy category from C to B.

11.0 CONCLUSIONS AND RECOMMENDATIONS

I believe that Janssen has submitted sufficient data to support the conclusion that risperidone is effective and acceptably safe in the management of the manifestations of psychotic disorders. I recommend that we issue the attached approval letter with labeling that we feel is appropriate for this product.

cc:
Orig NDA
HFD-120
HFD-120/TLaughren/PLeber/AMosholder/SHardeman
HFD-100/RTemple

DOC: MEMRSPRD.AP1

JANSSEN RESEARCH PRODUCTS INFORMATION SERVICE

Date: February 1992 Drug: Risperidone (R 64,766)

Title: An integrated summary of the effectiveness of risperidone

Sponsor: Janssen Research Foundation
40 Kingsbridge Road
Piscataway, New Jersey 08854 U.S.A.

CONTENTS Page

US02092

RISPERIDONE CONTROLLED TRIALS

Protocol Study ID	Investigator	Dates of Study	Report Vol. Page	Pt. Tabulations Vol. Page	CRFs Vol. Page	Study Design	Total N Sex (M-F) Age Range	Dose & Formulation	Control	Duration
Protocol 201 RIS-USA-9001	Borison, et al. Multicenter USA	10/88 - 6/90	1.45/00-00013 1.110/00-00013	1.161/00-00028	1.239/00-00021 AE	DB/PARA	160 (154-6)	r=2-10mg h=4-20mg tablets	placebo haloperidol	6 weeks
Protocol 204 RIS-INT-3	Small,et. al Multicenter USA/Canada	10/89 - 7/91	1.52/00-00001 1.117/00-00001	1.166/00-00073	1.234/00-00003 D 1.243/00-00001 AE	DB/PARA	523	r=2,6,10,16mg h=20mg tablets	placebo haloperidol	8 weeks
Protocol 024 RIS-INT-2	Multinat. al	3/89 - 3/91	1.69/00-00001 1.134/00-00001	1.183/00-00001	1.234/00-00100 D 1.254/00-00001 AE	DB/PARA	*1362 (894-467)	r=1,4,8,12,16mg h=10mg tablets	haloperidol	8 weeks
Protocol 006 RIS-BEL-5	Claus, et. al. Multicenter, Belgium	4/1/88 - 3/30/89	1.83/00-00001 1.148/00-00001	Not available	1.289/00-00001 AE	DB/PARA	44 (29-15)	r=2-20mg h=2-20mg oral sol.	haloperidol	12 weeks
Protocol 008 RIS-BEL-7	Mesotten, et. al. Multicenter, Belgium	12/87 - 9/88	1.84/00-00001 1.149/00-00001	1.225/00-00001	1.235/00-00412 D 1.290/00-00001 AE	DB/PARA	60 (37-23)	r-2-20mg h=2-20mg oral sol.	haloperidol	8 weeks
Protocol 022 RIS-FRG-9005	Klieser, E,; Kinzler, E. Germany	11/24/88- 4/4/90	1.85/00-00001 1.150/00-00001	1.227/00-00001	1.290/00-00203 AE	DB/PARA	59 (31-28)	r=4,8mg c=400mg tablets	clozapine	4 weeks
Protocol 041 RIS-FRA-9003	Tatossian, A. France	5/89 - 5/91	1.86/00-00001 1.151/00-00001	1.229/00-00001	1.291/00-00001 AE	DB/PARA	62 (38-24)	r=4-12mg h=4-12mg l=50-150mg tablets	haloperidol levomepro- mazine	4 weeks
Protocol 048 RIS-INT-7	Remivig, J. Denmark	2/90 - 8/91	1.87/00-00001 1.152/00-00001	1.231/00-00001	1.192/00-00001 AE	DB/PARA	107 (77-30)	r=5-15mg p=16-48mg tablets	perphenazine	8 weeks
Protocol 015 RIS-BEL-11	J. Geutjens Belgium	5/88 - 4/89	1.88/00-00001 1.153/00-00001	Not available	1.294/00-00001 AE	DB/XO	37 (18-19)	r=4-12mg oral sol.	placebo	3 weeks

*155 were recruited, 47 discontinued during placebo wash-out phase, 148 excluded from analysis due to sites failing a GCP audit.

DB = Double Blind PARA = Parallel Group r = Risperidone h = Haloperidol c = Clozapine l = Levomepromazine p = Perphenazine D = Death AE = Adverse Experience

Risperidone--Integrated Summary of Effectiveness

I. INTRODUCTION

In the 30 years since Haldol® was discovered, many antipsychotics have been developed. These compounds have been referred to as neuroleptics and they all share in common the ability to induce unwanted extrapyramidal side effects (EPS). Up to 30% of psychotic patients will not respond to neuroleptic treatment and they have little if any effect on negative symptoms.

The therapeutic effects and the extrapyramidal side effects of neuroleptics are known to result from antagonism of dopamine D_2 receptors. The association between dopamine-receptor blockade and antipsychotic activity derived from the observation that reserpine, a catecholamine-depleting agent, had antipsychotic activity, whereas classic antipsychotic agents such as haloperidol produce an (apparent compensatory) increase in dopamine metabolites.[1] With the development of receptor-binding techniques, the potency of antipsychotics at D_2 receptors was strongly correlated with therapeutic effect.[2]

Dopamine-receptor sensitivity has been reported to be upregulated in schizophrenics, but it remains controversial whether this results from the disease process or is a result of chronic neuroleptic treatment.[3] Repeated administration of neuroleptics to experimental animals has been shown to increase the density (number) of striatal D_2 receptors. This increase in receptor density is accompanied by increased response to dopamine agonists and spontaneous oro-facial movements resembling dyskinesia seen in humans following chronic neuroleptic treatment.[4,5]

The close relationship between neuroleptic activity and EPS has stimulated a search for atypical antipsychotics that would be free of these side effects. One possibility is suggested by reports that all antipsychotic agents also share the ability to bind to serotonin receptors.[6] Brain serotonin systems have close anatomical and functional rela..onships with dopamine systems. In particular, serotonin can influence the activity of dopamine neurons projecting to the frontal cortex and striatum.[7] Decreased dopamine activity in the frontal cortex may contribute to the negative symptoms of schizophrenia.[8] Thus, compounds with serotonergic as well dopaminergic antagonist activity could be more effective against negative symptoms and have a lower liability for producing EPS than traditional neuroleptics.

Risperidone--Integrated Summary of Effectiveness

An antipsychotic agent with equal or superior efficacy to standard neuroleptics would require a greater activity at serotonin receptors. Risperidone has a high affinity for 5-HT_2 receptors than all currently approved antipsychotic agents and has substantial affinity for dopamine D_2 receptors. In vivo risperidone was a potent serotonergic antagonist and was active in selected models predictive of antipsychotic efficacy. However, risperidone was less potent than haloperidol as a dopamine antagonist and in particular produced catalepsy only when administered in high doses. These data indicated that the effective dose of risperidone would be similar to haloperidol and may result in less EPS.

Three multicenter trials, one conducted in the United States (JRD 64,766/201), one conducted in the United States and Canada (JRD 64,766/204), and one conducted in countries within Europe, Africa, and Central and South America (R 64,766/024) are considered adequate and well-controlled studies. Six controlled studies also support the proposed indication. These studies provide the basis of the effectiveness of risperidone in the treatment of psychotic symptoms.

II. ADEQUATE AND WELL-CONTROLLED STUDIES

JRD 64,766/201 (RIS-USA-9001)

This study, conducted between October 1988 and June 1990, had eight centers and compared the effectiveness of risperidone to a classical neuroleptic, haloperidol, and placebo in the treatment of psychotic symptoms associated with schizophrenia. Based on the results of uncontrolled studies in Europe, a randomized, double-blind, placebo-controlled, parallel group study design was used.

Male and female patients between the ages of 18 and 65 and in good health were eligible. Patients had to meet DSM III-R criteria for schizophrenia and had to be inpatients at the start of the study to be included in the trial. They also had to have a minimum total score of 30 on the Brief Psychiatric Rating Scale (BPRS) and a minimum score of 4 (moderate) for any two of the following BPRS items: conceptual disorganization, suspiciousness, hallucinatory behavior, and unusual thought content. Patients with clinically significant pulmonary and cardiovascular diseases and psychotic disorders other than schizophrenia were excluded.

After a three-day washout period (two weeks for depot neuroleptics), patients received double-blind risperidone, haloperidol, or placebo. Since this study was the first parallel group, placebo-controlled trial with risperidone, an individual dose titration design was used. In each treatment group, upward titration was allowed if a sufficient response did not occur during the first two weeks of the double-blind treatment. After the first day, the investigator could adjust the dosage according to the individual patient's needs in increments of one tablet daily and no increases could occur in the final four weeks of the study. The maximum daily dose of 10 tablets (risperidone 10 mg and haloperidol 20 mg) was administered as 5 tablets BID. Improvement was assessed at each visit using the BPRS for psychotic symptoms, the Scale for Assessment of Negative Symptoms (SANS) for negative symptoms, and Clinical Global Impression (CGI) for overall efficacy.

Table 1 summarizes the schedule of evaluations.

Table 1: Schedule of assessments

Study JRD 64,766/201	Visit 1	Visit 2*	Visit 3*	Visit 4*	Visit 5**	Visit 6**	Visit 7**
Weeks on drug (per period)	-2 wks to -3 days	0	1	2[a]	1	2	4
BPRS	X	X	X	X	X	X	X
SANS	X	X	X	X	X	X	X
CGI	X	X	X	X	X	X	X
ECG	X			X		X	X
Chest x-ray	X						X
Vital signs	X	X	X	X	X	X	X
Laboratory tests	X		X	X		X	X

* dose-rising period
** maintenance period
[a] Visit 4 occurred between Days 10-18 of the study. At this visit the dose was stable and the patient began four weeks at a fixed dose, unless adverse experiences warranted a dose adjustment.

STATISTICAL ANALYSIS

An intent-to-treat approach (using all randomized patients) was used in the analysis and the interpretation of efficacy data. The intent-to-treat analysis included all randomized patients who had at least one on-treatment evaluation.

Two sets of analyses were performed for the intent-to-treat sample. The first set included only patients who were still in the study and for whom an observation was recorded at each visit. The second set included patients who dropped out by carrying forward their last observation to the end of the study (LOCF or endpoint analysis). In order to reduce the bias introduced by differential dropout rates and to have the endpoint analysis associated more closely to the effective duration of the study, the endpoint analysis results carried out to the latest point in time at which at least 70% of the patients assigned to each treatment remained in the study were also performed for all efficacy variables. In the present case, the 70% rule was at Week 1.

Risperidone--Integrated Summary of Effectiveness

The primary measures of effectiveness defined a priori were the total symptom score of the Brief Psychiatric Rating Scale (BPRS), the percent of patients with at least 20% reduction from baseline in the total BPRS score, and the score on the Clinical Global Impressions (CGI) scale of absolute severity. The analysis of the intent-to-treat population at endpoint was the primary effectiveness analysis.

An analysis was performed on the following secondary variables: total key BPRS items (sum of four items including conceptual disorganization, hallucinatory behavior, suspiciousness, and unusual thought content); overall change from baseline (Visit 2) measured in the Clinical Global Impressions (CGI-C) scale; total score of the Scale for the Assessment of Negative Symptoms (SANS) (sum of 25 items); total non-global symptom score of the SANS (sum of 20 non-global items); total global symptom score of the SANS (sum of five global items); and percent of patients who discontinued the study due to insufficient response; percent of patients showing clinical improvement, defined as a 20% or greater in the total BPRS score from baseline (Visit 2) and a CGI compared to baseline score of 3 (minimally improved) or less, as measured by the BPRS and CGI scales.

Within-treatment comparisons were performed for each symptom severity score of BPRS and SANS, total score of BPRS, total score of SANS, total non-global score of SANS, total global score of SANS, and CGI score of the severity of schizophrenia using the Wilcoxon signed rank test.

The test, stratified by investigator, was used to compare treatment groups with respect to the proportion of patients with clinical improvement, the overall change from baseline measured in the Clinical Global Impressions (CGI-C). The percent of patients who discontinued the study due to insufficient response was analyzed without stratification using the test.

Pairwise comparisons between any two treatment groups were performed using least significant difference (LSD) procedure from the two-way ANOVA results. The primary pairwise comparisons were risperidone vs. placebo and risperidone vs. haloperidol. For completeness the haloperidol vs. placebo comparison was also made. The reported p-values are two-tailed.

SUPPLEMENTAL ANALYSIS

A two-way analysis of covariance (ANCOVA) and a longitudinal data analysis was performed on the change from baseline of the total BPRS score. The baseline total BPRS score was used as a covariate in both analyses. A longitudinal data analysis was used to test for treatment differences across time instead of at each time point (visit). Survival analysis techniques were used to analyze the time to premature discontinuation of the study due to insufficient response.

PATIENT DISPOSITION

A total of 160 patients were randomized to double-blind treatment. Of the 160 patients, 66 (41%) completed the six-week treatment. Thirty-one percent in the placebo group, 51% in the risperidone group, and 42% in the haloperidol group completed the six-week treatment period.

A total of 94 patients (59%) prematurely discontinued (37 for placebo, 26 for risperidone, and 31 for haloperidol). The main reasons were adverse experiences, insufficient response, withdrawal of consent, and uncooperativeness.

There were no statistically significant differences between the three groups with respect to sex, race, age, weight, and height (Table 2). The duration of treatment was similar among groups. The mean duration was 24, 30, and 27 days for the placebo, risperidone, and haloperidol groups, respectively. During the dose-rising (titration) period, there was a gradual increase in the mean number of tablets in all treatment groups. The mean number of tablets dispensed at endpoint was 7.6 for the placebo group, 7.8 (7.8 mg) for the risperidone group, and 7.5 (15.0 mg) for the haloperidol group.

EFFICACY RESULTS

Brief Psychiatric Rating Scale (BPRS): At each visit, the investigator evaluated the patient using the BPRS. This scale consisted of 18 items: somatic concern; anxiety; emotional withdrawal; conceptual disorganization; guilt feelings; tension; mannerism/posturing; grandiosity; depressive mood; hostility; suspiciousness; hallucinatory behavior; motor retardation; uncooperativeness; unusual thought content; blunted affect; excitement; and disorientation. These items were assessed on a seven-point scale where 1=not present, 2=very mild, 3=mild, 4=moderate, 5=moderately severe, 6=severe, and 7=extremely severe.

Risperidone--Integrated Summary of Effectiveness

Table 2: Demographics

Study JRD 64,766/201		Placebo	Risperidone	Haloperidol	Total
Entered		54	53	53	160
Sex	M	51	53	50	154
	F	3	0	3	6
Race	White	29	29	26	84
	Black	24	23	24	71
	Oriental	1	0	1	2
	Hispanic	0	1	2	3
Age (years)	Mean	40.3	39.7	38.4	39.5
	Min.	23.0	21.0	22.0	21.0
	Max.	63.0	60.0	63.0	63.0
Weight (lbs)	Mean	167.2	175.2	172.7	171.6
	Min.	113.0	112.0	95.0	95.0
	Max.	257.0	340.0	264.0	340.0
Height (in.)	Mean	69.4	68.8	69.4	69.2
	Min.	55.0	55.0	52.0	52.0
	Max.	78.0	77.0	86.0	86.0

Risperidone--Integrated Summary of Effectiveness

Table 3 summarizes the mean change from baseline in symptom severity and the p-values at Week 1 (70% rule) and at endpoint. Visual displays for the total BPRS are shown in Figure 1.

Table 3: Mean change from baseline score

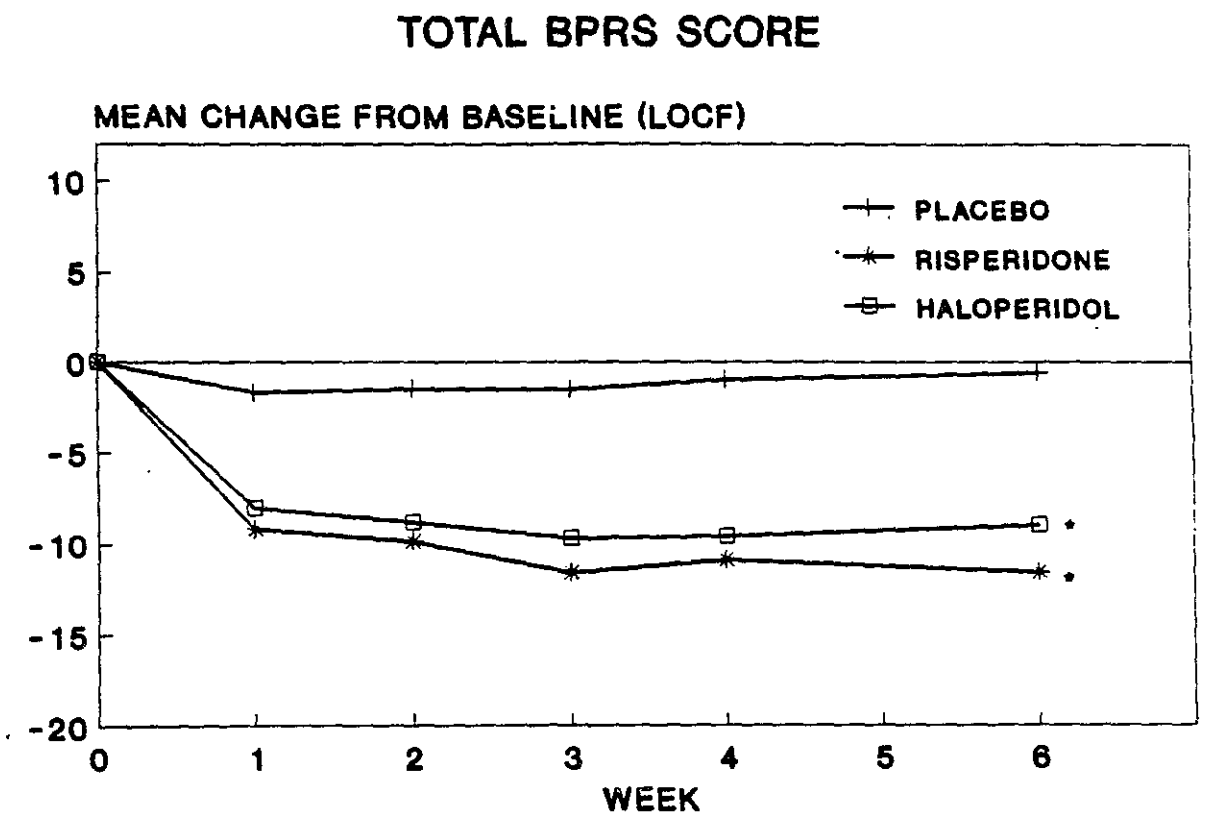
Study JRD 64,766/201		Mean Change from Baseline		
Parameter	Week	Placebo	Risperidone	Haloperidol
Total BPRS (18-126)[a]	Baseline	52.8	56.2	53.1
	Week 1	-1.7	-9.2*	-8.0*
	Endpoint	-0.6	-11.6**	-9.0*
Total key BPRS (4-28)	Baseline	16.7	17.2	16.7
	Week 1	-0.8	-3.5**	-3.4**
	Endpoint	-1.2	-4.8**	-5.0**
CGI-severity (0-6)	Baseline	3.9	4.1	3.9
	Week 1	-0.3	-0.5	-0.5
	Endpoint	-0.3	-0.7	-0.7

[a] Minimum and maximum possible scores

* $p \leq 0.05$ ** $p \leq 0.001$ compared to placebo

At endpoint, patients treated with risperidone and haloperidol showed a significantly greater reduction from baseline compared to placebo in total BPRS score and the key BPRS items. In general, these differences were observed in the first week (the week at which there were at least 70% of the patients remaining in all treatment groups). No pairwise significant differences were detected between the risperidone and the haloperidol groups in total BPRS or the key BPRS items at endpoint.

Figure 1: Total BPRS score--Mean change from baseline (LOCF)



Clinical global impression (CGI): The overall severity of the patient's schizophrenia was rated by the investigator at each visit as no symptoms, borderline, mild, moderate, marked, severe, or very severe.

At endpoint, risperidone was marginally more effective than placebo (p=0.067). No other pairwise treatment comparisons were found to be significant at endpoint (Table 3).

Clinical improvement: Table 4 summaries the percent of patients who improved via total BPRS, CGI-C, and BPRS/CGI-C.

Table 4: Percentage of patients with clinical improvement

		Study JRD 64,766/201--Clinical Improvement		
		Percent of Patients		
Parameter	Week	Placebo N=53	Risperidone N=51	Haloperidol N=52
Total BPRS	Week 1	28.3%	54.9%*	50.0%*
	Endpoint	30.2%	64.7%**	51.9%*
CGI-C	Week 1	43.4%	66.0%*	60.4%*
	Endpoint	35.8%	64.2%**	58.5%*
CGI-C/BPRS	Week 1	24.5%	51.0%*	48.1%*
	Endpoint	26.4%	56.9%*	42.3%

* $p \leq 0.05$ ** $p \leq 0.001$ compared to placebo

Clinical Improvement via total BPRS: At endpoint, a higher percentage of patients in the risperidone group (65%) showed improvement compared to placebo (30%) (p=0.001) and haloperidol (52%) (p=0.189). The clinical improvement in risperidone-and haloperidol-treated patients when compared to the placebo group was significant as early as Week 1.

Clinical Improvement via CGI-C: At Visits 3-7, the patient's present condition was compared to his or her condition at baseline (CGI-C): very much improved, much improved, minimally improved, no change, minimally worse, much worse, or very much worse. At endpoint, 64% of the patients in the risperidone group, 59% in the haloperidol group, and 36% in the placebo group showed improvement in CGI. The two active drugs were more effective than placebo beginning at Week 1. No significant differences were detected at any visit between the risperidone and haloperidol groups.

Clinical improvement via CGI and total BPRS: At endpoint, 57% of the patients in the risperidone group improved compared to 26% in the placebo group (p=0.003) and 42% in the haloperidol group.

Scale for the Assessment of Negative Symptoms (SANS): Each negative symptom was rated on a six-point scale where 0=none, 1=questionable, 2=mild, 3=moderate, 4=marked, and 5=severe. The individual categories are listed below: total SANS (sum of 25 items), total non-global (sum of 20 items), and total global (sum of 5 items). The individual items for each category are presented in Appendix I.

The risperidone group showed significantly greater reductions from baseline in the total SANS (p=0.056) and total non-global SANS (p=0.049) at endpoint. No other pairwise comparisons were significant.

Percent of patients discontinued for insufficient response: The placebo group had a significantly greater dropout rate ($p<0.05$) than the risperidone and haloperidol groups at Week 2. Table 5 summarizes the number of patients who discontinued treatment due to insufficient response.

Table 5: Number (percent) of patients who discontinued due to insufficient response

Week	Placebo (N=54)	Risperidone (N=53)	Haloperidol (N=53)
Week 1	3 (6%)	1 (2%)	1 (2%)
Week 2	12 (22%)	3 (6%)*	3 (6%)*
Week 3	18 (33%)	6 (11%)*	4 (8%)*
Week 4	19 (35%)	8 (15%)*	5 (9%)*
Week 6**	20 (37%)	8 (15%)*	6 (11%)*

* $p \leq 0.05$ compared to placebo group

** Total number of patients who discontinued during the study (Weeks 1-6)

By the end of the trial, 37% of the placebo patients discontinued the study due to insufficient response. The crude rate for risperidone and haloperidol groups were 15% and 11%, respectively.

Conclusions

- For each of the efficacy assessments the improvement between baseline and endpoint was greater for the risperidone-treated than for the placebo-treated group.

- Risperidone produced a significant improvement, relative to placebo, for each of the three primary efficacy variables at endpoint. Risperidone significantly decreased (improved) the total BPRS score ($p<0.001$ vs. placebo), significantly increased the percentage of patients showing clinical improvement via the total BPRS score ($p=0.001$ vs. placebo) and marginally decreased (improved) the CGI-severity rating ($p=0.067$ vs. placebo).

- Risperidone was effective in treating negative as well as positive symptoms. The total SANS score ($p=0.056$) and the SANS non-global item score ($p=0.049$) were both improved at endpoint in risperidone-treated patients, relative to placebo-treated patients.

- In comparison to placebo, haloperidol failed to significantly improve negative symptoms at endpoint, as assessed by the SANS scale. Additionally, the change in the CGI-severity score and the percentage of patients with improvement on both the BPRS and the CGI did not differ significantly between the placebo- and haloperidol-treated groups.

- The risperidone group had a significantly fewer dropouts than placebo for all reasons including insufficient response.

JRD 64,766/204 (RIS-INT-3)

This study differed from JRD 64,766/201 in two important ways: . 1) to gain experience with a range of risperidone doses and to identify the optimal effective dose for risperidone, a fixed-dose design was used instead of an individual dose titration; and 2) to evaluate the efficacy of risperidone in the treatment of psychotic symptoms, particularly negative symptoms, the Positive and Negative Syndrome Scale (PANSS)[9,10] was used instead of the BPRS and SANS. The PANSS consists of three subscales: positive, negative, and general psychopathology. All 18 items of the BPRS are included in the PANSS. This allows for comparison of these results with results of other studies. All investigators were trained in rating the PANSS scale by viewing a videotape of patient interviews prepared by Stanley Kay, Ph.D. A second tape was used to test inter-rater reliability. Inter-rater reliability data were collected from all investigators except Drs. Chouinard and Nair (Canada).

This was a randomized, double-blind, placebo-controlled, multicenter trial conducted at 26 (20 in the U.S and six in Canada) sites. Male and female patients between the ages of 18 and 65 with chronic schizophrenia were eligible. They had to meet DSM III-R criteria for schizophrenia and be inpatients at the start of the study. They also were required to have a minimum total score of 60 and a maximum total score of 120 on the PANSS. Female patients of childbearing potential were required to have a serum pregnancy test performed prior to entry to confirm they were not pregnant and used oral contraceptives to prevent pregnancy (Protocol Amendment dated September 7, 1990). Patients were excluded if they had: a history of mental disorders other than chronic schizophrenia; previously received risperidone; or clinically significant laboratory or ECG abnormalities at selection.

After a one-week single-blind placebo washout period (four weeks for depot neuroleptics), patients were randomly assigned to one of the six treatment groups: risperidone 2, 6, 10, or 16 mg, haloperidol 20 mg, or placebo. During the first week of the double-blind treatment (Days 1-7), fixed upward titration was required to reach the maximal dose within each treatment group. During the remainder of the study, the dose was constant. Symptoms were assessed at baseline and after 1, 2, 4, 6, and 8 weeks using the PANSS Clinical Global Impression (CGI) scale, and global evaluations were rated by both the investigator and patient at Week 8 or discontinuation. Table 6 summarizes the schedule of assessments.

Table 6: Schedule of assessments

Study JRD 64,766/204	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6	Visit 7
Days on drug	-7	0	7	14	28	42	56
PANSS	X	X	X	X	X	X	X
CGI	X	X	X	X	X	X	X
Global assessments							X
ECG	X		X*				X
Vital signs	X	X	X	X	X	X	X
Laboratory tests	X		X*	X*	X*	X*	X

* U.S patients only

STATISTICAL ANALYSIS

The statistical methods used in this study were similar to Study JRD 64,766/201. In the present case, the 70% rule was at Week 1.

The primary measures for effectiveness defined a priori were the total symptom score of the Positive and Negative Syndrome Scale (PANSS) and the percent of patients with at least 20% reduction from baseline in the total PANSS score. The analysis of the intent-to-treat population at endpoint was the primary effectiveness analysis.

An analysis was performed on the following secondary variables: Clinical Global Impressions (CGI) scale of the severity of schizophrenia; overall change from baseline (Visit 2) measured in the CGI scale (CGI-C); total positive subscale score of the PANSS (sum of seven items); total negative subscale score of the PANSS (sum of seven items); total general psychopathology subscale score of the PANSS (sum of 16 items); total derived BPRS subscale score of the PANSS (sum of 18 items); total key BPRS items (sum of four items including conceptual disorganization, hallucinatory behavior, suspiciousness, and unusual thought content); percent of patients who discontinued the study due to insufficient response; percent of patients showing clinical improvement, defined as a 20% or greater reduction in the total PANSS score from baseline (Visit 2) and a CGI compared to baseline score of 3 (minimally improved) or less, as measured by the PANSS and CGI scales; and global evaluation of the double-blind medication compared to the patient's previous neuroleptic treatment by both the investigator and the patient.

Pairwise comparisons between any two treatment groups were performed using least significant difference (LSD) procedure from the two-way analysis of variance results. The following pairwise comparisons were performed:

i. Each risperidone- or haloperidol-treated group was compared to the placebo group.

ii. The most effective risperidone-treated group based on the total PANSS score analysis from (i) was compared to the haloperidol group. The most effective risperidone-treated group was selected based on the smallest p-value obtained from (i).

The primary comparisons of interest were the risperidone-treated groups versus placebo. Secondary comparisons were the placebo group versus haloperidol and the most effective risperidone-treated group versus haloperidol. The reported p-values are two-tailed.

SUPPLEMENTARY ANALYSIS: The supplementary analyses used in Study JRD 64,766/201 were also used in this study for the total and subscales of the PANSS.

Risperidone--Integrated Summary of Effectiveness

PATIENT DISPOSITION

A total of 523 patients were randomized to double-blind treatment. Of the 523 patients, 253 (48%) completed the eight-week treatment period.

A total of 270 patients (52%) prematurely discontinued the study, (61 for placebo, 51 for risperidone 2 mg, 34 for risperidone 6 mg, 39 for risperidone 10 mg, 34 for risperidone 16 mg, and 51 for haloperidol 20 mg). The main reasons were adverse experiences, insufficient response, withdrawal of consent, and uncooperativeness.

There were no statistically significant differences between the groups with respect to sex, race, age, weight, or height (Table 7).

Table 7: Demographics

Study JRD 64,766/204		Placebo	Ris 2 mg	Ris 6 mg	Ris 10 mg	Ris 16 mg	Hal 20 mg	Total
Entered		88	87	86	87	88	87	523
Sex	M	74	72	71	75	70	74	436
	F	14	15	15	12	18	13	87
Race	White	61	64	64	61	61	60	371
	Non-white	27	23	22	26	27	27	152
Mean weight (kg.)		75.6	79.8	77.9	74.9	74.5	79.2	77.0
Mean height (cm.)		174.2	173.2	174.1	171.8	172.9	173.9	173.4

The mean age at onset of psychotic symptoms was 21.5 years with a range of years. Forty-five percent of the patients had a family history of mental illness. According to the DSM III-R criteria, 56.2% of the patients were the paranoid type; 32.1% were of the undifferentiated type; 8.8% were the disorganized type; 2.3% were the residual type; and 0.6% were the catatonic type.

There was a significant difference ($p<0.001$) among the treatment groups in the mean duration of treatment. The mean duration in the placebo, risperidone 2 mg, and haloperidol 20 mg groups was less than or equal to 35 days. The mean range in the risperidone 6, 10, and 16 mg groups was 39 to 43 days. The minimum duration was one day and the maximum was 64 days.

EFFICACY RESULTS

Positive and Negative Syndrome Scale (PANSS) for schizophrenia: At each visit, the investigator evaluated the patient using the PANSS. This 30-item scale consisted of three subscales: positive subscale (seven items); negative subscale (seven items); and general psychopathology subscale (16 items). These items were assessed on a seven-point scale where 1=absent, 2=minimal, 3=mild, 4=moderate, 5=moderate severe, 6=severe, and 7=extreme. The individual items evaluated in each part of the scale are presented in Appendix 2.

Clinical Global Impression (CGI): The overall severity of the patient's schizophrenia was rated by the investigator at each visit as not ill, very mild, mild, moderate, marked, severe, and extremely severe. At Visits 3-7, the patient's present condition was compared to his or her condition at baseline (CGI-C): very much improved, much improved, minimally improved, unchanged, minimally worse, much worse, and very much worse.

PANSS and CGI: Table 8 summarizes the mean change from baseline in symptom severity and the p-values at endpoint. Visual displays for the total PANSS is shown in Figure 2.

Comparison to placebo: At endpoint, patients treated with risperidone 6 mg, 10 mg, and 16 mg groups showed a significantly greater reduction from baseline with respect to total PANSS, positive, negative, and general psychopathology subscales of PANSS, total derived BPRS, total key BPRS items, and CGI. These differences were observed in the first week, the week at which there were at least 70% of the patients remained in each of the treatment groups. Patients treated with the risperidone 2 mg group did show significant improvement at endpoint in all of the above efficacy variables except in negative subscale of PANSS. However, these improvements were marginal compared to the other risperidone groups. Numerically, risperidone 6 mg demonstrated the greatest improvement in all of the efficacy variables studied. This improvement was maintained throughout the study and was consistent for all variables.

Risperidone--Integrated Summary of Effectiveness

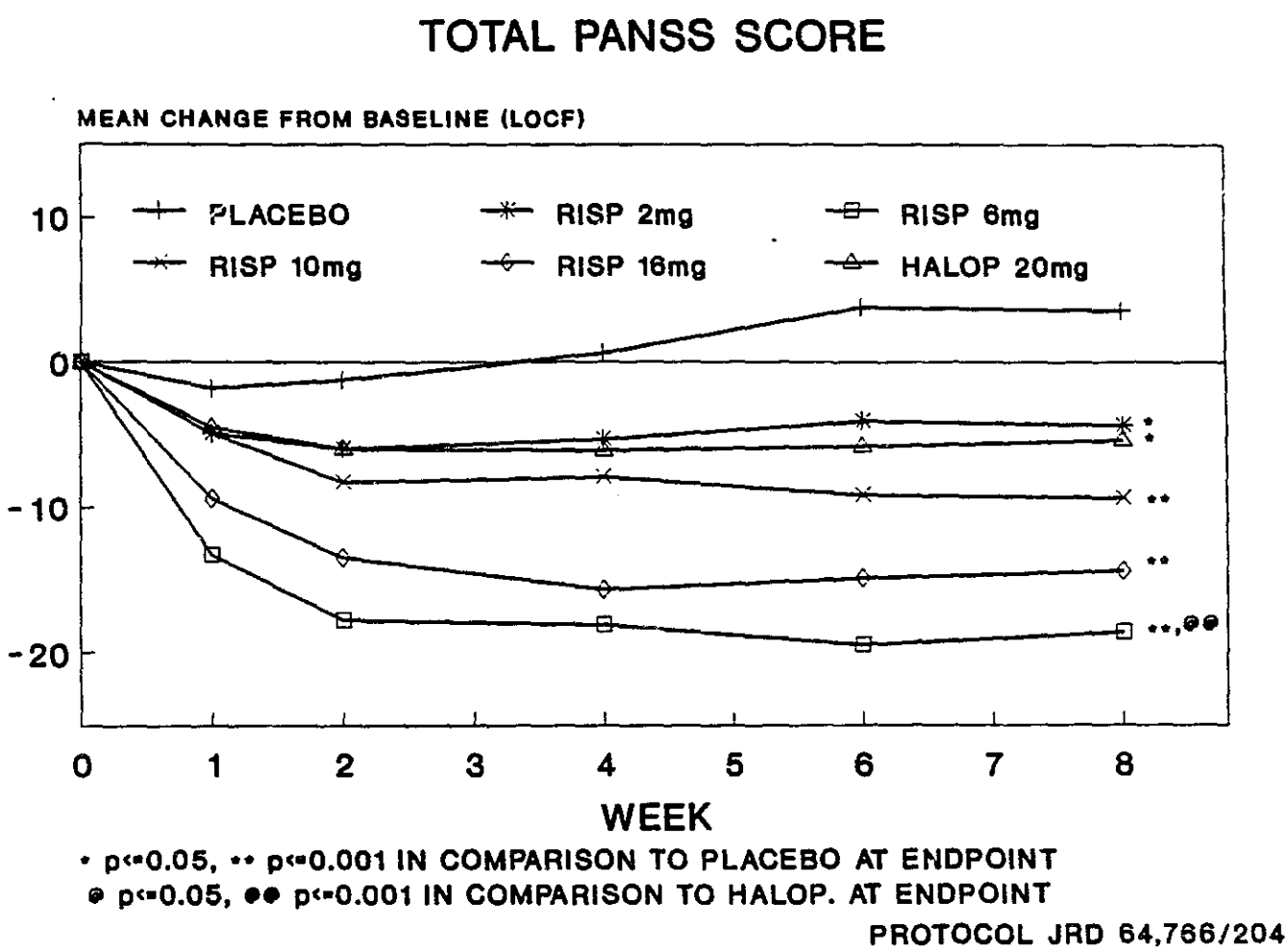
Table 8: Study JRD 64,766/204--Mean change from baseline score

Parameter[a]	Week	Placebo (N=86)	Risp 2mg (N=87)	Risp 6mg (N=85)	Risp 10mg (N=85)	Risp 16mg (N=85)	Hal 20mg (N=85)
Total PANSS (30-210)[b]	Baseline	92.6	89.2	94.9	91.8	93.9	93.6
	Week 1	-1.8	-4.9	-13.3**++	-4.9	-9.4*	-4.5
	Endpoint	3.6	-4.4*	-18.6**++	-9.4**	-14.4**	-5.4*
Positive Subscale (7-49)	Baseline	23.2	22.1	23.7	23.1	23.1	23.9
	Week 1	-0.8	-1.3	-3.4**	-1.9	-2.8*	-1.8
	Endpoint	1.5	-0.7	-5.4**+	-3.3**	-4.2**	-2.7**
Negative Subscale (7-49)	Baseline	24.0	23.8	25.5	24.5	24.7	24.9
	Week 1	0.1	-1.3	-3.3**+	-0.7	-1.9*	-0.8
	Endpoint	0.2	-1.3	-3.9**+	-1.9*	-3.1*	-0.7
General Psychopathology Subscale (16-112)	Baseline	45.5	43.2	45.8	44.2	46.1	44.7
	Week 1	-1.1	-2.3	-6.6**++	-2.4	-4.7*	-1.8
	Endpoint	1.9	-2.3*	-9.2**++	-4.2**	-7.1**	-1.9*
Derived BPRS (18-26)	Baseline	54.2	52.1	55.0	53.2	54.3	54.9
	Week 1	-1.2	-3.2	-7.2**+	-2.8	-5.4*	-2.8
	Endpoint	2.2	-2.9*	-11.2**++	-5.7**	-8.5**	-3.8*
Key BPRS items (4-28)	Baseline	15.4	14.9	15.7	15.4	15.4	15.8
	Week 1	-0.5	-1.2	-1.9*	-1.2	-1.5*	-1.3
	Endpoint	0.6	-0.8*	-3.5**	-2.2**	-2.8**	-2.1**
CGI-Absolute Severity (0-6)	Baseline	3.7	3.8	3.8	3.7	3.7	3.8
	Week 1	0.0	-0.2	-0.5**	-0.3*	-0.3*	-0.3*
	Endpoint	0.2	-0.2*	-0.9**+	-0.6**	-0.6**	-0.4**

[a] Higher values denote greater severity
[b] Minimum and maximum possible scores

* $p \leq 0.05$ ** $p \leq 0.001$ compared to placebo
+ $p \leq 0.05$ ++ $p \leq 0.001$ risperidone 6 mg compared to haloperidol

Figure 2: Total PANSS score--Mean change from baseline (LOCF)



* p<=0.05, ** p<=0.001 IN COMPARISON TO PLACEBO AT ENDPOINT
● p<=0.05, ●● p<=0.001 IN COMPARISON TO HALOP. AT ENDPOINT

PROTOCOL JRD 64,766/204

00-00021

The haloperidol group also showed a significant reduction from baseline with respect to all of the above mentioned efficacy variables except for the negative subscale of PANSS. The onset of action with haloperidol, however, was not as rapid as the effective risperidone group (6 mg). For example, the total PANSS scores in the haloperidol group were not significantly better than placebo until Week 4 of treatment.

Comparison to haloperidol: The risperidone 6 mg was more effective than the haloperidol group with respect to the total PANSS, positive, negative, and general psychopathology subscales of PANSS, total derived BPRS and CGI, and was marginally more effective with respect to the total key BPRS items. Risperidone 6 mg consistently improved the patients' symptoms throughout the study compared to haloperidol 20 mg.

Clinical improvement: Table 9 summarizes the number and percent of patients who improved in each treatment group and pairwise p-values at endpoint:

Table 9: Study JRD 64,766/204--Clinical improvement at endpoint

VIA	Placebo	Risp 2mg	Risp 6mg	Risp 10mg	Risp 16mg	Hal 20mg
Total PANSS	17/86 (19.8%)	34/87 (39.1%)*	52/85 (61.2%)**++	33/85 (38.8%)*	43/85 (50.6%)**	29/85 (34.1%)*
Total PANSS and CGI-C	14/86 (16.3%)	29/87 (33.3%)*	46/85 (54.1%)**+	32/85 (37.6%)*	40/85 (47.1%)**	27/85 (31.8%)*

* $p \leq 0.05$ ** $p \leq 0.001$ compared to placebo
+ $p \leq 0.05$ ++ $p \leq 0.001$ compared to haloperidol

At endpoint, a significantly higher percentage of patients in the risperidone and haloperidol groups showed clinical improvement as compared to placebo group. Relative to haloperidol group, patients treated with risperidone 6 mg showed a significantly greater clinical improvement at Week 1 (70% rule) ($p=0.032$) and at endpoint ($p=<0.001$) than the haloperidol-treated group. With respect to clinical improvement via total PANSS and CGI-C, 54% of the patients treated with risperidone 6 mg improved compared to 32% in the haloperidol 20 mg group and 16% in the placebo group.

CGI-change from baseline: Patients receiving risperidone or haloperidol showed improvement in CGI-C. Risperidone 6 mg showed the highest clinical improvement among the risperidone groups and was more effective than haloperidol. The percent of patients who improved in the CGI-C in each of the treatments was similar to the percent of patients whose total PANSS score decreased by at least 20% from baseline.

Global assessments: At Week 8 or discontinuation from the study, the investigator and patient each assessed the overall effect of the study drug compared to the patient's previous neuroleptic treatment as much better, slightly better, identical, slightly worse, worse, or much worse.

Both the investigator and patient rated risperidone 2, 6, 10, and 16 mg groups as more effective than previous neuroleptic therapy. Significant differences were also detected between the haloperidol and placebo groups. Risperidone 6 mg was rated as significantly ($p=0.001$) more effective when compared to haloperidol in both the investigator's and patient's assessments.

Percent of patients discontinued for insufficient response: Table 10 summarizes the number and percent of patients who discontinued due to insufficient response.

Table 10: Study JRD 64,766/204--Number and percent of patients who discontinued due to insufficient response

Week	Placebo (N=88)	Ris 2 mg (N=87)	Ris 6 mg (N=86)	Ris 10 mg (N=87)	Ris 16 mg (N=88)	Hal 20 mg (N=87)
Week 1	13 (15%)	7 (8%)	1 (1%)*	7 (8%)	6 (7%)	7 (8%)
Week 2	26 (30%)	18 (21%)	2 (2%)*	14 (16%)*	10 (11%)*	15 (17%)
Week 4	40 (46%)	31 (36%)	10 (12%)*	16 (18%)*	13 (15%)*	29 (33%)
Week 6	50 (57%)	38 (44%)	12 (14%)*	24 (28%)*	17 (19%)*	33 (38%)*
Week 8**	51 (58%)	41 (47%)	12 (14%)*	25 (29%)*	18 (21%)*	36 (41%)*

* $p<0.05$ compared to placebo
** Total number of patients who discontinued from the study (Weeks 1-8)

At the end of the study, a significantly greater number of patients from placebo (58%), risperidone 2 mg (47%), and haloperidol 20 mg (41%) groups discontinued the study due to insufficient response when compared to risperidone 6 mg (14%) group.

Risperidone--Integrated Summary of Effectiveness

Conclusions:

- For each of the efficacy assessments the improvement between baseline and endpoint was significantly greater for the 6, 10, and 16 mg risperidone-treated groups than for the placebo-treated group. Risperidone 6 mg showed the largest improvement in all the efficacy variables. Patients treated with risperidone 2 mg also improved relative to placebo but the magnitude of effect was smaller than the other doses.

- Patients treated with risperidone 6 mg improved ($p<0.001$) relative to placebo-treated patients on both of the primary efficacy assessments. The percentage of patients showing clinical improvement, as determined by the total PANSS score was approximately three times greater in the risperidone 6 mg group than in the placebo group.

- Risperidone was effective in treating negative as well as positive symptoms. Relative both to placebo and to baseline, risperidone 6, 10 and 16 mg significantly reduced the PANSS negative symptom subscale score. Risperidone 6 mg was significantly ($p=0.004$) more effective than haloperidol in reducing negative symptoms.

- Risperidone 6 mg was consistently superior to haloperidol. Patients treated with risperidone 6 mg improved ($p<0.001$) relative to haloperidol-treated patients on each of the two primary efficacy assessments. The percentage of patients showing clinical improvement, as determined by the total PANSS score was almost twice as great in the risperidone 6 mg group as in the haloperidol group (61 vs. 34%, respectively).

- The risperidone 6, 10, and 16 mg groups had a significantly fewer dropouts due to insufficient response than placebo at Weeks 2, 4, 6, and 8.

- In summary, risperidone had a rapid onset of action and was significantly superior to placebo and risperidone 6 mg was superior to haloperidol 20 mg in reducing both positive and negative symptoms of psychosis.

64,766/024 (RIS-INT-2)

This study was a multinational study designed to parallel the North American trial JRD 64,766/204. The primary purpose of this study was to establish the effective dose range for risperidone. Thus, risperidone doses of 1, 4, 8, 12, and 16 mg were chosen to interpolate between the doses in Study JRD 64,766/204. The design was the same as Study JRD 64,766/204 except a placebo group was not used. The effects of risperidone 1 mg were compared to the higher doses of risperidone and a daily dose of haloperidol 10 mg. The investigators were trained in the rating of the PANSS using the same videotape that was used in the U.S. and Canada.

This was a randomized, double-blind multicenter trial conducted at 110 sites in 15 countries in Europe, Africa, and Central and South America. Male and female patients between the ages of 18 and 65 with chronic schizophrenia were eligible. They had to meet the DSM III-R criteria for schizophrenia and to have a minimum total score of 60 and a maximum total score of 120 on the PANSS. Patients were excluded if they had mental disorders other than schizophrenia. After a one-week, single-blind, placebo washout period, patients were randomly assigned to one of the six treatment groups: risperidone 1, 4, 8, 12, and 16 mg, or haloperidol 10 mg.

During the first week of the double-blind period (Days 1-7), a fixed upward titration was required to reach the target dose within each treatment group; thereafter (Days 8-56), the dose remained constant. Patients were assessed at the end of the washout period (baseline) and after 1, 2, 4, 6, and 8 weeks of double-blind treatment.

STATISTICAL ANALYSIS

The same primary and secondary parameters were analyzed in this study as in Study JRD 64,766/204 except total key BPRS items. The statistical methods used in this study were similar to Study JRD 64,766/204. However, in the two-way ANOVA, the factors were treatment and country instead of treatment and investigator.

Pairwise comparisons (interpreted at the 5% level) were only performed when the overall test over the six treatment groups showed a significant difference at the 10% level. The pairwise comparisons between the risperidone 1 mg and the other risperidone treatment groups were considered primary comparisons. The comparisons of haloperidol versus risperidone 1 mg and haloperidol versus the most effective dose were considered secondary.

Risperidone--Integrated Summary of Effectiveness

PATIENT DISPOSITION

A total of 1510 patients entered the study. Data from 148 patients at six sites were excluded from the efficacy analysis because the sites were declared invalid due to failure to comply with Good Clinical Practices (elimination of these patients did not change the significance of intergroup differences for any of the assessments). The remaining 1362 patients received risperidone 1 mg (N=229), risperidone 4 mg (N=227), risperidone 8 mg (N=230), risperidone 12 mg (N=226), risperidone 16 mg (N=224), or haloperidol 10 mg (N=226). Of the 1362 evaluable patients, 1019 (75%) completed the eight-week treatment period. For the 343 patients who discontinued prematurely, insufficient response and adverse experiences were the most reported reasons for discontinuation.

There were no statistical differences between the groups with respect to sex, race, age, weight, and height (Table 11).

Table 11: Demographics

Study 64,766/024		Ris 1mg	Ris 4mg	Ris 8mg	Ris 12mg	Ris 16mg	Hal 10mg	Total
Entered		229	227	230	226	224	226	1362
Sex	M	166	152	144	142	140	150	894
	F	63	75	86	83[a]	84	76	467[a]
Race	Asian	11	3	10	7	8	11	50
	White	189	183	189	185	189	181	1116
	Hispanic	17	17	12	16	16	16	94
	Black	9	21	13	15	7	15	80
	Mixed	1	3	4	1	2	2	13
	NR	2	0	2	2	2	1	9
Mean age (yrs)		38.4	38.1	37.6	37.9	38.5	38.1	38.1
Mean weight (kg)		70.3	70.9	69.9	68.8	68.8	70.7	69.9
Mean height (cm)		170.3	168.4	168.8	168.8	168.1	168.5	168.8

[a]: the sex of one patient was not recorded
NR: Not recorded

Thirty percent of the patients had a known family history of psychiatric or neurological disorders. The mean age at onset of psychiatric symptoms was 22.8 years, and at first hospitalization was 25.2 years. The mean number of previous hospitalizations was 4.9; nine percent of the patients had not been hospitalized. The mean duration of the current hospitalization was 4 months.

EFFICACY RESULTS

PANSS and CGI: Table 12 summarizes the mean change from baseline in symptom severity and the p-values at endpoint.

Table 12: Study 64,766/024--Mean change from baseline score

Parameter[a]	Week	Ris 1mg (N=229)	Risp 4mg (N=227)	Risp 8mg (N=230)	Risp 12mg (N=226)	Risp 16mg (N=224)	Hal 10mg (N=226)
Total PANSS (30-210)[b]	Baseline Endpoint	90.1 -12.5	89.6 -18.6*	89.2 -17.9*	90.5 -16.6	89.8 -17.0*	88.8 -15.0
Positive Subscale (7-49)	Baseline Endpoint	19.5 -2.1	19.2 -4.2**	18.9 -4.5**	19.1 -3.9*	19.9 -4.9**	19.0 -3.9*
Negative Subscale (7-49)	Baseline Endpoint	26.6 -4.5	26.2 -5.5	26.8 -5.2	26.6 -5.0	26.2 -5.2	26.4 -4.8
General Psychopathology Subscale (16-112)	Baseline Endpoint	44.0 -6.0	44.2 -8.9*+	43.6 -8.2*	44.8 -7.7	43.7 -6.9	43.4 -6.4
Derived BPRS (18-26)	Baseline Endpoint	48.9 -6.7	48.6 -10.2*	48.1 -10.0*	49.1 -9.0*	49.5 -9.7*	48.1 -8.1
CGI-Absolute Severity (0-6)	Baseline Endpoint	3.9 -0.4	3.8 -0.8**	3.8 -0.8*	3.8 -0.7*	3.9 -0.8**	3.7 -0.6

[a] Higher values denote greater severity
[b] Minimum and maximum possible scores

* $p \leq 0.05$ ** $p \leq 0.001$ compared to risperidone 1 mg

Patients receiving risperidone 4 mg, 8 mg, and 16 mg showed a significant reduction from baseline to endpoint for the total PANSS score compared to patients receiving risperidone 1 mg. Similar patterns were obtained for the PANSS general psychopathology subscale and PANSS-derived BPRS. The patients in the risperidone 1 mg group differed from all other groups on the PANSS positive subscale, but did not differ significantly from any of the other groups on the PANSS negative subscale at endpoint. Numerically, risperidone 4 and 8 mg were the most effective doses of risperidone for each of the efficacy variables studied. Risperidone 16 mg was the more effective dose for improving positive symptoms. The CGI-severity of schizophrenia at endpoint was significantly lower in the risperidone 4, 8, 12, and 16 mg groups compared to risperidone 1 mg.

Clinical improvement: Of the 1362 patients, 814 (60.2%) showed clinical improvement via total PANSS at endpoint. No significant difference was observed among risperidone 4, 8, 12, and 16 groups versus risperidone 1 mg. The percentage of patients that showed clinical improvement via total PANSS and CGI-C varied between 47.8% in the risperidone 1 mg group and 59.4% in the risperidone 8 mg group. Table 13 summarizes the percent of patients who improved in each treatment group.

Table 13: Study 64,766/024--Clinical improvement at endpoint

VIA	Ris 1 mg	Ris 4 mg	Ris 8 mg	Ris 10 mg	Ris 16 mg	Hal 10 mg
Total PANSS	54.4%	63.4%	65.8%	58.2%	60.5%	58.7%
Total PANSS and CGI-C	47.8%	57.7%	59.4%	52.4%	52.5%	55.6%

CGI-change from baseline: Patients receiving risperidone 4 and 8 mg and haloperidol showed significant improvement versus risperidone 1 mg. The percent of patients showing improvement was similar among the risperidone 4 (69.2%) and 8 mg (67.2%) and haloperidol 10 mg (67.1%). Although the other groups showed improvement, significance was not reached.

Global assessments: At the end of the study, the investigator and patient compared the double-blind medication with previous neuroleptic treatment on a 7-point scale. The investigators rated the mean score as significantly better for risperidone 4 mg than risperidone 1, 12, and 16 mg. No significant differences were noted when the patients rated their study medication versus their previous neuroleptic treatment.

Percent of patients discontinued for insufficient response: Table 14 summarizes the number and percent of patients who discontinued due to insufficient response.

Table 14: Study 64,766/024--Number and percent of patients who discontinued due to insufficient response at endpoint

Ris 1 mg (N=229)	Ris 4 mg (N=227)	Ris 8 mg (N=230)	Ris 12 mg (N=226)	Ris 16 mg (N=224)	Hal 10 mg (N=226)
40 (17.5%)	16 (7.0%)**	24 (10.4%)*	32 (14.2%)	20 (8.9%)*	22 (9.7%)*

* $p \leq 0.05$ ** $p \leq 0.001$ compared to risperidone 1 mg

Conclusions

- Patients in the risperidone 4, 8, or 16 mg groups were improved ($p<0.05$) compared to patients in the risperidone 1 mg on the total PANSS score.

- The largest magnitude of effect was observed with risperidone 4 or 8 mg in all efficacy variables. For the total PANSS score, the PANSS positive subscale and general psychopathology subscale scores, the PANSS-derived BPRS scores, and the CGI-severity score, the improvement between baseline and endpoint was significantly greater for the risperidone 4 and 8 mg groups than for the risperidone 1 mg group. Additionally, the percentage of patients showing clinical improvement as assessed by the PANSS, the PANSS-derived BPRS and the CGI-change scores was higher and the percentage of patients who discontinued for insufficient response was lower in the risperidone 4 and 8 mg groups than in the risperidone 1 mg group. Only the PANSS negative subscale score failed to show a difference among these groups, and this may indicate an unexpected efficacy for the 1 mg dose rather than an insufficient response for the higher doses.

- Whereas risperidone 4 and 8 mg were superior to 1 mg risperidone on all but one of the efficacy assessments above, haloperidol was superior to the lowest dose of risperidone (1 mg) only with respect to the PANSS positive subscale score, key BPRS items and the CGI-severity scale. The optimal dose of risperidone (4 mg) was at least marginally superior to haloperidol in reducing symptoms of psychosis as determined by the total PANSS, the PANSS general psychopathology subscale, the PANSS-derived BPRS, and the CGI-severity scores. Together, these data are consistent with the previous findings that risperidone is more effective than haloperidol in reducing symptoms of psychosis.

III. ADDITIONAL CONTROLLED STUDIES

Table 15 summarizes the design of the six double-blind, controlled Phase II trials that have examined risperidone in the treatment of symptoms of psychosis. As with the adequate and well- controlled trials, described above, a consistent pattern emerged from these supportive studies. In every instance, risperidone-treated patients improved from baseline to endpoint. In each study, for each assessment, risperidone was at least as effective as (not significantly different from) the active control drug. In Study RIS-BEL-5, risperidone was significantly more effective than haloperidol in reducing symptoms of psychosis as assessed by the SADS-C scale. Additionally, risperidone produced approximately a 14-point decrease in the total PANSS score, whereas haloperidol produced only a 5-point decrease. Although these differences did not achieve significance because of the limited number of subjects per group, they are quite similar in magnitude to those seen in Study JRD 64,766/204. However, in Study RIS-BEL-7, no significant changes in the BPRS, NOSIE, and CGI were noted between risperidone 2-20 mg and haloperidol 2-20 mg.

In Study RIS-FRG-9005, risperidone 4 mg and clozapine each produced a 17-point improvement from baseline in the BPRS symptom score. Although there were no intergroup differences in this study, the magnitude of this effect was sufficient to suggest that both drugs were equally effective. In Study RIS-INT-7, 74% of patients treated with risperidone and 59% of patients treated with perphenazine showed a clinically significant improvement in PANSS scores ($p=0.11$). A similar difference was seen for the derived BPRS scale ($p=0.04$). In Study RIS-FRA-9003, according to the mean total PANSS score risperidone significantly improved psychotic symptoms compared to the haloperidol ($p=0.047$) and levomepromazine ($p=0.015$) groups. Finally, in Study RIS-BEL-11, risperidone was significantly more effective than placebo in reducing behavioral disturbances in mentally retarded patients as assessed either by a CGI ($p<0.01$) or an Aberrant Behavior Checklist ($p=0.01$).

Risperidone--Integrated Summary of Effectiveness

Table 15
Double-blind Controlled Trials of
Risperidone in the Treatment of Symptoms of Psychosis

Study	No. of patients	Population	Treatments (mg/day)	Duration	Assessments
RIS-BEL-5 (Belgium 006)*	44	Chronic schizophrenics	Risperidone 12 (2-20)[1] Haloperidol 10 (2-20)[1]	12 weeks	PANSS SADS-C NOSIE CGI-C
RIS-BEL-7 (Belgium 008)	60	Schizophrenics	Risperidone 9.1 (2-20)[1] Haloperidol 9.4 (2-20)[1]	8 weeks	BPRS NOSIE CGI
RIS-FRG-9005 (Germany 022)	59	Schizophrenics	Risperidone 4 [2] Risperidone 4 [2] Clozapine 400 [2]	28 days	BPRS CGI
RIS-FRA-9003 (France 041)	62	Chronic schizophrenics	Risperidone 9 (4-12)[1] Haloperidol 9 (4-12)[1] Levomepromazine 125 (50-150)[1]	4 weeks	PANSS PAS CGI
RIS-INT-7 (Den/Nor 048)	107	Chronic schizophrenics	Risperidone 8.5 (5-15) [1] Perphenazine 28 (16-48)[1]	8 weeks	PANSS CGI
RIS-BEL-11 (Belgium 015)	37	Mentally retardation with behavior disturbances	Risperidone 8.3 (4-12)[1] or Placebo add-on	21 days cross-over	ABC CGI VAS

1. Dose titrated to individual needs. Values are group mean (allowable range) in mg/day at endpoint.

2. Fixed dose in mg/day at endpoint.

PANSS	Positive and Negative Syndrome Scale
SADS-C	Schedule for Affective Disorders and Schizophrenic, change version
NOSIE	Nurses Observation Scale for Inpatient Evaluation
CGI-C	Clinicians Global Impression, change version
BPRS	Brief Psychiatric Rating Scale
CGI	Clinical Global Impression
ABC	Aberrant Behavior Checklist
VAS	Visual Analogue Scale, Severity of Target Symptom
PAS	Psychotic Anxiety Scale

* Protocol number

IV. UNCONTROLLED STUDIES

Table 16 summarizes the open-label experience with risperidone in the treatment of symptoms of psychosis. In each of these studies, risperidone-treated patients improved relative to baseline. Studies RIS-BEL-6 and the follow-up RIS-BEL-9 suggest effectiveness in an elderly population. The dose range at endpoint in this trial was slightly lower than that recommended based on the controlled studies above.

Table 16
Open Label or Single-blind Studies of
Risperidone in the Treatment of Symptoms of Psychosis

Study	No. of patients	Population	Treatments	Duration	Assessments
RIS-ITA-9001 (Italy 026)*	31	Chronic schizophrenics	6[2]	28 days	BPRS SANS
RIS-BEL-6 (Belgium 007)	50	Elderly with behavior disturbance (DAT, MID, and Schizophrenia)	3 (1-10)[1]	28 days	PBES VAS
RIS-BEL-9 (Belgium 013)	9	Elderly with behavior disturbance	2.4 (0.5-10)[1]	1 year	PBES GTI VAS
RIS-BEL-15 (Belgium 030)	5	Chronic schizophrenics	9.5 (1-20)[1]	1 year	PANSS NOSIE CGI
RIS-FRA-9001 (France 019)	12	Chronic schizophrenics	2 or 4[2]	6 weeks	BPRS SANS CGI
RIS-INT-1 (Flanders)	61	Chronic schizophrenics	3.7[1]	28 days	BPRS CGI
(Wallony)	40		5.6[1]		
(Portugal)	20		4.6[1]		
RIS-FRG-9003 (Germany 020)	13	Chronic shizophrenics	7 (1-10)[1]	28 days	BPRS CGI
RIS-FRG-9004 (Germany 021)	10	Chronic schizophrenics (negative symptoms)	8 or 12[2]	28 days	BPRS CGI SANS NOSIE AMDP 4&5
RIS-GBR-9003 (Gr. Brit 036)	7	Chronic Schizophrenics	16 (4-20)[1]	28 days	PANSS MSCS MADRS SANS
RIS-ITA-9002 (Italy 038)	10	Chronic schizophrenics	6[2]	1 month	BPRS SANS HAM-D STAI-X1
RIS-INT-8	17	Psychiatric with hallucinations	4.5[1]	up to 13 months	GTI BPRS

1. Dose titrated to individual needs. Values are group mean (allowable range) in mg/day at endpoint.
2. Fixed dose in mg/day at endpoint.

PBES Psychogeriatric Behavioral Evaluation Scale
VAS Visual Analogue Scale, Severity of Target Symptom
NOSIE Nurses Observation Scale for Inpatient Evaluation
CGI-C Clinicians Global Impression
MSCS Montgomery Schizophrenic Change Scale
MADRS Montgomery & Asberg Depression Rating Scale
SANS Scale for Assessment of Negative Symptoms
Ham-D Hamilton Depression Rating Scale
STAI-X1 State Trait Assessment Index

* Protocol number

Table 16--continued
Open label or Single-blind Studies of Risperidone in the Treatment of Symptoms of Psychosis

Study	No. of patients	Population	Treatments	Duration	Assessments
RIS-BEL-4 (Belgium 005)*	17	Psychotic	10-25[2]	4 weeks	BPRS SANS CGI-M
RIS-BEL-17 (Belgium 035) RIS-HOL-9002 (Holland 011) RIS-INT-8 (Int. 004)	264	Psychotic	7.6 (2-20)[1]	6 mos-1 year	BPRS GTI
RIS-INT-4 (Int. 033)	77	Chronic schizophrenics	9 (2-16)[1]	up to 1 year (Ongoing)	PANSS CGI
RIS-TCH-9001 (Czech. 008)	36	Psychotic	Risperidone 10.8 (2-20)[1] Haloperidol 9.7 (2-20)[1]	8 weeks	Serejki rating scale BPRS FKP DVP
RIS-JPN-9003 (Japan 045)	83	Schizophrenics	6.6 (1.5-15)[1]	8 weeks	BPRS GIR

1. Dose titrated to individual needs. Values are group mean (allowable range) in mg/day at endpoint.
2. Fixed dose in mg/day at endpoint.

PANSS	Positive and Negative Syndrome Scale for schizophrenia
SANS	Scale for the Assessment of Negative Symptoms
CGI-M	A modified Clinical Global Impressions Scale
BPRS	Brief Psychiatric Rating Scale
CGI	Clinical Global Impressions Scale
GIR	Global Improvement Rating Scale
GTI	Global Therapeutic Impression

* Protocol number

V. COMPARISONS ACROSS STUDIES

Efficacy of Risperidone to Improve Symptoms of Psychosis

The efficacy of risperidone was demonstrated in three adequate and well-controlled studies using three different designs to achieve slightly different goals. Study JRD 64,766/201 was designed to reflect the clinical practice of dose escalation. As expected, most patients received the maximum dose of risperidone (53%, 10 mg/day), haloperidol (51%, 20 mg/day) and placebo (56%, 10 tablets). Studies JRD 64,766/204 (conducted in the U.S. and Canada) and 64,766/024 (conducted in several countries outside of North America), were designed to systematically investigate risperidone dose-response relationships. These studies used complementary fixed-dose designs that differed only in the choice of doses and control conditions. Study JRD 64,766/204, the North American trial, compared daily doses of both placebo and haloperidol 20 mg with four doses of risperidone. Study 64,766/024, the multinational trial, compared a low daily dose (1 mg) of risperidone and haloperidol 10 mg with four other doses of risperidone. The exclusion of the placebo group outside of North America was based on restrictions many countries have about using a placebo group when approved treatments are available. The use of a lower dose of haloperidol in the multinational trial was based on clinical practice in Europe. The choice of "interlocking" dosages in these two trials was deliberate. In the North American trial, dosages of risperidone 2, 6, 10, and 16 mg daily were used, while risperidone doses of 1, 4, 8, 12, and 16 mg daily were studied in the multinational trial. Apart from the highest dose of 16 mg daily, which was thought to be close to the limit of tolerance, an extensive dose range of 1 to 12 mg daily with increments 1-2 mg daily was covered.

Study JRD 64,766/201 and the other two studies also differed in the assessments used. Study JRD 64,766/201 used the BPRS and SANS scales to measure treatment effects on overall/positive and negative symptoms, respectively. Studies JRD 64,766/204 and 64,766/024 used the PANSS as the primary efficacy assessment scale. The PANSS contains all 18 items from the BPRS scale as well as specific positive and negative symptom subscales. Thus, the total PANSS score combines information that in previous studies could only be obtained from a separate analysis of the BPRS and SANS scores.

These differences among the studies provide an opportunity to test whether risperidone would: A) be an effective antipsychotic agent; B) be effective against both positive and negative symptoms; C) be at least as effective, if not more effective than haloperidol; and D) be less likely than haloperidol to produce EPS.

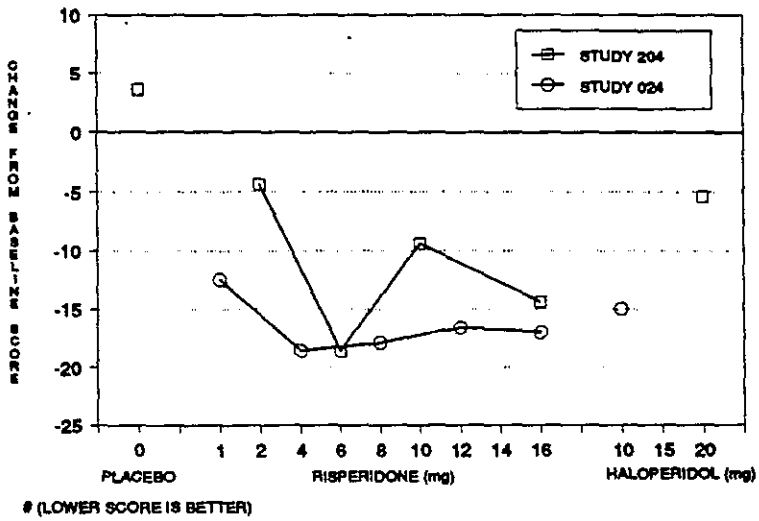
Risperidone--Integrated Summary of Effectiveness

Overall Efficacy

A. Symptom Scores and Clinical Improvement: PANSS and BPRS. The mean change from baseline to endpoint in each of the three adequate and well-controlled studies is shown as a function of drug and dose group, for the total PANSS and the total BPRS (or PANSS-derived BPRS) in Figures 3 and 4, respectively. Mean treatment difference and 95% confidence limits for the BPRS are shown in Figure 5. The percentage of patients showing clinical improvement (20% or greater reduction in symptom score) as determined by the PANSS or BPRS are shown in Figures 6 and 7, respectively. In order to facilitate comparison, the data from Study JRD 64,766/201 are plotted using the maximum dose allowed in the protocol.

Figure 3.

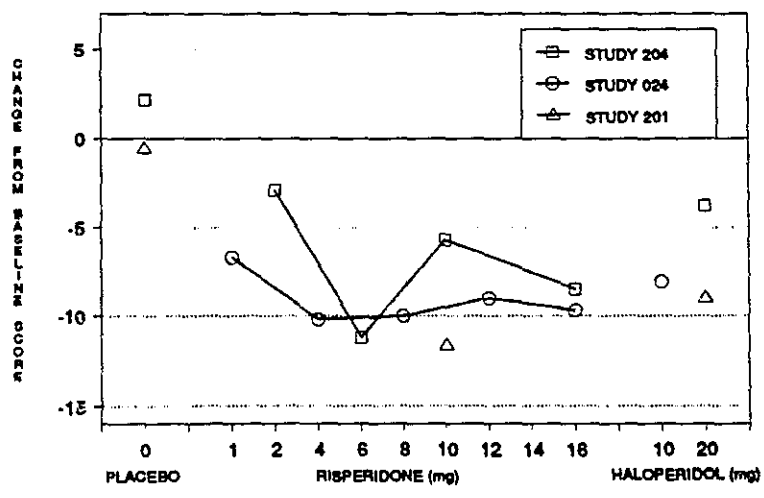
MEAN CHANGE IN SYMPTOM SEVERITY RATINGS
TOTAL PANSS AT ENDPOINT #



(LOWER SCORE IS BETTER)

Figure 4.

MEAN CHANGE IN SYMPTOM SEVERITY RATINGS
TOTAL BPRS AT ENDPOINT #



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00-00037

Risperidone--Integrated Summary of Effectiveness

Figure 5.

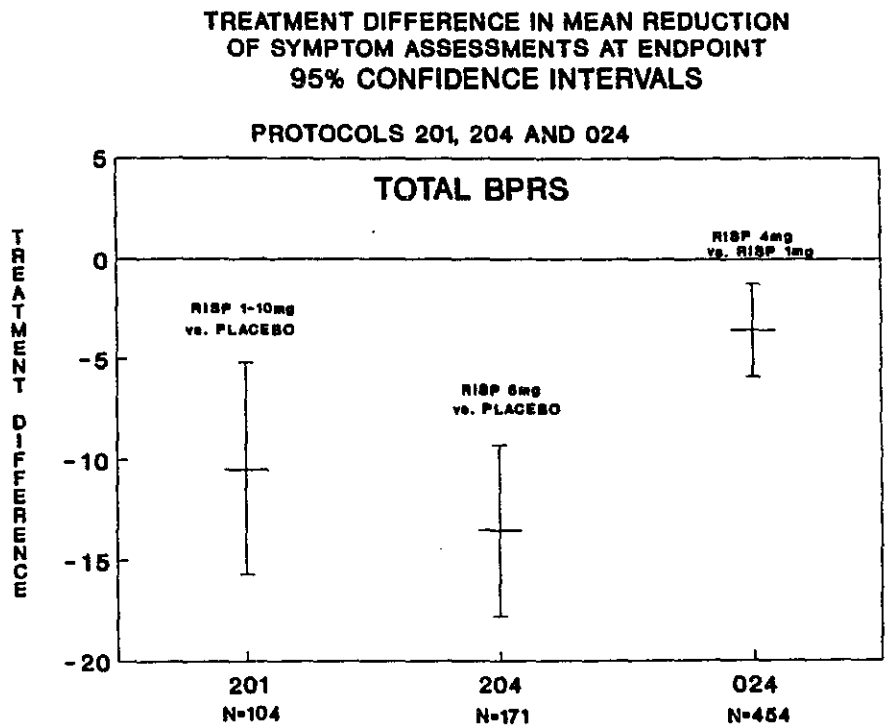


Figure 6.

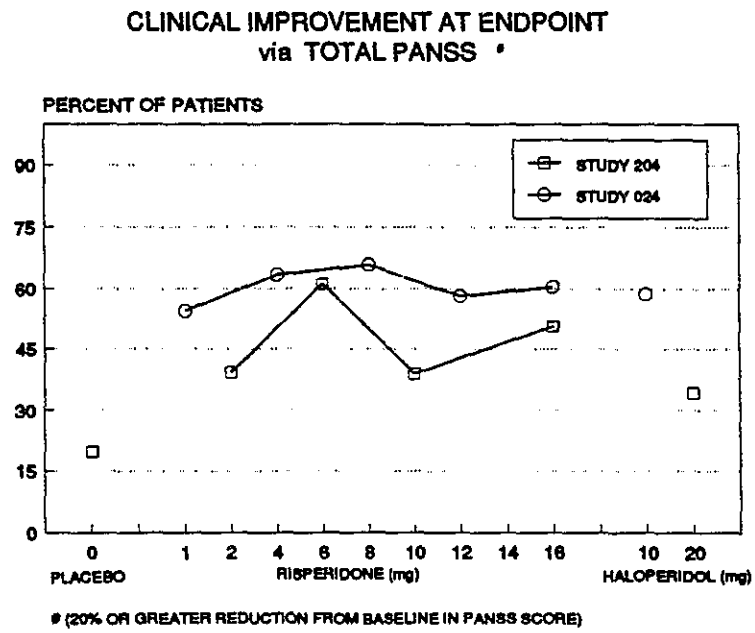
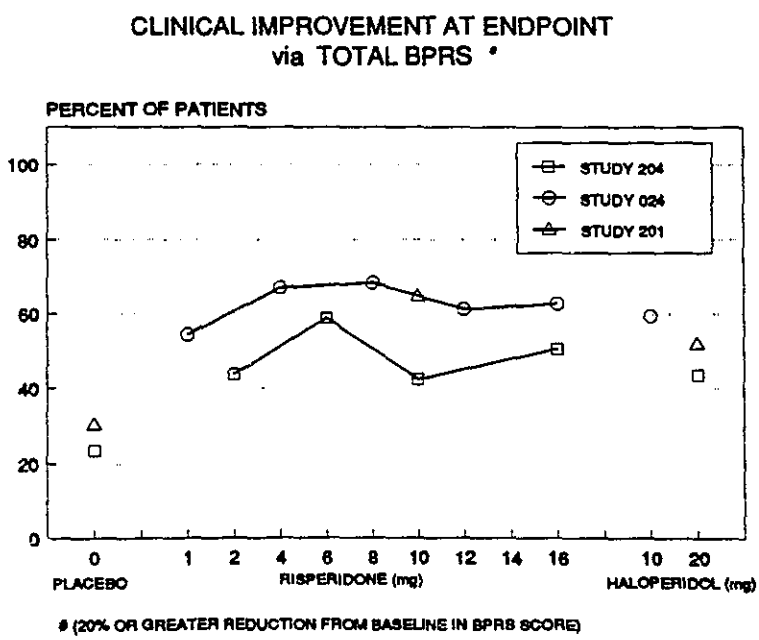


Figure 7.

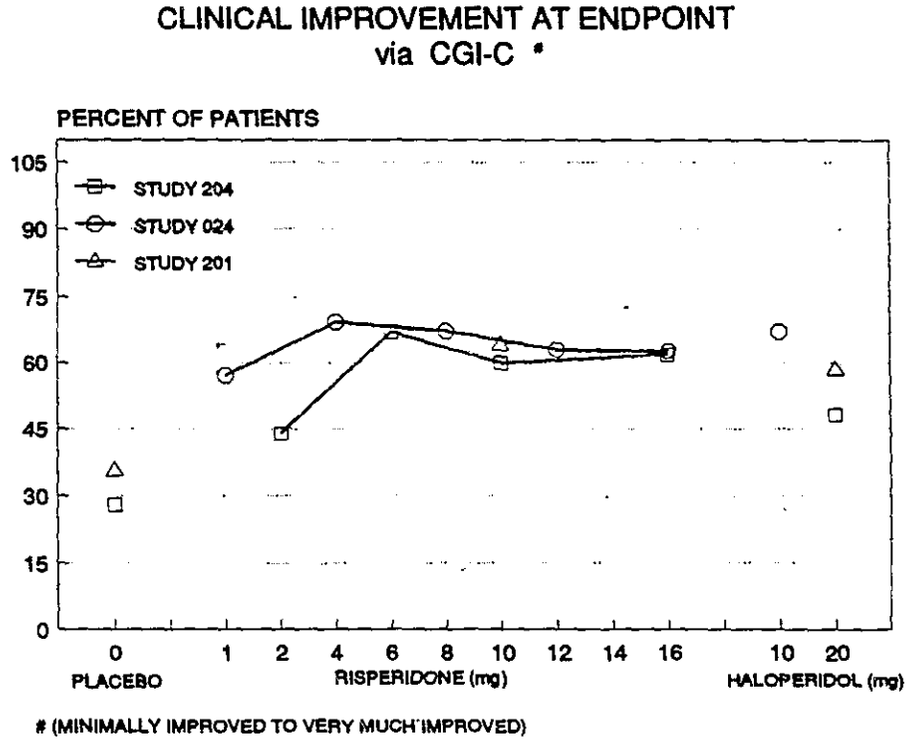


In each of the three studies, risperidone produced a significant improvement in the PANSS and the BPRS or PANSS-derived BPRS symptom scores and a corresponding increase in the percentage of patients with clinical improvement. Fifteen of 18 BPRS items improved significantly relative to baseline ($p \leq 0.05$) during risperidone treatment in Study JRD 64,766/201 and 29 of 30 PANSS items, including 17 of the 18 derived BPRS items improved significantly relative to baseline during risperidone (6 mg) treatment in Study JRD 64,766/204.

The range of effective doses was relatively broad, extending from at least risperidone 2 mg through 16 mg, the highest dose tested. Although statistical comparison is not appropriate, the use of risperidone 1 mg group from Study 64,766/024 suggests that even this low dose of risperidone may have some effect. In the two studies that systematically examined the dose-response relationship, the greatest magnitude of response was seen with doses in the range of risperidone 4 to 8 mg. Higher doses were not more effective and increased the risk of side effects (see Section VI).

B. Global Evaluations: Percent Improved CGI-Change Score. The percentage of patients showing improvement from baseline to endpoint, as assessed by the CGI-Change score, is shown in Figure 8, as a function of drug and dose group, for each of the three adequate and well-controlled studies. To facilitate comparison of dose-response relationships across studies, the data from Study JRD 64,766/201 are plotted as in previous figures. The pattern of results was similar to that described above for the total PANSS and BPRS symptom scales. In all three studies, risperidone significantly increased the percentage of patients showing improvement by the CGI-Change score. The range of effective doses, the magnitude of the maximum effect, and dose of peak effect was similar across studies.

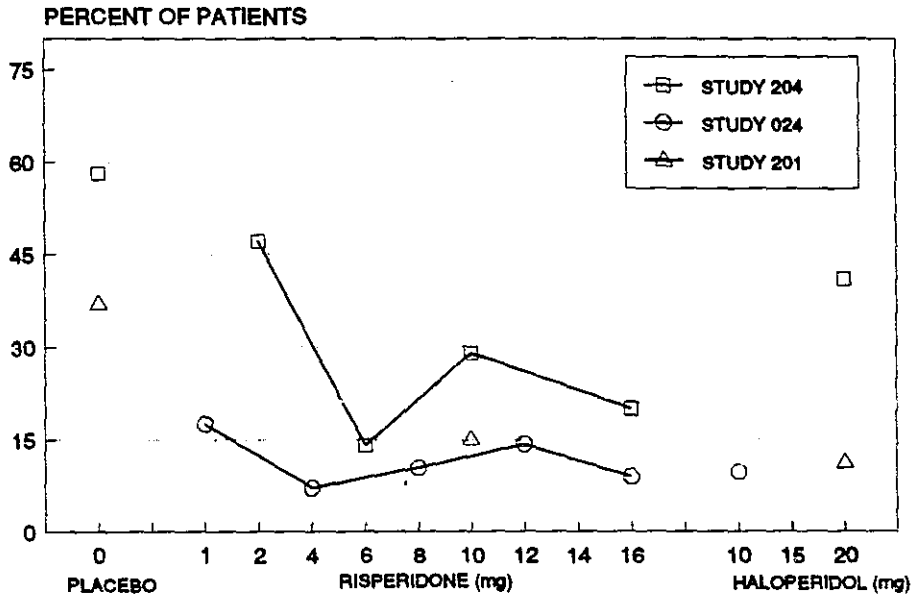
Figure 8.


CLINICAL IMPROVEMENT AT ENDPOINT
via CGI-C #
PERCENT OF PATIENTS
105
90
75
60
45
30
15
0
STUDY 204
STUDY 024
STUDY 201
0
1
2
4
6
8
10
12
14
16
10
20
PLACEBO
RISPERIDONE (mg)
HALOPERIDOL (mg)
(MINIMALLY IMPROVED TO VERY MUCH IMPROVED)

C. Outcome: Percent of Patients Discontinued for Insufficient Response. Figure 9 shows, as a function of dose group, the percentage of patients who discontinued for insufficient response in each study. Data from Study JRD 64,766/201 are plotted as in Figure 4. The pattern of results is similar to that described above. Risperidone was effective across a wide range of doses in all three studies. The maximum effect and dose of peak effect were similar across studies. However, there is a clear suggestion of a tendency for investigators in Study JRD 64,766/204 to be more conservative, (due to the possibility of ineffective doses of risperidone in addition to placebo), resulting in a higher overall proportion of patients discontinued for insufficient response. Treatment differences observed using the survival analysis techniques were similar to the crude rate results using test.

Figure 9.

PREMATURE DISCONTINUATIONS DUE TO INSUFFICIENT RESPONSE



Conclusion: There is consistency across the three trials regarding the overall effectiveness of risperidone. Despite differences in design, methods of assessment, dosages and controls, each of the three trials demonstrated a significant overall effect of risperidone in improving symptoms of psychosis.

D. Negative and Positive Symptoms

In Study JRD 64,766/201, no attempt was made to measure effects on positive symptoms. The primary efficacy measurements, the BPRS, as well as the key BPRS item subscale, examine positive symptoms. Effects of risperidone on negative symptoms in Study JRD 64,766/201 were evaluated with a separate scale, the Scale for Assessment of Negative Symptoms (SANS). In Studies JRD 64,766/204 and 64,766/024, effects of risperidone on positive and negative symptoms were evaluated using the corresponding subscales of the PANSS. Together, these analyses provided evidence that risperidone is effective in the treatment of both positive and negative symptoms of psychosis.

Positive Symptoms. Figure 10 shows the change in the PANSS positive symptom subscale from baseline to endpoint, as a function of drug and dose group, for Studies JRD 64,766/204 and 64,766/024. The results are consistent with those described above for the total PANSS. In both studies, the PANSS positive symptom scores at endpoint for the risperidone 4 through 16 mg groups were significantly improved relative to both the corresponding baseline score and to the scores for the placebo group.

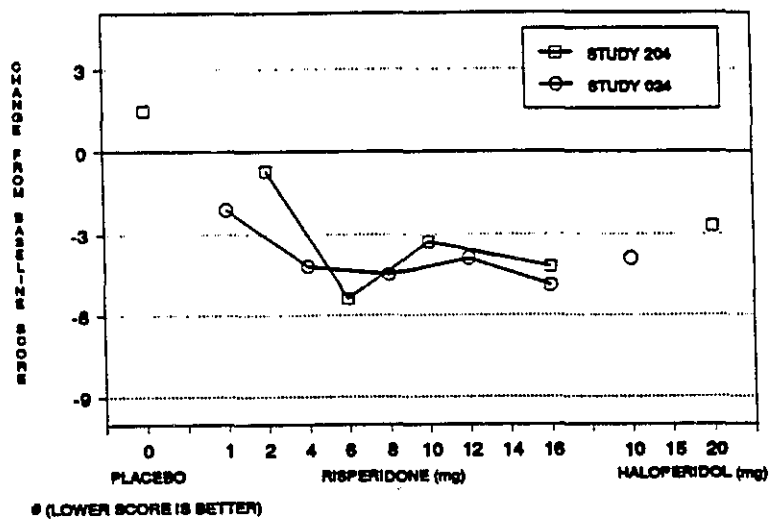
Negative Symptoms. In Study JRD 64,766/201, risperidone produced an almost 20% reduction in the SANS score; only a 6% reduction was observed in placebo-treated patients. This difference did not reach statistical significance ($p=0.056$). A statistically significant difference between risperidone and placebo was obtained when the scores for the SANS non-global items were evaluated ($p=0.049$, not shown).

Figure 11 shows the change in the PANSS negative symptom subscale from baseline to endpoint, as a function of drug and dose group, for Studies JRD 64,766/204 and 64,766/024. The results for Study JRD 64,766/204 were similar in direction and even greater in magnitude and consistency than those described above for Study JRD 64,766/201.

The PANSS negative symptom subscale scores at endpoint for the risperidone 4 through 16 mg groups were significantly improved relative both to the corresponding baseline score and to the scores for the placebo group. The larger, more consistent result in Study JRD 64,766/204 relative to Study JRD 64,766/201 probably is because of the greater power due to larger patient numbers and from the titration procedure used in Study JRD 64,766/201. The majority of patients in Study JRD 64,766/201 (54%) received the highest allowable risperidone dose of 10 mg daily. Subsequent experience suggests this dose may be too high to demonstrate optimal effectiveness.

Figure 10.

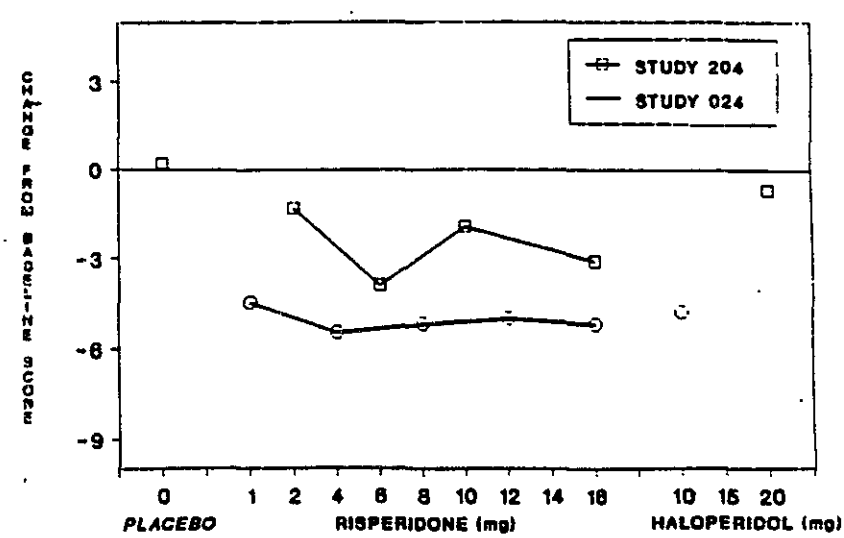
MEAN CHANGE IN SYMPTOM SEVERITY RATINGS
POSITIVE SUBSCALE OF PANSS AT ENDPOINT #



(LOWER SCORE IS BETTER)

Figure 11.

MEAN CHANGE IN SYMPTOM SEVERITY RATINGS
NEGATIVE SUBSCALE OF PANSS AT ENDPOINT #



(LOWER SCORE IS BETTER)

00-00044

In contrast to Studies JRD 64,766/201 and JRD 64,766/204, no significant difference was found among the groups in Study 64,766/024. However, the changes from baseline to endpoint for the PANSS negative symptom subscale scores between Study 64,766/024 and Study JRD 64,766/204 shows that all doses of risperidone in Study 64,766/024 may have been effective in reducing negative symptoms. No significant differences were noted among the treatment groups.

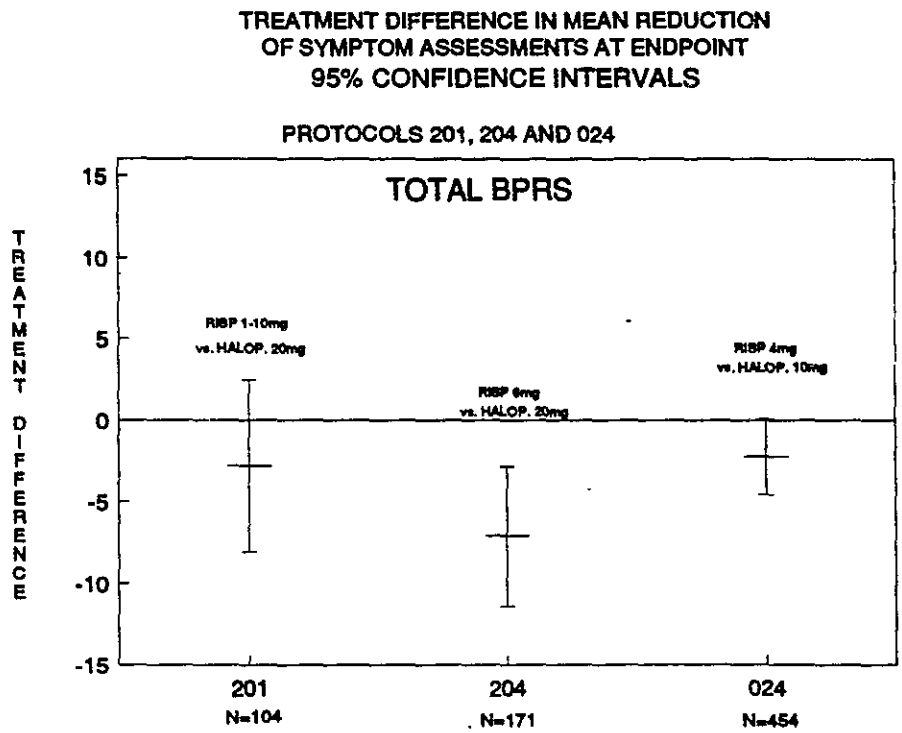
Conclusion: In all three studies, risperidone significantly improved positive symptoms of psychosis as assessed by the BPRS and key BPRS items scales or the PANSS positive symptom subscale. In two of the three studies, risperidone significantly improved negative symptoms as assessed by the SANS non-global scale (Study JRD 64,766/201) or the PANSS negative symptom subscale (Study JRD 64,766/204). In the third study, no difference was observed among the groups, but the lowest dose may have been effective, making it difficult to demonstrate intergroup differences.

E. Comparison with Haloperidol

Figures 3-11 show the effects of haloperidol in each of the three studies. The figures show that haloperidol was consistently less effective than risperidone. Because of the non-linear dose-response relationship, observed in Studies JRD 64,766/204 and 64,766/024, the apparent peak doses of risperidone, (i.e., 4 mg and 6 mg in Studies 64,766/024 and JRD 64,766/204), were selected for comparison to haloperidol. No attempt was made to stratify subjects in Study JRD 64,766/201 as a function of risperidone dose. Mean treatment differences and 95% confidence limits for these comparisons of risperidone and haloperidol are shown in Figure 12 for the BPRS scores for each of the studies.

Risperidone--Integrated Summary of Effectiveness

Figure 12.



Risperidone--Integrated Summary of Effectiveness

In Study JRD 64,766/201, there were no significant differences between risperidone and haloperidol. However, the data did show important trends in favor of risperidone. Risperidone was more effective than placebo for all of the efficacy assessments except the SANS global subscale; at endpoint, haloperidol did not differ from placebo as determined by the CGI-severity, the total SANS, non-global, or global scores, or the percent of patients improved on both the BPRS and CGI-Change scales. The difference between risperidone and haloperidol approached significance for this latter measure ($p=0.131$).

Study JRD 64,766/204 confirmed and extended the above findings. The apparent optimal dose of risperidone, i.e., risperidone 6 mg, was significantly more effective than haloperidol in reducing symptoms of psychosis as determined by the total PANSS ($p<0.001$), the PANSS positive ($p=0.023$), negative ($p=0.004$), and general psychopathology ($p<0.001$) subscales, the PANSS-derived BPRS ($p=0.001$) and the CGI-severity ($p=0.015$) scores. For the PANSS-derived key BPRS items the p-value was 0.059. The percentage of patients with clinical improvement as determined by the PANSS, CGI-Change, or the PANSS-plus-CGI-C scores was also greater ($p<0.004$) in the risperidone- than in the haloperidol-treated group.

Finally, in Study 64,766/024, haloperidol was no more effective than the lowest dose of risperidone 1 mg in reducing symptoms of psychosis as assessed by the total PANSS, the PANSS negative symptom and general psychopathology subscales, and the CGI-Change scores. In contrast, significant differences between risperidone 4 mg (the apparent optimal dose) and risperidone 1 mg were obtained for each of these variables. The difference between risperidone 4 mg and haloperidol 10 mg was significant or approached significance ($p<0.1$) for the total PANSS, the PANSS general psychopathology subscale, the PANSS-derived BPRS scale, and the CGI-severity score.

Figures 10 and 11 highlight an additional difference between haloperidol and risperidone. Haloperidol was ineffective in reducing negative symptoms of psychosis. In Study JRD 64,766/201, the SANS scale did not demonstrate an effect of haloperidol on negative symptoms. In Study JRD 64,766/204, the positive symptom subscale of the PANSS showed a significant difference between haloperidol and placebo whereas the negative symptom subscale did not. In Study 64,766/024, the patients treated with haloperidol (10 mg daily) showed a significant superiority over risperidone 1 mg with regard to the positive but not the negative symptom subscale of the PANSS. As noted above, the difference between risperidone- and haloperidol-treated groups on the negative symptom scale was significant for Study JRD 64,766/204.

In summary, potentially important differences between the effects of haloperidol and the effects of risperidone were observed in each of the three studies. These differences achieved consistent statistical significance in Study JRD 64,766/204. There are several reasons why Study JRD 64,766/204 might be expected to be the best-designed of the three studies for statistical demonstration of the superiority of risperidone to haloperidol. Study JRD 64,766/204 had greater statistical power than Study JRD 64,766/201 because the number of patients increased from approximately 60 to 90 per group. The dose-titration regimen in Study JRD 64,766/201 may have resulted in an underestimation of the effects of risperidone. Because a 10 mg target dose was specified, and because dose titration took place rapidly without the benefit of any formal assessment, the majority (54%) of patients in this study received the maximum allowed daily dose (10 mg). However, the two subsequent Studies (JRD 64,766/204 and 64,766/024) showed that 10 mg is not an optimally effective dose of risperidone.

Study JRD 64,766/204 also had greater statistical power than Study 64,766/024. Although the number of patients per group was larger in Study 64,766/024 than in JRD 64,766/204, Study 64,766/024 suffered from a larger intragroup variance, due in part to the large number of countries and sites participating in the trial. Additionally, lack of a placebo group may have influenced the results because comparison involved several active doses, including 1 mg/day.

F. Extrapyramidal Symptoms

Abnormal movements were monitored in all risperidone trials using several different methods. In the simplest form, volunteered complaints were recorded. Events were listed by investigators using either general terminology (such as EPS) or the specific abnormal movement (for example, tremor). The true incidence of EPS was determined by combining all complaints of abnormal involuntary movements such as dystonia, ataxia, choreoathetosis, abnormal gait, hyperkinesia, hypertonia, hypokinesia, oculogyric crisis, tongue paralysis, tremor, involuntary muscle contractions, hyporeflexia, or aggravated parkinsonism, as well as unspecified extrapyramidal disorder.

Risperidone--Integrated Summary of Effectiveness

Within the recommended dose range for risperidone, the incidence of EPS was similar to that of placebo (Table 17). For haloperidol (in doses up to 20 mg), the incidence of EPS was almost twice that of placebo. Even at lower doses of haloperidol (10 mg), the incidence of EPS was still higher than that of risperidone.

Table 17: Patient-volunteered Complaints of EPS[a] (Double-blind Studies)

	Placebo	Haloperidol	Risperidone (≤ 10 mg)	Risperidone (greater than 10 mg)
U.S./Canada	22/142 (15.5)	54/140 (38.6%)	54/324 (16.7%)	26/77 (33.8%)
Non-U.S.	4/34 (11.8%)	66/300 (22.0%)	96/878 (10.9%)	78/458 (17%)
Total	26/176 (14.8%)	120/440 (27.3%)	150/1,202 (12.5%)	104/535 (19.4%)

a) Patients who had at least one complaint of any abnormal involuntary movement.

In the large multinational trial (Study 64,766/024), the incidence of EPS was 12% (137 of 1,136) in the risperidone group compared to 24% (55 of 226) in the haloperidol group.

EPS was also determined by analysis of rescue medication that was allowed by protocol (Table 18).

Table 18: Patients Requiring Rescue Medication For EPS in Double-blind Studies

	Placebo	Haloperidol	Risperidone (≤10 mg)	Risperidone (greater than 10 mg)
Study 64,766/024	---	67/226 (30%)	106/686 (16%)	113/450 (25%)
U.S./Canada	32/142 (23%)	75/140 (54%)	88/313 (28%)	37/88 (42%)

In the two placebo-controlled studies, a total of 54% of patients on haloperidol required rescue medication compared to 42% for high dose risperidone (16 mg). Twenty-eight percent of risperidone patients receiving 10 mg or less required rescue medication, compared to 23% of placebo patients. In the large multinational trial (Study 64,766/024), 16% of the low-dose risperidone groups (1, 4, and 8 mg/day) required medication compared to 25% for high-dose risperidone (12 and 16 mg/day) and 30% for the 10 mg/day haloperidol group. Thus, almost 50% fewer patients receiving low-dose risperidone therapy required rescue medication than patients receiving haloperidol, and this reduced need was not significantly higher than that associated with placebo.

Finally, in Studies JRD 64,766/201 and 64,766/204, EPS was also determined with the Extrapyramidal Symptom Rating Scale (ESRS) of Chouinard[11] (Table 19). The ratings for parkinsonism parallel those seen with the previous methods for recording EPS. That is, for risperidone doses below 10 mg/day there were no significant differences compared to placebo. In Study JRD 64,766/204, there was marginally more parkinsonism with 10 mg/day than with placebo and significantly more with 16 mg/day. Haloperidol had significantly more parkinsonism than placebo in both trials.

Table 19: Worst ESRS Parkinsonism Scores (Mean Change From Baseline) in Double-blind Studies

Trial	Placebo	Risperidone				Haloperidol 20 mg
		2 mg	6 mg	10 mg	16 mg	
201 (Titration[1])	1.1			2.1		3.4[2]
204 (Fixed dose)	1.2	0.9[3]	1.8[3]	2.4[3]	2.6[2,3]	5.0[2]

[1] The mean dose of risperidone and haloperidol were 8 mg and 15 mg, respectively.
[2] Two-sided p-value ≤0.05 compared to placebo.
[3] Two-sided p-value ≤0.05 compared to haloperidol.

In conclusion, even at the maximal dose of 16 mg, the incidence of EPS with risperidone was significantly lower than that with 20 mg of haloperidol in direct comparison, and lower than a mean dose of 15 mg of haloperidol when compared across trials. In addition, the non-U.S. trials found significantly less EPS with risperidone compared to only 10 mg haloperidol.

G. Conclusions

Risperidone produced a consistent pattern of effects across the three adequate and well-controlled studies. In two studies (JRD 64,766/201 and 64,766/204), risperidone was significantly more effective than placebo in reducing psychotic symptom scores (PANSS, BPRS). In the third study (64,766/024), recommended doses of risperidone were significantly more effective than a low dose. Similar effects were seen in all three studies for secondary measurements, including global evaluations (CGI) and outcome measurements (percentage of patients discontinued for insufficient response). These effects were typically seen within the first week of treatment (the earliest timepoint for efficacy assessment) and were maintained throughout the trials. In the two studies that systematically manipulated risperidone dose, similar dose-effect relationships were observed; peak effects were consistently achieved by 4 to 10 mg/day, the recommended dose range.

Risperidone was consistently effective in reducing both positive and negative symptoms. It was significantly more effective than haloperidol in Study JRD 64,766/204 and this was consistent across all studies, particularly where negative symptoms were evaluated. Finally, risperidone doses in the recommended range were no more likely than placebo, and significantly less likely than haloperidol, to be associated with EPS.

VI. DOSE-RESPONSE RELATIONSHIP AND RECOMMENDED DOSAGES

In the two larger multicenter trials, a wide dosage range from 1 to 16 mg daily was used. Increasing the dosage over this range did not result in further improvement, and increasing the dose above 10 mg in Study JRD 64,766/204 and above 8 mg in Study 64,766/024 resulted in no greater response. These studies suggest that the optimal dosage range would be $\leq$10 mg daily in most patients. There was a suggestion of a bimodal relationship, that was most evident in Study JRD 64,766/204. Whether this is true remains to be confirmed, but it appears that the dose/response relationship may be bell-shaped. The mechanism for this relationship is unclear but presumably involves a subtle interplay among direct 5-HT_2 antagonism, D_2 antagonism, and dopamine release due to 5-HT_2 blockade.

In addition to the bell-shaped dose response curve for risperidone, the other reason for limiting drug dose is that the incidence of EPS is dose related over the range studied. A dose of 10 mg daily appears to be the critical cut off at which EPS may become a factor, judged by the need for increase rescue medication and the increase in ESRS Parkinsonism scores. Increasing the dose above a certain level, therefore, brings no greater benefit with an increased side effect liability. The preferred maximum recommended dose range is between 8 mg and 10 mg daily. The dosage of 10 mg daily was chosen because: 1) the 10 mg dose was studied in North America and was the dose at which side effects began to appear; and 2) on an individual basis, some patients may gain added benefit without significant EPS.

VII. DISCUSSION AND CONCLUSIONS

The efficacy of risperidone was demonstrated in three adequate and well-controlled studies using three different double-blind parallel-groups designs. Risperidone was effective in reducing psychosis as measured by symptom scores (PANSS, BPRS), global evaluation (CGI) or outcome (discontinuation due to lack of efficacy). In the two studies that systematically manipulated risperidone dose, consistent dose-effect relationships were observed; peak effects were consistently achieved by 4 to 10 mg/day, the recommended dose range. Risperidone was consistently effective in reducing both positive and negative symptoms. Finally, risperidone was significantly more effective than haloperidol in Study JRD 64,766/204 and this was consistent across all studies, particularly where negative symptoms were evaluated.

The phase II and open-label studies provide additional support for these hypotheses. In each case risperidone-treated patients improved relative to baseline. Despite the relatively small number of subjects per group, significant superiority to haloperidol or perphenazine was demonstrated in two studies for selected assessment variables. Risperidone in addition to multiple neuroleptic treatment was more effective than neuroleptic treatment alone in control of behavioral disturbance in mentally retarded patients. Finally, two open-label studies suggest that risperidone can be effective in control of symptoms of psychosis in elderly demented patients. Although the adequate and well-controlled studies, for reasons related to experimental design and control, were all conducted with chronic schizophrenics, these latter three studies suggest that the antipsychotic effects of risperidone are not limited to a single population.

VIII. EVIDENCE OF LONG-TERM EFFECTIVENESS, TOLERANCE, AND WITHDRAWAL EFFECTS

No controlled studies have been conducted to assess long-term effectiveness, tolerance, or withdrawal effects.

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APPENDIX 1

Scale of Assessment of Negative Symptoms

Affective flattening or blunting:	unchanging facial expression decreased spontaneous movements paucity of expressive gestures poor eye contact affective nonresponsivity inappropriate affect lack of vocal inflections global rating of affective flattening
Alogia:	poverty of speech poverty of content of speech blocking increased latency of response global rating of alogia
Avolition-Apathy:	grooming and hygiene impersistence at work or school physical anergia global rating of avolition-apathy
Anhedonia-Asociality:	recreational interests and activities sexual activity ability to feel intimacy and closeness relationships with friends and peers global rating of anhedonia-asociality
Attention:	social inattentiveness inattentiveness during mental status testing global rating of attention

APPENDIX 2

Positive And Negative Syndrome Scale (PANSS) For Schizophrenia

The items were rated using a seven-point scale where 1=absent, 2=minimal, 3=mild, 4=moderate, 5=moderate severe, 6=severe, and 7=extreme.

I. Positive Subscale

- P1 Delusions
- P2 Conceptual disorganization
- P3 Hallucinatory behavior
- P4 Excitement
- P5 Grandiosity
- P6 Suspiciousness/persecution
- P7 Hostility

II. Negative Subscale

- N1 Blunted affect
- N2 Emotional withdrawal
- N3 Poor rapport
- N4 Passive/apathetic social withdrawal
- N5 Difficulty in abstract thinking
- N6 Lack of spontaneity and flow of conversation
- N7 Stereotyped thinking

III. General Psychopathology Subscale

- G1 Somatic concern
- G2 Anxiety
- G3 Guilt feelings
- G4 Tension
- G5 Mannerism and posturing
- G6 Depression
- G7 Motor retardation
- G8 Uncooperativeness
- G9 Unusual thought content
- G10 Disorientation
- G11 Poor attention
- G12 Lack of judgement and insight
- G13 Disturbance of volition
- G14 Poor impulse control
- G15 Preoccupation
- G16 Active social avoidance

RISPERIDAL™ (R64,766) Caplets - New Drug Application

JANSSEN RESEARCH PRODUCTS INFORMATION SERVICE

Clinical Research Summary	Drug: Risperidone (R 64,766)
Date: March 1992	

Title: Integrated summary of information on the safety of risperidone (R 64,766).

Sponsor: Janssen Research Foundation
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00-00058

RISPERIDONE - CLINICAL PHARMACOLOGY

STUDY ID PROTOCOL	INVESTIGATOR	DATES OF STUDY	STUDY DESIGN	TOTAL N SEX (M-F) AGE RANGE	DOSE & FORMULATION	CONTROL	DURATION	N#	TYPE OF INFORMATION	LOC. IN NDA VOL./PG.
DOSE TOLERANCE STUDIES										
RIS-BEL-1 Protocol 001	Y. Gelders	1986	Open Volunteers	9 (9-0)	ris: 0.5+1.0mg oral sol. (n=6) ris: 2.0 mg oral sol. (n=6)	---	single dose	56687 --- 56466	dose tol., PK cardio. --- PK., cardio, prolactin	1.43/ 00-00015 --- 1.38/ 00-00332
RIS-FRG-9001 Protocol 017	P.W. Lucker, MD, PhD, FCP Institute fur Klinischer Pharmackologie Bobenheim, Germany	9/6/87 - 10/13/89	db ascending doses volunteers	24 (24-0)	ris: 1-4mg oral sol. (0.5mg/ml) i.m. 1mg/ml placebo: oral sol. i.m. (.9%NaCl)	placebo	single dose	84091 --- 64530 --- 85142	pharmacology --- endocrine --- pharmacokinetics	1.43/ 00-00035 --- 1.44/ 00-00038 --- 1.38/ 00-00267
RIS-FRG-9002 Protocol 018	P.W. Lucker, MD, PhD, FCP	10/87 - 12/87	db volunteers	13 (13-0)	ris: 2mg oral sol. x 1 day 1mg oral sol. x 20 day	placebo	20 days	84092 --- 85143	pharmacology --- pharmacokinetics	1.43/ 00-00084 --- 1.38/ 00-00349
RIS-JPN-9001 Protocol 042 & Protocol 044	J. Ishigooka Kitasato University School of Medicine/Japan	9/88 - 4/89	Open volunteers	6 (6-0)	.25-2mg --- 1.0 mg	haloperidol	single dose --- 7 days	85327	pharmacology & pharmacokinetics	1.43/ 00-00122
RIS-GBR-9004 Protocol 037	C. Idzikowski, BSC, PhD, CPsychol, FBPS Grove, Oxon, England	8/88 - 6/89	db-xo volunteers	15 (15-0)	ris: .5,2mg placebo	placebo	single dose	80987	sleep EEG	1.43/ 00-00296

00-00059

RISPERIDONE - CLINICAL PHARMACOLOGY

STUDY ID PROTOCOL	INVESTIGATOR	DATES OF STUDY	STUDY DESIGN	TOTAL N SEX (M-F) AGE RANGE	DOSE & FORMULATION	CONTROL	DURATION	N#	TYPE OF INFORMATION	LOC. IN NDA VOL./PG.
DOSE TOLERANCE STUDIES (cont'd)										
RIS-BEL-2 Protocol 003	P. Van Rooy Janssen Pharmaceutical Beerse, Belgium	1/87 - 3/87	x - over volunteers	6 (6-0)	ris: 2mg sol. 2mg tablets	----	single dose	54906 ----- 54946 ---------- 59726	effect of food: hr, bp, ECG ---------- effect of food: endocrine ---------- laboratory parameters	1.44/ 00-00001 ---------- 1.44/ 00-00008 ---------- 1.44/ 00-00023
RIS-BEL-16 Protocol 031	DeBuck, Belgium	11/88 - 9/90	Open	10 (10-0)	5, 10 mg tablets	N/A	4 weeks	84054	effect on sleep	1.44/ 00-00055

00-00060

RISPERIDONE - CLINICAL PHARMACOLOGY

STUDY ID PROTOCOL	INVESTIGATOR	DATES OF STUDY	STUDY DESIGN	TOTAL N SEX (M-F) AGE RANGE	DOSE & FORMULATION	CONTROL	DURATION	N#	TYPE OF INFORMATION	LOC. IN NDA VOL./PG.
PHARMACOKINETICS										
Protocol FRK949	G. Mannens Belgium	9/89 - 2/90	Open volunteers	3 (3-0)	1mg ^{14}C-risperidone	---	single dose	76677	abs., elim. 1/2 life, excre.	1.38/ 00-00114
RIS-HOL-9005 Protocol 073	J. Jonkman	5/91 - 8/91	Volunteers	12 (12-0)	1mg iv 1mg im 1mg oral soln.	___	single dose	---	PK	1.38/ 00-00167
RIS-HOL-9004 Protocol 068	J. Jonkman	2/91 - 5/91	open x-o volunteers	24 (24-0)	2mg sol. research 2mg tabs research 2x1mg caps market 2mg tabs market	---	single dose	---	Bioequiv/bioavail clinical vs. marketed	1.39/ 00-00001
Protocol 0001	R. Borison, MD, PhD Psychiatry Service 116A-D Downtown VA Medical Center Augusta, GA 30910	8/91- 10/91	Open, x-o psychotic patients volunteers	24 (24-0)	1x4mg tab research 1x4mg tab market	----	single dose	___	Dose prop. bio equiv.	1.39/ 00-00193
Protocol 0002	M. Sack, MD M.L. Crismon, PharmD L. Ereshefsky, PharmD Texas, USA	10/91 - 1/92	Open, x-o psychotic patients volunteers	36 (36-0)	1x4mg tab market 4x1mg tabs market 4x1mg tabs research	---	single dose	---	Dose prop. bio equiv.	1.40/ 00-00001
RIS-INT-3 Protocol 204	Small, et. al.	10/89 - 7/91	DB/PARA patients	223	2,6,10,16mg research tabs.	---	8 weeks	---	dose prop.	1.41/ 00-00001

RISPERIDONE CONTROLLED TRIALS

Protocol Study ID	Investigator	Dates of Study	Report Vol. Page	Pt. Tabulations Vol. Page	CRFs Vol. Page	Study Design	Total N Sex (M:F) Age Range	Dose & Formulation	Control	Duration
Protocol 201 RIS-USA-9001	Borison, et al. Multicenter USA	10/88 - 6/90	1.45/00-00013 1.110/00-00013	1.161/00-00028	1.239/00-00021 AE	DB/PARA	160 (154-6)	r=2-10mg h=4-20mg tablets	placebo haloperidol	6 weeks
Protocol 204 RIS-INT-3	Small,et. al. Multicenter USA/Canada	10/89 - 7/91	1.52/00-00001 1.117/00-00001	1.166/00-00073	1.234/00-00003 D 1.243/00-00001 AE	DB/PARA	523	r=2,6,10,16mg h=20mg tablets	placebo haloperidol	8 weeks
Protocol 024 RIS-INT-2	Multinational	3/89 - 3/91	1.69/00-00001 1.134/00-00001	1.183/00-00001	1.234/00-00100 D 1.254/00-00001 AE	DB/PARA	*1362 (894-467)	r=1,4,8,12,16mg h=10mg tablets	haloperidol	8 weeks
Protocol 006 RIS-BEL-5	Claus, et. al. Multicenter, Belgium	4/1/88 - 3/30/89	1.83/00-00001 1.148/00-00001	Not available	1.289/00-00001 AE	DB/PARA	44 (29-15) 20-66	r=2-20mg h=2-20mg oral sol.	haloperidol	12 weeks
Protocol 008 RIS-BEL-7	Mesotten, et. al. Multicenter, Belgium	12/87 - 9/88	1.84/00-00001 1.149/00-00001	1.225/00-00001	1.235/00-00412 D 1.290/00-00001 AE	DB/PARA	60 (37-23)	r-2-20mg h=2-20mg oral sol.	haloperidol	8 weeks
Protocol 022 RIS-FRG-9005	Klieser, E.; Kinzler, E. Germany	11/24/88- 3/4/90	1.85/00-00001 1.150/00-00001	1.227/00-00001	1.290/00-00203 AE	DB/PARA	59 (31-28)	r=4,8mg c=400mg tablets	clozapine	4 weeks
Protocol 041 RIS-FRA-9003	Tatossian, A. France	5/89 - 5/91	1.86/00-00001 1.151/00-00001	1.229/00-00001	1.291/00-00001 AE	DB/PARA	62 (38-24)	r=4-12mg h=4-12mg l=50-150mg tablets	haloperidol levomepro- mazine	4 weeks
Protocol 048 RIS-INT-7	Remivig, J. Denmark	2/90 - 8/91	1.87/00-00001 1.152/00-00001	1.231/00-00001	1.192/00-00001 AE	DB/PARA	107 (77-30)	r=5-15mg p=16-48mg tablets	perphenazine	8 weeks
Protocol 015 RIS-BEL-11	J. Geutjens Belgium	5/88 - 4/89	1.88/00-00001 1.153/00-00001	Not available	1.294/00-00001 AE	DB/XO	37 (18-19)	r=4-12mg oral sol.	placebo	3 weeks

*1557 were recruited, 47 discontinued during placebo wash-out phase, 148 excluded from analysis due to sites failing a GCP audit.

DB = Double Blind PARA = Parallel Group r = Risperidone h = Haloperidol c = Clozapine l = Levomepromazine p = Perphenazine D = Death AE = Adverse Experience

RISPERIDONE UNCONTROLLED TRIALS

Protocol Study ID	Investigator	Dates of Study	Reports Vol. Page	Pt. Tabulations Vol. Page	CRFs Vol. Page	Study Design	Total N Sex (M-F) Age Range	Dose & Formulation	Duration
Protocol 026 RIS TA-9001	Persani et. al. Multicenter, Italy	1/88 - 7/89	1.89/00-00021	Not available	1.294/00-00243 AE	Open	31 (17-14) --- 18 (10-8)	2-6mg tablets --- 2-6mg tablets	4 weeks --- 1 year
Protocol 007 RIS-BEL-6	Mertens, Belgium	11/87 - 9/88	1.90/00-00001	Not available	1.294/00-00305 AE	Open - geriatrics	50 (15-35)	1-10mg oral sol.	4 weeks
Protocol 013 RIS-BEL-9	Mertens, Belgium	3/88 - 5/89	1.90/00-00230	Not available	N/A	Open - geriatrics follow-up to RIS-BEL-6	9 (9-0)	1-6mg tablets	1 year
Protocol 030 RIS-BEL-15	De Cuyper Belgium	7/88 - 6/90	1.91/00-00001	Not available	N/A	Open- extension to RIS-BEL-5	5 (3-2)	Up to 10mg bid oral sol.	6-13 months
Protocol 019 RIS-FRA-9001	Monfort, France	9/88 - 5/89	1.92/00-00001	Not available	1.295/00-00001 AE	Open	12 (9-3)	2-4mg tablets	6 weeks
Protocol 002 RIS-INT-1	Belgium, Portugal	4/89 - 6/87	1.93/00-00001	Not available	1.295/00-00127 AE	Open	121 (64-57)	2-10mg oral sol.	4 weeks
Protocol 005 RIS-BEL-4	Mesotten, et. al. Belgium	5/87 - 9/87	1.95/00-00001	Not available	N/A	Open	17 (10-7)	10-25mg tablets	4 weeks
Protocol 020 RIS-FRG-9003	Moller, et. al. Germany	7/88 - 6/89	1.95/00-00118	Not available	N/A	Open	13 (5-8)	1-10mg	4 weeks
Protocol 021 RIS-FRG-9004	Hippius, Germany	5/89 - 12/89	1.96/00-00001	Not available	1.295/00-00221 AE	Open	11 (4-7)	Up to 10mg	4 weeks
Protocol 036 RIS-GBR-9003	Livingston, England	10/88- 6/90	1.96/00-00201	Not available	N/A	Open	7 (5-2)	4-20mg .5mg/ml oral susp.	4 weeks

DB = Double Blind PARA = Parallel Group r = Risperidone h = Haloperidol c = Clozapine l = Levomepromazine p = Perphenazine D = Death AE = Adverse Experience

RISPERIDONE UNCONTROLLED TRIALS

Protocol Study ID	Investigator	Dates of Study	Report Vol. Page	Pt. Tabulations Vol. Page	CRFs Vol. Page	Study Design	Total N Sex (M-F) Age Range	Dose & Formulation	Duration
Protocols: 035, 011, 004 RIS-BEL-17 RIS-HOL-9002 RIS-INT-8	Multinational Boom, Roose, Mertens	10/86 - 3/91	1.97/00-00001	Not available	RIS-INT-8: 1.296/00-00114 AE --- RIS-BEL-17: 1.237/00-00001 D 1.297/00-00001 AE --- RIS-HOL-9002: 1.237/00-00332 D 1.296/00-00209 AE	Open	264 (148-115)*	1-32mg	up to 19 months
Protocol RIS-BEL-SLT	DeWilde	3/86 - 8/91	1.99/00-00236	Not available	N/A	Open	38 (23-15)	2-25mg	1-4 years
Protocol 033 RIS-INT-4	Multinational	5/89 - 5/91	1.100/00-00001	Not available	1.236/00-00001 D 1.238/00-00001 D	Open	77 (42-35)	1-26mg	290-580 days

*1 patient's sex was not specified.

00-00064

DB = Double Blind PARA = Parallel Group r = Risperidone h = Haloperidol c = Clozapine l = Levomepromazine p = Perphenazine D = Death AE = Adverse Experience

RISPERIDONE UNCONTROLLED TRIALS - NO INDIVIDUAL DATA AVAILABLE

Protocol Study ID	Investigator	Dates of Study	Reports Vol. Page	Pt. Tabulations Vol. Page	CRFs Vol. Page	Study Design	Total N Sex (M-F) Age Range	Dose & Formulation	Duration
Protocol 038 RIS-ITA-9002	Meco, Italy	6/88 - 12/88	1.101/00-00001	Not available	N/A	Open	10 (5-5)	2-6mg tablets	4 weeks
Protocol 045 RIS-JPN-9003	Yagi, Japan	10/89 - 7/90	1.101/00-00097	Not available	1.296/00-00001 AE	Open	83 (57-26)	Up to 15mg tablets	8 weeks
Protocol 008 RIS-TCH-9001	Svestka Czechoslovakia	6/89 - 6/90	1.101/00-00186	Not available	N/A	DB	36 (21-15)	2-20mg oral sol.	8 weeks

DB = Double Blind PARA = Parallel Group r = Risperidone h = Haloperidol c = Clozapine l = Levomepromazine p = Perphenazine D = Dea.. AE = Adverse Experience

RISPERIDONE - OTHER

Protocol Study ID	Investigator	Dates of Study	Reports Vol. Page	Pt. Tabulations Vol. Page	CRFs Vol. Page	Study Design	Total N Sex (M-F) Age Range	Dose & Formulation	Duration
Protocol 009 RIS-BEL-8	Cosyns	5/88 - 10/89	1.101/00-00193	Not available	N/A	Open	17 (17-0)	up to 4mg tid. IM 1-10mg bid oral sol.	1 week
Case Report N69390	Mostmans	12/88- 9/89	1.101/00-00297	N/A	N/A	Open	1 (1-0)	2mg bid	9 months+
Case Report N72127	Buylaert	3/89 - 6/89	1.101/00-00300	N/A	N/A	Open	1 (0-1)	5mg bid	10 weeks

DB = Double Blind PARA = Parallel Group r = Risperidone h = Haloperidol c = Clozapine l = Levomepromazine p = Perphenazine D = Death AE = Adverse Experience

Risperidone--Summary of Safety Information

I. INTRODUCTION

Integrated international safety database

The anti-psychotic drug risperidone has been investigated in 30 clinical therapeutic trials in 21 countries. Of these, 24 studies from 20 countries have been incorporated into a single database of safety-related information (Table 1 and below). Five of these trials were international in nature. The integrated database includes a total of 2,322 patients who received risperidone (Table 2). The distribution of patients by treatment group and study is shown in Table 3 (by country) and Table 4 (by type of study).

Nine of the trials in the integrated database were double-blind, randomized controlled trials, as shown below.[1-13] They included 2,446 patients, of whom 1,737 received risperidone, 176 received placebo, 440 received haloperidol, and 93 patients received other active controls, clozapine, perphenazine, and levomepromazine. All nine studies have been completed.

Controlled Risperidone Trials Included in Integrated Safety Database			
Country	Protocol no.	System no.	Control
United States	JRD 64,766/201[1]	USA-9001	Placebo, haloperidol
United States/Canada	JRD 64,766/204[2]	INT-3	Placebo, haloperidol
Multinational	024[3]	INT-2	Haloperidol
Belgium	006[4-7]	BEL-5	Haloperidol
	008[8]	BEL-7	Haloperidol
	015[9]	BEL-11	Placebo
France	041[10]	FRA-9003	Haloperidol, levomepromazine
Germany	022[11-12]	FRG-9005	Clozapine
Denmark/Norway	048[13]	INT-7	Perphenazine

Risperidone--Summary of Safety Information

Seven hundred twenty-two patients received risperidone on an uncontrolled, open-label basis, 137 of whom had also received it in the controlled trials.[14-27] Three of these studies are ongoing.

Uncontrolled Risperidone Trials Included in Integrated Safety Database			
Country	Protocol no.	System no.	Description
United States	JRD 64,766/202*	USA-9005	Open-label extension of 201
	JRD 64,766/205*	USA-9006	Open-label extension of 204
Multinational	033[14]*	INT-4	Open-label extension of 024
Belgium	005[15]	BEL-4	
	007[16]	BEL-6	
	013[17]	BEL-9	Follow-up of 007
	031[18]	BEL-16	Sleep architecture
	035[19,20]	BEL-17	
France	019[21]	FRA-9001	
Germany	020[22]	FRG-9003	
	021[23]	FRG-9004	
Holland	011[20,24]	HOL-9002	
Belgium/Portugal	002[25]	INT-1	
Belgium/Austria/ Czechoslovakia	004[20,26]	INT-8	
Italy	026[27]	ITA-9001	

*Ongoing study.

The adequate and well-controlled trials included in the database used a standard case record form. Adverse events were both patient-volunteered and elicited. ECG's were obtained in all controlled trials, as were complete blood chemistries and urinalyses.

Risperidone--Summary of Safety Information

Risperidone dose and duration of exposure

The distribution of risperidone daily doses, grouped by ≤2 mg, >2-4 mg, >4-6 mg, >6-10 mg, and >10 mg, is shown by country in Table 5 (using the mode or 'most frequent' dose for each patient) and Table 6 (using the maximum dose for each patient). The distributions were unremarkable.

Figure 1 on page 4 summarizes the distribution of patients in the integrated database according to the duration of their exposure to risperidone. Eighty-six percent (1,994 of 2,322) had at least one month of treatment. Sixty percent (1,398 of 2,322) had at least two months of exposure. Two hundred thirteen patients were treated for approximately one year or more.

Primary studies

The majority of safety data on risperidone were derived from two North American (U.S. and Canada) placebo- and active-controlled effectiveness trials (Protocols JRD 64,766/201 and JRD 64,766/204), in which 401 patients received double-blind risperidone, and a large international multi-dose and active-controlled trial (Protocol 024; INT-2). These studies are considered the primary adequate, well-controlled effectiveness trials. Therefore both the safety and effectiveness of risperidone were defined using the same patient population from the same trials.

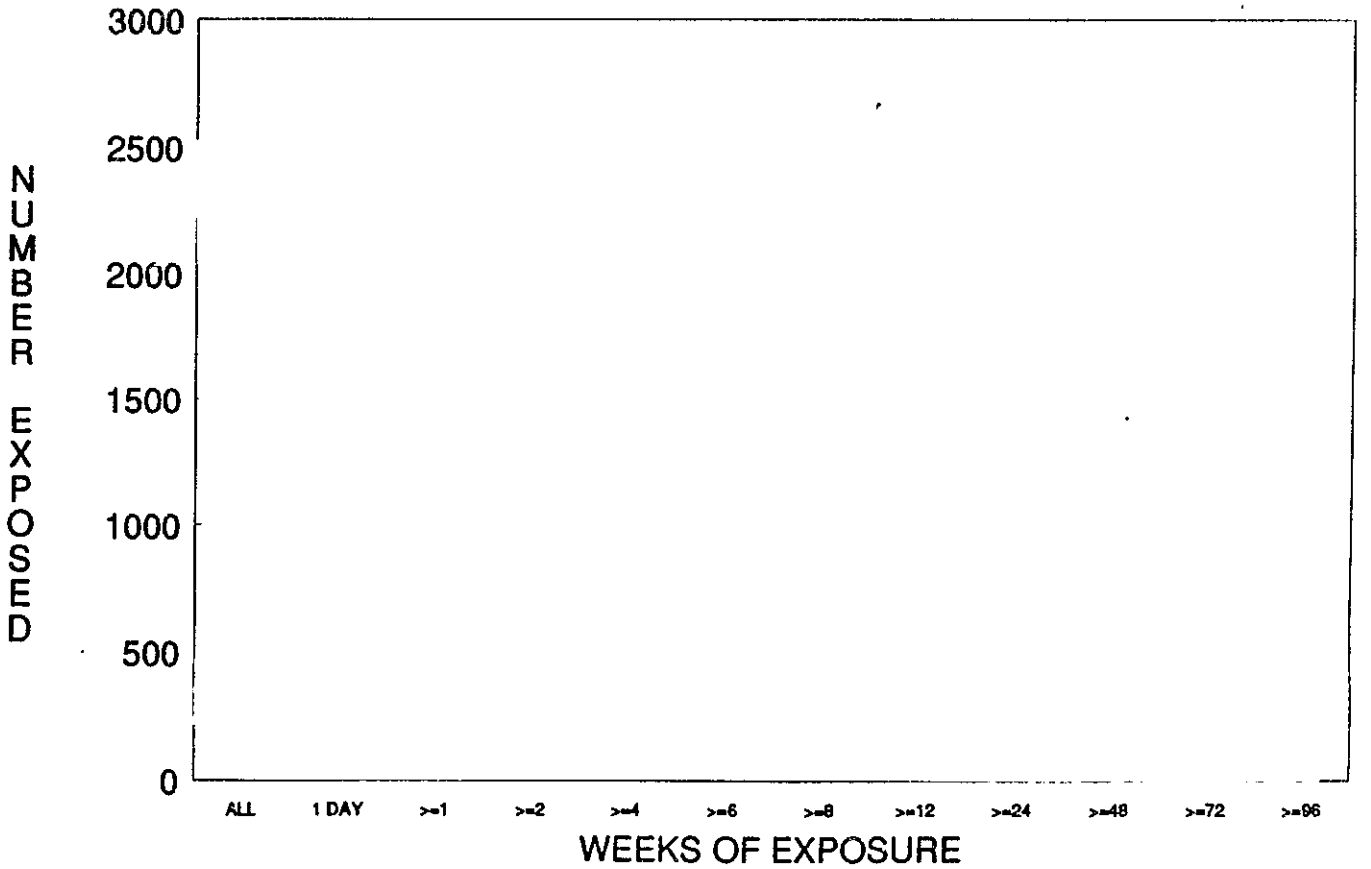
Presentation of data

Comparisons of risperidone with placebo and haloperidol are presented first (Section II), using data from the U.S./Canadian studies only. Comparisons with haloperidol follow, using data from non-U.S. studies only (Section III). Each table includes both sets of data, with U.S./Canadian double-blind (and open-label) data in tables with suffix A, non-U.S. double-blind (and open-label) data in tables with suffix B, and all data in tables with suffix C.

Six additional studies that were published and not included in the integrated safety database, including one placebo-controlled (10 risperidone patients), one active-controlled (18 risperidone patients), and four uncontrolled (112 patients), are described in the appropriate sections following discussion of the integrated database.

DURATION OF RISPERIDONE USE
ALL PATIENTS (U.S AND NON-U.S STUDIES)

FIGURE 1



ALL PATIENTS EXPOSED ARE INCLUDED IN THE FIRST BAR. THE REMAINING BARS REPRESENT THE DECLINING NUMBERS EXPOSED

Risperidone--Summary of Safety Information

Extrapyramidal symptoms reported in controlled trials in the integrated database are discussed separately in Section IV.

Uncontrolled therapeutic clinical trials are presented in Section V, using data from tables with suffix C.

All geriatric patients in the integrated database are discussed in Section VI.

The 11 single-dose Phase I safety and pharmacokinetic studies are described separately in Section VII. This is followed by sections on long-term safety, drug interactions, withdrawal effects, and animal studies.

II. PLACEBO-CONTROLLED TRIALS

Comparisons between risperidone and placebo are based on the two U.S./Canadian studies.[1-2] The one non-U.S. placebo-controlled study that was incorporated into the integrated database (BEL-11, 34 patients) is included in Section III with other controlled trials, since it was a crossover design.[9] Data for haloperidol are also presented in this section, but only for patients from the two U.S./Canadian studies. All patients met DSMIII-R criteria for schizophrenia.

A second non-U.S. placebo-controlled study that was not included in the database (ITA-9002) is summarized at the end of this section.

A. Patient characteristics

Enrollment: Four hundred one patients received double-blind risperidone, 142 received placebo, and 140 haloperidol.

Demographics: The distribution of patients by sex, age, height, weight, and race was comparable for patients treated with risperidone, placebo, and haloperidol (below and Table 7A). Eighty-five to 89% of each group were males and 61-70% were white. Mean age was 38 years in all three groups. Mean height ranged from 173 to 175 cm, and mean weight from 76 to 79 kg. The distribution of patients by sex is further broken down by age groups in Table 8A.

Patient Demographics--U.S./Canadian Controlled Trials

		Risperidone		Placebo		Haloperidol	
Sex	Males	341	(85%)	125	(88%)	124	(89%)
	Females	60	(15%)	17	(12%)	16	(11%)
Race	White	279	(70%)	90	(63%)	86	(61%)
	Black	84	(21%)	41	(29%)	42	(30%)
	Other	38	(9%)	11	(8%)	12	(9%)
Mean age (years)		37.6		38.4		37.9	
Mean height (centimeters)		173.2		175.0		174.8	
Mean weight (kilograms)		77.1		75.7		78.9	
Age at onset of psychotic symptoms (years)		21.6		22.5		23.3	
Duration of symptoms (years)		15.9		16.0		14.4	

Dose and duration of treatment: In the U.S./Canadian double-blind trials, the daily dose of risperidone ranged from 1 to 16 mg (Table 9A). The mean dose most frequently used by each patient was 7.9 mg. The average maximum dose was only slightly higher at 8.2 mg.

Double-blind treatment averaged 39 days (maximum: 64 days) (Table 10A). Duration of treatment is broken down by risperidone dose in Table 11A.

Premature discontinuation: A larger proportion of placebo patients (69%) and haloperidol patients (59%) than risperidone patients (46%) discontinued double-blind treatment prematurely (Table 12A). The proportions who discontinued specifically because of adverse events (including death, intercurrent illness, and abnormal laboratory values) were comparable: 8% for risperidone, 7% for placebo, and 9% for haloperidol. These dropouts will be discussed further under adverse events.

B. Adverse events

Incidences: For the two U.S./Canadian controlled studies, the overall incidences of adverse events were 75% for risperidone, 63% for placebo, and 79% for haloperidol (below and Table 13A).

These two trials were conducted at doses up to 16 mg/day, but the proposed recommended dosage is ≤10 mg/day. Therefore, the adverse event profile of risperidone is displayed in doses of 10 mg or less compared to doses above 10 mg (16 mg), or placebo (Tables 14A--by WHO body class and 15A--by WHO-preferred term). The table on page 8 lists the adverse events that occurred in at least 1% of risperidone patients treated within the recommended dose range based on the mode dose.

The adverse events most commonly observed in risperidone patients at doses ≤10 mg/day (that is, seen in at least 3%) and not seen at an equivalent incidence among placebo-treated patients test, two-tail, p≤0.10) were rhinitis (9.6%), abdominal pain (3.7%), and tachycardia (3.1%). At the higher-than-recommended dose of 16 mg/day, there was increased incidence of constipation (13.0%) and tachycardia (5.2%), but a decreased incidence of rhinitis (7.8%) and abdominal pain (1.3%). The higher dose was also associated with more anxiety (19.5%), somnolence (7.8%), dyspepsia (10.4%) and rash (5.2%) than was seen with either the lower doses or placebo.

Risperidone--Summary of Safety Information

Incidences of Adverse Events in >1% of Risperidone Patients Who Received ≤10 mg/day (Mode Daily Dose) in U.S./Canadian Placebo-controlled Clinical Trials– Percent of Patients Reporting				
Adverse event	Risperidone ≤10 mg/day (N = 324)	Risperidone 16 mg/day (N = 77)	Haloperidol ≤20 mg/day (N = 140)	Placebo (N = 142)
Psychiatric disorders				
Insomnia	25.6	23.4	25.7	19.0
Agitation	21.9	26.0	22.9	19.7
Anxiety	12.3	19.5	14.3	8.5
Somnolence	2.5	7.8	6.4	0.7
Nervousness	2.2	2.6	0.7	2.8
Aggressive reaction	1.2	2.6	0.7	1.4
Central and peripheral nervous system disorders				
Extrapyramidal symptoms (combined)	16.7	33.8	38.6	15.5
Headache	14.2	11.7	11.4	12.0
Dizziness	4.3	6.5	0.7	1.4
Gastrointestinal disorders				
Constipation	6.8	13.0	6.4	2.8
Nausea	6.2	3.9	2.9	2.8
Dyspepsia	5.2	10.4	3.6	3.5
Vomiting	4.9	6.5	5.0	4.2
Abdominal pain	3.7	1.3	1.4	0.0
Saliva increased	1.9	0.0	0.0	0.7
Tooth ache	1.5	0.0	1.4	0.0
Respiratory system disorders				
Rhinitis	9.6	7.8	2.9	3.5
Coughing	3.4	2.6	1.4	1.4
Sinusitis	2.2	1.3	0.0	0.7
Pharyngitis	1.9	2.6	1.4	0.0
Dyspnea	1.2	0.0	0.0	0.0
Body as a whole				
Pain	2.8	2.6	2.9	3.5
Injury	2.2	0.0	2.1	2.1
Back pain	2.2	0.0	2.9	0.7
Chest pain	1.5	2.6	0.0	0.7
Fever	1.5	2.6	0.7	0.0
Skin and appendages disorders				
Rash	2.2	5.2	1.4	0.7
Dry skin	2.2	3.9	0.7	0.0
Seborrhea	1.2	0.0	0.0	0.0
Resistance mechanism disorders				
Upper respiratory tract infection	2.8	2.6	0.0	1.4
Fungal infection	1.9	2.6	0.7	4.9
Infection	1.5	2.6	1.4	0.0
Vision disorders				
Abnormal vision	1.5	1.3	3.6	0.7
Musculo-skeletal system disorders				
Arthralgia	2.2	2.6	2.1	0.0
Heart rate and rhythm disorders				
Tachycardia	3.1	5.2	0.7	0.0

The incidence of extrapyramidal symptoms was calculated by adding together all events that were categorized as dystonia, ataxia, choreoathetosis, abnormal gait, hyperkinesia, hypertonia, hypokinesia, oculogyric crisis, tongue paralysis, tremor, involuntary muscle contractions, hyporeflexia, or aggravated parkinsonism, as well as unspecified extrapyramidal disorder. The incidence of all such events for patients taking ≤10 mg/day risperidone was 16.7%, which was comparable to the incidence for patients on placebo, 15.5%. The higher dose of risperidone (16 mg) produced a substantially higher incidence, 33.8%, which approached that seen with haloperidol, 38.6%. The analysis of extrapyramidal side effects is discussed further in Section IV.

Elicited events--In one placebo-controlled trial (Protocol JRD 64,766/204) adverse events were also elicited from patients at baseline and at each visit during treatment from a list of common events seen with psychotropic medications using the UKU scale (Udvalg for Kliniske Undersglese--Committee on Clinical Investigations) (Lingjærde et al., 1987) (Appendix A).[28] The scale was modified to exclude items pertaining to schizophrenia, which were monitored by the use of the PANSS (Positive and Negative Symptoms Scale). The scale also did not include extrapyramidal symptoms, which were recorded with the ESRS (Extrapyramidal Symptoms Rating Scale) (Chouinard et al., 1988)[29] (Appendix A). The table below lists the complaints occurring in at least 3% of risperidone ≤10 mg/day patients. For each UKU symptom, the table summarizes the proportion of patients whose UKU scores (range: 0-3) worsened (1-point increase from baseline) at least once during double-blind treatment.

The incidences of elicited events were generally higher for each group compared to the incidences of similar complaints that were volunteered. Elicited events that occurred at higher frequencies for risperidone ≤10 mg/day than for placebo (Fisher's exact test, two-tail, p≤0.10) and/or were not volunteered include increased duration of sleep, increased dream activity, accommodation disturbances, erectile dysfunction, ejaculatory dysfunction, and orgastic dysfunction. Similar differences between volunteered and elicited complaints were seen with sleepiness/sedation (compared to somnolence) and nausea/vomiting. Weight gain, which was volunteered as an adverse event by only two risperidone patients, was elicited from 26% through the UKU scale. Events that appear dose-related include sedation and (not shown on table) orthostatic dizziness and fatigue.

Risperidone--Summary of Safety Information

Elicited Events With Incidences ≥ [illegible] Patients Taking Risperidone ≤10 mg/day--Protocol RD 64,766/204				
UKU category UKU symptom	Total incidence (%)			
	Risperidone		Placebo (N=88)	Haloperidol 20 mg/day (N=87)
	≤10 mg/day (N=260)	16 mg/day (N=88)		
Psychic				
Sleepiness/sedation	29.6	40.9	15.9	40.2
Increased duration of sleep	18.5	19.3	8.0	19.5
Increased dream activity	15.8	12.5	6.8	14.9
Autonomic				
Accommodation disturbances	11.2	17.0	4.5	14.9
Reduced salivation	11.9	12.5	8.0	16.1
Nausea/vomiting	21.2	18.2	9.1	25.3
Micturition disturbances	7.3	9.1	3.4	8.0
Palpitations/tachycardia	17.7	22.7	10.2	10.3
Other				
Rash: not classifiable	4.6	2.3	0.0	1.1
Weight gain	25.8	26.1	11.4	16.1
Erectile dysfunction	7.3	14.8	3.4	6.9
Ejaculatory dysfunction	9.2	14.8	4.5	9.2
Orgastic dysfunction	3.8	11.4	2.3	5.7

Premature discontinuations due to adverse events--Of 401 double-blind risperidone patients, 30 (7.5%) discontinued treatment due to an adverse event, which included abnormal laboratory findings and intercurrent illnesses (Table 16A). Ten (7.0%) placebo patients and 13 (9.3%) haloperidol patients discontinued due to adverse events. Concise summaries for all dropouts, including placebo and haloperidol, for all North American patients are in Appendix B.

The events commonly associated with discontinuation in risperidone-treated patients, occurring for at least 1% of the total, were dizziness (1.5%), nausea (1.2%), and agitation (1.0%).

Five patients discontinued risperidone due to EPS compared to seven for haloperidol. Note that these cases reflect only cases where EPS rescue medication failed. Two placebo patients discontinued for dyskinesia and one for catatonia that was probably non-psychiatric. Note that catatonia and dyskinesia were not treated as EPS events in the database or in the combined calculation of EPS adverse events because they may have reflected preexisting conditions.

Only one risperidone patient discontinued for increased liver function tests compared to four placebo patients.

Each group had one dropout for suicide attempt; the risperidone patient died following burns to his body (listed in the database as injury).

The incidence of cardiovascular-related dropouts was 1% for both risperidone (4 of 401) and placebo (1 of 142); no haloperidol patients discontinued. Of the four risperidone patients, one dropped for syncope, one for increased heart rate, and two for hypotension. In addition, three risperidone patients discontinued due to dizziness, which may be orthostatic.

There were no dose-related differences in dropouts (Table 17A).

The table below lists the reasons for discontinuing treatment due to an adverse event for all North American patients.

Risperidone--Summary of Safety Information

Premature Discontinuations Due to Adverse Events--North American Patients		
Risperidone (n = 401)	Placebo (n = 142)	Haloperidol (n = 140)
Extrapyramidal symptoms 204/752 Not specified 534 Acute dystonia 604 Not specified 611 Hyperkinesia 492 Hyperkinesia	201/510 Catatonic state 515 Tardive dyskinesia 204/027 Tardive dyskinesia	201/215 Trismus 132 ↑ choreoathetosis 331 Tremor limb 402 Parkinson's Syndrome 204/033 Not specified 324 Dystonic reaction 360 Severe stiffness
Elevated liver function test 204/190 ↑ SGOT, SGPT	201/316 ↑ SGPT 910 ↑ SGPT 204/246 ↑ CPK 248 ↑ liver function test	204/409 ↑ CPK, LDH, SGOT; ↓ Hct, Hgb, MCV 535 ↑ GGT, SGOT
Suicide 204/326 Injury, ... n—probable suicide	201/502 Suicidal tendency	201/806 Suicide attempt
Cardiovascular 201/513 Hypotension 204/288 Increased heart rate 391 Orthostasis 578 Agitation, syncope	201/506 Atrial fibrillation	
Other 201/125 Asthma 207 Drowsiness, nausea 303 Marked restlessness 415 Marked restlessness 509 Dizziness, diarrhea, vomiting 204/046 Mouth ulcers 097 Pelger-Hu'it anomaly 129 Pruritus 172 Lightheadedness, psychomotor retardation, sedation, slurred speech 290 Auger 292 Diverticulitis 389 Nausea, emesis, viral infection 440 Dizziness 443 Dizziness 451 Insomnia, tension 468 Anemia, epistaxis, abdominal bloating, weight gain 403 Cholelithiasis 396 URI 436 Abdominal pain, weakness, dizziness, nausea	201/405 Confusion	201/203 Headache, nausea 408 Insomnia, lethargy 204/606 Sedation, reduced appetite

Deaths: As noted earlier, patient in Protocol JRD 64,766/204 died of burns probably self-inflicted during risperidone treatment at 6 mg/day (Table 18A, Appendix C). No other patients in the U.S./Canadian studies died.

C. Vital signs

In the placebo-controlled trials, supine and standing heart rate and blood pressure, as well as temperature and weight, were measured at each visit. The ranges used to establish clinically significant abnormalities are given for each parameter in Table 19. Standing heart rate was clinically increased (increased by ≥15 BPM to >120) in 10% of risperidone patients (35 of 339) compared to 2% of placebo (2 of 83) and 4% of haloperidol patients (3 of 83) (Table 20A). There were no differences relative to placebo in supine heart rate.

Supine systolic blood pressure was clinically decreased (decreased by 20 mmHg to ≤90 mmHg) in 5% of risperidone patients (20 of 393) compared to 4% of placebo (5 of 137) and 9% of haloperidol patients (12 of 137). Standing systolic pressure was clinically decreased (decreased by ≥20 mmHg to ≤90 mmHg) in 9% of risperidone patients (30 of 339) compared to 7% of placebo patients (6 of 83). Standing diastolic blood pressure was clinically lowered (decreased by ≥15 mmHg to ≤50 mmHg) in 3% (10 of 339) of risperidone patients compared to none of the placebo patients.

Weight gain was reported as an adverse event by two patients on risperidone. From elicited complaints, however, weight gain was found in 26% of risperidone patients compared to 11% of placebo patients (table on page 10). In analyzing measured weights, 18% of risperidone patients (65 of 363) had a clinically significant weight gain (≥7% of body weight) compared to 5% of placebo (6 of 119) and 9% of haloperidol patients (11 of 119). Consistent with this observation was the fact that placebo patients had the largest proportion with weight loss, 11% (13 of 119), compared to 2% of risperidone patients (8 of 363).

To determine whether weight gain was associated with fluid retention, the adverse event database was searched for edema. Three patients experienced edema while taking double-blind risperidone at ≤10 mg/day (Table 14A). In one case the edema was described as self-inflected to the right cheek bone. One patient taking risperidone 16 mg/day and one patient taking haloperidol also reported edema. No placebo patients reported edema.

D. Clinical laboratory data

Table 21A displays the numbers of patients tested for each laboratory parameter in each treatment group and the reference ranges, including the ranges outside which abnormalities were considered clinically significant. In Table 22A, each patient's baseline value for each parameter was classified as below, within, or above the reference range. Values obtained during treatment time points were further grouped according to whether they shifted classification. These categories are summarized in Table 22A, with mean and median values for each time point.

Table 23A displays, by parameter, the proportions of patients who had any abnormal values during treatment that were clinically significant. Those of most interest that included at least one risperidone patient are summarized on page 15. No distinction is made for the dose of risperidone. The following abnormalities occurred in more than 1% of risperidone patients: low hematocrit (3%), increased phosphorus (2%) and increased SGPT (1%) (Table 23A).

Although ranges of clinical significance were not established for creatine phosphokinase (CPK) values, 9-14% of risperidone patients had values above normal limits at each time point (Table 22A). Similarly, 6-14% of placebo patients and 4-14% of haloperidol patients also had above-normal values. Because of the large variation in reference ranges from study to study, mean CPK values cannot be compared to normal limits. However, because they occurred across groups, these changes are not considered related to risperidone treatment. CPK fractionation was performed on samples from six patients who had elevated CPK levels. In all six cases, the results showed MM (skeletal muscle) enzymes.

No consistent differences among treatments were noted in any other parameter.

Risperidone--Summary of Safety Information

Clinical Significant Laboratory Abnormalities in U.S./Canadian Controlled Trials (Percent)			
Abnormality	Risperidone	Placebo	Haloperidol
↓Hemoglobin	3/382 (0.8)	0/129	1/129 (0.8)
↓Hematocrit	10/364 (2.7)	1/125 (0.8)	1/123 (0.8)
↓Platelets	1/383 (0.3)	0/126	0/130
↓White blood cells	3/382 (0.8)	0/127	1/129 (0.8)
↓Segmented neutrophils	1/335 (0.3)	1/99 (1.0)	0/100
↑Eosinophils	1/309 (0.3)	0/94	2/95 (2.1)
↓Red blood cells	0/382	0/128	0/129
↓Sodium	0/383	1/130 (0.8)	1/131 (0.8)
↓Calcium	0/383	1/128 (0.8)	0/129
↑Phosphorus	7/357 (2.0)	1/112 (0.9)	0/114
↑Uric acid	3/349 (0.9)	0/118	0/119
↓Albumin	1/377 (0.3)	0/127	0/128
↑SGPT	4/370 (1.1)	0/124	0/129
↑SGOT	1/384 (0.3)	0/130	0/129
↑GGT	2/365 (0.5)	0/118	2/123 (1.6)
↑Total bilirubin	1/380 (0.3)	1/128 (0.8)	1/129 (0.8)

Figures 2-12 are scatterplots of data for each laboratory parameter by treatment, showing results for risperidone and placebo at Week 4 and Week 8.

For Protocol JRD 64,766/204, plasma samples were collected separately for determination of concentrations of prolactin, thyroid-stimulating hormone (TSH), human growth hormone (HGH), T_3, and testosterone. The proportions of patients with post-baseline abnormalities (but within normal limits at baseline) are summarized below.

At treatment endpoint, there were higher proportions of patients with prolactin levels above the normal limits in the risperidone and haloperidol groups than in the placebo group, reaching 37% in the risperidone 10 mg/day group and 50% in the 16 mg group. There were also higher proportions with abnormally low T_3 in the risperidone 6-16 mg groups and the haloperidol group--13% for 6 mg/day, 16% for 10 mg/day, 18% for 16 mg/day, and 23% for haloperidol, compared with 9% for placebo.

Incidences of Endocrinological Abnormalities at Treatment Endpoint-- Protocol JRD 64,766/204						
Abnormality	Placebo	Risperidone				Haloperidol 20 mg/day
		2 mg/day	6 mg/day	10 mg/day	16 mg/day	
↑Prolactin	1/32 (3.1%)	7/35 (20.0%)	5/31 (16.1%)	14/38 (36.8%)	17/34 (50.0%)	5/35 (14.3%)
↑TSH	0/32	0/35	0/31	0/38	2/34 (5.9%)	1/35 (2.9%)
↓T_3	3/32 (9.4%)	3/35 (8.6%)	4/31 (12.9%)	6/38 (15.8%)	6/34 (17.6%)	8/35 (22.9%)
↓Testosterone	0/20	2/17 (11.7%)	0/22	3/26 (11.5%)	1/20 (5.0%)	2/12 (16.7%)
↑HGH	5/32 (15.6%)	1/35 (2.9%)	0/31	5/37 (13.5%)	7/34 (20.6%)	2/35 (5.7%)

E. Electrocardiograms

ECG's were obtained for all patients in both placebo-controlled trials. In the larger trial (JRD 64,766/204) all tracings were read by a blinded rater, Charles Fisch, M.D., of the Krannert Institute of Cardiology at Indiana University. The criteria for identifying clinically significant changes in conduction parameters are presented in Table 24 and patients meeting these criteria are listed in Table 25A.

Overall there were few significant changes in the risperidone-treated patients. Two patients (0.5%) had abnormally low QRS duration (≤50 msec) and 8 patients (1.1%) had prolongation of the QTc (≥450 msec), the longest of which was to 478 msec. In his summary of the ECG changes seen in Study 204, Dr. Fisch concluded, "Risperidone has no clinically significant effect on the electrocardiogram." (See Appendix D.)

F. Cardiovascular events

Risperidone is a potent antagonist at α_1 receptors. Due to the hypotensive effects of alpha blockade, normal volunteers were unable to tolerate single doses above 2 mg. Therefore, pharmacokinetic studies using doses greater than 2 mg were done in patients. In these single-dose studies, the dose was 4 mg (Protocols JRD 64,766/0001 and JRD 64,766/0002). All patients were able to tolerate this dose, but most complained of somnolence and dizziness. The incidence of somnolence and dizziness was lower in clinical trials (U.S. Protocols JRD 64,766/201 and 204)[1-2] when therapy was initiated at 1 mg twice daily and increased by 1 mg once or twice daily.

G. Additional trial

A single-blind crossover trial of 10 patients meeting DSMIII-R criteria for chronic schizophrenia was conducted in Italy (ITA-9002) (Meco et al., 1989), for which case record form data were not available for inclusion in the integrated analysis.[30] All 10 patients received risperidone for 30 days, with fixed doses of 6 mg/day (3 mg b.i.d.) for the final 10 days.

ECG, EEG, blood pressure, glycemia, azotemia, SGOT, SGPT, and hematology were recorded, with no changes noted for risperidone. No adverse experiences were reported.

III. ACTIVE-CONTROLLED TRIALS

Comparisons between risperidone and haloperidol in this section are based on the non-U.S. studies only, consisting of the six active-controlled studies and one placebo-controlled crossover study that were incorporated into the integrated database.[1-13] An additional study not included in the database is summarized at the end of this section.

A. Patient characteristics

Enrollment: In these studies, 1,336 patients received double-blind risperidone and 300 haloperidol (Table 2). In a crossover study, 34 patients received both placebo and risperidone (BEL-11);[9] their placebo data are included in summary tables but are not discussed here.

Demographics: The distribution of patients by sex, age, height, weight, and race was comparable for patients treated with risperidone and haloperidol (below and Table 7B). Sixty-five percent of risperidone patients and 65% of haloperidol patients were males and approximately 83% of both groups were white. In both groups, the mean age was 38 years and mean height was 169 cm. Mean weight was 70-71 kg.

Patient Demographics--Non-U.S. Studies		
	Risperidone	Haloperidol
Sex		
Males	865 (65%)	195 (65%)
Females	470 (35%)	105 (35%)
Missing	1	
Race		
White	954 (83%)	199 (82%)
Black	66 (6%)	16 (7%)
Other	129 (11%)	29 (12%)
Missing	187	56
Mean age (years)	38.1	37.9
Mean height (centimeters)	169.3	168.6
Mean weight (kilograms)	69.8	70.5

The distribution of patients by sex is further broken down by age groups in Table 8B.

Dose and duration of treatment: In the non-U.S. trials, the daily dose of risperidone ranged from 1 to 24 mg (Table 9B). The mean dose most frequently used by each patient was 7.8 mg and the mean maximum dose 8.2 mg.

The duration of risperidone treatment in the non-U.S. trials averaged 47 days (maximum: 84 days) (Table 10B). Duration of treatment is broken down by risperidone mode (most frequent) daily dose in Table 11B. The majority of patients were treated for eight weeks.

Premature discontinuation: The proportion of patients who discontinued treatment prematurely was comparable for risperidone (25%) and haloperidol (26%) (Table 12B). It was slightly higher (30%) for all other active controls. The proportions who discontinued due to adverse events were also comparable: 9% for risperidone, 10% for haloperidol, and 13% for all others. These dropouts will be discussed further under adverse events.

B. Adverse events

Incidences: Adverse experiences occurred in 36% of risperidone patients (486/1,336), 48% of haloperidol patients (143/300), and 37% of patients on other active controls (34/93) (Table 13B). As before, incidences are further broken down by risperidone mode (most frequent) dose (Table 14B). Events that occurred in more than 1% of patients at the risperidone recommended dose range, based on mode daily dose, are shown below.

Extrapyramidal symptoms (combined) occurred in 11% of risperidone patients taking ≤10 mg/day, less than the 17% seen in U.S./Canadian placebo-controlled trials. The higher-dosed patients had an incidence of 17%, about half the incidence in the U.S./Canadian trials. Haloperidol patients had a lower incidence in these studies, 22%, vs. 39% in the U.S./Canadian trials. This may be due to the lower dose of haloperidol used (10 mg vs. 20 mg). Extrapyramidal events are discussed later, in Section IV.

With the exception of insomnia, anxiety, and agitation, all volunteered complaints occurred less frequently with risperidone than with haloperidol.

Risperidone--Summary of Safety Information

Incidence of Adverse Events in ≥1% of Risperidone Patients Who Received ≤10 Mg/day (Mode Daily Dose) in Non-U.S. Active-controlled Clinical Trials-- Percent of Patients Reporting			
Adverse event	Risperidone ≤10 mg (N = 878)	Risperidone >10 mg (N = 458)	Haloperidol 20 mg (N = 300)
Psychiatric disorders			
Insomnia	8.5	8.1	7.7
Anxiety	4.6	3.3	2.7
Somnolence	4.0	1.5	6.0
Agitation	3.5	3.9	2.3
Concentration impaired	1.7	0.0	3.0
Nervousness	1.3	1.3	2.0
Central and peripheral nervous system disorders			
Extrapyramidal symptoms (combined)	10.9	17.0	22.0
Dizziness	2.4	1.1	1.7
Headache	2.3	1.3	5.0
Gastrointestinal disorders			
Saliva increased	1.7	1.7	1.7
Constipation	1.6	0.4	1.0
Anorexia	1.4	0.2	2.0
Nausea	1.4	0.9	3.0
Body as a whole			
Fatigue	2.5	0.7	5.0
Vision disorders			
Abnormal vision	1.5	0.0	1.3

Elicited events--In one haloperidol-controlled trial (Protocol 024/INT-2) adverse events were also elicited from patients from a list of common events seen with psychotropic medications using a modified UKU scale. For purposes of comparison, the table below lists the elicited events that occurred in at least 3% of patients taking risperidone ≤10 mg/day in the U.S./Canadian placebo-controlled trials (page 10).

Risperidone--Summary of Safety Information

UKU-Elicited Events* in Non-U.S. Study 024						
UKU category UKU symptom	Total incidence (%)					
	Risperidone					Haloperidol 10 mg (N=225)
	1 mg (N=226)	4 mg (N=227)	8 mg (N=228)	12 mg (N=225)	16 mg (N=224)	
Psychic						
Sleepiness/sedation	23.5	31.7	33.3	32.9	47.8	39.6
Increased duration of sleep	20.4	24.2	27.2	28.4	33.9	28.4
Increased dream activity	15.0	13.2	18.0	18.7	16.5	17.3
Autonomic						
Accommodation disturb.	8.9	8.8	14.0	13.3	17.0	17.3
Nausea/vomiting	15.0	10.6	12.7	14.2	15.6	18.2
Micturition disturbances	8.4	5.7	5.7	6.7	7.6	8.0
Orthostatic dizziness	15.0	20.7	18.4	29.3	30.4	23.1
Palpitations/tachycardia	17.7	14.6	16.7	19.6	28.1	12.0
Other						
Rash: not classifiable	1.8	0.9	0.9	0.9	1.3	1.8
Weight gain	26.1	31.3	33.8	30.2	38.8	24.9
Erectile dysfunction	4.2	10.5	8.5	17.7	10.7	12.8
Ejaculatory dysfunction	3.6	7.9	9.2	17.7	11.4	6.7
Orgastic dysfunction	2.2	3.5	3.5	7.6	6.3	3.6

*Based on elicited events occurring in at least 3% of patients taking risperidone ≤10 mg/day in the U.S./Canadian placebo-controlled trials (page 10).

For risperidone-treated patients taking ≤10 mg/day, higher incidences of events were elicited in these studies than in the U.S./Canadian studies for increased duration of sleep (20-27% vs. 19%) and weight gain (26-34% vs. 26%). Lower incidences were elicited for nausea/vomiting (11-15% vs. 21%), rash--not classifiable (1-2% vs. 5%). Otherwise, the results generally agreed.

Events that appeared to be dose-dependent were sleepiness, increased duration of sleep, accommodation disturbances, orthostatic dizziness, palpitations, weight gain, erectile dysfunction, ejaculatory dysfunction, and orgastic dysfunction. Some higher doses of risperidone were associated with higher incidences of sleepiness, orthostatic dizziness, weight gain, erectile dysfunction, ejaculatory dysfunction, and orgastic dysfunction than haloperidol.

Premature discontinuations from treatment: A total of 9% (123 of 1,336) of risperidone patients discontinued from the controlled non-U.S. trials due to adverse events (Table 16B, Appendix B). The most common reasons for dropouts (1% or greater) were: suicide attempt (1%) and EPS (2.0%--combined events, as before). Of the 13 suicide attempts on risperidone, 7 were on doses within the recommended range (0.8% incidence) and 6 were at higher doses (1.3% incidence) (Table 17B). One occurred with haloperidol (0.3% incidence). Eleven patients on low doses of risperidone discontinued for combined EPS (1.3%) versus 16 on high doses (3.5%) and 9 on haloperidol (3.0%).

Deaths: There were two deaths reported from controlled non-U.S. studies (Table 18B, Appendix C). Patient in Study BEL-7 committed suicide by drowning after 30 days of treatment. Patient in Study INT-2 died following a myocardial infarction after 41 days of treatment.

There were also follow-up reports of the deaths of five patients in Study INT-2, which occurred from one week to four months following discontinuation of risperidone: -suicide by carbon monoxide poisoning, --suicide by jumping, -myeloma, -pneumonia, and -carcinoma). Patient who had received haloperidol in Study INT-2, committed suicide after completing the study. These patients are not included in Table 18, but individual summaries are provided in Appendix C.

C. Vital signs--In non-U.S. active-controlled trials, standing heart rate was clinically increased (increased by ≥15 BPM to >120) in 4.8% of risperidone patients compared to 1.4% of haloperidol patients (Tables 19 and 20B).

Supine systolic blood pressure was clinically decreased (decreased by ≥20 mmHg to <90 mmHg) in 6.0% of risperidone patients compared to 4.4% of haloperidol patients. Standing systolic pressure was clinically decreased (decreased by ≥20 mmHg to ≤90 mmHg) in 7.3% of risperidone patients compared to 7.2% of haloperidol patients. Standing diastolic blood pressure was clinically lowered (decreased by ≥15 mmHg to ≤50 mmHg) in 3.6% of risperidone patients compared to 4.5% for haloperidol.

D. Clinical laboratory data

Table 21B displays numbers of patients tested and reference ranges for each laboratory test parameter. Table 22B shows shifts in values into or out of the reference range.

Table 23B displays, by parameter, the proportions of patients who had any abnormal values during treatment that were clinically significant. Those of most interest that included at least one risperidone patient treated with ≤10 mg/day are summarized below. No distinction is made for the dose of risperidone.

Clinically Significant Laboratory Abnormalities in Non-U.S. Controlled Trials (Percent)		
Abnormality	Risperidone	Haloperidol
↓Hemoglobin	2/1,012 (0.2)	0/215
↓Hematocrit	4/400 (1.0)	0/71
↓White blood cells	3/1,018 (0.3)	2/216 (0.9)
↑Eosinophils	17/807 (2.1)	2/186 (1.1)
↓Sodium	3/975 (0.3)	5/216 (2.3)
↓Calcium	1/934 (0.1)	0/202
↑Phosphorus	9/812 (1.0)	1/179 (0.6)
↑Uric acid	1/852 (0.1)	0/186
↓Albumin	1/812 (0.1)	0/180
↑GGT	1/940 (0.1)	1/185 (0.5)
↑Total bilirubin	6/943 (0.6)	1/210 (0.5)
↑Urea	2/757 (0.3)	0/160

The following abnormalities occurred in at least 1% of risperidone patients: low hematocrit (1%) and high phosphorus (1%) and eosinophils (2%) (Table 23B). No consistent differences among treatments were noted in any other parameter.

Figures 13-22 display scatterplots of risperidone data for each parameter at Week 4 and Week 8.

E. Electrocardiograms

Clinically significant prolongations of QTc interval (≥450 msec) occurred in approximately 3% of both risperidone (27 of 869) and haloperidol patients (6 of 199) (Table 24 and 25B). PQ intervals were significantly decreased (≤120 msec) in 6% of risperidone patients and 7% of haloperidol patients.

F. Additional trial

In a published trial not included in the database (Svestka et al., 1990--Study TCH-9001),[31] 36 patients with schizophrenia and schizoaffective disorder (according to ICD-9) were randomized to either risperidone or haloperidol up to 20 mg/day for eight weeks. There were no reports of adverse events except to state that the incidences of parkinsonism, akathisia, tremor, and fatigue were less (but not significantly) for risperidone. Risperidone, however, at equal doses to haloperidol, was associated with significantly less use of antiparkinson medications.

IV. EXTRAPYRAMIDAL SYMPTOMS IN CONTROLLED TRIALS

Abnormal movements were monitored in all risperidone trials using several different methods. In the simplest form, volunteered complaints were recorded. Events were listed by investigators using either general terminology (such as EPS) or the specific abnormal movement (for example, tremor). These data are found in Tables 13A (U.S./Canadian studies), 13B (non-U.S. studies), and 13C (all studies). The true incidence of EPS was determined by combining all complaints of abnormal involuntary movements from Table 13: dystonia, ataxia, choreoathetosis, abnormal gait, hyperkinesia, hypertonia, hypokinesia, oculogyric crisis, tongue paralysis, tremor, involuntary muscle contractions, hyporeflexia, or aggravated parkinsonism, as well as unspecified extrapyramidal disorder.

Within the recommended dose range for risperidone, the incidence of EPS was similar to that of placebo (see table below and Table 14A). For haloperidol (in doses up to 20 mg), the incidence of EPS was almost twice that of placebo. Even at lower doses of haloperidol (10 mg) the incidence of EPS was still higher than that of risperidone. Similar results were obtained in the U.S./Canadian double-blind studies.

Patient-volunteered Complaints of EPS[a] (Double-blind Studies)				
	Placebo	Haloperidol	Risperidone (≤10 mg)	Risperidone (greater than 10 mg)
U.S./Canada	22/142 (15.5)	54/140 (38.6%)	54/324 (16.7%)	26/77 (33.8%)
Non-U.S.	4/34 (11.8%)	66/300 (22.0%)	96/878 (10.9%)	78/458 (17%)
Total	26/176 (14.8%)	120/440 (27.3%)	150/1,202 (12.5%)	104/535 (19.4%)

a) Patients who had at least one complaint of any abnormal involuntary movement.

In the large multinational trial (Protocol 024, INT-2), the incidence of EPS was 12% (137 of 1,136) in the risperidone group compared to 24% (55 of 226) in the haloperidol group.

EPS was also determined by analysis of rescue medication that was allowed by protocol.

Patients Requiring Rescue Medication For EPS in Double-blind Studies				
	Placebo	Haloperidol	Risperidone (up to 10 mg)	Risperidone (greater than 10 mg)
INT-2	—	67/226 (30%)	106/686 (16%)	113/450 (25%)
U.S./Canada	32/142 (23%)	75/140 (54%)	88/313 (28%)	37/88 (42%)

In the two U.S./Canadian placebo-controlled studies, a total of 54% of patients on haloperidol required rescue medication compared to 42% for high dose risperidone (16 mg). Twenty-eight percent of risperidone patients receiving 10 mg or less required rescue medication, compared to 23% of placebo patients. In the large multinational trial (Protocol 024, INT-2), 16% of the low-dose risperidone groups (1, 4, and 8 mg/day) required medication compared to 25% for high-dose risperidone (12 and 16 mg/day) and 30% for the 10 mg/day haloperidol group. Thus, almost 50% fewer patients receiving low-dose risperidone therapy required rescue medication than patients receiving haloperidol, and this reduced need was not significantly higher than that associated with placebo.

Finally, in Studies JRD 64,766/201 and /204, EPS was also determined with the Extrapyramidal Symptom Rating Scale (ESRS) of Chouinard. The ratings for parkinsonism parallel those seen with the previous methods for recording EPS. That is, for risperidone doses below 10 mg/day there were no significant differences compared to placebo. In Study 204, there was marginally more parkinsonism with 10 mg/day than with placebo and significantly more with 16 mg/day. Haloperidol had significantly more parkinsonism than placebo in both trials.

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Worst ESRS Parkinsonism Scores (Mean Change From Baseline) in Double-blind Studies						
Trial	Placebo	Risperidone				Haloperidol 20 mg/day
		2 mg/day	6 mg/day	10 mg/day	16 mg/day	
201 (Titration[1])	1.1	—	—	2.1	—	3.4[2]
204 (Fixed dose)	1.2	0.9[3]	1.8[3]	2.4[3]	2.6[2,3]	5.0[2]

[1] The mean dose of risperidone and haloperidol were 8 mg and 15 mg, respectively.
[2] Two-sided p-value ≤0.05 compared to placebo.
[3] Two-sided p-value ≤0.05 compared to haloperidol.

In conclusion, even at the maximal dose of 16 mg, the incidence of EPS with risperidone was significantly lower than that with 20 mg of haloperidol in direct comparison, and lower than a mean dose of 15 mg of haloperidol when compared across trials. In addition, the non-U.S. trials found significantly less EPS with risperidone compared to only 10 mg haloperidol.

V. UNCONTROLLED TRIALS

Seven hundred twenty-two patients were treated with risperidone in the 15 open-label trials that were incorporated into the integrated database. There were 124 patients in the two U.S./Canadian trials and 598 in non-U.S. studies.[14-27] For the three ongoing studies, the database includes only patients who completed treatment or discontinued prematurely as of the cut-off date of May 31, 1991. Therefore the total number of patients presented here does not include all patients enrolled. Four trials that were not included in the database are summarized at the end of this section.

A. Patient characteristics

Demographics: Sixty percent of the patients were male and 82% were white (Table 7C). The mean age was 41 years. Mean height was 172 cm and mean weight 73 kg. The distribution of patients by sex is further broken down by age groups in Table 8C.

Dose and duration of treatment: In the uncontrolled trials, the daily dose of risperidone ranged up to 60 mg (Table 9C). The mean dose most frequently used by each patient (mode dose) was 7.4 mg. The average maximum dose was 10.1 mg. Treatment averaged 150 days (maximum: 583 days) (Table 10C). Duration of treatment is broken down by risperidone dose in Table 11C.

Premature discontinuation: A larger proportion of the patients (40%) discontinued treatment prematurely, compared to 30% of double-blind risperidone patients in controlled studies (Table 12C). However, a lower proportion of open-label patients (6%) than double-blind patients (9%) discontinued because of adverse events.

In the U.S./Canadian trials, data from 124 patients treated with open-label risperidone were available for analysis as of the cut-off date (Table 12A). Eighty-eight percent of these patients discontinued prematurely, 11% for adverse events and 51% for inadequate response. These trials are ongoing, and only patients who have completed all 12 months or who prematurely discontinued are included in this safety analysis. Therefore, the dropout percentages do not accurately reflect the entire study population and the comparisons should be interpreted with caution since the estimated incidences may be biased.

B. Adverse events

Incidences: The overall incidence of adverse events was 50%, similar to the 45% incidence for risperidone patients in all the controlled trials (U.S./Canada and non-U.S.) (Tables 13C, 14C, 15C). The incidences of the more common events tended to be lower in uncontrolled trials. Specifically, the incidence of insomnia was 6% compared to 12%; agitation 4% compared to 8%, and anxiety 3% compared to 6%. Somnolence occurred more frequently in the uncontrolled studies (6% compared to 3%). Events that occurred in more than 1% of risperidone patients are shown below.

Incidences of Adverse Events in Uncontrolled Clinical Trials--Percent of Patients Reporting	
Adverse event	Risperidone (N = 722)
Psychiatric disorders	
Somnolence	6.4
Insomnia	6.0
Agitation	4.2
Anxiety	2.6
Depression	1.2
Nervousness	1.1
Central and peripheral nervous system disorders	
Extrapyramidal symptoms (combined)	18.6
Headache	3.3
Dizziness	1.5
Gastrointestinal disorders	
Saliva increased	3.3
Dyspepsia	1.2
Anorexia	1.2
Nausea	1.0
Body as a whole--general disorders	
Fatigue	2.8
Adverse event--not specified	2.6
Asthenia	1.7
Pain	1.5
Respiratory	
Rhinitis	2.9
Cardiovascular	
Hypertension	1.0
Vision disorders	
Abnormal vision	1.0
Musculo-skeletal	
Arthralgia	1.1

Neuroleptic malignant syndrome (NMS): A 33-year-old male Canadian patient hospitalized with severe chronic schizophrenia was treated with risperidone on a compassionate basis. Following 1 mg/day for two days, the dose was raised to 2 mg/day. He then developed severe catatonia, tremors, pallor, urinary incontinence, intense diaphoresis, fever (to 42°C), hypotension, and tachycardia. He also had associated axial rigidity with cogwheel rigidity of upper extremities and increased somnolence. Creatinine was elevated to 221 µMol/L the following day (normal range: 35-115 µMol/L) and creatine kinase was elevated to 17,268 IU/L within two days (normal range: 55-190 IU/L). NMS was diagnosed and the patient was treated with rehydration, dantrolene, and antibiotics. Rigidity improved within two days and he became afebrile within three.

The patient had taken other neuroleptics and experienced "unbearable" tremors, but he had no prior episodes of NMS. He was taking diphenhydramine HCl, lorazepam, trifluoperazine, and methotrimeprazine concurrently with risperidone. NMS has been associated with phenothiazine-like antipsychotic drugs such as trifluoperazine and methotrimeprazine.

Hyponatremia: Two risperidone-treated patients developed hyponatremia with resultant seizures, both in U.S. Protocol JRD 64,766/205 in July, 1991, during an extremely hot summer. Both cases resolved with no sequelae (see discontinuation summaries in Appendix B). (They do not appear in Tables 13B, 14B, or 15B because they occurred after the cut-off date--May 31, 1991).

Psychotic patients suffer from polydipsia and polyuria (Jose and Perez-Cruet, 1979;[32] Vieweg et al., 1988,[33] 1989[34]) with an incidence between 6 and 17% (Illowsky and Kirsch, 1988[35]). These patients may develop episodes of symptomatic dilutional hyponatremia leading to lethargy, confusion, seizures, and death. In a study of hospital admissions, the incidence of hyponatremia among schizophrenic patients was 5.8% compared to 0.36% for all other admissions (Gleadhill et al., 1982).[36]

Premature discontinuations due to adverse events--Six percent of the patients (45 of 722) discontinued because of adverse experiences (Table 16C). Seven patients (1%) discontinued due to extrapyramidal symptoms (combined). Thirteen patients (2%) discontinued because of unspecified events. No other specific reason accounted for as much as 1% of dropouts.

Deaths: There were no deaths during open-label treatment in the U.S. In non-U.S. trials, there were two deaths in Study INT-4. French patient who was enrolled in Study INT-2 as patient committed suicide by drowning after 290 days of risperidone treatment (Table 18C, Appendix C). Partuguese patient committed suicide by hanging after 105 days of treatment; since this was reported after the cut-off date for the integrated database, the patient does not appear in Table 18C but a summary is included in Appendix C.

Two other patients committed suicide within 30 days of stopping treatment, both from Study 035 (BEL-17)--patients A third post-treatment suicide, patient from Study 011 (HOL-9002), was learned of after the cut-off date and is therefore not included in Table 18B. Similarly, in ongoing study BEL-14, patient died of renal failure too recently for inclusion in the database. There were also three reports of patient deaths following compassionate use of risperidone, one in Austria (suicide), one in Belgium (cardiac arrest), and one in Canada (AIDS). Summary reports of these deaths can be found in Appendix C.

C. Vital signs

The incidence of clinically significant increases in supine heart rate (increase of ≥15 BPM to >120 BPM) in open-label studies was higher than that seen for controlled studies, 4% vs. 1%, though the incidence of clinically significant increases in standing heart rate was lower, 5% vs. 6% (Tables 19, 20C). Supine and standing systolic blood pressure reduction was clinically significant in 6% and 11% of patients.

D. Clinical laboratory data

Table 21C displays numbers of patients tested and reference ranges for each laboratory test parameter. Table 22C shows shifts in values into or out of the reference range. Because of the large variations in reference ranges from study to study, mean and median values were not calculated. Instead, values were normalized using the corresponding reference ranges to generate the shift table.

Table 23C displays, by parameter, the proportions of patients who had any abnormal values during treatment that were clinically significant. Those of most interest that included at least one risperidone patient are summarized below. No distinction is made for the dose of risperidone.

Clinically Significant Laboratory Abnormalities in Uncontrolled Trials	
Abnormality	Risperidone
↓Hemoglobin	1/441 (0.2%)
↓Hematocrit	6/168 (3.6%)
↑Eosinophils	2/426 (0.5%)
↓Sodium	5/423 (1.2%)
↑Phosphorus	6/356 (1.7%)
↑Glucose	4/427 (0.9%)
↑Creatinine	1/442 (0.2%)
↑Uric acid	2/357 (0.6%)
↑Alkaline phosphatase	2/440 (0.5%)
↑SGPT	4/443 (0.9%)
↑SGOT	2/442 (0.5%)
↑GGT	4/325 (1.2%)
↑Total bilirubin	1/432 (0.2%)

The following abnormalities occurred in more than 1% of risperidone patients: low hematocrit (4%) and sodium (1%) and high phosphorus (2%) and GGT (1%) (Table 23C).

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E. Electrocardiograms

In open-label studies, 26 of 235 patients (11.1%) had clinically significant prolongation of the QTc interval (≥450 msec) (Table 25C). Clinically significant decreases in PQ interval (≤120 msec) occurred in 13% of patients and increases (≥200 msec) in 5%.

F. Additional trials

There were four uncontrolled trials of risperidone that were either published or for which case record form data are not available for inclusion in the integrated analysis.[37-40] One hundred twelve patients were treated with risperidone in these four trials. Daily doses ranged from 0.75 to 20 mg. Treatment was for up to one year. The 17 patients in Study BEL-8 received risperidone as an intramuscular injection and as an oral solution; all others received tablets.

Four patients discontinued from one trial (JPN-9003) due to side effects, one for EPS (present at baseline), one for rash, one for anemia, and one for sinus tachycardia and increased ST and T waves. Akathisia was reported in one trial in Japan in 23 of 83 patients. This incidence of akathisia was not seen in controlled trials. In fact, the incidence of akathisia was not different from placebo in the two U.S./Canadian placebo-controlled trials. Across all four studies, sedation/sleepiness was reported in 16 (14%) of patients. Dizziness was seen in 3 (3%) of patients.

The table below lists the uncontrolled trials that do not appear in the database.

Uncontrolled Risperidone Studies Not in Integrated Database				
Study	N	Dose (mg b.i.d.)	Length	Adverse events (number of patients)
JPN-9003[37]	83	0.75-7.5	8 weeks	Akathisia (23), tachycardia (3), ↑SGOT, SGPT (2), sleepiness (10), dysarthria (10), tremor (9), insomnia (8) weakness (7), fatigue (5)
GBR-9003[38]	7	2-10	28 days	Postural hypotension (1), sleepiness (2), dizziness (1), salivation (2)
BEL-8[39]	17	4-12 mg IM 4-20 mg PO	≤3 days 4-6 days	Extrapyramidal symptoms (1), malaise (1), dry mouth (1), sedation (1)
BEL-15[40]	5	2-10	52 weeks	Dizziness (2), nausea/vomiting (2), sedation (3), concentration difficulty (3), fatigue (4)

VI. GERIATRIC PATIENTS

Sixty patients aged 65 or older received risperidone, seven in double-blind studies only, 51 in open-label studies only, and three in both (Table 26A-C). In all, 20 of these patients experienced adverse events, an incidence of 33% (Table 26C), lower than the 47% for the general population (Table 13C).

Two patients in the U.S./Canadian controlled studies were aged 65 years or older, one of whom received risperidone and the other placebo (Table 26A). The risperidone patient experienced blepharitis, anxiety, insomnia, and coughing. The placebo patient reported agitation, eczema, and a fungal infection.

There were 11 risperidone-treated patients in the non-U.S. active-controlled studies who were aged 65 years or older (Table 26B). Of the eight who received double-blind risperidone, four had adverse experiences. Agitation occurred in two and somnolence, insomnia, impaired concentration, extrapyramidal disorder, dizziness, headache, increased appetite, and fatigue each occurred in one. Both haloperidol patients had adverse events, including one instance each of anxiety and peripheral edema; both also had extrapyramidal symptoms, including hyperkinesia in one case. One other active control patient reported no adverse events.

Of the 53 geriatric patients in uncontrolled studies, 17 (32%) reported adverse events (Table 26C). Somnolence occurred in five patients (9%) and extrapyramidal disorder, confusion, stupor, and increased saliva in two patients each. The following were reported in one patient each: agitation, insomnia, anxiety, dizziness, dyskinesia, hyperkinesia, hypertonia, tremor, increased appetite, nausea, and seborrhea. Three events were not specified.

VII. PHASE I SAFETY AND PHARMACOKINETIC STUDIES

There was a total of 11 single-dose pharmacokinetic studies.[41-54] It was agreed at a meeting held in August, 1991, with representatives of the FDA Neuropharmacology Division that reports of adverse events in these studies would not be part of the integrated safety analysis but would be reported separately.

In normal volunteers, a dose of 1 mg resulted in sedation and dizziness in most subjects in four of six studies. In one 26-subject trial (HOL-9004), one subject collapsed and a second nearly collapsed following a 2 mg dose. In another trial (GBR-9001), four of six subjects collapsed after receiving a single dose of 4 mg. It was therefore decided that single-dose studies of doses greater than 2 mg would be conducted in patients.

Single doses of 4 mg risperidone were given to 60 patients in two studies (JRD 64,766/0001 and JRD 64,766/0002) comparing market vs. research formulations.[51-52] This was the highest single initial dose of risperidone given in the U.S.

In these two studies, the most common events seen at the first dosing were somnolence/sedation (50% of the patients), dizziness (33%), insomnia (32%), and headache (28%). Postural hypotension was seen in five patients with one patient having a syncopal incident. No patients discontinued from either trial due to adverse events.

These two trials demonstrated that if patients ignored instructions to begin dosing at 1 mg b.i.d., and began dosing at 4 mg, the expected side effects would be somnolence and dizziness and these would probably be tolerated by most patients. The following events were noted in these trials.

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Phase I Single-dose Safety Studies Not in Integrated Database				
Protocol	Population	Dose	Number	Adverse events (number of patients)
BEL-1[41]	Normal subjects	0.5 mg	6	None reported
		1.0 mg	6	Sedation (3) ↑HR first 2 hours (6)
BEL-2[42-44]	Normal subjects	2.0 mg	6	↑HR
FRG-9001[45]	Normal subjects	1 mg IM	24	1 mg--↑HR 2 mg--↑HR 3 mg--↑HR, ↓BP, dizziness (4/10), fatigue (6/10) 4 mg--↑HR (5), ↓BP (5)--4 pts. collapsed. TRIAL TERMINATED
FRG-9002[46]	Normal subjects	1,2 mg (20 days)	11 +2 plac	↓BP, ↑HR, ↑SGPT (2), tiredness (9), dizziness (7), headache (6)
FRK-49[47]	Normal subjects	1 mg	3	None reported
HOL-9004[48]	Normal subjects	2 mg	26	2 subjects collapsed (BP <45 mmhg), dizziness (9), drowsiness (25)
HOL-9005[49]	Normal subjects	1 mg IV, IM, and orally	12	Dizziness (8), drowsiness (12), lightheaded (3)
GER-9004[50]	Normal subjects	0.5, 2 mg	15	Tiredness and lethargy (2), headache (2)
JPN-9001[51]	Normal subjects	0.25-2 mg	6	0.25 mg--sleepiness (6), fatigue (1), muscle rigidity (1) 0.5 mg--sleepiness (5), fever (1), 1 mg--sleepiness (5), tremor (1), stuffy nose (2) 2 mg--sleepiness (6) orthostatic hypotension (1), concentration disturbed (1)
	Normal subjects	1 mg (1 week)	6	Sleepiness (6), fatigue (3)
JRD 64,766/ 001[52]	Patients	4 mg	24	Somnolence (20), dizziness (8), agitation (5), insomnia (5), headache (4), postural hypotension (1)
JRD 64,766/ 002[53]	Patients	4 mg	36	Somnolence (13), dizziness (13), insomnia (14), headache (13), postural hypotension (4), syncope (1)

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VIII. LONG-TERM SAFETY

A total of 213 patients in the integrated database have been treated for approximately one year. Incidences of adverse events for these patients are displayed in Table 27A-C. **Note: for the non-U.S. patients (in Table 27B and included in Table 27C), the date of onset for adverse events was not recorded; therefore events for these patients may have occurred at any time during treatment.**

Incidences of the most common events (≥3%) seen with risperidone ≤10 mg/day are listed. The data are insufficient to make meaningful comparisons to the results of the controlled trials.

Incidences of Adverse Events in Patients Treated For at Least One Year (≥275 days)		
WHO-preferred term	Risperidone ≤10 mg/day (n = 150)	Risperidone >10 mg/day (n = 63)
Extrapyramidal (combined)	20.7%	25.4%
Insomnia	8.0%	15.9%
Fatigue	3.3%	0
Anxiety	3.3%	19.0%
Somnolence	2.0%	3.2%
Agitation	2.0%	23.8%
Increased saliva	4.0%	3.2%

An additional 38 chronic psychotic patients at four Belgian centers received long-term risperidone on a compassionate basis, 21 after completing open-label Studies BEL-17 and INT-8.[54] These data were not included in the integrated database. Treatment lasted from 8.6 months to 3.3 years (mean: 25.1 months). Doses at endpoint ranged from 2 to 25 mg/day (mean: 9.4 mg/day). Four adverse events occurred: amenorrhea and weight increase in one patient and cough and rhinitis in another. There were decreases in mean heart rate (7.7 beats per minute), QTc (19.2 msec), and QTm (12.4 msec), none of which was considered clinically significant (20 patients). No clinically relevant laboratory abnormalities were observed (34 patients).

IX. DRUG-DRUG INTERACTIONS

In animal studies, there did not appear to be drug-drug interactions when risperidone was given in combination with warfarin. No formal interaction studies have been performed in humans to date.

X. WITHDRAWAL EFFECTS

There was no systematic attempt to follow patients after they stopped treatment. Two non-U.S. patients committed suicide upon stopping risperidone treatment.

XI. ANIMAL STUDIES

As in man, the adverse changes found in animal studies were those usually present following the administration of anti-psychotics. Almost without exception, the relevant adverse changes present in the animal studies were limited to those due to exaggerated pharmacologic activity or to those which are commonly found after the administration of potent dopamine D_2-receptor-binding agents. Examples of those considered to be due to pharmacologic activity in animals were sedation, palpebral ptosis, hypotonia, hypothermia, and, at near lethal dosage levels, convulsions and loss of righting reflex.

Examples of changes that were associated with the expected increase in prolactin release were: 1) in rodents--stimulation of the pituitary gland, the mammary gland, and the endocrine pancreas, sometimes to the point of neoplasia; neoplasia was present only in the rodent carcinogenicity studies; and 2) in both rodents and dogs--changes in the reproductive tracts. The neoplastic changes present in the carcinogenicity studies (adenomas of the pituitary gland, adenocarcinomas of the mammary gland, and adenomas of the endocrine pancreas [male rats only]) were considered to be unique responses of rodents to prolonged increases of prolactin release. Serum prolactin levels were increased in man, mice, and rats following the administration of risperidone. Whereas increased ejaculatory dysfunction was present in both dog and man, other clinical signs of hyperprolactinemia, such as gynecomastia and breast enlargement, were not reported in human clinical studies.

Tachycardia, which was observed in man, was not found during ECG examinations which were conducted as a part of dog multidose toxicity studies even at toxic dosage levels. Body weight was increased in human studies. In contrast, body weight was almost always decreased in animal studies. Exceptions (increased body weight) were occasionally found in female rats at lower dosage levels.

In mouse, rat, and dog toxicity studies, marginally decreased hemoglobin, hematocrit and/or erythrocyte levels were present which correlates with the findings in humans. In contrast to pharmacology studies, where the ED_{50} for slight catalepsy was 0.59 mg/kg and for moderate catalepsy was 3.02 mg/kg following subcutaneous administration, no catalepsy or signs of extrapyramidal effects were present in any multidose toxicity or carcinogenicity study (all oral administration; maximum levels in mouse and rat were 10 mg/kg/day--62.5-125 times the recommended human use level [RHUL]: in rabbit and dog were 5 mg/kg/day--31.25-62.5 times RHUL). Catalepsy was present in acute oral, subcutaneous, and intravenous toxicity studies in only rats at dosage levels of 20 mg/kg, which was the minimum dosage level in this study (125-250 times RHUL), and above. In humans, the incidence of extrapyramidal symptoms at dosage levels of 10 mg/day of less was comparable to that seen with placebo and much less than that seen with haloperidol.

There was good reversal of all non-neoplastic changes present in animals following a recovery period of 2-8 weeks when risperidone was not administered.

In animal reproduction studies, neither embryotoxicity nor teratogenicity were present even at maternally toxic dosage levels. During fertility studies, prolactin-dependent decreases of and delays in mating were present and the cohabitation-mating period was increased. However, where copulation occurred, the fertility rates were unaffected even at dosage levels where paternal and maternal toxicity were present. In studies where risperidone was administered during lactation, maternal toxicity and decreased mothering were also present at dosage levels where decreased pup survival was found. The male and female reproductive tract changes reported in toxicity studies of mice, rats, and dogs may have been expressed in humans by the elicited (and not-unexpected) complaints regarding the reproductive systems.

More detailed information regarding animal studies conducted with risperidone is presented in separate summaries of the non-clinical pharmacology, toxicology, and pharmacokinetics information.

XII. CONCLUSIONS

Risperidone was well tolerated in most patients. The alpha-blocking effects were minimal and transient at the recommended dosing regimen. In patients who received risperidone in doses up to 10 mg/day, there was no greater risk of extrapyramidal symptoms than that associated with placebo. Doses above 10 mg/day were associated with extrapyramidal symptoms, but at an incidence significantly lower than that seen with haloperidol (at doses of 10 and 20 mg/day).

The most common volunteered adverse events not seen at equivalent rates with placebo were rhinitis, abdominal pain, and tachycardia (increased heart rate). Elicited complaints not volunteered included accommodation disturbances, rash, menorrhagia, erectile dysfunction, ejaculatory dysfunction, and orgastic dysfunction.

Increased heart rate and decreased blood pressure were found with risperidone. Although weight gain was measured in a substantial proportion of patients, it was only rarely considered an adverse event. There were no clinically significant changes in the ECG, and the only clinically significant changes in laboratory values were decreased hematocrit and T_3 and increased phosphorus, SGPT, and prolactin.

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TABLES

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Pharm./Tox.
Review

REVIEW AND EVALUATION OF PHARMACOLOGY AND TOXICOLOGY DATA

Date: 4/30/93

NDA #: 20,272

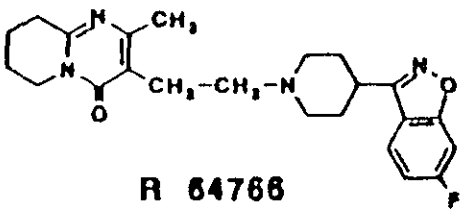
Sponsor: Janssen Research Foundation
1125 Trenton-Harbourton Road
Titusville, N.J. 08560-0200

Drug: Risperdal (risperidone) Caplets

Code Number: R 64766

Chemical Name: 3-[2-[4-(6-fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]ethyl-6,7,8,9-tetrahydro-2- methyl 4H-pyrido[1,2-a]pyrimidin-4-one

Structure:



R 64766
Risperidone

Molecular Wt: 410.40

Dosage Form: Oral caplets: 1, 2, 3, 4, and 5 mg

Clinical Dose: Optimum: ≤10 mg/day
Maximum: 16 mg/day

Related IND #

Studies were performed by the sponsor

Bold-face type denotes portions from reviews by Gary Evonick, Ph.D.

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PHARMACOLOGY

Receptor studies and behavioral pharmacology

In vitro receptor binding of risperidone has been determined for a variety of neurotransmitter systems, and comparisons have been made to other typical and atypical antipsychotic agents (see table from sponsor).

Risperidone was found to have a subnanomolar affinity for the $5HT_2$ receptor (K_i=0.12 nM), and a sub-to low nanomolar affinity for the α_1 and α_2 adrenergic, D_2, and the H_1 receptors.

Dissociation half-times for these receptors were on the order of 5-30 min.

Risperidone had higher affinity for the $5HT_2$ receptor than for any other receptor subtype. Haloperidol had only low nanomolar affinities for D_2 and the haloperidol-sensitive sigma receptor. Haloperidol did not react with the α_2 receptor. At the D_2 receptor, risperidone was 2-fold less potent than haloperidol, having a 25-fold weaker affinity for D_2 than for $5HT_2$.

Risperidone had weak/no affinity for D_1, H_2, ß-adrenergic, or haloperidol sensitive-sigma receptor. Risperidone was also shown to have little or no affinity for the $5HT_3$ receptor, as evidenced by the inability to inhibit 2-methyl-5HT suppression of medial prefrontal cortical cells. In vitro binding to D_2 revealed a K_i for risperidone of 1.4-3.1 nM in rat striatum, nucleus accumbens, olfactory tubercle, and in cloned D_2 receptors in human kidney. By comparison, the K_i for haloperidol binding to the D_2 receptor in these areas was 0.5-1.2 nM.

Risperidone was found to antagonize 5HT-stimulation of the PI cycle in human platelets, as measured in vitro both by changes in intracellular calcium and release of ^{3}H-PA, with an IC_{50} of 1.2 nM. This response was comparable to that of ritanserin, a known potent and selective $5HT_2$ antagonist, and greater than that of either chlorpromazine (IC_{50}=18 nM) or clozapine (IC_{50}=210 nM).

In vivo D_2 and $5HT_2$ receptor binding in rat brain was examined using ^{3}H-spiperone. Risperidone inhibited ^{3}H-spiperone labelling at $5HT_2$ sites at an ED_{50} of 0.03 mg/kg. This was 40-fold more potent than haloperidol and 100-fold more potent than clozapine. At D_2 sites, risperidone was less potent than haloperidol, binding with an ED_{50} of 1 mg/kg as compared to an ED_{50} of 0.14 mg/kg for haloperidol. Clozapine only partially inhibited ^{3}H-spiperone binding, with an ED_{50} of 3-5 mg/kg.

In synaptosomal preparations, risperidone was a weak inhibitor of monoamine uptake. Apparent IC_{50}s of 525, 2350 and 4500 nM were measured for the inhibition of serotonin, noradrenaline and dopamine uptake, respectively. GABA uptake was unaffected.

In rats, risperidone, but not haloperidol, (both at 1 mg/kg, i.p.), increased brain dopamine levels; however, both drugs increased brain levels of dopamine metabolites, DOPAC and HVA, to a similar extent (DOPAC: 228-245%; HVA: 216-275% of controls).

In tests of in vivo 5-HT antagonistic activity, risperidone (ED_{50}s=0.002-0.1 mg/kg s.c.) was 2.5 to 10-fold more potent than ritanserin (ED_{50}s=0.02-1.0 mg/kg s.c.) in blocking effects of seizures and cyanosis in rats. The onset of action of risperidone was faster (0.5 vs. 1 hr) but

lasted for a shorter period of time (2 vs. 4 hr) compared to ritanserin. A similar potency difference (risperidone>ritanserin) was observed for blockade of 5-HTP mediated head twitching and mast-cell mediated lesions induced by compound 48/80. The potency of the two drugs was comparable in inhibiting mescaline-induced (20 mg/kg i.v.) head twitching. Risperidone (0.028 mg/kg s.c.) antagonized the LSD cue in a drug discrimination test in rats without producing generalization.

Risperidone (ED_{50}s=0.6-1.2 mg/kg s.c.) was 5 to 10-fold less potent than haloperidol (ED_{50}s=0.1-0.26 mg/kg s c.) in tests of in vivo antidopaminergic activity in rats, including blockade of apomorphine (1.25 mg/kg i.v.), amphetamine (2.5 mg/kg s.c.) or cocaine (5 mg/kg i.v.) induced hyperactivity and/or stereotypy. However, risperidone (ED_{50}s=0.06 mg/kg s.c.) was more potent than haloperidol (ED_{50}=0.15 mg/kg s.c.) in preventing cocaine-induced oxygen hyperconsumption. A 5 to 10-fold potency difference (haloperidol > risperidone) between the two drugs was observed for inhibition of several learned responses including intracranial self stimulation and conditioned food consumption in rats and shuttle box avoidance in the dog. Risperidone was approximately equipotent to haloperidol in preventing apomorphine-induced emesis in the dog. Emesis was prevented at doses of 0.011-0.016 mg/kg by s.c., i.v. and p.o. routes of administration. The onset of action was rapid (<30 min) after p.o. administration and persisted for 8 hr or more. Risperidone produced hypoactivity, slight to marked catalepsy, ptosis and hypotonia at doses of 0.2-3.5 mg/kg s.c.; these doses were generally 2 to 10-fold higher than those blocking dopaminergic responses (e.g., stereotypy, emesis) and were also 2 to 5-fold higher than doses of haloperidol needed to produce similar cataleptic effects.

Both risperidone and haloperidol reduced apomorphine-induced rotation in mice after 6-hydroxydopamine lesions at low doses (0.1 mg/kg, i.p). At higher doses, risperidone was less potent than haloperidol. Rotation was reduced to 40% of controls by 0.5 mg/kg risperidone, compared with 0.2 mg/kg haloperidol, and to 20% of controls by 1.0 mg/kg risperidone, compared to 0.5 mg/kg haloperidol.

Risperidone inhibited conditioned avoidance behavior in squirrel monkeys at an ED_{50} of 84 nM/kg with less potency than haloperidol (ED_{50}= 23 nM/kg). Haloperidol data were collected in a separate experiment; therefore, the comparison may not be valid.

Study Of Risperidone Metabolites:

The pharmacological activity of the main metabolite of risperidone, R 76477 and its enantiomers, R 78543 (+) and R 78544 (-), was examined using a variety of behavioral measures. In rat (Wistar) studies, the metabolites (s.c., doses not given) were effective against apomorphine-induced agitation and stereotypies (ED_{50} of 0.19-0.39 mg/kg), tryptamine-induced convulsions (ED_{50} of 0.17-0.22 mg/kg) and tremors (ED_{50} of 0.34-1.0 mg/kg), and norepinephrine-induced mortality (ED_{50} of 0.22-0.34 mg/kg; however, they were, in general, slightly less potent (1.3-2.6 times) than risperidone (s.c., doses not given), especially in antagonism of tryptamine-induced tremors (3-9 times). In Beagle dogs, all three metabolites (s.c., p.o.) prevented apomorphine-induced emesis (ED_{50} of 0.004-0.1 mg/kg s.c; 0.0094-

0.59 mg/kg oral) (not all metabolites were tested at all doses). The metabolites (primarily R 76477) were, in general, equipotent to or slightly less potent than risperidone (up to 2 times).
General observations after R 76477 and risperidone (both 40 mg/kg, i.p.) were similar and consistent with antagonism of α-adrenoceptors and central dopamine receptors. The major observations were prostration, catalepsy, muscular hypotonia, sedation, decreased palpebral opening, reduced body temperature, decreased pupil diameter, protection from castor oil diarrhea (presumed local effect). Tremors and ataxia were seen only with risperidone. Neither risperidone or its metabolite had effects on tail withdrawal reaction or anticonvulsant activity. The data indicate that it is unlikely that R76 477 has any secondary pharmacological effects not seen with risperidone.

The effects of ^{3}H-labeled risperidone, 9-hydroxy-risperidone (racemic mixture), and the corresponding enantiomers, R 78,543 (+) and R 78 544 (-), on in vitro receptor binding and neurotransmitter uptake were studied in rat brain synaptosome preparations. There were no differences among risperidone and its metabolites in terms of the profile of receptor binding. The metabolites were similar to slightly less (0.9-7.1 fold) potent than the parent compound. All showed highest affinity to the 5-HT_2 receptor (K_i=0.12-0.24 nM) and nanomolar affinity to the α_1-adrenergic, D_2, and the H_1-receptors (K_i=0.81-1.4, 2.6-4.1, and 2.1-10 nM, respectively). Risperidone and its metabolites had little or no affinity for the other receptor binding sites examined, e.g., cholinergic (muscarinic), sigma, ion channels, peptide. Inhibition of uptake of serotonin, dopamine, NE, and GABA occurred at micromolar concentrations (IC_{50}s ranged from 544-2170 nM for serotonin to 4740-10690 nM for GABA).

Other In Vivo Studies:

Lethality after mast cell activation by compound 48/80 was reduced by risperidone with an ED_{50} of 0.028 mg/kg s.c. The drug also reduced skin reactions to s.c. injections of 5-HT, histamine or ovalbumin. The ED_{50} for protection against noradrenaline induced lethality was 0.1-0.3 mg/kg s.c. Similarly, risperidone antagonized the antidiarrheal effect of clonidine and the ataxia produced by xylazine; ED_{50}s against both α_2 agonists were in the 0.5-3 mg/kg range. At doses up to 10 mg/kg s.c. risperidone had no effect on the antidirrheal effect of loperaminde, nor was any analgesic effect observed in the tail flick test. Risperidone also lacked any significant ability to prevent physostigmine induced mydriasis and lethality, nicotine or KCN induced lethality, or metrazol seizures.

Risperidone (10 mg/kg, s.c.) had no effect on gastrointestinal motility as measured in rats by the phenol red and charcoal tests. Risperidone had no effect on hepatic drug-metabolizing enzymes at doses up to 10 mg/kg (gavage) as assess by comparison to vehicle-treated and positive (phenobarbital, 3-methylcholanthrine, dexamethasone, ethanol) controls

Endrocrine Studies

In a study of the endocrine effects of risperidone, fasted rats were dosed with risperidone, haloperidol or clozapine. Risperidone (0.028-2.0 mg/kg p.o.) produced dose related, 3 to 14-fold increases in serum prolactin levels within 20 min which persisted for up to 4 hr. These increases were of similar magnitude but shorter duration than those produced by haloperidol (2-3 mg/kg). There were no changes in serum corticosterone, insulin or glucose levels after risperidone or haloperidol

administration. By contrast, clozapine (10-90 mg/kg) increased these parameters by up to 500, 600 and 100%, respectively.

The effect of risperidone on serum prolactin levels was studied further (in male rats) because of the apparent discrepancy observed in the early study between affinity of haloperidol and risperidone for the D_2 receptor and the effect of these drugs on serum prolactin levels.

1. In vitro studies using rat anterior pituitary cell cultures indicated that haloperidol was 3 times more effective in effecting the release of prolactin than risperidone. Pretreatment of haloperidol and risperidone with S-9 ("a postmitochondrial fraction containing induced microsomal and cytosolic enzymes of hepatic metabolism") for two hours rendered haloperidol ineffective in releasing prolactin, whereas, the effect of risperidone on prolactin release remained unchanged. The data indicated that hepatic metabolism resulted in the conversion of risperidone (40-54%) to a metabolite (R 76477) equipotent with risperidone in the release of prolactin. The data were consistent with previous reports that haloperidol is metabolized to inactive metabolites. In vivo studies in rats confirm the previous report that serum prolactin levels were up to 3 times higher after risperidone [p.o.(gavage), i.p.] than after haloperidol [p.o.(by gavage), i.p.] when expressed per dose. When expressed per serum concentration of drug, haloperidol was found to be 3-4 times more potent than risperidone. After 1 hr (0.01-4.0 mg/kg, p.o., i.p.), serum levels of R 76477 were 3-15 fold higher than those of the parent compound. In addition, serum levels of risperidone and R 76477, at equivalent doses, were 2-10 fold higher than those of haloperidol.

Serum corticosterone levels were unchanged by risperdone, whereas they increased 2-3 fold after haloperidol.

2. In vivo studies were conducted in female SPR Wistar rats to examine the effect of haloperidol, risperidone, and R76477 on serum prolactin levels. All drugs were given by gavage at doses of 0.01, 0.05, 0.25, 1, and 5 mg/kg. A small effect of risperidone and R76477, but not haloperidol, on serum prolactin levels was seen at 0.01 mg/kg. At 0.25 mg/kg, haloperidol increased serum prolactin levels. At 0.25 and 1.0 mg/kg the AUC's for serum prolactin were similar for haloperidol and risperidone. At 5.0 mg/kg, the AUC for serum prolactin was 1.7 times higher for risperidone than haloperidol. In female rats, the ratio of serum levels of R76477 to risperidone was 1.4-1.6, indicating less metabolism of risperidone in female rats than previously shown to occur in male rats. The AUC's for serum haloperidol were ≈4-6 fold lower than those of either risperidone or R76477 at all doses. Therefore, haloperidol was more potent than risperidone or R76477 based on serum concentrations of drug. R76477 elevated serum prolactin at 0.01 mg/kg. At 0.05 amd 0.25 mg/kg, R76477 elevated prolactin levels comparable to those observed after similar doses of risperidone, and 1.3-3.7 fold higher than similar doses of haloperidol. As with risperidone, R 76477 was less potent than haloperidol in affecting serum prolactin levels when comparisons were made on the basis of serum concentrations, and not dose, of the drugs.

3. The effect of a single oral (gavage) dose of risperidone on serum prolactin levels was studied in male and female mice. Risperidone was administered at doses of 0, 0.16, 0.63, 2.5, 10 mg/kg and blood samples were collected at 0.5, 2, and 4 hrs. This study confirmed the effect of risperidone on serum prolactin levels observed in male and female rats. In both male and female mice, serum prolactin levels were highest at 0.5 hr; however, in females, only the increase in mean serum prolactin level at the highest dose was significant due to high control values in females. At 0.5 hr postdosing, serum prolactin levels in risperidone-treated mice were 2-4 fold higher than in controls. At 0.5 hr, there was no clear dose-response effect in males, as there was in females over the dose range. At 2 and 4 hr, serum prolactin levels, at all doses, were still significantly elevated above control levels.

4. The effect of risperidone administration in the diet for 6 wks on serum prolactin, testosterone, and LH was examined in male and female SPF Wistar rats. The doses of risperidone were 0, 0.63, 2.5, and 10 mg/kg. Calculation of dose based on food consumption and body weight indicated that actual doses were

0, 0.62, 2.48, and 9.61 mg/kg for males and 0, 0.58, 2.3, and 9.32 mg/kg for females. Blood samples were collected on Day 7, 14, 28, and 42 at 7:00 am and 11:00 am. In males, body weight was decreased at the HD (92-96% of control) at all time points. In females, body weight was significantly increased (107-115% of control) at the LD and MD, starting on wk 1-2, weekly weight gains being 200-500% of control. Food consumption was decreased in males at HD (90-97% of control) and increased at all doses in females (111-130% of control).

In males, serum prolactin levels were elevated (165% of control) at the LD only on day 42 at 7:00 am. At the MD, serum prolactin was elevated on day 28 and 42 (11:00 am) (164-186% of control) and on day 7 and 14 (11:00 am) (268-357% of control). At the HD, serum prolactin was elevated on all days (7:00 am) (160-590% of control). Testosterone levels remained unchanged, except for a significant increase (244% of control) on day 28 (7:00 am). Changes in LH levels were not consistent. Serum LH was elevated at LD and HD on day 7 (7:00 am), but decreased at HD on day 28 (7:00 am). For the 11:00 am samples, serum LH levels were decreased at the MD on day 7 and at the HD on day 42.

In females, serum prolactin levels were elevated at all doses of risperidone. At the LD, increases were seen on day 7 and 28 (7:00 am) (2.5-5.5 fold); at the MD and HD, serum prolactin was increased (5-22 fold) on days 7, 14, and 28. On day 42, increased serum prolactin was only observed in the HD group (7:00 am) (2.3-fold); this was apparently due to high control levels on this day.

5. The effect of daily oral (diet) administration of ripseridone on serum prolactin levels were studied in male and female SPF Albino Swiss mice. Doses of ripseridone were 0, 0.63, 2.5, and 10 mg/kg. Blood samples were collected on day 28 and day 90 (7:00 and 11:00 am). Clinical observations revealed no drug related effects. There were body weight changes. In males, there was a significant, but slight (95-97% of control), decrease in body weight at 2.5 (wk 2,3,5) and 10 (wk 2,3,5-9) mg/kg. In females, significant increases in body weight (103-118% of control) were evident at all doses throughout the experiment. Weight gain was studied in both males and females. No general drug effect on food consumption was observed. This is curious in light of weight differences between drug-treated and control animals. The lack of an effect may reflect imprecise food intake measurement due to documented incidence of food wastage.

Serum prolactin was elevated in risperidone-treated male and female mice. The data (means $\pm$ SEM, 7:00 am) for females are presented below. All data for drug-treated animals are significantly different from control data except for 0.63 mg/kg on Day 28.

Dose (mg/kg)	Day 28	Day 90
0	11.7 $\pm$ 6.5	9.7 $\pm$ 3.6
0.63	35.9 $\pm$ 18.1	120.9 $\pm$ 39.0
2.5	382 $\pm$ 78	573 $\pm$ 123
10	527 $\pm$ 46	1059 $\pm$ 218

In females, elevations in serum prolactin levels were dose- and duration dependent. On Day 28, serum prolactin levels in drug-treated females were 3, 33, and 45-fold higher than control values for LD, MD, and HD, respectively. Prolactin levels in drug-treated rats increased to 12.5, 59, and 109-times control levels on Day 90 for LD, MD, and HD, respectively. This was an increase of 1.5-3.5 fold over prolactin levels measure on Day 28.

In males, elevations in serum prolactin levels were dose-, but not duration, dependent. The data (mean $\pm$ SEM, 7:00 am) are presented in the following table.

Dose (mg/kg)	Day 28	Day 90
0	2.2 $\pm$ 0.2	2.0 $\pm$ 0
0.63	5.4 $\pm$ 1.9 *	2.0 $\pm$ 0
2.5	10.2 $\pm$ 3.5 *	10.3 $\pm$ 2.4 **
10	57.9 $\pm$ 15.7 **	56.3 $\pm$ 12.1 **

*$p \leq 0.05$; **$p \leq 0.005$

At 0.63, 2.5, and 10 mg/kg, serum prolactin levels were 2.4, 4.6, and 26-fold higher in drug-treated than in control animals. The levels remained elevated at Day 30.

Cardiovascular Studies

In cardiovascular studies, risperidone was administered to 7 conscious dogs. A low dose (0.08 mg/kg p.o.) produced 25% decreases in systolic and diastolic blood pressures, which occurred within 90 min of dosing and persisted for at least 4 hr. Heart rates were decreased, but by no more than 10%. Myocardial oxygen demand, as indicated by the pressure rate product, was decreased. ECG analysis indicated a 5% increase in corrected QT interval duration. There were no changes in left ventricular dP/dt. A higher dose (0.31 mg/kg p.o.) caused an increase in heart rate of up to 25 bpm. The corrected QT interval was prolonged by approximately 10%.

In a separate study, anesthetized dogs were dosed with 0.005-1.25 mg/kg i.v. Systolic and diastolic blood pressures were decreased, beginning at the lowest dose of 0.005 mg/kg. Large changes were observed beginning at 0.08-0.32 mg/kg doses, where pressure decrements of 30 to 50 mmHg were observed. Heart rates were increased slightly (~10 bpm) at doses up to 0.08 mg/kg; much larger increases (50 bpm or more) were observed at doses of 0.32 mg/kg and higher. Cardiac output, LVdP/dt and the pressure-rate product were increased in parallel with the heart rate. No ECG changes were observed except for frequency-related decreases in PQ and QT intervals.

Cardiovascular and behavioral effects of risperidone (0.08 mg/kg orally) in conscious dogs, chronically medicated with the compound.

This study was initiated after a single oral dose study in dogs indicated that risperidone doses of 0.08 mg/kg elicited 25% decreases in systolic and diastolic pressures for 4 hr or more. Seven unanesthetized instrumented dogs were dosed with 0.08 mg/kg i.p. for 6 days. Cardiovascular parameters were measured prior to the first day of dosing and then again during the first 4 hr after dosing. There were no significant changes in heart rate, ECG, LVEDP or overt behavior. The sponsor concludes that these results suggest development of tolerance to the hypotensive effect of risperidone in dogs. However, a much more convincing case would have been made had measurements been taken on the first day of dosing in order to confirm the magnitude of the initial cardiovascular effect.

Pharmacokinetic Studies

Pharmacokinetic studies were performed in the dog, rabbit and rat. Some of the results are summarized in the following table:

Table 2 - Pharmacokinetic Parameters

Species (Dose, mg/kg)	Dog (0.63)	Rabbit (0.63)	Rat (1.25)
$t_{1/2}$ (terminal) (hr)	0.8	5.7	2.8
t_{max} (oral) (hr)	0.5-0.75	2.0	0.5-1.0
C_{max} (ng/ml)	462	200	416
V_d	0.64	1.5	1.84
Cl (ml/kg/hr)	575	200	58
F (%)	60	64	32

1. Fasted beagle dogs dosed intravenously exhibited rapid clearance of the unchanged drug. The volume of distribution was close to that of total body water (this volume is not specified, but in humans it is ≈60% of body weight). After intragastric dosing, peak plasma levels of unchanged drug were reached within 1 hr. Bioavailability ($AUC_{oral}/AUC_{i.v.}$) was 60%.

   Fasted New Zealand white rabbits were dosed with ^{14}C-risperidone by i.v. and oral routes. Oral absorption was slower than in the dog (t_{max}=2 hr), and a longer elimination half-life was observed (5.7 vs. less than 1 hr in the dog). Comparing AUCs, the levels of unchanged drug accounted for an average of 64% of plasma radioactivity observed, indicating the presence of labelled risperidone metabolites in the blood.

2. After administration of ^{14}C-risperidone in the rat, a smaller percentage of radioactivity was accounted for by unchanged drug (11 and 41% after oral and s.c. administration, respectively). Oral bioavailability (unchanged drug) was 41%. Elimination of total plasma radioactivity was slower than that of unchanged drug, with a terminal half-life on the order of 8 hr. Highest levels of radioactivity were observed in the liver (initially 16-20% of the original dose), kidney (2-5%) and lung (1-2%) after i.v., s.c. and i.g. dosing. Brain levels of radioactivity were 3 to 7-fold lower than plasma levels. As G.I. radioactivity was not measured, it was not possible to determine whether the decrease in AUC after oral dosing was due to incomplete absorption or first pass metabolism of the parent compound.

3. The distribution of ^{14}C-risperidone in the rat was also studied by whole-body autoradiography after i.v. injection of 1.2 mg/kg. Fifteen minutes after dosing, highest concentrations of radioactivity were present in the kidney, liver, lung, pancreas, adrenal, salivary and lachrymal glands, stomach (probably the result of ion trapping), and the small intestine (apparently due to biliary excretion). Low concen' ations of radioactivity were detected in the brain - far lower than most peripheral tissues. After 2-4 hr, most tissue radioactivity levels had fallen significantly, except in the kidney, bladder and prostate where label persisted for 4 hr or more. Tissue radioactivity was negligible 24 hr after dosing except in the liver and large intestine.

4. In an excretion and metabolism study, rats were dosed with 0.63 mg/kg i.g. ^{14}C-risperidone. Urine and feces were collected over the following 96 hr. Of the original dose of radioactivity, 95% was recovered within 24

hr. Urinary excretion accounted for approximately 25% of the dose, fecal elimination accounted for more than 70%. Unchanged drug accounted for 3% of urinary radioactivity; 10 metabolites were detected in urine but not characterized. Two metabolites appeared to be glucuronides. In the feces, unchanged drug accounted for less than 1% of the radioactivity. The remainder was divided among a large (15 or more) number of metabolites, including 2 major peaks accounting for 5 and 6% of the dose, respectively. Neither was identified or characterized.

5. ^{3}H or ^{14}C-risperidone was administered orally as a single dose (0.63 mg/kg by gavage) to male and female rats (5/sex/grp) in order to identify metabolites in feces and urine. The majority of the radiolabel was excreted in the feces (78-82%) rather than the urine (14-20%). Overall, 96-98% of the dose was excreted after 96 hr. Seven major metabolites were excreted in urine after both ^{3}H and ^{14}C-risperidone; however, there were a number of metabolites specific for one radiolabel. In general, the more lipophilic metabolites were labeled with ^{14}C and the more hydrophilic metabolites with ^{3}H. The results in rats were compared to those in human volunteers given 1 mg ^{14}C-risperidone. In addition to the parent compound, there were 4 metabolites detected in both human and rat urine: 7-hydroxy-risperidone (R 79242), 9-hydroxy-risperidone (R 76477), 6,7,8,9-tetrahydro-2-methyl-oxo-pyrido[1,2-a]pyrimidine-3-acetic acid (R 78256) and its 9-hydroxy-metabolite (V-908-4).

Following ^{14}C-risperidone (0-24 hr), R 78256 (2.7-5.4% of dose) and V-908-4 (0.3-1.4% of dose) were higher in male than in female rat urine, indicating greater metabolism of risperidone via this pathway (i.e., oxidative N-dealkylation at the piperidine nitrogen) in males. Fifteen other metabolites were detected in rat urine, with each of 4 accounting for 1-2% of the dose. Following ^{3}H-risperidone, there were numerous metabolites. The metabolites detected only with ^{3}H-risperidone in rat urine were all presumed to be secondary metabolites of the nor-metabolite 6-fluoro-3-(4-piperidinyl)-1,2-benzisoxazole (R 56109), and were all detected in greater amounts in male than female rat urine. Levels of parent compound were higher in the urine of female rats than that of male rats (1.4 vs 0.7% of dose, respectively).

In feces, the same metabolites were detected in feces after either ^{3}H or ^{14}C-risperidone. The two major metabolites (0-24 hr) were dihydroxy-risperidone (7-10% of dose) and hydroxy-keto-risperidone (5-6% of dose in male, 4-5% of dose in females). The parent compound (0.8-1.0% of dose) and 4 metabolites [dihydroxi-risperidone, 3 not completely characterized (3.6-5.5% of dose)] were detected in rat and human feces (1 mg ^{14}C-risperidone).

In plasma, total radioactivity was higher in female than in male rats. In both sexes, however, 9-hydroxy-risperidone was the main plasma metabolite (27-63 and 15-46% of total plasma radioactivity in males and females, respectively). Four other metabolites accounted each for 3-10 (males) and 2-6% (females) of total radioactivity.

The data suggest the following metabolic pathways for orally administered risperidone: (1) hydroxylation at the alicyclic part of the 6,7,8,9-tetrahydro-2-methyl-4H-pyrido[1,2-a]pyrimidin-4-one ring system, (2) oxidative dealkylation at the piperidine nitrogen, (3) scission of the isoxazole in the benzisoxazole ring system.

6. **In a preliminary metabolic study using a single beagle dog, elimination of ^{14}C-risperidone appeared to be somewhat slower than in the rat, requiring 48 hr to eliminate 78% of the original dose of radioactivity. Urinary and fecal excretion accounted for equal fractions of the eliminated drug. Both contained large numbers of metabolites, including several major glucuronide metabolites in the urine. Unchanged drug accounted for less than 0.1% of either urinary or fecal radioactivity.**

7. PK and absolute bioavailability of risperidone were studied after i.v. and oral (gavage) administration to 4 male Beagle dogs. Risperidone (0.31 mg/kg) was given according to a crossover

design, all dogs receiving both p.o. and i.v. risperidone. Blood was collected prior to and at 8, 15, and 30 min (15, 30, and 45 min for p.o.) 1, 1.5, 2, 3, 4, 6, 8, 12, 25, 32, 48, 56, 72, and 80 hr after dosing. Plasma was analyzed for risperidone and 9-hydroxy-risperidone. After i.v. dosing, peak levels of risperidone and 9-hydroxy-risperidone occurred at 8 min and 4 hr, respectively. At 2 hr postdosing, metabolite levels were higher than those of risperidone. By 8 hr, plasma risperidone levels were undetectable; by 80 hr, the metabolite was also undetectable in plasma. After oral dosing, peak levels of risperidone and metabolite were 1 and 3 hrs, respectively. By 2 hrs postdosing, plasma levels of the metabolite were higher than those of risperidone. By 6 hr, plasma levels of risperidone were low to undetectable, whereas levels of the metabolite were measurable up to 72-80 hrs postdosing. By 1.5 hrs postdosing, plasma levels of the metabolite were the same or higher than those of risperidone.

Risperidone

parameter	i.v.	p.o.
C_{max} (ng/ml)*	473±94.3	248±65
T_{max} (h)		0.9
AUC (ng*hr/ml)	845±478	612±336
% bioavailability	100	76±28 (range)

*for i.v., C_0

9-hydroxy-risperidone

parameters	i.v.	p.o.
C_{max} (ng/ml)	210±54	226±54
T_{max} (h)	4.5±2.4	3.8±1.7
AUC (ng*hr/ml)	4893±2152	5686±3449

The $t_{1/2}$ (β) was similar after both routes of administration: 1.2-1.4 hr for risperidone and 19.9-21.1 hr for the metabolite. There was some variability in bioavailability (based on AUC; 39-98%), however, bioavailability was 98% in 2 of 4 dogs. C_{max} after p.o. was a maximum of 53% (39-66%) of that after i.v. dosing. C_{max}, T_{max}, and AUC for the metabolite were similar after i.v and p.o. dosing. The ratio of AUCs for metabolite to risperidone were 5.1-7.8 and 6.6-14.1 for i.v. and p.o. dosing, respectively.

8. PK and absolute bioavailability of 9-hydroxy-risperidone were studied after i.v. and oral (gavage) administration (0.31 mg/kg) to 4 male Beagle dogs (the same animals used in the previous study, i.e., #7). The dosing regime and blood collection times were the same. Plasma samples were analyzed for 9-hydroxy-risperidone using HPLC. After i.v. dosing, peak levels were obtained by 8 min (the first collection time). Levels were undetectable at 80-144 hr. $t_{1/2}$ (β) was 14.4 hr (range: 10.3-19.1), slightly less than after i.v. risperidone. After oral dosing, peak levels were obtained at 45 min-3 hr. $t_{1/2}$ (β) was 17.5 hr (13.1-22.4), similar for that after i.v. and p.o. risperidone.

9-hydroxy-risperidone

parameters	i.v.	p.o.
C_{max} (ng/ml)*	470±122	352±114
T_{max} (h)		1.4±1.1
AUC (ng*hr/ml)	6794±2631	6431±3029
% bioavailability		94.4±15.0

*C_0 for i.v.

AUCs were similar after i.v. and p.o dosing and were 16-35% higher than after i.v. and p.o. risperidone.

9. Metabolism and excretion of ^{14}C-risperidone was studied after a single oral (gavage) dose (low: mg/kg; high: 1.25 mg/kg) in 3 male Beagle dogs. Each dog received the low and high doses separated by a washout period of 5 wks. One additional dog received 1.25 mg/kg by gavage to determine the main urinary metabolites. Blood samples were collected prior to and at 0.5, 1, 2, 4, 8, 24, 48, and 72 hr (also, 96 and 168 hrs after the high dose) after dosing. Urine samples were collected up to 96 hr post dosing. Feces were collected for 96 hrs -7 wks after dosing.

In **plasma**, risperidone and 9-hydroxy-risperidone were the main radioactive compounds, with 7-hydroxy-risperidone being a minor metabolite (2.9-5.8% of plasma radioactivity). At 1 hr after dosing, risperidone accounted for 57-59% of plasma radioactivity, while the 9-hydroxy metabolite accounted for 40%. At 4 hr post dosing, the 9-hydroxy metabolite accounted for 82-86% of plasma radioactivity. At 8 and 24 hrs, 9-hydroxy-risperidone was the only detectable metabolite (75-90% of plasma radioactivity). Peak levels of risperidone (643-892 ng/ml) and 9-hydroxy-risperidone (625-886 ng/ml) occurred at 1-2 and 4 hr postdosing, respectively. $t_{1/2}$ was 0.9-1 hr for risperidone and 15.6-18.6 hr for 9-hydroxy-risperidone. AUC (μg*h/ml) was 1.49-1.94 for risperidone and 11.1-13.3 for 9-hydroxy-risperidone.

Excretion: At 4 days after dosing, 43% of the dose was excreted in urine and 46% in feces. The total excretion was 87% of the dose. After 7 days, 49.7% of the dose was excreted in urine and 40.1% in feces, with total excretion being 92.3% of dose. **Urine** was co-chromatographed with urine samples from rat and human collected previously. Risperidone and 4 major metabolites (A, B, G, H) were excreted in the urine of all three species: **H**: 9-hydroxy-risperidone; **G**: 7-hydroxy-risperidone, **B**: 6,7,8,9-tetrahydro-2-methyl-4-oro=4H-pyrido[1,2-a]pyrimidin-3-acetic acid; **A**: 9-hydroxy-metabolite of B. 3 minor metabolites were not observed in all species. In dog urine, there were only a few glucuronic acid or sulphate conjugates of risperidone metabolites. 9-hydroxy-risperidone (H) was the main metabolite in dog, making up 37-49% of total radioactivity or 8.3-24.4% of the dose at 24 hr and 14-33% of the dose at 96 hr. At 24 hr postdosing, A, B, and G accounted for 4-10% of sample radioactivity (1.2-3.2% of dose), 6-12% of sample radioactivity (1.7-4.7% of dose, and 6-9% of sample radioactivity (1.3-3.1% of dose), respectively. At 96 hr, A, B, and G accounted for 1.9-3.5%, 1.8-5.0%, and 1.5-3.2% of the dose, respectively. Risperidone (along with its metabolite with an opened benzisoxazole ring) made up 1.4-4.3% of sample radioactivity and 0.5-1.2% of dose. The pattern of metabolites indicates that in human and dog risperidone is metabolised first to B, which is in turn metabolized to A, since B appears first in urine, but later the concentration of A in urine is greater than that of B.

The recovery of radioactivity from **feces** was low (43-52%), therefore, quantitation of the metabolites and parent compound was not possible. Most fecal metabolites were different from urinary metabolites. The following metabolites were identified: **M**: 3-[2-[4-(4-fluoro-2-hydroxybenzoyl)-1-piperidinyl]ethyl]-6,7,8.9-tetrahydro-2-methyl-4H-pyrido[1,2-a]pyrimidin-4-one, **I**: the corresponding 9-hydroxy compound, **L**: urinary metabolite G, **K**: dihydroxy-risperidone. Risperidone and metabolites H, I, and G were present in both urine and feces. Risperidone and metabolites K, L, I, and M were present in feces of all three species. As in plasma and urine, 9-hydroxy-risperidone was the main metabolite, accounting for 1.0-2.9% of fecal radioactivity.

The main pathways for risperidone metabolism appear to be: (1) hydroxylation at the alicyclic part of the 6,7,8,9-tetrahydro-2-methyl-4H-pyrido[1,2-a]pyrimidin-4-one ring system [an aliphatic hydroxylation], (2) oxidative N-dealkylation at the piperidine nitrogen, and (3) scission of the isoxazole in the benzisoxazole ring system. 9-hydroxy-risperidone is metabolized only to I and A. In dogs, the first pathway predominates at the 9-position in a way similar to humans. In rats 7-hydroxy risperidone is somewhat more abundant than in human or dog; however, in all three species, 9-hydroxy risperidone is the most abundant metabolite (more so in human than either dog or male rat). Metabolites K, L, I, and M appear to be most abundant in rat and is detected almost exclusively in feces, perhaps being formed by intestinal microorganisms. In general, human metabolites, both quantitatively and qualitatively, resemble more the pattern in dog than in rat.

10. Regional brain distribution of ^{3}H-risperidone and 9-hydroxy-risperidone was studied in rats given 0.02 mg/kg ^{3}H-risperidone s.c.

Total brain radioactivity

	C_{max} (ng/ml)	T_{max} (h)	$t_{1/2}$ (h)	AUC(ng*h/ml)
plasma	5.9	1		24.6
frontal cortex	7.55	1		61.4
striatum	6.85	1		42.7
cerebellum	1.72	1		12.0
rest of brain	4.35	1		24.6

Parent compound

	C_{max} (ng/ml)	T_{max} (h)	$t_{1/2}$ (h)	AUC(ng*h/ml)
plasma	4.19	0.5	1.0	8.57
frontal cortex	6.89	1	3.9	43.3
striatum	5.84	1	2.5	24.3
cerebellum	1.39	1	0.8	2.46
rest of brain	4.18	1	2.6	15.3

R 76477 (9-hydroxy-risperidone)

	C_{max} (ng/ml)	T_{max} (h)	$t_{1/2}$	AUC(ng*h/ml)
plasma	1.9	2	1.4	7.14
frontal cortex	0.893	4	7.2	12.5
striatum	0.857	4	6.4	8.58
cerebellum	0.183	2	$\leq$2	0.878
rest of brain	0.394	4	4.4	3.49

The parent compound rapidly entered the brain, reaching C_{max} in all brain areas and in plasma at 1 hr. The maximum concentrations were in frontal cortex and striatum. Levels of parent compound declined more gradually in brain than in plasma ($t_{1/2}$=2.5-3.9 vs 1.0, respectively). Tissue/plasma ratios, based on AUC, were 2.8 for striatum and 5.1 for frontal cortex. Lower C_{max} and tissue/plasma ratio was lower in cerebellum (1.39 ng/ml at 1 hr and 0.3, respectively). Higher levels and a longer $t_{1/2}$ were observed in frontal cortex than in striatum, reflecting the greater affinity for the $5HT_2$ than for the D_2 receptor. Concentrations of 9-hydroxy-risperidone were lower (6.8-10.6 fold) and reached C_{max} later (2-4 vs 1 h) than the parent compound. The $t_{1/2}$ for the metabolite was longer; therefore, the AUC for 9-hydroxy-risperidone was only 3-4 fold lower than the parent. For the frontal cortex and striatum, the parent compound account for the majority of total radioactivity up to 8-12 hr after dosing, whereas, in plasma and cerebellum, parent compound only accounted for <50% of total radioactivity (AUC/total radioactivity equalled 0.71, 0.57, 0.21, for frontal cortex, striatum, and cerebellum, respectively). The sponsor stated that the other metabolites (not specified) showed no regional distribution.

11. Plasma levels of risperidone and 9-hydroxy-risperidone were measured at the end of a 3-mo oral (dietary) toxicity study in SPF Albino Swiss mice (10/sex/grp). Doses of risperidone were 1.25, 5, and 20 mg/kg. Diet was corrected for body weight and food intake resulting in actual doses of 0.95-1.26, 3.96-5.38 and 16.3-22.0 mg/kg. Plasma levels were calculated in pooled (n=5) samples. In both males and females, levels of 9-hydroxy-risperidone were higher than those of risperidone (ratio of metabolite to

parent compound: 2.72-3.93 for males, 2.52-3.29 for females), more so at the higher doses than at 1.25 mg/kg. Plasma levels of both compounds were higher in males than females. The sponsor suggests this may have been due to the fact that males were sacrificed sooner after diet withdrawal than were females.

Plasma levels (male; female) of risperidone and 9-hydroxy-risperidone (ng/ml) (recalculated to exact theoretical dose):

Dose (mg/kg/day)	risperidone (male)	risperidone (female)	9-hydroxy-risperidone (male)	9-hydroxy-risperidone (female)	ratio (R:9-OH-R) (male)	ratio (R:9-OH-R) (female)
1.25	2.4	2.7	6.7	7.5	2.72	2.52
5	7.1	5.6	27.9	14.4	3.95	3.11
20	28.7	20.1	110	65.2	3.93	3.29

12. Plasma levels of risperidone and 9-hydroxy-risperidone (ng/ml) were measured at the end of an 18-mo carcinogenicity study conducted in SPF Albino Swiss mice (50/sex/grp). Risperidone was administered orally (in diet) at doses of 0.63, 2.5, and 10 mg/kg. Diet was corrected for body weight and food intake; actual doses were 0.499-0.736, 2.11-3.27, and 8.01-10.6 mg/kg. Blood samples were collected 1-8 hr after diet removal. Plasma levels of both risperidone and 9-hydroxy-risperidone following 0.63 mg/kg and 2.5 mg/kg (only in females) were undetectable; in males, plasma levels of risperidone were near the lower limit of detectability. Plasma 9-hydroxy-risperidone levels were higher than risperidone levels in both males and females. Plasma levels of 9-hydroxy-risperidone tended to be lower in females than in males and to increase somewhat linearly with increase in dose from 2.5-10 mg/kg.

Dose (mg/kg/day)	risperidone (male)	risperidone (female)	9-hydroxy-risperidone (male)	9-hydroxy-risperidone (female)	ratio (R:9-OH-R) (male)	ratio (R:9-OH-R) (female)
0.63	n.d.	n.d	n.d.	n.d.	n.d.	n.d.
2.5	5.3	≤5	14.9	9.7	2.8	—
10	14.5	14.3	50.6	40.9	3.5	2.86

13. Plasma levels of risperidone and 9-hydroxy-risperidone (ng/ml) were measured at the end of the 24 mo carcinogenicity study conducted in Wistar rats (50/sex/grp). Risperidone was administered orally in the diet at doses of 0, 0.63, 2.5, and 10 mg/kg. Drug concentrations in the diet were changed as necessary to provide the appropriate doses of risperidone. Blood samples were collected at autopsy, i.e., 1-6.5 hr after removal of the medicated diet. Individual or pooled (2-6) serum samples were analyzed for drug levels by HPLC (limit of detection was 2.0 ng/ml for both compounds). Concentrations were corrected to theoretical doses. The data were analyzed according to the length of time between removal of medicated diet and blood collection (at autopsy) and according to the highest concentrations at each dose. Clearly the time interval between diet removal and blood sampling had a marked effect on plasma concentrations. Therfore, the data are of questionable value, especially since the analyzes were based partly on pooled samples, in which each sample potentially could have been collected at a different time after removal of the medicated diet. The highest plasma levels (ng/ml) of risperidone and 9-hydroxy-risperidone are presented in the following table:

Dose (mg/kg)	risp male	9-OH male	sum male	risp female	9-OH female	sum female
0.63	4.1	9.0	13.1	5.0	10.5	15.5
2.5	10.1	24.3	34.4	15.1	41.1	56.2
10	40.5	104	145	46.9	126	173

14. Plasma and tissue (brain, heart, lung, liver, kidney, muscle) radioactivity was measured after a single i.v., oral, and s.c. dose of risperidone (1.25 mg/kg) in male Wistar rats. Total radioactivity was higher after s.c. and i.v. than after oral administration (s.c. 30% higher than p.o.), indicating fecal (unabsorbed and/or biliary) excretion of radioactivity after oral administration. In addition, plasma exposure to radiolabeled risperidone (based on AUC) was also higher after s.c. and i.v. than after p.o. dosing (i.v. was 3.7-fold higher and s.c. was 5.4-fold higher than p.o.); this suggests a significant first-pass effect after p.o. dosing. T_{max} was 1 hr after p.o. and 0.5 hr after s.c. and i.v. dosing. The elimination $t_{1/2}$ was similar for all routes of administration (0.5-0.6 hr). Tissue radioactivity peaked rapidly, indicating rapid absorption and equilibration with plasma radioactivity. Highest levels of radioactivity were detected in liver (especially after p.o. dosing) and kidney (AUC of 14.3-16.5 ng*h/ml for liver, 5.98-9.97 for kidney), moderate levels of radioactivity were detected in lung (3.42-4.28), and the lowest amounts were detected in heart (0.76-1.00), muscle (0.54-0.73), and brain (0.20-0.31). Brain total radioactivity varied from a maximum of 0.013 to 0.179% of the dose, depending upon route, being highest after i.v. and lowest after p.o. dosing. Regardless of the route, brain total radioactivity fell to $\leq$0.005% of the dose by 8 hr.

15. The effect of nutritional status (fed vs fasted) on absorption of a single oral dose of risperidone (0.63 mg/kg) was studied in male Wistar rats. Plasma levels of total radioactivity, risperidone, and 9-hydroxy-risperidone were measured up to 8 hr after dosing. At 0.5 hr, total radioactivity was higher in fasted than in fed rats 205 vs 92.2 ng/ml, respectively); however, even at this early time point, plasma levels of risperidone were similar in fasted and fed rats (36.6-39.7 ng/ml). There was slightly greater metabolism of risperidone to 9-hydroxy-risperidone in fasted rats (ratio of parent to metabolite: 0.77 and 1.32, for parent and metabolite, respectively). This is reflected in the AUCs for parent and metabolite: AUC (ng*h/ml) for risperidone was higher (40.2 vs 30.9), and that for 9-hydroxy-risperidone was lower (141 vs 186) in fed than in fasted rats, respectively. The data suggest that, although nutritional state delays absorption of risperidone slightly and somewhat decreases its metabolism to 9-hydroxy-risperidone, overall absorption seems to be fairly similar.

16. Plasma and organ/tissue radioactivity was measured in male and female Wistar rats up to 24 hr after oral (gavage) administration of ^{14}C-risperidone (0.63 mg/kg). The following tissues were examined: brain, pituitary gland, eyeballs, lacrimal glands, lymph nodes, salivary glands, thyroid, thymus, heart, lung, liver, kidney, adrenal gland, pancreas, spleen, esophagus, stomach, small and large intestine (tissue and contents separately), urine-bladder, muscle, skin and fur, ears, peri-renal and subcutaneous fat, brown fat, bone-marrow, bone, trachea, testicles, seminal vesicles, epididymis, prostate, ovaries, vagina, uterus.

	total radioact. (male)	total radioact. (female)	risperidone (male)	risperidone (female)	9-hydroxy-risperidone (male)	9-hydroxy-risperidone (female)
T_{max} (h)	0.5	0.25	0.25	0.25	1	2
C_{max} (ng/ml)	102	335	48 2	265	51.4	61.5
$t_{1/2}$ (h)		0.9	1.4	2.0	3.6 2.0	3.6
AUC (ng*h/ml)	492	1084	58.4	327	172	433

Blood collections for analysis of radioactivity were not serial samples. There were 4/sex/time point, resulting in 4 individual time course curves/sex. Plasma total radioactivity reached a peak at the same time or slightly earlier than did plasma risperidone, whereas, peak levels of 9-hydroxy-risperidone tended to be reached somewhat later than did levels of plasma risperidone. Plasma levels of total radioactivity and risperidone were higher (3.3 and 5.5-fold, respectively) in females than males. On the average, plasma

levels of 9-hydroxy-risperidone were 20% higher in females than males; however, individual data indicate that 2 groups (4/time point) of females had higher levels and 2 groups had lower levels of the metabolite. In males, risperidone and 9-hydroxy-risperidone accounted for 12% and 35% of total radioactivity exposure (based on AUC). In females, the percentages were 30 and 40%. Therefore, the extent of metabolism of risperidone was greater in males, but the extent of metabolism of risperidone to 9-hydroxy-risperidone was less than in females. The additional metabolite(s) in males was not identified. The organ/tissue data indicate rapid, but incomplete, absorption and distribution of risperidone (and/or 9-hydroxy-risperidone) into various tissues. Organs with rapid ($\leq$0.5 hr) peak concentrations of radioactivity (expressed as % of dose) include brain (0.028), heart (0.062), lung (0.346), liver (12.8), kidney (0.717), adrenal gland (0.028), pancreas (0.138), and spleen (0.172). Highest levels of radioactivity were detected in stomach contents (22.4-47.3 up to 2 hr after dosing), liver (12.8%), small intestine contents (increased from 0.25 to 8 hr after dosing; 0.08-41.4%). Lowest levels of radioactivity were detected in pituitary gland (0.001-0.002%), eyeballs (0.003-0.011%), thyroid (0.002%), ears (0.003-0.008%), and trachea (0.002-0.008%). Analysis of GI contents indicates that 50-60% of total dose is either not absorbed or is secreted in bile. At 24 hr after dosing, tissue/organ (non-GI) levels of radioactivity are low to undetectable, indicating little if any accumulation. Total (non-reproductive) organ exposure (based on AUC of total radioactivity) was 1.5-3 fold higher in females than in males, except for bladder (female 0.6 fold lower than male), and adipose tissue (female 0.9 fold lower than male).

17. Plasma levels of risperidone and total radioactivity were determined after a single oral (gavage) administration of ^{14}C-risperidone (0 63 mg/kg) to 4 male New Zealand white rabbits Plasma risperidone was measured using HPLC with UV detection (limit 2.5 ng/ml). Blood samples were collected prior to and 0.25, 0.5, 1, 2, 4, 8, and 24 hr after dosing. T_{max} was 2 hr for both total radioactivity and risperidone. C_{max} (ng-eq/ml) was 195 for total radioactivity and 131 for risperidone. AUC (µg-eq*hr/ml) was 2.01 for total radioactivity and 1.27 for risperidone. The $t_{1/2}$ for risperidone was 5.1 hr. Data were expressed as means of 3 rabbits; the data from 1 rabbit were significantly different from those of the others presumably due to misdosing.

18. Tissue distribution of ^{14}C-risperidone after a single i.v. (1.25 mg/kg) or oral (2.5 mg/kg; gavage) dose in male and pregnant (18th day of gestation) female Wistar rats was studied using whole body autoradiography. Only selected autoradiographs were submitted with the report since no quantitative analysis was performed. After i.v. administration in male rats, the highest levels of radioactivity appeared to be in stomach, GI, lung, liver, pancreas, spleen and glandular tissue (e.g., adrenal, salivary, lacrimal, and preputial glands). Very low levels of radioactivity were detected in brain and only in the pineal and pituitary glands, and the lateral and 4th ventricles. At 4 hrs postdosing, the highest levels of radioactivity appeared to be in intestine, bladder, and urethra By 24 hrs, radioactivity was detectable only in liver, salivary glands and large intestine. Distribution of radioactivity was similar in pregnant females, except there appeared to be high levels of radioactivity in fetal membranes. In fetal tissue, only the liver contained low, but detectable radioactivity. Elimination of radioactivity from tissue appeared to be somewhat slower in females than in males. After oral administration of of ^{14}C-risperidone, tissue distribution appeared to be similar to that after i.v. dosing, except that liver appeared to have higher levels of radioactivity after oral dosing.

19. Melanin-binding of risperidone was studied in 3 male spotted pigmented Dunning rats after i.v. injection of ^{14}C-risperidone. Tissue was examined by whole body radioautography at 4, 24, and 96 hr postdosing. Autoradiographs were not quantitated. Overall distribution of radioactivity was similar to that seen in albino rats with the exception of melanin-containing structures. Eye, especially the chroid, retinal pigment epithelium, and iris, and skin appeared to have high levels of radioactivity; in the albino rat, there was low to undetectable radioactivity in eye. In pigmented rat brain, marked radioactivity was detected in the meninges, which was also not observed in the albino rat. Over time, radioactivity decreased; however,

even at 96 hr postdosing, there appeared to be high levels of radioactivity in melanin-containing tissue, especially in eye.

20. Placental transfer of ^{14}C-risperidone was studied in female rats receiving 1.25 mg/kg as a single dose (i.v., p.o.) on Day 18 of gestation. As observed previously, plasma exposure (based on AUC) to risperidone and 9-hydroxy-risperidone was higher after i.v. than oral dosing, while metabolism of risperidone was greater after oral than after i.v. dosing. Absolute bioavailability of the parent compound was 40%, whereas, the ratio of AUCs for total radioactivity (oral:i.v.) was 0.6 (or 60%). Radioactivity was detected in all tissues and fluids examined (placenta, uterus, fetus, fetal membranes, amniotic fluid, fetal blood, ovaries, mammary gland) and at higher levels (1.2-5 fold) after i.v. than after oral dosing. Plasma exposure to total radioactivity in fetal blood was 80% of maternal values. Based on AUCs, exposure (total radioactivity) was highest in fetal membrane (8.75 µg*h/ml), moderate in ovaries (2.79), mammary gland (2.58), and placental (2.70), and lowest in maternal blood (1 20), fetus (0.516), and amniotic fluid (0.477). In all tissues examined, risperidone accounted for 31-38% of total radioactivity, whereas, 9-hydroxy-risperidone accounted for a larger percentage (≈40%) (except mammary gland, 30%). Total radioactivity declined over a 24-hr period after dosing to ≤5.0% of peak levels, except in fetal membranes and amniotic fluid which retained 30 and 10% of peak levels, respectively.

21. Milk levels of risperidone and 9-hydroxy-risperidone were measured in 3 lactating Beagle dogs after a single oral administration (0.16 mg/kg) of oral risperidone. The dogs were dosed on day 11-16 after delivery. Milk samples were collected prior to and a 0.5, 1, 2, 4, 8, 24, 48, and 96 hr after dosing. Pups were removed for ≈30 min prior to each milk collection. (It is not certain that this collection method would provide representative samples of total drug content of milk.) Blood samples were collected immediately after milk sampling. Absorption of risperidone and its secretion into milk was rapid. Peak levels of risperidone and 9-hydroxy-risperidone in both plasma (101, 110 ng/ml) and milk (99.1, 180 ng/ml) were observed at 0.67 and 2.0-2.3 hr. AUCs for risperidone were similar in plasma and milk (178 and 166 ng•h/ml, respectively); however, AUC for 9-hydroxy-risperidone in milk was 2.6 fold larger than in plasma, reflecting both a greater concentration of the metabolite in milk, relative to risperidone, and a longer $t_{1/2}$ for the metabolite in milk (12.7 vs 9.5 hr). The milk/plasma ratio was 1.0 for risperidone and 2.6 for 9-hydroxy-risperidone. The ratio of metabolite to risperidone was higher in milk than in plasma (21.5 vs 8.2).

Other studies

Protein-binding studies

1. The binding of ^{3}H-risperidone to various plasma protein was studied (in vitro) in human, rat and dog plasma. The effects of pH (5.16-8.2) and cold risperidone concentrations ng/ml; ng/ml was the concentration used to assess other effects) on plasma protein binding was assessed, as well as the distribution of ^{3}H-risperidone binding in blood. Binding to the following plasma proteins was measured: human serum albumin (HSA), α_1-acid glycoprotein (AAG), α-globulin, α_1-globulin, ß-globulin, gamma-globulin. In vivo binding was also assessed using plasma samples from humans (1 mg/kg), rat (0.63 mg/kg), and dog (1.25 mg/kg) receiving ^{14}C-risperidone. Binding to human plasma proteins increased with increasing pH from 70% at pH 6.8 to 88% at pH 8.1, and was independent of cold drug concentration within the range of 0.5-200 ng/ml. At 500 ng/ml risperidone, % binding fell slightly to 87%. Binding was highest to HSA and AAG (83-85%). Binding to the other plasma proteins ranged from %: % to the α-globuins and % to the ß and gamma-globulins. In blood, the majority of ^{3}H-risperidone was bound to plasma proteins (73.8% human, 65.3% rat, 84.9% dog); 18.1, 24.2, and 7.5% in human, rat, and dog, respectively, was distributed to the rbc. In an rbc suspension (buffer), distribution to rbc was similar to that in plasma, 71.5-74.9% in all three species. In vivo, binding of total radioactivity to plasma proteins was high (77.2-87%) at 1 hr and decreased with time. Low values were 63.4-90.7% in

human at 8 hr, 61.6-78.2% in rat at 4 hr, and 79.5% at 24 hr postdosing in dog. This decrease in binding is consistent with formation of the more polar metabolite, 9-hydroxy-risperidone which is 77.4% protein-bound in human plasma.

2. The effect of various drugs on the plasma protein binding of ^{3}H-risperidone and and ^{3}H-9-hydroxy-risperidone was studied in vitro using human plasma samples. ^{3}H-9-hydroxy-risperidone was prepared by incubating ^{3}H-risperidone with dog hepatocytes followed by purification by radio-HPLC. Plasma protein binding interactions were assessed by adding 10 ng/ml ^{3}H-risperidone or 50 ng/ml ^{3}H-9-hydroxy-risperidone to human plasma followed by the addition of the following drugs at concentrations corresponding to a high therapeutic level: imipramine, diphenylhydantoin, diazepam, tolbutamide, sulfamethazine, indomethacin, warfarin, digitoxin, haloperidol, carbamazepine, and either 9-hydroxy-risperidone (in the case of ^{3}H-risperidone) or risperidone (in the case of ^{3}H-9-hydroxy-risperidone). In an additional experiment, unlabeled risperidone and 9-hydroxy-risperidone were added to human plasma containing various radiolabeled drugs (imipramine, diphenylhydantoin, warfarin, digitoxin, propranolol, haloperidol, diazepam, risperidone, or 9-hydroxy-risperidone) in order to determine the effect of risperidone and its metabolite on the binding of these drugs to plasma proteins. 87.7% of risperidone and 77.4% of 9-hydroxy-risperidone was bound to plasma protein. Imipramine, haloperidol, and digitoxin nad no affect on binding of either risperidone or its metabolite. Sulfamethazine, warfarin, and carbamazepine decreased the % binding of both compounds. Diphenylhydantoin, tolbutamide, and indomethacin increased the % binding of risperidone only, whereas diazepam decreased the % binding of 9-hydroxy-risperidone only. In all cases, however, the changes were extremely small; all values were 96-101% of the control value (i.e., in the absence of any unlabeled drug). Neither risperidone nor 9-hydroxy-risperidone affected the binding of any of the drugs tested.

Melanin-binding study

1. The in vitro study of melanin-binding properties of ^{3}H-risperidone and ^{3}H-9-hydroxy-risperidone were studied using synthetic melanin. Effects of time, concentration, and ionic strength on melanin-binding of risperidone were assessed. In addition, the reversibility of binding was determined using solvent and buffer washes and dialysis. Comparisons were made to melanin-binding of other compounds: haloperidol, chlorpromazine, and glucose. Maximum binding of ^{3}H-risperidone to melanin (77.2%) was observed after 10 min of incubation (the first time point) and remained at this level up to 120 min of incubation. Increasing concentration of risperidone from μM did not result in saturation of binding which increased linearly from %. The Scatchard plot was curvilinear, indicating multiple binding sites (at least two). The low affinity site had a K_2=1.70 x 10^2 M^{-1} and B_{max2}=3.67 μmol/mg melanin. The high affinity site had a K_1=1.91 x 10^4 M^{-1} and B_{max1}=2.49 nmol/mg melanin. This strength of binding is 5-50 fold lower than that for haloperidol or chlorpromazine. Increasing the ionic strength of the incubation medium (NaCl) reduced melanin-binding of risperidone. With no additional NaCl, percent bound was 78.7%; at NaCl concentrations of M, binding was decreased to %, respectively. These data suggest that electrostatic forces have a role in binding; this is not observed with chlorpromazine. A comparison of the melanin-bind of risperidone to other compounds indicated that chlorpromazine and haloperidol bound to melanin to a significantly greater extent (97.1% and 81.9%, respectively) than either risperidone or 9-hydroxy-risperidone (76% and 73.9%, respectively). Very little glucose bound to melanin (8.5%). Solvent (dichloromethane) and buffer washes resulted in the release of risperidone from melanin. Following repeated extraction with solvent, only 3.4-5.7% of previously bound risperidone remained bound; after 4 successive washes with buffer, 43% of previously bound risperidone was released. Dialysis resulted in the release of 56.6% of bound risperidone.

Microsomal enzyme induction study

Possible microsomal enzyme induction properties of risperidone were studied in hepatic microsomal fractions from male Wistar rats (5/grp) treated with **0, 0.63, 2.5, and 10 mg/kg** of risperidone (orally by gavage) for seven consecutive days. Phenobarbital, 3-methylcholanthrene, dexamethasone, ethanol, and clofibrate were administered to additional groups of rats (5/grp) and served as positive controls. Risperidone had no effect on relative liver weight or any microsomal enzyme studied. All positive controls had expected effects on specific microsomal enzyme systems.

Biliary excretion study

Seventeen male and 6 female Wistar rats were used to study biliary excretion after a single dose of orally administered (gavage) ^{14}C-risperidone. Thirteen males and 6 females received single bile duct cannulations. Of these, five males and 6 females received 0.63 mg/kg and 4 males received 10 mg/kg ^{14}C-risperidone/risperidone. Each of four male "acceptor" rats received a proximal and a distal bile cannula. The biliary excretions of 4 male rats dosed with 0.63 mg/kg radiolabeled risperidone were delivered to acceptor rats by linking the bile cannulas of the "donor" rats with the distal cannulas of the acceptor rats. Bile was collected at varying intervals up to 48-50 hrs postdosing. Biliary excretion of total radioactivity peaked between 0.5 and 2.0 hr postdosing. Peak excretion was 10.02-12.54% of dose in rats receiving 0.63 mg/kg and 21.74% of dose in those receiving 10 mg/kg. In acceptor rats, peak concentration of bile radioactivity (0.541% of donor dose) was reached at 6-7 hr postdosing. Total biliary excretion of radioactivity was 71.67-79.15% of dose in rats receiving ^{14}C-risperidone. In acceptor rats, 14% of the dose received was excreted via bile; thus, only about 14% of biliary radioactivity entered the enterohepatic circulation. Excretion rate and % of dose excreted were slightly higher in females than in males. An analysis of biliary metabolites indicated that the two major metabolites, hydroxy-keto-risperidone ((P) and dihydroxy-risperidone (R), had previously been identified as urinary metabolites. Other biliary metabolites corresponded to the fecal metabolites, 7-hydroxy-risperidone, ring-open risperidone, M, and S (sufated conjugate of M). No unchanged risperidone was detected in bile. There were a few bile metabolites (B_1, B_2, etc) which did not co-elute with any fecal or urinary metabolites. In bile from acceptor rats, the metabolite pattern was more complex; the fraction of conjugated metabolites (glucuronide and sulfate) was larger. The major metabolites, B_1, B_2, B_3, P, R, and S, accounted for 43.5-57.2% of dose, with P and S accounting for 15-12.6% and 17.7-23.9% of dose, respectively. The metabolite pattern was the same regardless of dose. In acceptor rats, P and R were the major metabolites at 0-6 hr; however, the amount of other metabolites increased after 6 hr. At 48 hr, S made up 2% of dose, whereas, P and R accounted for 0 4% and 0.8% of dose, respectively

Human ADME Study

Three male volunteers received a single oral (solution) dose of 1 mg ^{14}C-risperidone. They had previous been designated as a poor metabolizer (PM), an intermediate metabolizer (IM), or an extensive metabolizer (EM) based on the ability to metabolize debrisoquin to 4-hydroxy debrisoquin. Blood samples were collected prior to dosing and at various intervals up to 168 hr (1 wk) after dosing. Plasma was analyzed for risperidone and 9-hydroxy-risperidone. Complete urine output was collected at varying intervals up to 168 hr. Stools were collected up to 1 wk postdosing (a minimum of 7 samples per individual). Total blood radioactivity (based on AUC) was similar in PM and IM, and 45% lower in EM. Peak blood radioactivity was highest in PM (1.6 fold higher than in EM) and lowest in EM. $t_{1/2}$ was similar in all three individuals. Plasma levels of risperidone and 9-hydroxy-risperidone differed dramatically among the three individuals. Plasma exposure to risperidone (based on AUC) was 12.5 fold higher in PM, and 9.5 fold higher in IM than in EM. $t_{1/2}$ for risperidone was 6.7 and 5.2 fold greater in PM and IM, respectively, than in EM Plasma exposure to 9-hydroxy-risperidone was similar in EM and IM, but was not assessable in

PM; 9-hydroxy-risperidone levels were undetectable in PM 8 hr after dosing. C_{max} for risperidone was 3.2 and 2.0 fold higher in EM and IM, respectively, than in PM. The ratio of 9-hydroxy-risperidone to risperidone was higher in EM than in IM (7.4 vs 0.82). 9-hydroxy-risperidone accounted for 69.9% of total plasma radioactivity in EM and 40.4% of total plasma radioactivity in IM. Risperidone accounted for 9.9, 51, and 71% of total plasma radioactivity in EM, IM, and PM, respectively

In urine, total radioactivity was similar in all three volunteers (68.62-70.32% of dose after 1 wk); however, the urinary metabolite pattern differed. In IM and EM, the major urinary metabolite was 9-hydroxy-risperidone (21.6 and 30.5% of dose, respectively), whereas, in PM, unmetabolized risperidone was the major metabolite (36.1% of dose). Fecal radioactivity was highest in EM, intermediate in IM, and lowest in PM (17.68, 13.35, and 11.91% of dose, respectively).

Toxicology

A. Acute Toxicity

1. **Studies carried out in mice, rats and dogs utilizing risperidone (batch #A0101) are summarized in the following table** (LD_{50}).

Species	Sex	i.v.	p.o.
Mice	male	29.7	82.1
	female	26.9	63.1
Rats	male	34.3	113.
	female	35.4	56.6
Dogs	male	14.1	18.3
	female	18.3	18.3

Overt signs of toxicity included ptosis, prostration, sedation, hypothermia and tremor. At or near lethal doses, ataxia, convulsions and GI erosions and bleeding were also observed. In rodents, risperidone appeared to be slightly less toxic in males vs. females.

2. Acute toxicity of risperidone was studied in Wistar rats administered **0, 20, 40, 80, 160, and 320 mg/kg s.c.** (10/sex/grp). In males, **mortality** was observed at 160 and 320 mg/kg. In females, deaths occurred at all but the LD. The earliest deaths occurred within 3 hrs of dosing in the HD groups. All deaths occurred within 5 days of dosing. LD_{50}s were 172 mg/kg for males and 98 mg/kg for females. The most prominent **clinical signs of toxicity** were catalepsy, dyspnea, hypotonia, hypothermia, palpebral ptosis, prostration, sedation, tremors, and inflammation at the injection site. Catalepsy, ptosis, and prostration occurred in all drug-treated animals. Occurrence of other observations were: hypotonia: 5 at LD and all at 40-160 mg/kg in males, all but 1 LD female; hypothermia: 7 at 80 mg/kg and 10 at 160 mg/kg in males, 1 at 10 mg/kg, 10 at 40 and 80 mg/kg, and 6 at 160 mg/kg in females; sedation: 7-10 at 20-160 mg/kg in males, 4-10 at 20-160 mg/kg in females; tremors: 2,5, and 10 at 40, 80, and 160 mg/kg in males, 2, 4, 10, 7, and 5 at 20, 40, 80, 160, and 320 mg/kg in females. At all doses, onset of clinical signs was immediate upon dosing and persisted from 6 hr to Day 5, depending upon the dose. All animals that died spontaneously exhibited symptoms until death; survivors did not show clinical symptoms by Day 5. **Body weight** was decreased compared to controls at all doses in both males and females. **Gross pathology** indicated no abnormalities in any animal sacrificed at the end of the observation period, except for inflammation at the injection site (seen in vehicle and drug-treated). Of animals that died spontaneously,

all but 2 (which appeared normal) had evidence of multiple, hemorrhagic, stomach lesions, and 5 showed evidence of autolysis. **Histopathology** was positive in 4 rats: 2 (160 mg/kg male) had stomach abcess, 1 (160 mg/kg male) had foci of erosive gastritis and bleeding, and 1 (160 mg/kg female) had erosive gastritis and bleeding and atrophic spleen and thymus.

3. Acute toxicity of risperidone was studied in Mongrel dogs (4/sex/grp) at doses of **0, 2.5, 5, 10, and 20 mg/kg** administered orally by gavage. **Mortality** occurred in 3 HD males and 3 HD females. The LD_{50} was 18.3 mg/kg for both males and females. Deaths occurred at 3 hr, Day 1, and Day 2 after dosing in females and on Days 1,2 and 7 in males. The most frequent **clinical signs of toxicity** were: diarrhea, defecation, ataxia, loss of righting reflex, prostration, salivation, sedation, and tremors. Defecation/diarrhea was observed in some dogs at all doses in both males and females, except at 5 mg/kg in males (0 incidence). Ataxia occurred in some dogs at all doses in both males and females, with no clear dose-response effect. Prostration was observed in LD and HD males (1/4 at LD, 3/4 at HD), and at 5 (2/4), 10 (2/4), and 20 (3/4) mg/kg in females. Sedation was observed at all doses: 3/4 at LD males and females, 3/4 at 5 mg/kg in males, and 4/4 at 5-20 mg/kg in females and at 10-20 mg/kg in males. Clonic convulsions, salivation, loss of right reflex, and tremors were only observed at the HD, except that tremors were observed in 1 females at 5 mg/kg. Hyperventilation was only observed in 2 females at 10 mg/kg. Onset of clinical signs was immediate or up to 6 hr after dosing, depending upon dose. In dogs which died spontaneously, at least some clinical signs persisted until death; in survivors, all appeared normal by Day 1, except for 1 male that was sedated on Day 1. One male dog receiving 2.5 mg/kg showed no clinical signs. **Gross pathology** indicated the following abnormalities in drug-treated dogs (all at 20 mg/kg): 1 male: lung, apical lobe (left) abcess, pneumonia; diaphragm lobe, catarrhal pneumonia, pyothorax; 1 male: right heart dilation, congested spleen (severe) and liver, lung (apical lobe) catarrhal pneumonia; 1 male: right heart dilation, congested spleen; 1 female: congested spleen (severe) and liver, lung (apical lobe, left) catarrhal pneumonia; 1 female: moderately congested spleen and liver; 1 female: right heart dilation, slightly congested spleen. **Histopathology** indicated the cause of death in two males: adenovirus pneumonia and canine distemper pneumonia. Other abnormalities included necrotizing enteritis (1 male) and lung catarrhal pneumonia (1 female). The results at 10 mg/kg were verified in a separate experiment on 2 Beagle dogs at a dose of 10 mg/kg.

4. Acute toxicity after single doses of risperidone at **0, 2.5, 5, 10, 20, and 40 mg/kg** i.v. was studied in Mongrel dogs (4/sex/grp). No vehicle control was included. All dogs died immediately after a dose of 40 mg/kg. At 20 mg/kg, all males died (at 3 hr, and Days 1, 2, and 4) and 3/4 females died (2 on Day 1 and 1 on Day 2). The LD_{50} for males was 14.1 mg/kg and for females, 18.3 mg/kg. The most frequent **clinical signs of toxicity** were: diarrhea, ataxia, clonic convulsions, loss of righting reflex, prostration, salivation, sedation, and tremors. Catalepsy was noted occasionally. The dogs which died immediately upon dosing exhibited clonic convulsions, loss of righting reflex, salivation, and sedation (females). Ataxia, diarrhea, and prostration were observed at all doses in males and females. Salivation was noted in males and females at doses $\geq$10 mg/kg. Clonic convulsions were observed at 10, 20, and 40 mg/kg in males, and at 20 and 40 mg/kg in females. Loss of righting reflex was observed in all dogs at 20 and 40 mg/kg. Tremors were observed in males at doses of 5, 10, and 20 mg/kg and in females at all but the HD. Onset of clinical signs was immediate in all drug-treated groups. After Day 4, survivors appeared normal. The most common observations at **gross pathology** were: organ congestion (heart, intestines, spleen, liver, kidney, lung), lung edema (20 mg/kg: 1 male, 1 female; 40 mg/kg: 3 males, 1 female), catarrhal pneumonia (40 mg/kg: 1 male; 20 mg/kg: 1 female).

5. Acute toxicity of 9-hydroxy-risperidone (R 76477), the major and active metabolite of risperidone, was studied in Wistar rats (5/sex/grp) at doses of **0, 20, 40, 80, 160. and 320 (males only) mg/kg**. Dosing was orally by gavage. **Mortality** occurred at 40 mg/kg (2 females), 80 mg/kg (1 male, 2 females), 160 mg/kg (2 males, 4 females), and 320 mg/kg (5 males). The LD_{50} was 149 mg/kg for males,

and 65 mg/kg for females. Reduced body weight gain was observed at 80 mg/kg in males (35-85% of control) and females (0-68% of control) and at 160 mg/kg in males (0-66% of controls). The most frequent **clinical signs of toxicity** were: diarrhea, catalepsy, clonic convulsions, hypotonia, ptosis, prostration, ataxia, tremor, and sedation. Catalepsy and ptosis were observed in all drug-treated rats. In males, convulsions, hypothermia, and tremors occurred only at doses of 80, 160, and 320 mg/kg. In females, hypothermia occurred in all but one (LD) drug-treated rat; convulsions occurred in all HD rats, and tremors occurred at 20 mg/kg (3), 40 mg/kg (4), 80 mg/kg (all), and 160 mg/kg (all). Prostration was exhibited by all drug-treated females, in 1 LD male, in 4 males at 40 mg/kg and in all males at ≥80 mg/kg. Ataxia was only observed in 1 female at 80 mg/kg. Sedation occurred at all doses in males, and at 20, 80, and 160 mg/kg in females; however, there was no dose-response effect. Onset of clinical signs was immediate in all drug-treated rats at all doses. All survivors appeared normal by Day 5 (range: 6 hr-Day 5). All rats dying spontaneously exhibited some clinical signs until death. The main observations at **gross pathology** were petechia and/or vibex in stomach (in all but 2 spontaneously dead rats). One female (40 mg/kg) was found to have hemorrhagic areas in the stomach and 1 female (80 mg/kg) showed evidence of autolysis. No animal sacrificed at the end of the study had any symptoms at pathology; of rats dying spontaneously, 3 (2 males at 320 mg/kg and 1 female at 160 mg/kg) had normal pathology.

B. Subchronic and Chronic Toxicity

6. Pilot subchronic toxicity study in Wistar rats (repeated dosage for 1 month). Conducted by Janssen Pharmaceutica, Beerse, Belgium.

A total of 40 Wistar rats were subdivided into the following groups:

Group	# of Animals M	F	Dose (mg/100 g food)
C	5	5	Control
LD	5	5	0.63
MD	5	5	2.5
HD	5	5	10.0

Risperidone (batch #A0301) was administered in the diet for 1 month followed by sacrifice and necropsy.

Observations:

Daily - Mortality
Weekly - Clinical observations
Food Consumption
Body Weight
Terminal- Hematology
Clinical chemistry
Urinalysis
Organ weights
Gross pathology
Histopathology (C and HD only)

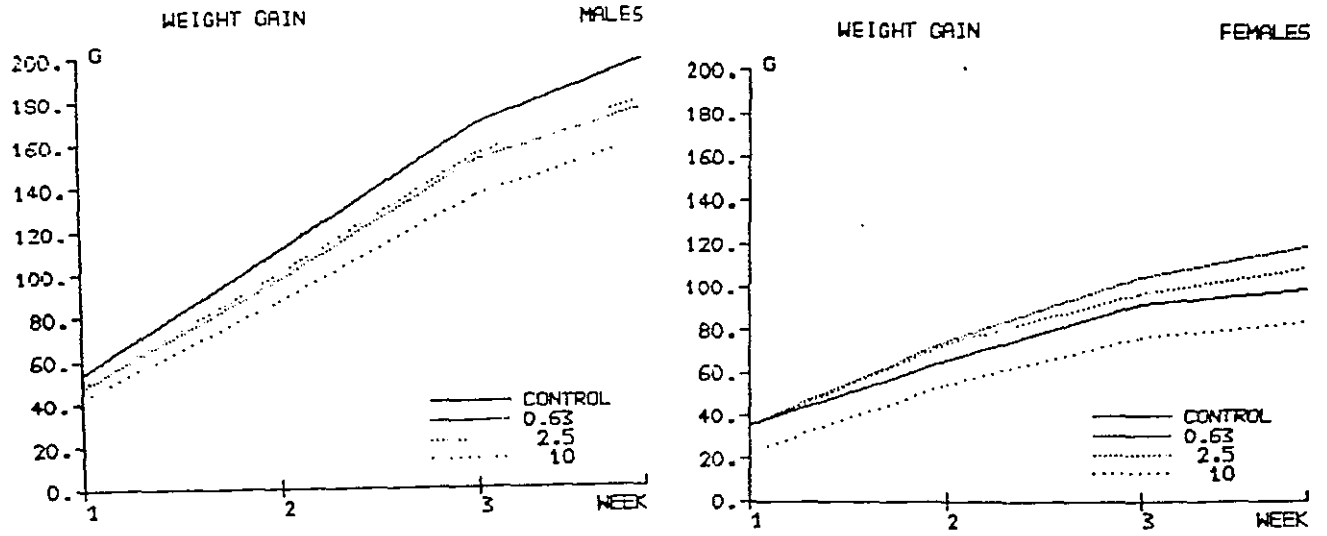
Results:

1. **There was no unscheduled mortality during the study.**

2. **There were no remarkable clinical observations.**

3. **Body weight gains are depicted in figure 1. Weight gains were significantly reduced by 14-19% in HD animals of both sexes. LDM and MDM also exhibited reduced (9-12%) weight gains which were not statistically significant; LDF and MDF weight gains were increased by 10-21% compared to controls.**

Figure 1



4. **Food consumption was decreased by 15% in HDM during weeks 3 and 4. During weeks 1 and 2, HDF food consumption appeared to be increased by 40-60%, but this may have been an artifact caused by food wastage in this group. Drug consumption was maintained at or above targeted levels. Intake of risperidone relative to body weight is summarized in the following table.**

(The sponsor indicated that food wastage was observed in 1/5 HD during weeks 1-3.)

Dose (mg/kg)

Group	Males	Females
LD	0.84±0.09	0.88±0.10
MD	3.29±0.40	3.23±0.38
HD	12.7±1.7	18.4+3.9

5. **HD animals exhibited slight (4-5%) decreases in hematocrit, HBG and RBC levels which remained within the range of historical controls. HDM platelets were reduced by 15% compared to controls. ALKP was reduced in drug-treated males by 34-47% and in HDF by 45%. AST was decreased by 27% in MDF. The latter 2 parameters remained within the range of historical controls.**

6. **There were no remarkable urinalysis findings.**

7. Relative and absolute liver weights were significantly decreased in drug-treated males by 7-20% and in HDF by 4-11%. Kidney weights were also decreased by 4-16% in MDM and HDM only. Relative heart weights were increased by 6-12% in treated males; however there was a 6% decrease in absolute weight for HDM. In females, there were increases of 6-10% in relative heart weights for MD and HD groups and of 9-12% in absolute weights for LD and MD groups. Absolute and relative lung weights were decreased in HD groups of both sexes by 3-14%. Relative and absolute adrenal weights were decreased by 16-31% in females but were increased in MDM. Spleen weights were increased significantly by 18-25% but in MDF only. Relative brain weights were increased in HD animals by 5-8%.

8. Mammary hyperplasia (increased glandular development and secretion) was noted in 0, 3, 4 and 4/5 females in C, LD, MD and HD groups, respectively. A significant decrease of recent corpora lutea and granulocytic infiltration of the uterus was present in HDF as well as a decrease in vaginal epithelial thickness. These changes were attributed to hyperprolactinemia.

7. Subchronic (3 month) toxicity study in Wistar rats. Conducted by Janssen Pharmaceutica, Beerse, Belgium.

A total of 160 SPF Wistar rats were subdivided into the following groups:

Group	# of Animals M F	Dose (mg/100 g food)
C	20 20	Control
LD	20 20	0.63
MD	20 20	2.5
HD	20 20	10.0

Risperidone (batch #A0101) was administered in the diet for 3 months followed by sacrifice and necropsy.

Observations:

Initial	Physical examination
	Ophthalmological examination
	Body weight
Daily	Physical examination
Weekly	Food consumption
	Body weight
Terminal	Ophthalmological examination
	Hematology
	Clinical chemistry
	Urinalysis
	Gross pathology
	Organ weights
	Histology

Results:

1. One LDF died during week 6 - autopsy revealed no apparent cause of death. One HDF was sacrificed in extremis during week 5. Autopsy revealed a pale liver and small sized uterus, but cause of death was not determined.

2. No overt signs of toxicity were reported.

3. Body weight gains are summarized in figure 2. HD groups gained 5-14% less weight compared to controls throughout the study. LDM and MDM displayed slight (1-10%) decrements in weight gain, whereas LDF and MDF displayed 20-25% increases during the study.

4. Changes in food consumption generally paralleled body weight gains. HD groups consumed 8-10% less food and water than controls, whereas LDF and MDF increased food consumption by 6-12%. Median dosage rates were consistently lower than targeted doses by 25% in males and by 10-18% in females. Average doses of risperidone consumed relative to body weight are summarized in table 5. In general, drug consumption exceeded these averages during the first 2 study weeks but was less than the averages during the last 6 weeks.

Figure 2

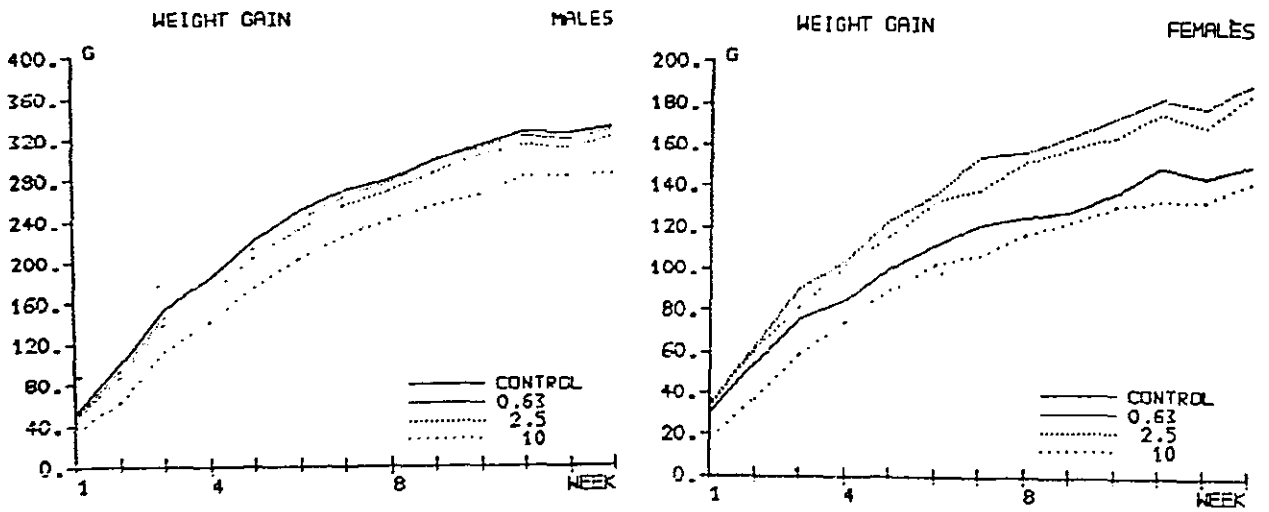


Table 5

Dose (mg/kg)

Group	Males	Females
LD	0.50±0.04	0.61±0.04
MD	2.04±0.14	2.34±0.14
HD	8.19±0.55	9.07±0.51

5. **No drug related ophthalmic lesions were observed.**

6. **Platelet counts were reduced by 11-18% in all drug-treated groups, but not in a dose-related manner. Clotting times were unaffected. Other changes in hematologic parameters, although occasionally reaching statistical significance, were small in magnitude (<5%) and within the range of historical controls. Clinical chemistry revealed decreases in ALKP and AST of 20% in HD animals and decreases in LDH of 30-40% in the same animals.**

7. **There were no remarkable urinalysis findings.**

8. **Relative spleen weights were increased in all treated groups by 6-19%; absolute spleen weights increased by 10-20% in LDF and MD groups. Relative liver weights were increased by 7-15% in drug treated females only. Absolute liver weights were decreased by 10% in HDM. There were small (2-11%) decrements in relative kidney weights in drug-treated groups and in relative lung weights in treated males. Adrenal weights were increased by 20% or more in HDM but were decreased by approximately the same amount in drug-treated females. Relative testicular weights were increased by 8% in MDM and HDM. Relative ovarian weights were decreased by 8% in treated females.**

9. **Stimulation of mammary development was observed in 0, 17, 19 and 18 females from C, LD, MD and HD groups, respectively. This was manifest as increased glandular development and secretion and are probably related to elevated levels of prolactin in these animals. In addition, there was a decrease in the number of corpora lutea, decreased uterine glandular development, and a lesser degree of vaginal cornification and epithelial thickening in these animals. MDM and HDM had a significant increase in neutrophilic infiltration of the prostate with occasional focal inflammation of the prostatic tubules. Two HDM had slight increases in the number of giant cells observed in their seminiferous tubules. Mammary tissue of MDM and HDM displayed significant feminization accompanied by the presence of secretion.**

Serum risperidone concentrations were determined at the end of the study in individual and pooled (4-5 rats) blood samples, using HPLC (detection limit 2 ng/ml using 1 ml serum). There was, however, no indication as to when blood samples were collected in relation to removal of medicated diet. Serum concentrations were corrected to theoretical drug intake. At the LD, serum drug levels were undetectable in both males and females. At the MD, serum risperidone was 5.3 ng/ml in males and 15.5 ng/ml in females, and at the HD, levels were 21.6 and 71.2 ng/ml for males and females, respectively. Calculated on a per mg basis, serum levels were higher in females than in males. There was a fairly linear increase in serum levels as dose was increased.

8. **A 3 mo subchronic oral toxicity study** followed by a 1 mo recovery period (control and HD) was conducted in SPF **Wistar rats** (10/sex/grp plus an additional 5/sex/grp at 0 and 10 mg/kg studied at end of the recovery period). Risperidone was administered by gavage at doses of **0, 0.16, 0.63, 2.5, and 10 mg/kg**. There was only one death, a female control; evidence of congested lungs suggested the cause of death was most likely a gavage accident. There were no drug-related clinical observations. There were sporadic cases of alopecia and skin irritation. Body weight was significantly affected in both males and females. In males, body weight was decreased at 2.5 and 10 mg/kg (10 and 19%, respectively, at end of dosing). There was some evidence of recovery; however, body weight was still decreased (11-15% at HD) at the end of the recovery period. In females, body weight was increased at 0.16 and 0.63 mg/kg (5-10 and 6-11%, respectively). At the HD, there was a slight, but nonsignificant decrease in body weight (5%), which was evident during the recovery period (7-10%). In general, food consumption reflected changes in body weight. Water consumption was increased at all doses in females (25-30%) during dosing, and was still elevated at the end of the recovery period.

There were several hematological changes which appeared drug-related:

(1) Increased hematocrit in males and females; however, there was no clear dose-related effect. In males, there was a 5-8% increase at 0.16, 2.5, and 10 mg/kg; in females, there was a 3-4% increase at 0.63 and 2.5 mg/kg.

(2) Increased hemoglobin in males and females; however, there was no clear dose-related effect. In males, there was a 5-8% increase at 0.16, 2.5, and 10 mg/kg; in females, there was a 3-4% increase at 0.63, 2.5, and 10 mg/kg.

(3) Increased mean cell hemoglobin at 10 mg/kg in both males and females (4 and 3%).

(4) Increased rbcs at 0.16, 2.5, and 10 mg/kg in males (5%), and at 0.63 and 2.5 in females (4%).

All effects were reversed at the end of the recovery period.

Serum analysis indicated the following drug-related changes:

(1) In males, there was a 5% decrease in serum calcium at 10 mg/kg,

(2) Total protein was decreased by 7 and 12% at 2.5 and 10 mg/kg, respectively, in males, and by 8% at 10 mg/kg in females,

(3) Albumin was decreased by 8% at 10 mg/kg in males,

(4) Glucose was decreased by 15% at 10 mg/kg in females,

(5) Triglycerides were decreased by 63% at 10 mg/kg in males; decreases of 17-26% were seen at lower doses but these decreases were not significant,

(6) BUN was increased by 22 and 51% at 2.5 and 10 mg/kg, respectively, in males, and by 21% at 10 mg/kg in females.

All effects were reversed by the end of the recovery period except BUN which was still elevated (31%) in HD females.

Urinalysis tests indicated the following drug-related effects:

(1) decreased creatinine at 2.5 and 10 mg/kg (23 and 34%, respectively) in males and at 0.16, 2.5, and 10 mg/kg (33, 49, and 55%, respectively) in females,
(2) decreased specific gravity at 10 mg/kg (1%) in males, and at 2.5 and 10 mg/kg (2 and 3%, respectively) in females,
(3) pH was increased at 10 mg/kg in both males and females (7 and 11%, respectively).
(4) bacteria was increased in males at 10 mg/kg (29%) and in females at 0.16 and 10 mg/kg (67 and 111%, respectively).
(5) volume was increased in females at 0.16 and 10 mg/kg (80-84%).
(6) decreased protein at 2.5 (67%) and 10 mg/kg (56%) in males and at 0.16, 2.5, and 10 mg/kg in females (59, 39, and 54%, respectively).

All effects were reversed by the end of the recovery period except that decreases were still noted in specific gravity (2%) and protein (45%) in HDM.

Analysis of organ/tissue weights indicated the following drug-related effects:

<u>in males</u>

(1) increase in relative lung weight at 2.5 and 10 mg/kg (9 and 13%, respectively).
(2) decreased absolute liver weight at 2.5 and 10 mg/kg (13 and 23%, respectively).
(3) decrease in absolute heart weight at HD (13%).
(4) decrease in absolute pancreas weight at 0.63 and 10 mg/kg (12 and 16%, respectively).
(5) decrease in absolute (2.5 mg/kg: 16%, 10 mg/kg: 22%) and relative (2.5 mg/kg: 8%) kidney weight.
(6) Increase in relative brain weight (5, 7, and 18% at 0.63, 2.5, and 10 mg/kg, respectively).
(7) increase in absolute (16% at 2.5 mg/kg) and relative (2.5 mg/kg: 27%, 10 mg/kg: 38%) adrenal weight.
(8) increase in absolute (8%) and relative (11%) gonad weight at the HD.

<u>in females</u>

(1) increase in absolute (13-20% at 0.16-2.5 mg/kg, not dose-related) and relative (8, 8, 10, and 24% at 0.16-10 mg/kg, dose-related) liver weight.
(2) increased relative adrenal weight at the HD (18%).
(3) decreased absolute (14%) and relative (12%) pancreatic weight at HD and 0.63 mg/kg, respectively.
(4) increase in relative heart weight at the HD (9%).

At the end of the recovery period, the only changes noted were increased relative weight of heart (14%) and adrenals (16%) in HD males and decreased absolute weight of lung (8%) and kidney (15%) in HDF

Gross pathology indicated evidence of mammary gland stimulation at all doses in females (60-100% incidence; no clear dose related effect), with no recovery apparent by the end of the rcovery period (evident in 5/5 HD females). Histopathology indicated mammary gland changes in males and females. A few males at 0.63, 2.5, and 10 mg/kg (1-2/grp) showed "female" type mammary glands. In females, there was histopathological evidence of mammary glandular development at 0.63, 2.5, and 10 mg/kg, with

evidence of secretion at 2.5 and 10 mg/kg. Males exhibited a slight increase in prostatic granulocytes which was significant only at 2.5 mg/kg (28% increase). 1 male in each dose grp showed presence of pituitary cyst. There were a variety of drug-related effects on the female reproductive system. Ovarian effects included increased incidence of atretic follicules, clear interstitial tissue, and eosinophilic corpora lutea in HD females. Basophilic corpora lutea was decreased at all doses, and tertiary follicles were reduced at 0.16, 0.63, and 2.5 mg/kg. Uterine changes included decreases in glandular development and dilated lumina at all doses, and decreased subepithelial granulocytes at 0.63, 2.5, and 10 mg/kg. Vaginal changes included decreased cornified epithelium and thickness of epithelium at all doses. Most changes reversed by the end of the recovery period; however, in females, there was still evidence of mammary gland development and increased dilated lumina of the uterus one month after dosing.

Plasma levels of risperidone and 9-hydroxy-risperidone were measured in a sallelite group (2/sex/grp; data on following page) on Day 2, 5, 12, 19, 33, 47, 61, 75, and 93 and in the HD animals (enrolled in the regular toxicology study) on Day 7, 14, and 28 of recovery. The satellite group received the same batch and formulation of drug; blood samples for these animals were drawn 1 hr after dosing.

	0.16	0.63	2.5	10
risperidone	nd 10.1-17.2*	8.7-13.2 32.9-77.3	43.6-109 77-128	211-412 330-990
9-hydroxy-risperidone	4.7-9.1 6.5-12.2	16.5-35.3 23.9-63.7	88.2-193 56.8-110	524-1191 395-966

*ng/ml (range); data for males (top) and females (bottom) in each cell.

Serum levels were measured for all drug-treated animals in the toxicology study in blood samples collected at necropsy. Drug levels were assayed by HPLC; limits of detection were 5 ng/ml for plasma and 2-4 ng/ml for serum. Levels of risperidone were undetectable at 0.16 mg/kg in males. Plasma concentrations of risperidone and 9-hydroxy-risperidone were fairly stable throughout the assay, except at the HD. At the lower doses, steady state levels of both risperidone and 9-hydroxy-risperidone appeared to be reached by Day 47. At the HD, plasma concentrations of parent compound and metabolite tended to increase to the end of the study. Plasma levels became undetectable by 1 wk after the end of dosing.

Previous PK data show that peak plasma levels of risperidone are reached within 0.5-1 hr of dosing and that the decline from peak levels is rapid. A comparison of the satelite and regular study data revealed the importance of controlling the time from last feeding to blood sampling interval. Within dose groups, plasma risperidone levels declined as time interval increased. Therefore, studies of plasma risperidone and 9-hydroxy-risperidone levels in which the time between last feeding and blood sampling is not carefully controlled are probably of no value.

9. Chronic toxicity study in Wistar rats (repeated dosage for 12 months, orally in the diet) (conducted by Janssen Pharmaceutica N.V., Beerse, Belgium)

A total of 160 SPF Wistar rats were subdivided into the following groups:

Group	# of Animals		Dose (mg/kg)
	F	M	
C	20	20	Control
LD	20	20	0.63
MD	20	20	2.5
HD	20	20	10

Risperidone (batch #PFA 021) was administered in the diet for 12 months, followed by sacrifice and necropsy of all animals.

Observations:

Daily	Behavior and appearance
Weekly	Body weights
	Food consumption
Months 6, 9 & 12	Ophthalmoscopy
	Hematology
	Clinical chemistry
	Urinalysis
Month 12	Necropsy
Month 12 (cont'd.)	Gross examination
	Organ weights
	Histopathology (C & HD only, except for positive findings)

Results:

1. Premature deaths are summarized in table 1. A total of 9 animals died during the 1 year study period. Three deaths, all in the MD group, were not diagnosable due to extensive autolysis. Of the remainder, 2 C and 1 LD were diagnosed as anemic, 1 LD and 1 MD had tissue masses in the thoracic cavity and kidney, respectively, and 1 HDF had a herniated diaphragm. Neither the overall rates nor individual causes of death appeared to be related to risperidone dosing.

Dosage (mg/100 g food)	Males	Females
control	1/20	1/20
0.63	2/20	0/20
2.5	1/20	3/20
10	0/20	1/20

2. Subcutaneous masses were found during physical examination in 2 LD and 3 HD animals. All were later characterized as tumors at necropsy (see item #9, below). There were no other gross or behavioral findings from general observations of the animals.

3. Overall body weight gains during the study were reduced in the HD group by 16-26% (fig. 1). Similarly, gains in LDM and MDM were also reduced, but by only 7-9%. LDF and MDF had an increase in weight gain of 10-14%.

4. Food consumption was affected by risperidone administration in a manner parallel to that of body weights. Actual intake of risperidone was generally lower than the targeted doses, especially in males, and in some cases was below the nominal

doses by as much as 30-50%. The true doses were calculated as LDM=0.42, LDF=0.51, MDM=1.7, MDF=2.0, HDM=7 and HDF=8 mg/kg, but all references in the sponsor's report continued to refer to nominal doses.

5. There were no drug-related ophthalmologic findings.

6. WBC counts were decreased in HD animals at all time points by 9-21%. Thrombocytes were reduced in HDM at all time points by ~15%. There were also dose-related increases in MCV and MCH in males, but values were still within normal limits. RBC counts in risperidone-treated males were also elevated at month 12 by 2-7%, but the changes were not dose-related. Serum potassium levels were decreased by 4-12% in HDM only. Inorganic phosphate levels tended to increase by 10-40% in all dosed females, but the changes were not dose-related. Total protein and albumin levels were decreased by up to 10% in HDF. A number of other statistically significant changes did not appear to be biologically significant, due to either their small magnitude or lack of dose relationship.

7. Urinalysis revealed a slight increase in urine volume and a small (30%) but consistent decrease in creatinine content in HDM. Other minor changes did not appear to be biologically significant.

8. HDM absolute and relative adrenal weights were increased by 24-55%. There was a similar, but smaller trend in MDM. However, adrenal weights in females tended to be decreased by 10-20%. MDF and HDF absolute thymus weights were decreased by 10-20%. HDM absolute liver weights were decreased by 22%. The remaining organ weight changes were not consistent when relative and absolute changes were compared.

9. Gross examination at autopsy indicated an increase in mammary development in HDM and all females treated with risperidone. Histopathology revealed an increase in the extent of glandular development and secretion in these groups. In addition, 4 mammary masses were detected, 1 in an LDF and 3 in the HD group. These were characterized histologically as 1 fibroadenoma in a HDM and 3 adenocarcinomas (1 LDF, 2 HDF). Uterine glandular development appeared to be retarded in all risperidone-treated females. HDM had an increased incidence of swelling of the pituitary accompanied by microscopic evidence of diffuse hyperplasia, and of swelling and/or inflammation of the prostate. Other notable findings included a case of lymphocytic-lymphoblastic leukemia in a LDM, a renal adenocarcinoma in a MDF, squamous carcinomas in a LDM and a HDF, and various neoplasms in controls including a case of lymphocytic leukemia, a meningioma, and a thyroid adenoma.

Serum concentrations of risperidone and its major metabolite, 9-hydroxy-risperidone, were measured in individual blood samples at the end of the 1-yr study. Blood samples were collected at autopsy, 1-8 hr after removal of diet containing risperidone. Analyses were performed using HPLC, detection limit was 2.5 ng/ml for both the parent compound and the metabolite. Levels of parent were undetectable in all males and all but 3 females at the LD, and all but 3 males at the MD (n=19). At the LD, levels of 9-hydroxy-risperidone were detectable in only 5/19 males.

Median plasma levels (ng/ml; male/female)

Dose (mg/kg)	Risperidone	9-hydroxy-risperidone	sum
0.63	n.d. n.d	n.d 7.2	- -
2.5	n.d. 9.2	14.3 25.1	- 34.6
10	17.2 34.3	73.8 81.3	91.0 116

The ratio of plasma levels of metabolite to parent compound was 60% higher in males (at HD) than in females (4.3 vs 2.4, 2 8). Unit exposure, however, was 1.1-2 fold greater in females than in males. Plasma levels of parent compound and metabolite increased fairly linearly with increased dose.

10. Pilot subchronic toxicity study in beagle dogs (repeated dosage for 1 month). Conducted by Janssen Pharmaceutica, Beerse, Belgium.

A total of 16 beagle dogs were subdivided into the following groups:

Group	# of Animals		Dose (mg/kg)
	M	F	
C	2		Control
LD	2	2	0.16
MD	2	2	0.63
HD	2	2	2.5

Risperidone (batch #A0301, no formulation specified) **was administered p.o. for 1 month. Animals were monitored for signs of toxicity but were not sacrificed at the end of the study. Consequently no organ weight, gross pathology or histopathology data were available.**

Observations:

Daily - Mortality
Clinical observations
Weekly - Body Weight
Biweekly- Hematology
Clinical chemistry
Monthly - Urinalysis Results:

1. There was no unscheduled mortality.

2. A dose related decrease in general activity and alertness was observed in all treated animals. HD animals displayed slight catalepsy. Moderate to severe stimulation of the mammary glands with secretion was noted in MDF and HDF.
3. All animals gained weight over the course of the study except HD animals, which exhibited slight weight loss during weeks 2 and 3.
4. There were no unusual ophthalmic findings.
5. There were no hematologic changes (differential counts were not provided). Serum haptoglobulin levels were elevated in MD and HD groups by 43-82% at weeks 2 and 4. Potassium and inorganic phosphate levels were decreased by 10-30% in HD animals at week 2 only.
6. There were no significant urinalysis findings.

11. Subchronic toxicity study in beagle dogs (repeated dosage for 3 months). Conducted by Janssen Pharmaceutica, Beerse, Belgium.

A total of 32 beagle dogs were subdivided into the following groups:

Group	# of Animal		Dose (mg/kg)
	M	F	
C	4	4	Control
LD	4	4	0.31
MD	4	4	1.25
HD	4	4	5.0

Risperidone (batch #A0301) was administered p.o. (gelatin capsule) for 3 months, followed by sacrifice and necropsy.

Observations:

Daily - Mortality
Clinical observations
Weekly - Body Weight
Food consumption
Monthly- Hematology
Clinical chemistry
Urinalysis
Pre & Post Study-
Ophthalmologic examination
Heart rate, ECG
Terminal- Organ weights
Gross pathology
Histopathology

Results:

1. There was no unscheduled mortality.

2. LD animals exhibited slight to moderate sedation. MD and HD animals exhibited moderate to severe sedation and miosis with occasional conjunctival congestion. Tremor and decubitus was apparent in some HD animals.

3. Body weight gain in HD animals was decreased slightly (0.2-0.3 kg/week) during weeks 1-9. Weight gains were decreased slightly in LD and MD animals only during the first 3 study weeks. Thereafter, gains were at or above control levels.

4. There were no significant ophthalmic findings except for the occurrence of miosis in MD and HD animals.

5. There appeared to be no drug-related changes in heart rate or E.C.G. when measured at weeks 6 and 12. However, the time of day that measurements were taken (in relation to time of dosing) was not specified. Therefore, it is not possible to determine whether the lack of effect in this study is the result of tolerance to the drug's cardiovascular effects or is due to pharmacokinetic factors (see section I.D. Cardiovascular effects p. 4-5).

6. All three treatment groups exhibited gradual decreases in hematocrit, HBG and RBC which were small (5-10%) in magnitude but dose proportional. Serum haptoglobulin levels were increased by 56-115% in drug treated groups beginning at week 2. Potassium levels were decreased by 4-7% in the same groups at weeks 8 and 12. Serum glucose was increased slightly (12-27%) in all drug groups at weeks 8 and 12. Over the same time period, serum cholesterol and phospholipids were increased in MD and HD groups by as much as 45 and 37%, respectively.

7. There were no remarkable urinalysis findings.

8. Treated animals exhibited dose-related increases in absolute and relative spleen weights of 16-25% and 8-23%, respectively. Absolute and relative testes weights were decreased by 18-44% in a dose related manner. Ovarian weights were also decreased by 19-30%, but the changes were not dose proportional. Relative and absolute prostate weights were decreased by 50% or more in MDM and HDM. Relative adrenal weights were decreased by 9-18% in LD and MD but not HD groups. Relative liver weights were increased in MD and HD animals by 5 and 13%, respectively. Brain (relative) weights were decreased by 6-19% in the same groups.

9. Increased mammary glandular development was found in LDF and MDF. All treated females exhibited increased resting state of the uterus and decreased vaginal epithelial thickness. The absence of corpora lutea in 15/16 females in the study indicated sexual immaturity. Incomplete spermatogenesis was observed in 1, 0, 3 and 3 males from C, LD, MD and

HD groups, respectively. An increase of clear basal cells, fibrotic interstitial tissue and immature aspect of the prostate was noted in MDM and HDM. HD animals exhibited an increase in the incidence of congested lymph nodes containing phagocytized erythrocytes and an increase in red cell content of the spleen.

PK data were collected during this 3 mo subchronic study in Beagle dogs (2/sex/grp) which were enrolled in the toxicity study. Doses of risperidone were 0.31, 1.25, and 5.0 mg/kg given as in gelatin capsules. Blood samples were collected prior to and at 0.5, 1, 2, 4, 6, 8, 12, and 24 hr after dosing on Day 1 and on day 93 (the last day). Other samples were collected just before dosing on Days 3, 8, 15, 29, 43, 57, and 71. Plasma samples were analyzed for risperidone and 9-hydroxy-risperidone by HPLC.

Dose (mg/kg)	Day	risperidone	9-hydroxy-risperidone
0.31	1	76.3±29.8	156±24
	93	49.6±24.1	188±50
1.25	1	243±75	946±52
	93	101±24	765±21
5	1	815±459	1588±718
	93	530±267	1248±727

Unit exposure (based on C_{max}) decreased with increasing dose and with repeated dosing for both risperidone and its metabolite. T_{max} for risperidone increased slightly with repeated dosing [1.1-2.0 fold; range: SD: 0.9-1.1 vs MD: 1.0-2.3]. For 9-hydroxy-risperidone, T_{max} increased slightly with increasing dose during acute administration (2.8 to 4.0 hr) and decreased slightly with increasing dose after repeated dosing (3.3-2.3). Unit exposure (based on AUC) decreased (10-40%) with multiple doses at all doses and for both risperidone and its metabolite. There was no consistent trend across doses for either risperidone or its metabolite.

12. **Subchronic oral toxicity was studied in male Beagle dogs** (6/grp) dosed with risperidone, orally in gelatin capsules, at doses of 0, 0.31, 1.25, and 5.0 mg/kg, for **3 mo followed by a 2-month recovery period** in selected dogs (2/grp of the 6/grp). There was no mortality at any dose The only clinical sign was sedation. Sedation was observed in all drug-treated dogs. Severity was dose-related, ranging from slight at the LD to moderate at the MD to severe at the HD. The effect decreased with time in all groups; however, in all drug-treated dogs, there was evidence of sedation to the end of the dosing period. There was no evidence of sedation throughout the recovery period. Body weight tended to be decreased in drug-treated dogs. Body weight was significantly decreased during the first 4-6 weeks (maximum decrease of 6-8%); the effect was not dose-related. By wk 10 of dosing, body weights were similar among groups. Food consumption could not be reliably estimated due to wastage.

Hematology: blood samples were collected on wks 0, 4, 8, 12, 16, and 20. Hematocrit, hemoglobin, and rbcs were decreased on wk 12 at the HD (9, 7, and 10%, respectively). Thrombocytes were decreased at all doses on wks 4, 8, and 12 wks (72-92%, no dose-response effect). Monocytes were decreased at the HD on wk 12 (38%). No differences were observed at the end of the recovery period.

Serum chemistry: Serum cholesterol was increased on wks 8 and 12 (20 and 18%) at the HD. Phospholipids were increased on wk 8 (16%) at the HD. Haptoglobin was increased in treated animals at

all doses; however, the data were quite variable and increases were only significant between MD (3.2 fold) and HD (3.7 fold) and control at Wk 4 and between control and HD (2-fold) at Wk 8. Other observations were sporadic and apparently not drug-related. No differences among groups were noted at the end of the recovery period.

Serum hormone levels: Serum samples were analyzed for testosterone and LH. No changes were observed in LH levels; however, there was a dose-related decreased in serum testosterone (C: 9.1, LD: 6.3, MD: 3.4, HD. 2.3 nmol/L). At the end of the 2-mo recovery period, serum testosterone increased in 1 MD and 1 HD (although still below control levels), but decreased further in 1 MD (from 4.8 to 2.7 nmol/L) and 1 HD (from 3.2 to 0.9 nmol/L) rat.

Urinalysis: Analysis was performed on samples collected prior to and during Wk 5 and 13, and at the end of the recovery period. There were no clear dose-related findings. pH, in general, was lower in treated animals than in controls and was signifcantly lower during Wk 5 at LD and MD and during Wk 13 at the HD. Bacterial content was elevated during Wk 5 in the MD group. No differences were noted at the end of the recovery period, although the pH still tended to be lower in treated groups.

Sperm analysis: Sperm examination was conducted at the end of the main study and the end of the 2-mo recovery period. Sperm collection met with variable success. At the end of the main study, samples could be collected only in 5/6 control and 2/6 LD animals. At the end of the recovery period, samples could be collected in 2/2 control and LD (the volume collected was low in 1/2 LD), but only 1/2 MD and HD animals. The sperm sample from the MD dog at the end of the recovery appeared normal; however, the sperm collected from the HD dog indicated reduced motility and low concentration. Risperidone clearly inhibited ejaculation and, although the sample sizes are too small, appeared to reduce sperm quantity and quality even after a 2-mo recovery period.

Organ/tissue weights: The following organs/tissues were weighed: adrenal, brain, heart, hypophysis, kidneys, liver, lungs, pancreas, prostate, spleen, testes, thymus, and thyroids. At the end of the main study, there was an increase in absolute and relative weight of pancreas at the LD (41-48%) and a dose-related decrease in absolute and relative prostate weight (15-22, 39-42, and 55-59% at LD, MD and HD, respectively). The decrease in prostate was only significant at the HD. Although not significant, there was a dose-related tendency for gonad weight to be reduced in treated animals (20-27, 27-29, and 38-43% in LD, MD, and HD, respectively) Drug effects were reversible in that there were no differences among groups at the end of the recovery period. Prostate weight (absolute and relative), however, still tended to be lower at MD and HD (59-62 and 32-34%, respectively) compared to control.

Gross pathology: Urinary bladder petechia were noted only in treated dogs. However, there were no clear, drug-related findings.

Histopathology: Histopathology was conducted only on the following organs/tissues: male genital tract (testes, epididymes, prostate), mammary gland, pituitary gland, spleen, and on tissues showing macroscopic abnormality. At the end of the main study, the following were noted: a dose-related decrease in prostate glandular development (LD:39, MD:54, and HD:69%, significant only at the HD) and a dose-related increase in spleen, red pulp (LD: 170, MD: 270, and HD: 370% above control; significant at MD and HD). There was also an increase in prominent basal cells in the prostate in MD and HD dogs (300% above control). These effects showed reversibility in that there were no significant differences among groups at the end of the recovery period. There was still a tendency, however, for prostate glandular development to be reduced in treated animals (22-33%, not dose-related).

13. Chronic toxicity study in Beagle dogs (repeated dosage for 12 months, orally in capsules) (conducted by Janssen Pharmaceutica N.V., Beerse, Belgium)

A total of 32 Beagle dogs were subdivided into the following groups:

Group	# of Animals		Dose (mg/kg)
	F	M	
C	4	4	Control
LD	4	4	0.31
MD	4	4	1.25
HD	4	4	5.

Risperidone (batch #PFA 021) was administered in gelatin capsules for 12 months, followed by sacrifice and necropsy of all animals.

Observations:

Daily	Behavior and appearance
Weekly	Body weights
Monthly	Hematology
	Clinical chemistry
Months 0, 6 & 12	Urinalysis
	Ophthalmoscopy
Weeks 0, 4, 12, 27, 41 & 52	Heart rate and ECG
Month 12	Necropsy
	Gross examination
	Organ weights
	Histopathology

Results:

1. There was no premature mortality.

2. Dose-related sedation, moderate to severe in extent, was observed in most of the risperidone-treated dogs during the first few study weeks. Other findings, more sporadic in nature, included swelling of female mammary glands, dry nose and miosis.

3. Body weight gain during the study is summarized in figure 2. During the first 6 study weeks, animals dosed with risperidone had minimal body weight gains or lost weight compared to controls. Thereafter, weight gain was increased by up to 100% in dosed animals.

4. There were no unusual ophthalmic findings.

5. A slight (10-35 bpm) bradycardia was observed in risperidone-dosed animals at varying time points during the study. The sponsor attributed this finding to the sedated condition of these animals. Some increases in uncorrected PQ, QRS and QT intervals were also observed in these animals, but the effect was not dose-related

6. **There were small (10-15%) dose-related reductions in HCT, HBG and RBC levels in MD and HD groups during the first 12 study weeks. Subsequent values returned to normal. Serum calcium levels were consistently elevated by 10-20% in risperidone-treated animals. HD animals exhibited 5-10% reductions in potassium levels late in the study (weeks 32-48). There were dose related elevations in haptoglobin levels in all risperidone-treated groups of 50-70%, which began at week 4 and continued throughout the study. Serum cholesterol and phospholipid levels were elevated in a similar manner by 30-70% and 20-40%, respectively. There was a large (2 to 10-fold) increase in urinary white and red cell counts for the HD group at week 25. Urobilinogen excretion was increased in the MD group at week 37. Urinary creatinine was increased by up to 70% in risperidone-treated animals throughout the study.**

7. **Absolute and relative spleen weights were doubled in risperidone-treated animals. Liver weights were also increased, but by only 10-35%. Prostate, testicular and ovarian weights were decreased in a dose-dependent manner in all risperidone groups by up to 50%.**

8. **Gross examination confirmed the organ weight data, in that risperidone-treated animals had an increased incidence of swollen spleen and small testes and/or prostate. This was accompanied by microscopic evidence of increased splenic retention of red blood cells** at all doses **and, in males, fibrotic prostatic development and degeneration of testicular tubules. MDF and HDF had histological evidence of decreased mammary and uterine development,** decreased **vaginal epithelial thickening** (all doses), **and absence of corpora lutea** at the MD and HD.

PK was studied in part of the animals (2/sex/grp) used in this study. Blood samples were collected prior to and 0.5, 1, 2, 4, 6, 8, and 24 hr after the first dosing on Day 1. Samples were also collected on Days 3, 4, 8, 15, 29, 57, 120, 176, 239, and 302 just before dosing, and on Day 373 immediately after dosing. Plasma samples and selected tissues (muscle, lung, kidney, brain, fat, and liver) were analyzed for both risperidone and 9-hydroxy-risperidone by HPLC.

Plasma risperidone (ng/ml):

Parameter	Day	0.31 mg/kg	1.25 mg/kg	5 mg/kg
C_{max} (ng/ml)	1	105±87	245 ±251	503 ±171
	366	117 ±85	325 ±351	726 ±181
T_{max} (h)	1	0.6 ±0.3	1.6 ±1.6	3.3 ±1.5
	366	1.0 ±0.0	1.5 ±0.6	2.0 ±0.0
$AUC_{(0-\infty)}$ (ng·h/ml)	1	166 ±111	609 ±374	1987 ±490
	366	205 ±153	761 ±531	1954 ±142

Plasma 9-hydroxy-risperidone:

Parameter	Day	0.31 mg/kg	1.25 mg/kg	5 mg/kg
C_{max} (ng/ml)	1	160 ±92	587 ±353	1576 ±182
	366	251 ±121	766 ±474	2236 ±246
T_{max} (h)	1	4.0 ±2.3	4.3 ±3.3	5.0 ±2.0
	366	1.8 ±0.5	3 0 ±1.2	3.3 ±1.2
AUC $_{(0-\infty)}$ (ng-h/ml)	1	3745 ±3537	7903 ±4691	22485 ±4610
	366	3252 ±1701	10704 ±6155	30421 ±2640

Unit exposure (based on both C_{max} and AUC) and "trough" (minimum) plasma levels (decreased with increasing dose for both risperidone and 9-hydroxy-risperidone. There were no differences in unit exposure (based on AUC) between LD and MD; there was, however, large interanimal variability which may have masked small, but significant, differences. T_{max} for both risperidone and 9-hydroxy-risperidone tended to increase (slightly) with increasing dose; there were no differences between LD and MD. The ratio of metabolite to risperidone was higher at the LD than the MD and HD (21.9,19.6 for LD vs 14.4, 15.5 for MD and 11.5, 16.0 for HD).

Tissue levels of risperidone 24 hr after the last dose were undetectable in all tissues examined. For 9-hydroxy-risperidone, the amount of drug in all tissues examined did not increase linearly with increases in dose; unit exposure decreased with increasing dose. The highest concentrations of metabolite at each dose were measured in lung ng/g) and liver ng/g). Moderate levels were detected in kidney (412-2431 ng/g) and lower levels in brain (77.6-324 ng/g) and muscle (83.0-453 ng/g). Lowest levels were detected in fat (43.5-162 ng/g). Brain/plasma ratio was 0.5-0.7, which was lower than that observed with haloperidol (22) and chlorpromazine (7.0).

REPRODUCTIVE AND TERATOLOGY STUDIES

1. Male and female fertility study in Wistar rats (Segment I, administration orally through the diet) (conducted by Janssen Pharmaceutica N.V., Beerse, Belgium)

A total of 192 SPF Wistar rats were subdivided into the following groups:

Group	# of Animals		Dose (mg/kg)
	F	M	
C	24	24	Control
LD	24	24	0.31
MD	24	24	1.25
HD	24	24	5.

Risperidone (batch #PFA 041) was administered in the diet to females for two weeks prior to mating through day 8 of gestation, and to males for 60 days prior to, and through mating.

Observations:

Daily	Behavior and appearance
Weekly	Body weights
	Food consumption
Gestational day 22	Necropsy
	Gross examination
	Reproductive parameters
	Fetal examination:
	Radiographic examination
	Alizarin staining (as indicated - two-thirds)
	Visceral dissection (one third)

Results:

1. One LDM died before the mating period. Autopsy revealed a cerebellar abscess. One MDM died of pneumonia, also before the mating period was begun. Neither premature death appeared to be related to risperidone dosing.

2. The only notable behavioral observation for risperidone-treated animals was an increase in food wastage for the HDF group. This effect could have led to an overestimation of drug intake in this group (see item #4 below).

3. Body weight gain in males was reduced by 5-21% in a dose-dependent manner. Premating female body weights were reduced in the HD group by 50%. These dams also had a 10% deficit in gestational weight gain while dosing continued, but exhibited recovery afterward (gestational days 10-22).

4. **Food consumption was reduced by 10% or less in the HD group** (food wastage was reported in HDF). **Actual intake of risperidone was: LDM 0.29, LDF 0.36, MDM 1.2, MDF 1.5, HDM 4.6 and HDF 6.0 mg/kg. Thus drug intake was maintained at or near (within 20%) of targeted levels.**

5. **Reproductive parameters are summarized in table 2. There was a dose-related decrease in the rate of copulation, so that in risperidone-treated pairs, mating was delayed or failed to occur in 30-80% of the cases. Fertility upon actual mating was unaffected. There were no changes in rates of pre- or postimplantation loss. There were no fetal deaths nor were there any significant differences in fetal weights.**

There were a total of 13 malformations: 1 MD fetus had encephalocele, spina bifida and polydactyly, the remainder were cases of short and/or wavy ribs. As the cohort of HD fetuses was so small (n=61), the highest incidence that could have been detected in this group with 95% confidence was 4%, well above the incidence observed in any other group. There were a number of skeletal variations (e.g. wavy ribs, split vertebrae) observed in all groups, with the highest incidence (12-13%) observed in the C and HD groups.

	C	LD	MD	HD
# Dams	24	24	24	24
# Mated	24	17[a]	12[a]	6[a]
# Pregnant	22	16	12[a]	5[a]
% Fertility	91.7	94.1	100	83.3
Time to mate (days)	2.0	5.0[a]	3.0	9.5[a]
# Corpora lutea	14.0	15.2	15.6	14.8
# Implantations	12.6	14.0	13.9	12.8
# Viable fetuses	12.2	13.1	13.0	12.2
Fetal weight (g)	5.4	5.3	5.3	5.1
% Fetal malformations	2	< 1	< 3	≤4
% Fetal variations	12	3	5	13

[a]p<0.05 vs controls

Data from the sponsor (12/9/92) indicated that the % incidence of wavy ribs was 2.6, 3.3, 5, and 13% for control, LD, MD, and HD, respectively. Expressed as % of litters with an affected fetus, the data were 9, 38, 33, and 40% for control, LD, MD, and HD, respectively.

2. **Male fertility study in Wistar rats (Segment I)**

Male Wistar rats (24/grp) received risperidone orally (by gavage) at doses of **0, 0.16, 0.63, and 2.5 mg/kg** for ≥60 days prior to mating and during cohabitation (maximum of 3 wks). Each treated and control male was cohabited with one untreated female until there was evidence of mating (vaginal smear), up to a maximum of 3 wks. Neither males or females were pre-evaluated for mating or estrus behavior.

The following observations were made: behavior and appearance, body weight [weekly; data only presented for prior to and at end of 60 day treatment (prior to cohabitation)], food consumption, and cohabitation-mating interval. Terminal studies included: # of corpora lutea, weight of uterus, # of live and dead fetuses, presence of empty implantation sites and resorption sites, weight of live fetuses, live and dead fetuses examined for external anomalies, radiographic analysis of all fetuses, visceral analysis of 1/2 of each litter, Alizarin stain of 1/2 of litter. Fetal measures were statistically analyzed using a test. There was no necropsy or histopathology conducted on adult males.

The results indicate no drug-related effects on any **clinical observations**. One LD male died during the pre-cohabitation period. The cause of death was unknown, but was not considered drug-related. One female also died. Body weight was significantly decreased (91% of control values) as was body weight gain (80% of control values) only in the HD males. Food consumption was similar in all drug-treated and control groups. There were no drug-related effects on **copulation index, fertility index, gestation index**, or **cohabitation mating interval**, on **# of corpora lutea**, the **# of implants**, or on the **# of live, dead, or resorbed fetuses**. In addition, **pup weights** at sacrifice were the same for all groups. (It was indicated, however, that gross examination revealed 11 "small" pups in the MD group.)

There were no drug-related effects on skeletal data, except perhaps a slight increase in the incidence of wavy ribs expressed as % affected/total fetuses (4.8, 4.6, 5.8, and 9.2% for control, LD, MD, and HD, respectively).

3. Female fertility study in Wistar rats (Segment I)

Female Wistar rats (24/grp) received risperidone at doses of 0, 0.16, 0.63, and 2.5 mg/kg orally by gavage 14 days prior to mating, during the cohabitation period (maximum of 3 wks), and up to Day 8 of pregnancy. Males were untreated.

The following observations were made: behavior and appearance (once per day), body weight (pre-cohabitation, and Days 1, 9, and 22 of pregnancy), and food consumption (pre-cohabitation and during Days 1-8 and 9-21 of pregnancy). Females were sacrificed on Day 22 of pregnancy. Terminal studies consisted of: autopsy of males and females, gravid uterus wt, # of corpora lutea, # of live and dead fetuses, presence of empty implantation sites and resorption sites, condition of uterus. Fetuses were weighed individually and examined for external anomalities. Radicgraphic exams were conducted on each fetus; 1/2 of the fetuses were randomly selected for dissection, and 1/2 were examined for skeletal anomalies using the Alizarin red staining method.

There was no premature mortality during the study. Clinical signs were noted in females at MD and HD. The primary clinical sign was sedation. During the pre-cohabitation dosing period, severe sedation was noted in 2/24 HD females, moderate sedation was noted in all HD females, and slight sedation was noted in 19/24 MD and 11/24 HD females. In addition, 2/24 HD females exhibited circling behavior. During pregnancy, sedation (moderate in all HD females, slight in all MD females) and circling behavior (1/19 HD females) were observed. Body weight and body weight gain were affected only at the HD (decreased by 5% and 22%, respectively, compared to control), and only during the pre-cohabitation dosing period. During pregnancy, body weight and body weight gain were comparable. There were no dose-related effects on food consumption. The only observed difference was an 8% decrease in food consumption at the MD during pregnancy.

There were no drug-related effects on copulation index, fertility index, or gestation index. Cohabitation-mating intervals were, however, increased at all doses. The median interval was significantly increased at LD and HD (2, 5, 4.5 and 11 days, for control, LD, MD, and HD, respectively). In addition, the number of animals with an interval greater than two normal cycles ($\geq$8 days) increased from 10.5% in

control, to 44-44.7% in LD and MD, to 70.6% in HD animals. The number of corpora lutea were similar among all groups.

There were no drug-related effects on the mean number of live dead, or resorbed fetus, on number of implantations, or on mean weight of the pups. There were no clear drug-related effects on fetuses. Necropsy of adult (male or female) indicated no drug-related findings.

4. **Embryotoxicity and teratogenicity study in Sprague-Dawley rats (Segment II). Conducted by Laboratoires Janssen, Aubervilliers, France.**

A total of 96 pregnant female Sprague-Dawley (CD non-inbred COBS, Charles River) rats were subdivided into the following groups:

Group	# of Animals	Dose (mg/kg)
C	24	Control
LD	24	0.63
MD	24	2.5
HD	24	10.0

Risperidone (batch #A0101) was administered by gavage during gestational days 6 through 16. Dams were sacrificed and necropsied on day 22.

Observations:

Daily	Clinical observations
Days 1, 6, 17, 22	Body weight
	Food consumption
Terminal	Physical examination
	Necropsy - Gross pathology
	Uterine weight
	Numbers of resorbtions, corpora lutea
	Fetal survival, weights
	Fetal necropsy - Soft tissue
	Skeletal development (radiographic analysis was performed on all fetuses; "if indicated", 2/3 of fetuses were examined using Alizarin red stain)

Results:

1. **One HD dam died on the second day of dosing due to intubation error.**
2. **HD animals exhibited palpebral ptosis.**
3. **Compared to controls, MD and HD dams registered decreased body weight gains of 17 and 43% during dosing. Overall gestational body weight gains were decreased by 2 and 13% in these 2 groups.**
4. **Food consumption was decreased by 2-8% in MD and HD groups.**
5. **Reproductive parameters are summarized below:**

Table 6

Group	C	LD	MD	HD
Pregnancy rate (%)	91.7	87.5	87.5	83.3
Litter size	11.3	11.9	12.5	12.1
Resorbtions/dam	1.2	0.5	0.6	1.3
Dead fetuses/dam	0.0	0.0	0.0	0.1
live fetuses/dam	11.3	11.9	12.5	12.0
survival (%)	90.4	96.0	95.4	89.6
fetal body weights (g)	5.3	5.3	5.2	5.0*

*$p \leq .01$

There were no significant changes in postimplantation survival (as corpora lutea were not examined, preimplantation survival could not be assessed). HD fetal body weights were decreased by 6%. No other parameters were affected by drug treatment.

6. **Talipes (clubfoot) was found in 1 fetus each from LD and MD groups for an incidence in each group of 0.4%. Soft tissue and skeletal variations were not recorded.**

An ammendment to the original report was submitted and included results of "an additional examination of radiographs" of the fetuses. The original description of the evaluation of skeletal findings involved an initial radiographic analysis. Only "if the results of the radiographic examination..." 2/3 of the fetuses were to be examined using Alizarin red stain. Apparently no evidence of a drug effect was noted using the radiographic technique; therefore, no analysis by Alizarin red stain was performed. The data provided in the addendum indicated no drug-related effect. However, this would not be considered an adequate examination for skeletal abnormalities/variations due to the relative insensitivity of the radiographic technique, especially in rats.

5. **Risperidone: Embryotoxicity and teratogenicity study in Sprague-Dawley rats (segment II)** (conducted by Janssen Laboratories Research Department, Aubervilliers, France)

A total of 96 pregnant Sprague-Dawley rats were subdivided into the following groups:

Group	# of Animals	Dose (mg/kg/day)
C	24	Vehicle
LD	24	0.63
MD	24	2.5
HD	24	10.0

Risperidone (batch RFA121) was administered by gavage from days 6 to 16 of gestation, followed by sacrifice and necropsy on day 22.

Observations:

Daily	Mortality and general behavior
	Body weights
	Food consumption

Day 22 **Necropsy**
Reproductive parameters
Litter size, weights, viability, sex distribution
Visceral and skeletal (radiographic and alizarin red staining) examination

Results:

1. **There was no premature mortality.**

2. **Palpebral ptosis was noted during the treatment period in 1 LD dam and in most of the dams in the MD and HD groups.**

3. **HD maternal weight gains were reduced by 28% during the dosing period, so that body weights on day 22 were significantly reduced. Most of the weight gain reduction was still evident when uterine weights were subtracted, indicating relative sparing of the fetuses.**

4. **Food consumption was comparable in all dosage groups.**

5. **Reproductive parameters are summarized in table 1. Litter size appeared to be reduced slightly following risperidone dosing, but this trend was not statistically significant. There were no significant differences in the frequency of fetal resorptions, and all remaining fetuses were alive at the time of necropsy except for a single control. There were no drug-related effects on fetal weights or sex distribution. Malformations were limited to a control with hydrops and a HD with missing subclavian artery. There were no changes in the frequency of visceral variations, but there did appear to be an increase in the number of skeletal variations, primarily missing phalanges** (expressed as % of affected litters: 2.7, 3.2, 5.1, and 7.6% for control, LD, MD, and HD, respectively). **The frequency of other common skeletal variations including wavy or extra ribs and misshapen sternebrae did not appear to be affected by risperidone treatment.**

6. **Embryotoxicity and teratogenicity study in Wistar rats (Segment II)**

Virgin female Wistar rats (36/grp) were dosed with risperidone by gavage at doses of 0, 0.63, 2.5, and 10 mg/kg on Day 8 through Day 18 of pregnancy. On Day 22 of pregnancy, 24 females in each group were sacrificed and fetuses were removed for analysis. The remaining females (12/grp) were allowed to deliver naturally

The following observations were made during the study: behavior and appearance (1/day), body weight (daily during dosing, and on Days 1, 8, 19, and 22 of pregnancy), and food consumption (Day 8, Day 19, and Day 22 of pregnancy) Twenty-four females/grp were delivered by cesarean section on day 22 of pregnancy. Terminal studies included: autopsy of all females, condition and weight of uterus, live and dead fetuses, implantation sites, resorptions, fetal weights, external exam of fetus, 1/2 of each litter dissected for examination of viscera, 1/2 of each litter examined (Alizarin red) for skeletal effects Twelve females/grp were allowed to deliver naturally. Pups were observed daily for clinical signs, and were weighed at 4, 14, and 21 days of age. At 21 days after birth, in 4 pups/sex/grp, physical development was

evaluated. Observations included pinna unfolding, tooth eruption, ear and eye opening. In addition, on Day 42 postpartum, testis descent and vaginal opening were evaluated. In 2 pups/sex/grp, the following behavioral observations were made (Day 21 postpartum): righting on surface, wire grasping, walking, righting in air, climbing down a rope, auditory startle, pain response, and corneal reflex. At 5 wks of age, horizontal activity was also evaluated in 5 pups/grp.

One male and female from each litter were randomly selected for mating. At this time, remaining pups were sacrificed and necropsied. At 3 mo of age, pups (10/sex/grp) were mated for a maximum of 2 wks. Clinical observations, body weight, and food consumption were recorded on Day 1 and Day 22 of pregnancy. Cesearean sections were performed on Day 22, and terminal studies were performed similar to those for the F_0 generation adults and F_1 generation pups.

Results

I. **F_0 generation; cesarean section**

No unexpected deaths occurred during the study

The primary clinical sign observed during the dosing period was sedation. Sedation was observed in all females; however, the severity increased with increasing dose (slight: 24/24 LD, moderate: 24/24 MD, severe. 24/24 HD). Red vaginal discharge was noted in 1 HD female and circling was noted in 1 LD female during and after the dosing period.

There was no significant drug effect on body weight or body weight gain at the LD and MD. There was, however, a slight (9%) decrease in body weight gain at the MD on Day 19-21 of pregnancy. At the HD, body weight and body weight gain were significantly decreased (5-7 and 20%, respectively) on Day 19-22 of pregnancy.

There was no significant drug effect on food consumption at the LD or MD, except for a slight reduction (8-9%) on Day 8-21 at the MD. At the HD, food consumption was reduced 12-13% below control levels on Days 8-21. Food consumption had not normalized by 3 days postdosing.

Pregnancy data:

The pregnancy index (# preg/# mated) was comparable across groups. It ranged from %, being lowest at the LD.

The # of corpora lutea/female tended to be higher in all treated females (6-8%), although, it was significantly higher only at the MD and HD (13.4, 14.3, 14.5, and 14.2 for control, LD, MD, and HD, respectively).

Offspring data:

No drug effect was observed on litter size; the # of live and dead pups (only 1 HD pup was dead) were comparable.

The number of resorptions was significantly elevated at the LD (0-2/female) compared to control (means of 1.05 and 0.55 per litter, respectively). Increased resorption, although not significant, was also observed at the HD, primarily due to a high number in two females (8 and 12 vs 0-2 in the other HD females).

The only effect observed on birth weight of the pups was an 11% decrease in HD pups. The mean sex ratio of the pups ranged from 46.2 to 49.2% and was comparable among groups.

Examination of viscera (pups) revealed no drug-related effects. Skeletal abnormalities were noted in all groups. There was an increased incidence of the following at the MD: short 13th pair of ribs, one rudimentary 14th rib, rudimentary 14th pair of ribs, small ossification point between 5th and 6th sternum bone, and asymmetrical sternum bone. At the HD, there was an increased incidence of one rudimentary 14th rib and decreased # of metatarsal bones (48/258 vs 18/266 and19/236 at the LD and control). Decreased # of metacarpal bones (not significant) was observed in 2 LD and 2 MD pups. Split center of thoracic vertebra(e) was observed in 1 LD, 1 MD, and 3 HD pups.

II. **F_0 generation; natural delivery**

No mortality was observed.

The primary clinical sign was sedation, which increased with severity with increasing dose (slight: 12/12 LD, moderate: 12/12 MD, severe: 12/12 HD). Piloerection was noted in 2 MD and 2 HD females; circling was observed in 1 HD female. During nondosing periods, behavior appeared normal.

During pregnancy, body weight was decreased at the HD only (by 11%) on Days 19 and 22. Overall body weight gain was reduced at MD (by 16%) and at HD (by 36%). At the HD, body weight was reduced throughout lactation (7-9%)

Food consumption was comparable among all groups, except for a 14% decrease at the HD during Days 19-21 of pregnancy (postdosing).

Pregnancy data:

Pregnancy rates were similar among all groups.

The duration of gestation was increased at the HD (23.0 vs 22.3-22.7); however, the duration in the HD group was within historical control values.

Offspring:

The number of live pups per litter was decreased at the LD compared to control (10.6 vs 12.4). Although not significant, the number of live pups were also slightly lower at the MD and HD compared to control (10.8 and 10.9 vs 12.4).

The number of dead pups per litter was comparable among groups. In control and LD groups, 1 litter had at least 1 dead pup, and in MD and HD groups there were 2 such litters.

Drug-treatment was associated with increased body weight of pups at all doses. On Day 4 postpartum, body weights were comparable; however, by Day 14 the body weight of MD males was 14% higher than controls, and by Day 21 the body weight of all treated males, and LD females was elevated (males: 15-29%, females: 24%) compared to controls.

Pup survival rate was comparable among groups.

All physical and behavioral developmental landmarks examined on Day 21 postpartum had been reached by all pups. In addition, the incidence of testis descent and vaginal opening was similar among groups. The only drug-related observation was an increase in horizontal activity (as measured by animex at 5 wks) in HD pups (total mean activity: control: 1999, LD: 2344, MD: 2140, and HD: 2939). The sponsor indicates that this significant finding is due to the low value obtained in control pups, and cites mean control values obtained in 2 previous studies of 2136 and 2922. However, in the present study, data for LD and MD groups were similar to control data. Therefore, this observation should be considered to be possibly drug-related.

Pups were analyzed only for external abnormalities. The only drug-related finding was a decreased incidence of ringtail in pups with increased dose, with the incidence at HD being significantly lower than in control.

III. F_1 generation

There was no mortality observed.

The only dose-related clinical sign was food wastage: 1 control, 2 LD, 3 MD, and 5 HD.

Body weight was similar among groups, except for a small, but significant, elevation in body weight (7%) at the HD on Day 1 of pregnancy. At the end of pregnancy, body weight and body weight gain were comparable among groups.

There was no drug-related effect on food consumption.
Pregnancy data:

Pregnancy rate and # of corpora lutea were similar among groups.

Offspring data:

Number of live and dead fetuses, as well as number of resorptions were comparable among groups.

Body weight of fetuses was comparable among control, MD, and HD fetuses; at the LD, there was a small, but significant, increase (6%) in body weight compared to control.

The sex ratio (% of male fetuses) was somewhat higher in drug-treated groups compared to control: 45 3, 49.7, 49.5, and 59.3% for control, LD, MD, and HD, respectively.
Histopathology indicated only one dose-related observation, an increased incidence of rudimentary 13th pair of ribs (0, 0, 1, and 3 in control, LD, MD, and HD, respectively). Other observations noted in drug-treated fetuses (but not dose-related) were: small size in 1 LD fetus, split center of the thoracic vertabra(e) in 3 LD, 3 MD, and 1 HD fetus, rudimentary 14th pair of ribs in 1 LD and 1 MD fetus, incomplete ossification of sternum bone in 1 LD and 4 MD fetuses, abdominal parumbilical hernia in 1 LD fetus, and reduced metacarpal bones in 1 LD and 2 MD fetuses. The only statistically significant finding was an increased incidence of dumbbell-shaped sternum bone at the LD (4 fetuses); this observation was also noted in 2/132 MD and 2/142 HD fetuses.

7. **Embryotoxicity and teratogenicity study in white rabbits (Segment II). Conducted by Laboratoires Janssen, Aubervilliers, France.**

A total of 60 white rabbits rats were subdivided into the following groups:

Group	# of Animals	Dose (mg/kg)
C	15	Control
LD	15	0.31
MD	15	1.25
HD	15	5.0

Risperidone (batch #A0301) was administered by gavage during gestational days 6 through 18. Does were sacrificed and necropsied on day 28.
Observations:

Daily	Clinical observations
Days 1, 6, 19, 28	Body weight
Terminal	Physical examination
	Necropsy - Gross pathology
	Uterine weight
	Numbers of resorbtions, corpora lutea
	Fetal survival, weights
	Fetal necropsy - Soft tissue
	Skeletal development (radiographic analysis followed up with Alizarin red stain)

Results:

1. Three HD does died during the study, one each on days 9, 19 and 20. No other details were provided, but the deaths were considered to be drug-related.

2. No behavioral abnormalities were noted.

3. HD does lost an average of 100 g body weight during dosing, in contrast to 100-200 g gains for other groups. Final body weights in MD and HD does were 95 and 91% of controls, respectively.

4. Reproductive parameters are summarized below:

Group	C	LD	MD	HD
Pregancy rate (%)	73.3	73.3	80.0	73.3
Litter size	7.7	5.9	8.5	8.1
Resorption/doe	1.7	0.7	0.5	0.4
Dead fetuses/doe	0.1	0.0	0.0	0.0
Live fetuses/doe	7.6	5.9	8.5	8.1
Survival (%)	80.0	89.4	94.4	95.3
Fetal body weights (g)	31.4	33.0	29.7	30.6

There were no significant changes in fetal survival or body weights.

5. There were 3 fetal abnormalities which were considered major: 1 C fetus had anouria, 1 LD fetus had anouria and 4 fused ribs, and 1 HD fetus had 2 fused ribs. In addition, 2 C fetuses had talipes. The incidence of minor skeletal anomalies (fused or extra ribs) was 44, 48, 54 and 77% for C, LD, MD and HD fetuses, and was thus increased significantly in the latter group.

An addendum to this report was submitted which provided individual adult and fetal data.

8. Oral peri- and postnatal study in Wistar rats (Segment III). Conducted by Janssen Pharmaceutica, Beerse, Belgium.

A total of 96 female Wistar rats were subdivided into the following groups:

Group	# of Animals	Dose (mg/100 g food)
C	24	Control
LD	24	0.31
MD	24	1.25
HD	24	5.0

Risperidone (batch #PFA 021) was administered in the diet from day 16 of pregnancy through day 21 of lactation.

Observations:

Daily	Clinical observations
Gestational days 1, 16 & 21 and Lactation days 4, 14 & 21	Body weight
Gestational days 1, 16 & 22	Food consumption
Delivery	Pup weights
	Physical examination

Results:

1. One CF died during pregnancy. Autopsy revealed a dilation of the renal pelvis with nephritis. In addition, 1 CF and LDF died at the end of the lactation period. These deaths were classified as "accidental" but no other details were provided.

2. Body weight gain in the HD group was reduced by 43% during gestational days 16-22 (dosing period of pregnancy). Body weights of all drug treated groups were reduced during lactation by 6-19% in a dose proportional manner.

3. Food consumption was reduced in a dose-proportional manner by 7-43% during dosing. Drug intake calculated from data provided by the sponsor was approximately 0.55, 2.43 and 6.43 mg/kg/day for LD, MD and HD dams, respectively.

4. Reproductive data are summarized in table 7. Fertility rates were unaffected by drug administration. There was a small increase in

gestational length for HD dams which did not appear to be biologically significant. Pup survival at birth was unaffected, but survival over the next 4 days was reduced by more than 50% in the HD group. Pup weights were also decreased in this group by 20%. Survival and body weight gains were comparable thereafter.

Groups	C	LD	MD	HD
Pregnancy rate (%)	95.8	91.7	100	100
Gestation length (days)	22.6	22.7	22.9	22.9*
Litter size	10.9	10.5	10.9	10.5
Dead pups/dam	0.5	0.2	0.6	0.7
live pups/dam	10.4	10.3	10.3	9.8
Survival day 0 (%)	95.4	98.1	94.5	93.3
Survival day 4 (%)	86.5	85.4	83.1	40.3*
Survival day 14 (%)	84.7	82.3	78.6	34.7*
Survival day 21 (%)	83.1	81.7	78.2	32.2*
Birth weight (g)	6.5	6.4	6.4	6.4
Weight on day 4 (g)	10.0	9.8	10.2	8.0*
Weight on day 14 (g)	28.6	28.0	28.7	27.0
Weight on day 21 (g)	45.5	42.8	45.0	41.2
Abnormal pups	0	2	0	0

*p<.05

5. **Two pups from the LD group had arthrogryposis.**

8. **Peri- and postnatal reproduction study with a second generation evaluation in Wistar rats (Segment III).**

Female Wistar rats (24/grp) were dosed (by gavage) with risperidone at 0, 0.16, 0.63, and 2.5 mg/kg from Day 18 of pregnancy through lactation (3 wks). The following observations were recorded: behavior and appearance (1/day), body weight (Day 1, 18, and 22 of pregnancy and Day 1, 4, 14, and 21 postpartum), food consumption (Day 18, 21 of pregnancy and during the lactation period), duration of gestation, and # of live and dead pups. Pups were weighed at birth and examined for external anomalies. Terminal studies were performed on Day 26 if natural delivery had not occurred by Day 23-24 of pregnancy and included: examination of uterus, # of live and dead fetuses, empty implantation sites, and resorptions.

Postnatal observation of F_1 generation included: evaluation of behavior and appearance (daily during lactation), body weight (Days 4, 14, and 21 postpartum), and survival rates. Physical development was assessed on Day 21 in 4/sex/grp (pinna unfolding, tooth eruption, ear and eye opening), and on Day 42 postpartum (testis descent, vaginal opening). Behavioral development was assessed in 2/sex/grp on Day 21 postpartum (righting on surface, wire grasping, walking, righting in air, climbing down a rope, auditory startle, pain response, corneal reflex). Horizontal activity was assessed at 5 wks of age in 5/sex/grp.

One male and female from each F_1 litter were selected for mating. Pups not mated were sacrificed and necropsied. At 3 mo of age, rats were mated for a maximum of 3 wks. Observations were recorded on Days 1 and 22 of pregnancy and included clinical signs, body weight, and food consumption. All females were sacrificed on Day 22 of pregnancy, and autopsies were performed. Terminal studies similar to those

listed for the F_0 generation were performed, and in addition, rat fetuses from each litter were dissected for examination of viscera (1/2 of litter) or examined (using Alizarin red) for skeletal anomalies (1/2 of litter). All fetuses were radiographically examined.

Results

F_0 generation

Clinical signs are reported for three separate periods, Day 18-21 of pregnancy, birth-sacrifice Day 26, and lactation (Day 0-3, 4-13, 14-20). It is unclear which animals are included in the "birth-sacrifice Day 26" period; it is not just the animals that were sacrificed on Day 26. The primary clinical signs were sedation and decreased nursing behavior. No drug-related effects were observed at the LD. During Day 18-21 of pregnancy, slight sedation was noted in 18/24 MD and moderate sedation was noted in 18/24 HD rats. During the birth-sacrifice Day 26 period, slight sedation was noted in 14/24 MD and 6/24 HD rats. Moderate sedation was observed in 16/24 HD rats. Sedation was observed at the MD and HD throughout the lactation period. On Days 0-3 of lactation, slight sedation was noted in 17/24 MD and 5/22 HD rats, whereas, moderate sedation was observed only at the HD (15/22). During mid-lactation (Days 4-13), slight sedation was noted at both MD and HD (19/24 and 15/22, respectively), whereas, moderate sedation was, again, noted only at the HD (7/22). By the end of lactation (Days 14-20), only slight sedation was observed (19/23 at MD, 19/21 at HD).

During early lactation (Day 0-3), there was a dose-related increase in the percentage of females exhibiting a decrease in nursing behavior (8, 30, 42, and 64% for control, LD, MD, and HD, respectively). By Day 4-13 of lactation, nursing behavior had returned to normal, except in 1 HD female that continued to show decreased nursing behavior up to Day 13 of lactation.

There were 4 unscheduled **deaths**. One female in each dose group was sacrificed. At necropsy, the LD female was found to have an absess on the pharynx, the MD female had purulent pneumonia, and the HD female had vaginal prolapse. The 1 HD female was found dead, death being due to a dosing accident (traumatic performation of the esophagus).

Body weight was decreased throughout lactation (6-9%) only at the HD.

Food consumption was decreased at all doses during lactation. During the latter part of lactation (Days 14-20), there was a dose-related decrease in food consumption (80, 79, and 61% of control at LD, MD, and HD, respectively). At the earlier lactation periods, food consumption was reduced only at the LD (80-85% of control) and HD. At the HD, the reduction in food consumption increased over time (Day 0-3: 75%, Day 4-13: 69%, Day 14-20: 61% of control). Reduced food consumption in drug-treated females may be due, at least in part, to reduced litter size (control: 8.9-7.8, LD: 6.4-5.8, MD: 6-5.1, HD: 3.5-2.9 pups).

Pregnancy data

Pregnancy and gestation indexes were comparable among groups. The gestation index was slightly decreased at the HD (95.7 vs 100%) due to one female with no live pups at birth

The **duration of gestation** was increased at the HD (23.3 vs 22.8-22.9 days), but was within the range of historical control.

Offspring

At the HD, there was an increase in the **number of dead pups** per litter (1.27 vs 0.08, for HD and control, respectively). A slight, but not significant, decrease in the **number of live pups** was also noted at the HD (10.2 vs 11.0 for control).

Body weights of the pups were comparable among groups by the end of the lactation period. During early lactation (Days 0 and 4), body weight was decreased by 7-16% at the LD. During mid-lactation (Day 14), body weight was increased by 13% in HD females pups.

Physical and behavioral development was similar on all tests among all groups, including the horizontal activity test assessed at 5 wks.

Survival rate for pups was reduced at all doses.

Survival (%) during lactation

Dose group (mg/kg)	Day 4	Day 14	Day 21
0	80.8	73.2	70.6
0.16	55.1*	52.1*	49.6*
0.63	56.0*	52.9*	48.4*
2.5	34.7*	28.9*	28.8*

*p<0.001

[It is not noted whether or not the greater decrease in survival rate at the HD is significantly different from the other dosage groups.] Most pups died during Days 0-4 of lactation. The sponsor attributes the decreased survival rate to the decreased nursing behavior observed in the dams during this period. This may, indeed, be an important contributory factor; however, a comparison of pup survival rates between control and drug-treated dams indicates that it may not be the sole factor.

Pup survival (%) presented according to lactation performance of dams. n=number of dams.

Dose	Lactation Performance	Day 4	Day 14	Day 21	n
control	decreased	79	62	58	2
	normal	82	75	74	22
0.16	decreased	3	3	3	7
	normal	72	69	68	15
0.63	decreased	15	14	12	10
	normal	84	79	70	13
2.5	decreased	9	4	4	14
	normal	86	83	83	7

Although the number of controls with decreased lactation performance was small, a comparison of the survival rate of pups of these dams is considerable higher than the survival rate of drug-treated dams exhibiting decreased lactation performance. This suggests that a direct drug effect on the pups may have contributed to the decreased survival rate.

Pups were examined only for external anomalies. Omphalitis was noted in 2 LD pups. A decreased incidence of ringtail was noted at MD and HD (3 MD and 5 HD vs 24 control), but was only significant at the MD.

F_1 generation

No mortality or clinical signs were noted.

Body weight and body weight gain during pregnancy were comparable. There was a tendency for food consumption to be lower in drug-treated animals (by 16-19%) than in controls; however, the effect was not significant.

The pregnancy index was comparable among groups (90, 100, 80, 80 for control, LD, MD, and HD, respectively).

Offspring

The number of live and dead fetuses per dam was comparable among groups; however, there was an increased number of resorptions at the HD (1.5 at HD vs 0.3-0.63 and LD, MD and in control). The sponsor attributes this observation to the increased number of corpora lutea in the HD group; however, the number of corpora lutea was comparable among groups (16.8, 16.6, 16.8, and 17.3 corpora lutea/female for control, LD, MD, and HD, respectively).

The sex ratio of pups was similar among the groups, ranging from 47.5% at the HD to 56.9% at the LD.

No dose-related findings were noted in fetuses. The only possibly drug-related observation was an increase in the incidence of rudimentary 13th pair of ribs at the HD (0.8, 0.7, 0.9, and 8.8% in control, LD, MD, and HD, respectively).

9. **Reproductive capacity study in Wistar rats. 2-generation reproductive study with 1 litter per generation.**

Male and female Wistar rats (24/sex/grp) were dosed with risperidone (in diet) at 0, 0.16, 0.63, and 2.5 mg/kg. Males were dosed for 60 days prior to and during mating (maximum of 14 days). Females were dosed for 14 days prior to and during mating, and throughout pregnancy and lactation. F_1 rats were not directly dosed. From each F_1 litter, one male and one female were selected for subsequent mating (at 3 mo of age). The remaining pups were sacrificed and necropsied.

The following observations were made: behavior and appearance (1/day), body weight (for males and females, weekly prior to mating; for females, Day 1 and 22 of pregnancy, and Day 4, 14, and 21 of lactation), food consumption (for males and females, weekly prior to mating; for females, during pregnancy and lactation). After weaning of the F_1 generation and ceserean delivery of F_2 generation, parents were sacrificed and necropsied. The offspring of each litter were examined for: body weight, # of live and dead pups, survival rate (Days 4, 14, and 21 of lactation), external anomalies, physical and behavioral development (Day 21: ear opening, ear pinna folding, auditory startle, eye opening, corneal reflex, tooth eruption, pain response, righting on surface, wire grasping, walking, righting in air, climbing down a rope; Day 42: testis descent, vaginal opening; wk 5: horizontal activity (Animex). Terminal studies (F_2 pups) included: radiographic analysis of all fetuses, and 1/2 of each litter was dissected for examination of viscera, and 1/2 examined by Alizarin stain for skeletal anomalies.

Results

F_0 generation

Males were observed for **clinical signs** only during the pre-cohabitation period. Skin irritation was noted in all dose groups, but incidence was significantly increased only in MD and HD males (1/24 control, 6/24 LD, 8/24 MD and 8/24 HD). Also, there was a greater incidence of food wastage in MD males (2/24 control, 4/24 LD, 13/24 MD, 6/24 HD). A subcutaneous mass was observed in 1 HD male. In females during the co-habitation period, there was an increased incidence of food wastage which was significant only at the MD and HD (5/24 control, 9/24 LD, 14/24 MD, 14/24 HD).

Females were also observed for clinical signs during pregnancy and lactation. Comparisons in pregnant and lactating females are more difficult because of the greatly reduced rate of pregnancy at the HD. Therefore, there were 21 control, but only 9 HD pregnant females. The major clinical sign was food wastage. Although only significantly increased in HD females during the first few days of lactation (Days 0-3), an increased incidence of food wastage was noted during pregnancy and throughout lactation, especially in HD females.

Incidence (%) of food wastage during pregnancy and lactation in F_0 adult females

Observation period	control	0.16 mg/kg*	0.63 mg/kg*	2.5 mg/kg*
pregnancy	3/21 (14%)	6/20 (30%)	6/17 (35%)	4/8 (50%)
lactation, Day 0-3	1/22 (5%)	3/19 (16%)	6/19 (32%)	4/9 (44%)#
lactation, Day 4-13	2/21 (10%)	2/18 (11%)	2/19 (11%)	2/9 (22%)
lactation, Day 14-20	3/21 (14%)	1/18 (6%)	4/19 (21%)	5/9 (56%)

*doses are theoretical (i.e., not calculated based on food consumption and diet concentration)
#p<.05

Piloerection was observed in 2/19 LD and 1/19 MD adult females at birth and during Days 0-3 of lactation in 2 LD adult females.

Mortality occurred in 1 control and 1 MD male during the pre-cohabitation period. Deaths did not appear to be drug-related. Observations at necropsy indicated fibrinous hemorrhagic pneumonia (control) and purulent otitis media (MD). One control and 1 LD female died during lactation. No cause of death could be determined in the control; swollen spleen, liver, and lymph nodes were noted in the LD female at necropsy.

During the pre-cohabitation period, there was no apparent drug-effect on **body weight** in either males or females. During pregnancy, there was a slight, nonsignificant, decrease (9%) at the MD and HD. During lactation, body weights were comparable among groups on the day of birth and on Day 4 of lactation. During Day 14-21 of lactation, body weight was reduced by 9% (compared to control) at the HD only.

During the pre-cohabitation period, **food consumption** was comparable among males. In females, however, food consumption was increased at the MD and HD (14 and 11%), presumably due to food wastage. During pregnancy, food consumption was comparable among groups. During lactation, there were no significant differences among group; however, there was a tendency for food consumption to be decreased (11-18%) on Days 4-20 at the HD. This observation may be due, in part, to decreased litter size in this group. Validity of food consumption data is questionable due to incidences of food wastage, especially at the HD.

Based on food consumption data (not taking into account extent of food wastage), the **calculated doses** were:

pre-cohabitation: 0.14, 0.56, 2.20 mg/kg for males
0.20, 0.86, 3.32 mg/kg for females

during pregnancy: 0.16, 0.59, 2.48 mg/kg

No calculated doses were reported for the lactation period. One of the weaknesses of using dosing through diet during reproductive studies, especially those involving an evaluation of lactation performance, is the fact that later in the lactation period, pups do consume the adult diet; therefore, it is impossible to calculate dose for either dam or pups during this period.

Pregnancy data

The **pregnancy and copulation indexes** were markedly lower at the HD; although not significant, both indexes tended to be lower at the LD andMD as well.

Dose (mg/kg)*	Pregnancy Index (%)	Copulation Index (%)	Fertility Index (%)	Cohabitation Mating Interval (days)
0	95.7	95.7	100	2.4
0.16	79.2	83.3	95.0	6.3#
0.63	82.6	82.6	100	9.4##
2.5	37.5##	37.5##	100	11.6##

*theoretical doses #p<0.05 ## p<0.001

The **fertility index and duration of gestation** were comparable among groups.

There was a marked and dose-dependent increase in the **cohabitation-mating interval**.

Offspring data

The number of **live and dead pups** were comparable among groups, except for an increase in the number of dead pups (0.59 vs 1.89 per litter for control and LD, respectively). This increase was primarily due to a high incidence of deaths in one litter. **Birth weight** of pups was decreased at the HD (6.4 vs 6.0 g for control and HD, respectively); no effect was noted at the lower doses.

Body weight of pups was increased in MD pups (15%) on Day 4 and in MD females (24% above control value) on Day 14 of lactation. By Day 21 of lactation, body weights were comparable. **Survival rate** was decreased at the LD and HD on Day 4 of lactation (81.9, 70.8, 75.1, and 72.2% for control, LD, MD, and HD, respectively). However, by Day 14 no significant differences were apparent among groups, and rates remained similar throughout the remainder of lactation Survival rate at the HD was slightly, although not significantly, lower on Days 14 and 21 of lactation (Day 14: 61.6 vs 54.0; Day 21: 60.9 vs 50.0; control vs HD). The sponsor attributes the lower survival rates to decreased nursing behavior of the dams; however, such an observation was reported for only 1 LD female during Days 0-3 of lactation.

All **physical and developmental landmarks** examined on Day 21 were met by all pups in all groups. There was a delay in vaginal opening in HD females on Day 42 postpartum. Horizontal activity, assessed at 5 wks, was comparable among groups, although overall activity was slightly reduced (10%) in MD pups.

An examination of **external abnormalities** indicated only one drug-related finding: a dramatic decrease in the incidence of ringtail in HD pups (70, 57, 34, and 0 for control, LD, MD, and HD, respectively).

F_1 generation

The only **clinical signs** noted during pregnancy were an increased incidence of food wastage in the HD group (4/24 control vs 9/18 HD), and circling in 1 LD animal.

No **mortality** occurred males or females.

During pregnancy, **body weight** was increased in LD and MD dams (28 and 33% above control, respectively). No effect was seen in HD dams.

Food consumption was increased at all doses (8-13%) compared to controls. However, food wastage at all doses reduces the validity of these data. The incidence of food wastage was increased only in the HD; however, whether or not the quantity of food wasted in the different groups was similar or not is unknown.

Pregnancy data:

There was no drug-related effect on **pregnancy index, cohabitation-mating interval, # of live and dead fetuses, sex ratio, or body weight of fetuses.**

The number of **corpora lutea** was sightly higher at the LD and MD, but significantly higher at the HD (13.8, 15.0, 14.9, and 15.5 for control, LD, MD, and HD, respectively).

Increased incidence of **skeletal** abnormalities was only observed in MD fetuses. Observations included: hydrocephalus in 1 MD fetus, and increased incidence of one rudimentary 13th rib, and incomplete ossification of the frontal and supra-occipital bones, and a decrease in the # of metatarsal bones.

Observation	Control	LD#	MD	HD
incomplete ossification of frontal bone	11 (4%)	10 (3.5%)	27* (9.8%)	13 (6%)
incomplete ossification of supra-occipital bone	3 (1%)	4 (1.4%)	13* (4.7%)	7 (3%)
one rudimentary 13th rib	0 (0%)	4 (1.4%)	5* (1.8%)	1 (0.5%)
reduced number of metatarsal bones	24 (8.7%)	28 (9.7%)	72** (26%)	41 (19%)

*p<.05 **p< 01 #Doses are theoretical

SUMMARY OF REPRODUCTIVE STUDIES

Study	Species Strain	n	Dose (mg/kg)	Route	Duration of Treatment
Segment I: ♂ ♀	Wistar Rat	24/sex/grp	0, 0.31, 1.25, 5	diet	♀: 2 wks prior to mating - Day 8 of gestation. ♂: 60 Days prior to mating & throughout the mating period.
Segment I: ♂	Wistar rat	24/grp	0, 0.16, 0.63, 2.5	gavage	60 Days prior to mating & throughout the mating period.
Segment I: ♀	Wistar rat	24/grp	0, 0.16, 0.63, 2.5	gavage	14 Days prior to mating - Day 8 of gestation.
Segment II	Sprague Dawley rat	24/grp	0, 0.63, 2.5, 10	gavage	Day 6 - Day 16 of gestation
Segment II	Sprague Dawley rat	24/grp	0, 0.63, 2.5, 10	gavage	Day 6 - Day 16 of gestation
Segment II, F_1 generation	Wistar rat	36/grp, 24/grp sacrificed Day 22 of pregnancy 12/grp followed through lactation & weaning	0, 0.63, 2.5, 10	gavage	Day 8 - Day 18 of gestation
Segment II	New Zealand White rabbit	15/grp (9-12 pregnant does/grp)	0, 0.31, 1.25, 5.0	gavage	Day 6 - Day 18 of gestation
Segment III	Wistar rat	24/grp	0, 0.31, 1.25, 5.0	diet	Day 16 of gestation - Day 21 of lactation
Segment III, F_1 generation	Wistar rat	24/grp	0, 0.31, 0.63, 2.5	gavage	Day 18 of gestation through Day 21 of lactation
Multigeneration study F_0 ♂ and ♀ dosed	Wistar rat	24/sex/grp	0, 0.16, 0.63, 2.5	diet	♂: 60 days prior to mating & throughout the mating period. ♀: 14 Days prior to, during mating, & throughout mating & lactation.

Summary of Sl al Observations

STUDY	SPECIES	DOSE (mg/kg)	OBSERVATION	C	LD	MD	HD	PARENT STATUS
Segment I ♂ and ♀ dosed	rat	0, 0.31, 1.25, 5	wavy ribs	7/268[1] (2.6)	7/210 (3.3)	8/156 (5%)	8/61 (13%)	♀: Transient ↓ BW gain HDF (>10%) ♂: dose-dep ↓ BW gain (5-21%)
Segment I ♂ dosed	rat	0, 0.16, 0.63, 2.5	wavy ribs	11/227 (4.8)	11/240 (4.6)	13/224 (5.8)	26/282 (9.2)	♂: ↓ BW at HD (9%)
Segment II	rat	0, 0.63, 2.5, 10	missing phalanges	6/225 (2.7)	8/247 (3.2)	13/254 (5.1)	17/225 (7.6)	ptosis, ↓ BW gain HDF (28%)
Segment II, F1 generation	rat	0, 0.63, 2.5, 10	split center of thoracic vertebra(e)	0/250 (0)	1/236 (0.4)	1/266 (0.4)	3/258 (1%)	sedation: slight 24/24 LDF moderate 24/24 MDF severe 24/24 HDF
			rudimentary 14th pair of ribs	0/250 (0)	1/236 (0.4)	5/266* (1.9)	4/258 (1.6)	
			one rudimentary 14th rib	0/250 (0)	1/236 (0.4)	8/266* (3%)	8/258* (3%)	
			asymmetrical sterum bone	0/250 (0)	0/236 (0)	5/266* (1.9)	4/258 (1.6)	
			reduced number of metatarsal bone	18/250 (7.2)	19/236 (8.0)	18/266 (6.8)	48/258* (19.6)	
Segment II	rabbit	0, 0.31, 1.25, 5	13th extra rib	21/85 (25)	14/65 (21)	40/102 (39)	44/73* (60)	3 HDF died; absolute loss of BW (x=100g) in HDF
Segment III, F_1 generation, F_0 ♀ dosed	rat		F_2 fetuses: rudimentary 13th pair of ribs	1/128 (0.8)	1/142 (0.7)	1/109 (0.9)	10/114 (8.8)	F_1 exposed in utero and in milk. No drug-related skeletal variations observed in F_1 pups.
Multigeneration study ♂ and ♀ dosed	rat	0, 0.16, 0.63, 2.5	F_2 fetuses: incomplete ossification frontal bone(s)	11/277 (4)	10/288 (3.5)	27/277* (9.8)	13/217 (6)	F_1 exposed in utero, in milk, and possibly in diet. No drug-related skeletal variations observed in F_1 pups.
			interparietal bone(s)	19/277 (6.9)	14/288 (5)	39/277 (14)	28/217 (13)	
			parietal bone(s)	27/277 (10)	29/288 (10)	50/277 (18)	29/217 (13)	
			reduced number of metatarsal bones	24/277 (8.7)	28/288 (9.7)	72/277** (26)	41/217 (19)	

[1] # of affect fetuses/total # of fetuses (%) * $p \leq .05$ ** $p < .01$

HISTORICAL CONTROL DATA

Observation	Species/Strain	Studies	Total	%
wavy ribs	Wistar rat	3/67 2/144 1/61 14/130 7/134 4/139 19/146 8/141 11/137 13/130	85/1355	6.3%
missing phalanges	Sprague Dawley rat	6/116 19/145	25/261	9.6%
one rudimentary 14th rib	Wistar rat	2/67 1/144 3/61 1/139 5/146 8/141	20/1355	1.5%
rudimentary 14th pair of ribs	Wistar rat	1/144 1/61 2/146 6/141 1/137	11/1355	0.81%
asymmetric sterum bone	Wistar rat	4/67 4/144 1/61 2/141 2/137	13/1355	0.96%
reduced # of metatarsal bones	Wistar rat	18/130 11/67 11/144 9/61 1/134 20/146 19/141 16/137	105/1355	7.8%
13th extra rib	New Zealand White rabbit	4/76 9/93 4/96 8/102 4/75 12/127 13/151 4/113 5/124	63/1243	5.1%

MUTAGENICITY

A. **Ames reverse mutation test: with and without metabolic activation.**

A pilot study was conducted to assess mutagenicity of risperidone using the Salmonella histidine reverse mutation assay, with and without metabolic activator (Aroclor 1254-induced rat liver microsomes, S9). The strains examined were TA1535, TA97, TA98, and TA100. Positive controls were 2-nitrofluorene, sodium azide, and 2-aminoanthracene. Risperidone was tested at 7 doses (500-2000 µg/plate). At the highest dose, risperidone was not cytotoxic; however, this dose was the upper limit of solubility. There was no increase in the number of reverse mutations in any of the strains tested at any dose of risperidone.

B. **Ames Salmonella/Microsomal Activation Test - Risperidone (50-5000 µg/plate) with or without metabolic activator (Aroclor-induced rat liver microsomes) had no effect on the number of revertant colonies in 5 Salmonella strains. The positive controls were 2-nitrofluorene, sodium azide and 2-aminoanthracene.**

C. **Escherichia coli gene reverse mutation test (Ames test): incubation with or without rat liver metabolic activation system.**

Risperidone was tested at 7 concentrations (25-2500 µg/plate) to assess mutagenicity using E. coli strain WP_2 uvrA, with and without metabolic activator (Aroclor-induced rat liver microsomes, S9). 2-Aminoauthracene and 4-nitroquinoline-N-oxide were used as positive controls. There was no dose-related increase in reverse mutations with risperidone; however, in two separate tests (without S9), reverse mutations were increased 1.5 fold over control at 25 µg/plate risperidone.

D. **Evaluation of the ability of R64766 to induce chromosome aberrations in cultured peripheral human lymphocytes.**

Risperidone was tested at 3 concentrations µg/plate) in the absence and at 3 concentrations µg/plate) in the presence of S9 (Aroclor-induced rat liver microsomes). These concentrations were determined from tests of inhibition of the mitotic index. Apparently, metabolic conversion of risperidone results in diminished cytotoxicity. Mitomycin C and cyclophosphamide were used as positive controls. No evidence of chromosomal aberrations was noted in human lymphocyte cultures exposed to risperidone (with and without metabolic activation) up to the highest concentrations tested.

E. **Chromosomal aberration test of risperidone on CHL cells in vitro.**

Chinese hamster lung fibroblasts were used to assess mutagenicity of risperidone with and without metabolic activator (S9, rat liver microsomes induced with pentobarbital and 5,6-benzoflavone). Preliminary cytotoxicty screening determined the IC_{50} for cell growth inhibition of risperidone to be 0.09 mM without S9, and 0.49 mM with S9. Mutagenicity was assessed at risperidone concentrations cf mM and mM (4 concentrations under each concentration). There was no evidence of risperidone-induced chromosomal aberrations.

F. **Evaluation of the mutagenic activity of risperidone in an <u>in vitro</u> mammalian cell gene mutation test with L5178Y mouse lymphoma cells (with independent repeat).**

Mutagenicity of risperidone was tested at concentrations of μg/ml, with and without metabolic activator (S9, rat liver microsomes, Aroclor-induced). Positive controls were ethylmethanesulphonate and dimethylnitrosamine. There was no evidence of increased mutation frequency with risperidone.

G. **Evaluation of DNS repair inducing ability of risperidone in a primary culture of rat hepatocytes (with independent repeat).**

DNA repair inducing ability of risperidone was tested at concentrations of μg/ml . At the HD, cell viability was reduced by 76%. Positive controls used were 4-nitroquinolinoxide and 7, 12-dimethylbenzathracene. There was no evidence that risperidone induced DNA repair at the concentrations tested, either with or without metabolic activity (however, it is unclear which data tables represent results with and without S9 mix).

H. **Micronucleus Test in Mice - Male and female mice dosed with 2.5-40 mg/kg i.g. risperidone displayed no structural chromosome aberrations in bone marrow erythrocytes 30 hr later. The positive control was cyclophosphamide.**

I. **Sex-Linked Recessive Lethal Test in Drosophila Melanogaster - Risperidone (250 and 750 ppm) was fed to male fruit flies for 3 days followed by mating to females. F_1 females were then pair-mated to siblings and the F_2 progeny were examined for recessive lethal mutations. None of these type mutations were detected in any stages of the Drosophila male germ cells. The positive control was diethylnitrosamine.**

CARCINOGENICITY

1. **Oral toxicity study in Swiss mice.**

This study was the dose-ranging study for the mouse 18-mo carcinogenicity study.

SPF albino Swiss mice (10/sex/grp) were dosed orally (in diet) for 3 mo at intended doses of 1.25, 5, and 20 mg/kg (corresponding to 0.63, 2.5, and 10 mg/100 g diet). Clinical observations were made daily. Body weight and food consumption were measured weekly. Ophthalmoscopy, hematology, and clinical chemistry parameters were tested at the end of the study. At necropsy, organ weights (relative and absolute) were recorded and gross pathology was assessed.

Results

Mortality: There were no **unscheduled deaths**.

Clinical observations: The only **clinical sign** observed was food wastage. In males, food wastage was noted in control (1/10) and in LD and MD groups (3/10 in each group). In females, food wastage was noted in all groups (3/10 control, 5/10 LD, 6/10 MD, and 1/10 HD).

Ophthalmology: There were no drug-related **ocular abnormalities** according to the sponsor (no data presented)

Body weight and food consumption: **Body weight** was only affected in females. In males, there was a transient decrease in body weight (compared to control) at wk 1 in HDM. In females, body weight was elevated above control levels at all doses. At the LD, body weight was increased by ≈10% above controls at Wk 10 and 12. At the MD, increased body weight was evident from Wk 8 on (7-16% above controls). At the HD, body weight was 6-13% higher than control at Wks 9, 11, and 13. **Body weight gain** was reduced at Wks 1 and 2 in HDM (50-100%), but increased at Wks 6, 11, and 13 in MDM (27-30%). In females, body weight gain was elevated (17-57%) from Wk 6-7 on at MD and HD and at Wks 6, 8-10, and 12-13 at the LD.

Food consumption could not accurately be measured because of food wastage in most groups.

Actual dose could not be determined because of food wastage. However, the sponsor stated that actual doses must have been close to the intended doses, and perhaps somewhat higher in females. Since no food wastage was noted in HDM, the actual dose may have been close to the intended dose for that group (calculated dose = 20.1 mg/kg in this group).

Hematology: There were no drug-related effects on **hematology** paramenters in females. In males, there was a small, but non-dose related increase in MCV (2.3-4.8%). In HDM, there were increases in MCHgb (4%) and segmented neutrophils (80%), and a decrease in lymphocytes (8%). The values for segmented neutrophils and lymphocytes were outside the range of historical controls.

Clinical chemistry: For **clinical chemistry** parameters in males, decreases noted in LDM [ALT (20%)], MDM [K (16%), BUN (18%), AST (32%)], and HDM [inorganic phosphate (16%), albumin (7%), and creatinine (20%)] were within the range of historical control. In HDM, decreases in total protein (6%) and phospholipids (14%) were outside the range of historical controls. There were no clear dose-related findings in males, although some effects were observed only in HDM.

In females, there was a dose-related reduction in glucose (LD: 15%, MD: 20%, HD: 25%), all values falling below historical control levels. Non-dose related findings included elevated cholesterol and phospholipid at all doses (34-43% and 24-29%, respectively), and decreased AlkPhos in HDF (35%); however, levels fell within the range of historical control. In MDF, AlkPhos was reduced by 46%, which fell below the level of historical control.

Organ/tissue weights: Organ weights were affected in both males and females. In HDM, there was an increase in relative and absolute spleen weight (18-19%) and an increase in absolute weight of pancreas (15%). Increased kidney weight (relative and absolute) was elevated at all doses (15-23%). Absolute and relative adrenal weight was elevated at all doses (50-75% and 27-45%, respectively), although, values fell within the range of historical control. There were no clear dose-related findings.

In females, absolute liver weight was increased at all doses (12-23%). Relative liver weight was elevated only at the LD (11%). Relative heart weight was decreased at the MD (9%), while elevated pancreas [absolute (22%) and relative (10%)] and thymus weight [absolute (27%)] was noted at the HD. Relative brain weight was decreased (12-13%) at the MD and HD, but absolute brain weight remained unchanged. Altered weight of spleen [relative (9%), HD], adrenals [absolute (9%, MD) and relative (19-24%, all doses)], kidney [absolute (12-14%) at all doses], and gonads [absolute (24-29%) and relative (32-35%) at all doses] were within historical control values.

Gross pathology: There were no drug-related **gross pathology** findings in males. In females, there was a dose-related stimulation of the mammary gland (1/10 control, 6/10 LD, 7/10 MD, 10/10 HD). Swollen pituitary gland was noted in 0/10 control, 2/10 LDF, 3/10 MDF, and 3/10 HDF. Pale liver was detected in 0/10 control, 2/10 LDF, 1/10 MDF, and 1/10 HDF.

Histopathology: No histopathology was performed. Also, there was no analysis of plasma drug levels to confirm dosing.

2. Mouse carcinogenicity study report

Methods

Animals: SPF Swiss mice were obtained from Charles River Labs (France). All mice (50/sex/grp) were <6 wks old at start of study.

Drug Preparation and Dose: Risperidone was administered orally in the diet at doses of **0, 0.63, 2.5, and 10 mg/kg**. Doses were based primarily upon the results of the dose range-finding study (No. 1926). Fresh diet was mixed at least each month.

Stability analysis was conducted using two separate extraction techniques followed by uv spectroscopy and/or HPLC. Originally, diet mix samples were assayed for risperidone after initial extraction using dichloromethane followed by uv specroscopy. Data indicated a risperidone concentration of % of the intended concentration. Data from the mice dose range-finding study, using the same extraction and detection procedure, indicated a recovery of 92-100%. The method was then changed to detection with HPLC to increase the specificity of analysis. Following this change, recovery fell to 51.9-80.4%. According to the sponsor, modification of the extraction procedure (substitution of 0.1% N HCl for dichloromethane) increased recovery to 97.5-102.9% in one test and to 91.1-116.7% in another (during a different study). The sponsor concluded that the low recovery noted

previously with the old extraction technique and uv spectroscopy was due, not to a low concentration of drug in the diet, but to incomplete recovery. This does not, however, explain why recovery was close to 100% using the old extraction procedure and uv spectroscopy. It is also troublesome that the new extraction procedure and HPLC detection results in recovery >100%. These stability data do not, therefore, provide a confident estimate of drug concentration in the diet mixtures.

Observations:

Behavior and appearance: at least once per day.
Record of palpable masses: conducted weekly. Time of appearance, location of mass, and dimensions of the mass were recorded.
Body weight: recorded weekly for the first 12 mo, then monthly (4 wks) thereafter.
Food consumption: recorded weekly for the first 12 mo, then monthly (4 wks) thereafter.
Water consumption: not accurately monitored.
Hematology: analyzed at 12 mo and at terminal sacrifice. Tests included hct, hgb, rbc, wbc, thrombocyte count, MCV, MCH, MChgb.
Clinical chemistry: analyzed at terminal sacrifice. Tests included: Na, K, Cl, Ca, Pi, total protein, albumin, haptoglobin, glucose, cholesterol, triglycerides, phospholipids, BUN creatinine, total bilirubin, AlkPhos, AST, ALT, cholinesterase.
Postmortum studies: organ weights (adrenals, brain, heart, kidneys, liver, lungs, pancreas, ovaries, spleen, testes, thymus) for terminal sacrifices and gross pathology for all animals. Histopathology for all animals for the following organs: adrenals, kidneys, liver and gall bladder, lungs, mammary gland, overies, pancreas, pituitary gland, mesenteric lymph nodes, salivary glands, spleen, testes with epididymes, thymus, uterus, vagina, and any organ suspect for neoplasm. Histopathology for all controls and HD animals: bone with bone marrow, brain, esophagus, heart, seminal vesicles, stomach, thyroids, trachea, urinary bladder.

Results

Mortality: There were no drug-related effects on mortality (or moribund sacrifice).

Mortality rates (%)

Dose (mg/kg)	Males	Females
0	46%	52%
0.63	32%	50%
2.5	48%	64%
10	50%	66%

Mortality for historical controls was 21.2-22.2% for males and 28.6-30.1% for females (percentages interpolated from tables provided by sponsor), considerably less than the percentages in the current study for both males and females. Therefore, spontaneous tumor incidences in the historical controls may be higher by virtue of decreased mortality.

Clinical observations. The most common clinical signs in both males and females were "bad" condition and food wastage. In males, there were no clear drug-related findings. Food wastage was increased in the LD group (43/50 vs 25/50 in LD and control, respectively) in males. In females, there was a high incidence of food wastage in all groups (27-37/50). An increased incidence of abdominal distension was noted in HDM (3/50 vs 3/50 in HD and control, respectively). There was a non-significant increase in the incidence of subcutaneous mass at the

HD (4/50 control, 3/50 LD, 3/50 MD, and 9/50 HD). In females, there was an increased incidence of subcutaneous mass at all doses (1/50 control, 8/50 LD, 17/50 MD, and 16/50 HD).

Body weight: In males, body weight was decreas ' compared to controls during the first 4-5 wks of the study at all doses (3-6%). There was a tendency for body weight to be elevated (5-7%) at the LD and MD during weeks 41-60; however, body weight was similar among groups at the end of the study.

In females, body weight was 4-18% higher than control at all doses throughout the study.

Food consumption: Food wastage precluded accurate analysis of food consumption. Overall, however, the data suggest that food co isumption was increased (4-15%) in dosed males and females compared to control throughout most of the study; therefore, food consumption was probably similar or slightly higher (especially in females) in dosed animals as compared to control.

Test article intake: Accuracy of calculated dose data are compromised by food wastage and problems of quantitation of risperidone in the diet mixture. Overall, the doses, calculated from body weight and food consumption data, were 0.697, 2.83, and 10.5 mg/kg for males, and 0.673, 2.68, and 10.7 mg/kg for females.

Hematology: There were no clear drug-related findings in males. At 1 yr, there was a decrease in wbc at the MD and HD (16 and 25%, respectively) and a small, but significant, increase in MCHgb (pg) of 1-3% at all doses. Leucocytosis was noted in 6 control, 7 LD, 3 MD, and 3 HD males. Of these, 1 LDM had a confirmed tumor of the hematopoietic system. At the end of the study, rbcs were decreased by 2% at the LD and small, but significant, increases in MCV (2% at all doses) and HCHgb (pg) (<1% at LD). Hematology results were similar among non-terminal deaths.

In females, the following were noted at 1 yr: decreased Hct (9%) at HD, decreased Hgb at MD (5%) and HD (9%), decreased rbc at MD (7%) and HD (11%), increased thrombocytes (9) at MD, and increased MCV and MCHgb (2.3%) at HD. Leucocytosis was noted in 2 control, 5 LD, 1 MD, and 3 HD females. Of these, 2 had confirmed tumors of the hematopoietic system. At the end of the study, Hct was decreased at all doses (6% LD, 16% MD, 16% HD), Hgb was decreased at MD (14%) and HD (13%), rbc was decreased at all doses (9% LD, 18% MD, 15% HD), thrombocytes were increased by 40-41% at LD and MD, and MCHgb was increased by 3% at LD and MD. Hematology results were similar among non-terminal deaths.

Clinical chemistry: In males, the following were noted: increased Na (1%) at MD and HD, decreased glucose at MD (13%) and HD (26%), a dose-related increase in cholinesterase (10% LD, 28% MD, 48% HD), tendency for haptoglobin to be increased (6% LD, 75% MD, 194% HD).

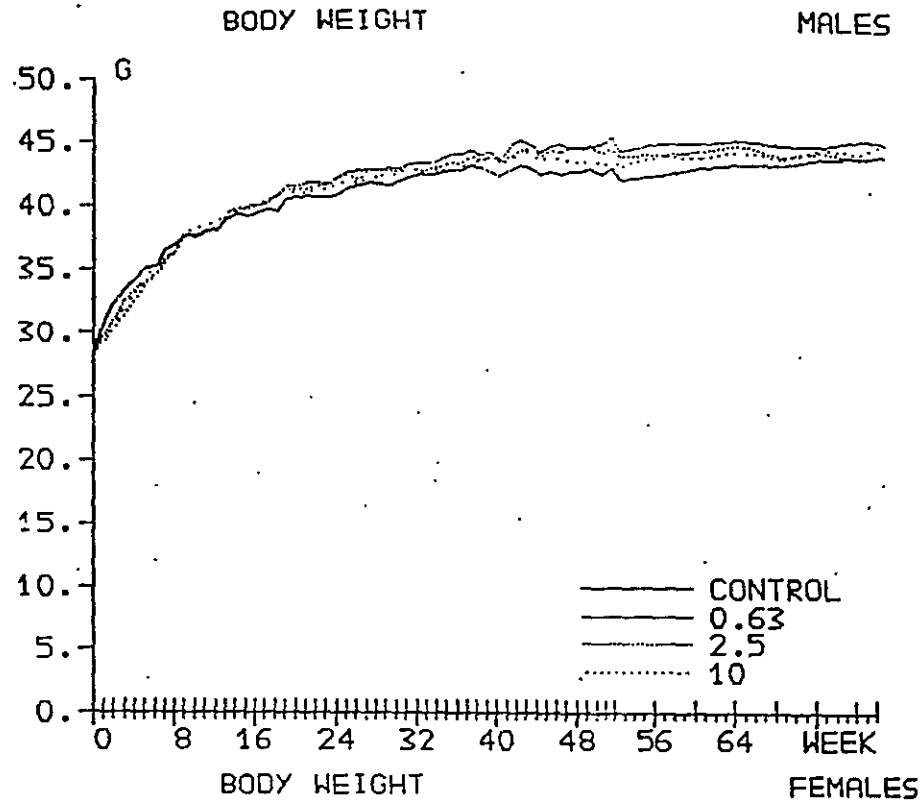
In females, the following were noted: increased Ca at MD (7%) and HD (10%), increased total protein at MD (6%) and HD (20%), increased albumin at HD (9%), increased haptoglobin at MD (6.8 fold) and HD (14-fold), a dose-related decrease in glucose (10% LD, 18% MD, 21% HD), dose-related increase in cholesterol [23% LD, 41% MD (not sign.), 61% HD), decreased TG at HD (36%), a dose-related increase in phospholipids [21% LD, 22% MD (not sign.), 52% HD], decreased total bilirubin at the HD (9%), decreased alkphos at LD (51%), MD (74%), and HD (73%), increased cholinesterase at HD (24%).

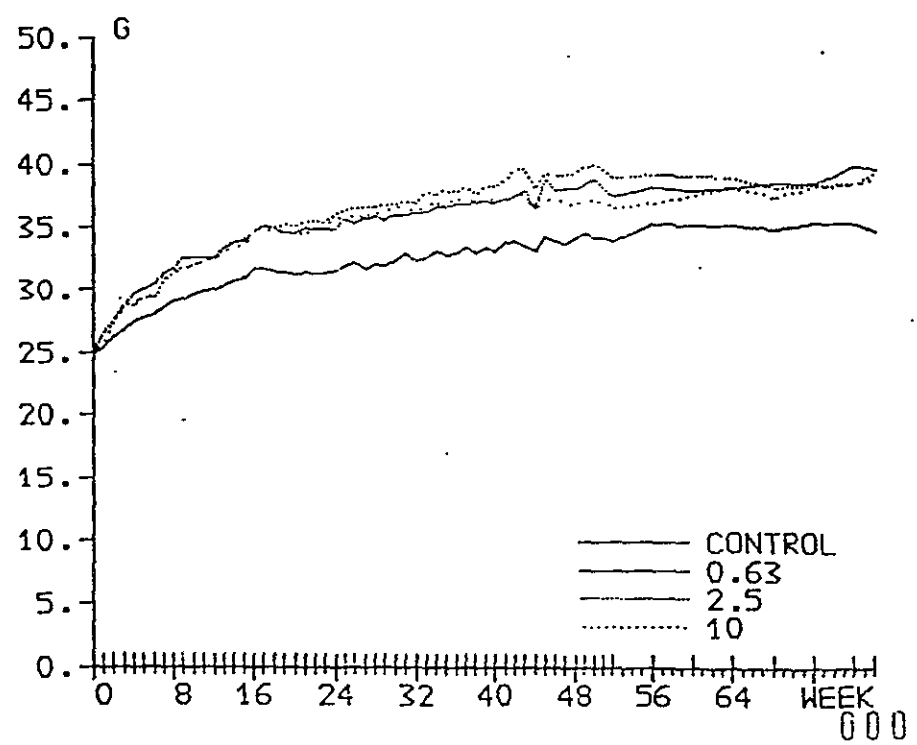
Organ weights: In males, the following were noted: increase in absolute lung weight at HD (8%), increase in absolute and relative spleen weight at MD (12-13%) and HD (30-35%), increased absolute and relative liver weight at HD (22-24%), increased absolute (7% LD, 12% MD, and 18%

Department of toxicology

EXPERIMENT: 1927
Carcinogenicity study
R 64766 - FOOD - MICE - 18 MONTH

| BODY WEIGHT
| Mean values per dosage group in g |





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HD) and relative (12% MD and 15% HD) weight of heart, increased absolute kidney weight at LD (8%) and HD (16%) and a dose-related increase in relative kidney weight (6% LD, 7% MD, and 13% HD), and a decrease in relative gonad weight at MD (9%) and HD (12%).

In females, the following were noted: increase in absolute lung weight at LD (10%) and MD (15%), increased absolute spleen weight at MD (27%) and HD (29%), increased absolute (31% LD, 42% MD, 31% HD) and relative (14% LD, 26% MD, 18% HD) liver weight, a dose-related increase in absolute heart weight (10% LD, 12% MD, 15% HD), increased absolute weight of pancreas at LD (17%) and of kidney at MD (12%), decreased relative weight of brain at LD (12%) and MD (13%), decreased absolute (10% MD, 20% HD) and a dose-related decrease in relative (18% LD, 22% MD, 25% HD) adrenal weight, decreased absolute gonad weight at MD (28%) and HD (33%), and a dose-related decrease in relative gonad weight (19% LD, 38% MD, 40% HD). No data were presented for animals that died or that were sacrificed moribund.
Gross pathology: Drug-related macroscopic changes were noted in kidney (swollen), testis (small), mammary gland (stimulation, tissue mass), pituitary gland (swollen, tissue mass), spleen (swollen), and seminal vesicles (dilated) and are summarized in the following table (from sponsor's submission). In addition, there were drug-related decreases in incidence of ovarian (cyst), uterus (swollen, cystic), and mammary gland (edematous) changes. No drug-related macroscopic findings were noted in LDM.

Additional observations include a tendency for increased incidence of liver mass (0/50 control, 3/50 LD, 3/50 MD, 4/50 HD), brown seminal vesicles (0/50 control, 0/50 LD, 2/50 MD, 5/50 HD), swollen spleen (8/50 control, 9/50 LD, 10/50 MD, 12/50 HD), and stomach wall thickening (1/50 control, 7/50 LD, 3/50 MD, 5/50 HD) in males. In females, there was a tendency for increased anemia (10/50 control, 14/50 LD, 15/50 MD, 15/50 HD, eye and adnexal mass (0/50 control, 0/50 LD, 2/50 MD, 2/50 HD), jaw, tissue mass in 2/50 HD, and lung nodule (4/50 control, 10/50 LD, 7/50 MD, 6/50 HD). None of these observations were statistically significant or dose-related.

Histopathology:

Non-tumorous changes (summary data are presented in sponsor's table):

Males: Histopathological changes were noted in pancreas, pituitary gland, seminal vesicle, and spleen. Hyperplasia of the pituitary gland was noted at the HD (8/47) and hyperplasia of the spleen (red pulp) was noted at the MD (16/48) and HD (20/49). Incidence of "large islets" was increased at the HD (28/50). It is unclear whether this refers to hypertrophy of the islet cells or not. There appeared to be a dose-related impairment of seminal vesicles function (accumulated contents, dilated lumen, inspissated material).

Females: Histopathological changes were noted primarily in mammary gland and indicated marked stimulation of secretion and growth. Fibrosis, focal hyperplasia, secretion, glandular development, and metaplasia were noted at all doses. Reduced glandular development of the uterus and hyperplasia (diffuse and focal) of the pituitary gland were noted at all doses. Vaginal changes indicative of disruption of the estrus cycle were noted, e.g., increased anestrus and decreased estrus at all doses.

Tumorous changes:

Males: There were no drug-related increases in tumors in males. The incidence of some tumors in males was considerably lower than in historical controls, e.g., hepatic neoplastic nodule, neoplasia, and carcinomas. The incidence of malignant primary lung tumors was lower than in

historical controls, whereas, the incidence of benign primary lung tumors was similar to that in historical controls. The differences may be due, in part, to the decreased mortality rate in the historical controls compared to the current study.

Females: There were drug-related increases in mammary gland neoplasms (specifically, adenocarcinomas) and pituitary gland adenomas.

Mammary gland neoplasms:

	Control	LD	MD	HD
adenocarcinoma	0/50	7/50*	18/47**	17/48**
carcinosarcoma	0/50	0/50	1/47	0/48
fibroadenoma	0/50	0/50	1/47	0/48
sarcoma	0/50	0/50	1/47	0/48
Total	0/50	7/50*	18/47**	17/48**

*p<0.01, **p<0.001,

Pituitary gland neoplasms:

	Control	LD	MD	HD
adenoma	1/48	2/46	13/45**	21/48**

**p<0.001

Primary lung tumors in female mice:

	Control	LD	MD	HD
Benign	2/50	5/50	4/50	6/50
Malignant	1/50	1/50	3/50	1/50
Total	3/50	6/50	7/50	7/50*

*asymptotic p-values, Peto's trend statistic (no correction for continuity)

Incidence of benign, malignant, and total primary lung tumors in the historical controls (7 studies):

	#1308	#1548	#1649	#1580c	#1580d	#1987	#1881
Benign	7/50	4/50	12/50	9/50	6/50	4/49	8/50
Malignant	5/50	3/50	4/50	3/50	7/50	1/49	3/50
Total	12/50	7/50	16/50	12/50	13/50	5/49	11/50

3. **Carcinogenicity study in Wistar rats.**

Methods

Animals: SPF Wistar rat were obtained from Charles River Germany. All rats (50/sex/grp) were <6 wks old at the start of the study.

Drug Preparation and Dose: Risperidone was administered orally in the diet at doses of 0, 0.63, 2.5, and 10 mg/kg. The doses were chosen on the basis of cumulative information on risperidone toxicity in rats. The dietary concentration of risperidone was adapted to changes in body weight and food consumption.

Study duration: The study duration was 25 mo. when the mortality rate for control and LD animals was ≈50%.

Observations:

Behavior and appearance: all animals were observed daily.
Records of palpable masses: all animals were palpated weekly. Time of appearance, location and dimensions of palpable masses were recorded.
Mortality: rats sacrificed moribund or found dead were examined macroscopically, and, if possible, complete tissue samples were preserved.
Body weight: individual body weights were recorded weekly during the first 6 wks, and monthly thereafter, and at sacrifice.
Food consumption: individual food consumption records were recorded weekly during the first 6 wks and monthly thereafter.
Water consumption: monitored daily, but no records kept.
Hematology: the following hematology parameters were assayed in all animals at 12 and 18 mo of dosing, in all terminally sacrificed animals, and if possible, in animals found dead: hct, hgb, rbc, wbc, thrombocyte count, differential count (only if wbcs are elevated), MCV, MCH, and MCHC. The methology was changed from "Ortho methodology" tc "Sysmex methodology" at wk 55.
Clinical chemistry: the following clinical chemistry parameters were assayed in all terminally sacrificed animals: Na, K, Cl, Ca, Pi, total protein, albumin, haptoglobin, glucose, cholesterol, TG, PL, BUN, creatinine, total bilirubin, alkphos, AST, ALT, and cholinesterase.
Necropsy: terminal studies included organ/tissue weights (adrenals, brain, heart, kidneys, liver, lungs, pancreas, ovaries, spleen, testes, thymus, thyroid), gross pathology, and fixation of the following organs/tissues for histopathology:

for all animals: adrenals, kidneys, liver, lungs, mammary gland, ovaries, pancreas, pituitary gland, prostate, mesenteric lymph nodes, salivary glands, seminal vesicles (with coagulating gland), spleen, testes with epididymes, thymus, thyroids (with parathyroid), uterus, vagina, any organ/tissue suspect for neoplasm.

for controls and HD animals: bone (with bone marrow), brain, caecum, colon, duodenum, esophagus, eye, exorbital lacrimal gland, external ear (Zymbal gland), heart, ileum, jejunum, nasal turbinates, rectum skeletal muscle, spinal cord, stomach, trachea, urinary bladder.

On occasion, autolysis precluded examination of some tissue. In only one animal was histopathology not performed because of extensive autolysis.

Results

Mortality: Mortality was assessed at 24 mo (26 lunar months) and was 28% in males and females. Because of this rate of mortality, the study was extended for an additional month (25 mo; 28 lunar months). Calculated for the last 3-4 mo, the mortality rate was significantly higher at the MD and HD than in controls in males and was somethat, but not significantly, higher at the HD than in controls in females.

Overall, mortality was 54-62% higher in LD and MD males and 20% higher in HD females than in corresponding controls.

Mortality at 25 mo:

Group	Males	Females
control	48%	50%
LD	58%	42%
MD	78%	54%
HD	74%	60%

Clinical observations: In males, the only drug-related clinical signs were increased incidence of "bad condition" (26/50 vs 15/50) and swollen paws (6/50 vs 0/50) at the MD compared to controls. Subcutaneous mass was detected in 13/50 control, 19/50 LD, 20/50 MD, and 21/50 HD animals. A cutaneous mass was detected in 2/50 control, 6/50 LD, 4/50 MD, and 1/50 HD.

In females, the only findings were decreased incidence of alopecia (7/50 control, 2/50 LD, 1/50 MD, and 0/50 HD) and abdominal distension (6/50 control, 2/50 LD, 1/50 MD, and 0/50 HD) at all doses, but significant at the HD. Subcutaneous mass was detected in 20/50 control, 26/50 LD, 27/50 MD, and 21/50 HD. A cutaneous tissue mass was only detected in 1/50 HDF.

Body weight and food consumption:

Body weight

Males: In males, body weight was decreased at the MD and HD compared to controls throughout the study. In LDM, body weight was reduced by 4-5% compared to controls until wk 40 and by 4-11% from wk 80 to wk 111. At the end of the study, body weight was reduced by 11 (LDM), 14% (MDM), and 27% (HDM) Body weight gain data showed similar trends. Body weight gain was reduced by 16 (LDM), 20 (MDM), and 37% (HDM) at the end of the study.

Females: In females, body weight was elevated compared to controls by 5-15% in LDF throughout most of the study and by 2-6% in MDF until wk 56. From wk 76 on, body weight in MDF was reduced compared to controls by 12-14%. At the HD, body weight was reduced compared to controls, begining at wk 24 and continuing for the rest of the study. At the end of the study, body weight was similar to control levels at the LD and MD, but was 23% lower in HDF. Body weight gain data showed similar trends. Body weight gain was decreased only in HDF (35%) by the end of the study, that of the LDF and MDF being similar to control.

Food consumption

Males: In males, the only consistent observation was decreased food consumption in HDM through wk 76, and during wks 81-84 and 97-100.

Females: Food consumption was elevated in LDF through wk 49-52, and occasionally thereafter. There were sporadic changes in food consumption in MDF, but a consistent reduction in HDF throughout the study (5-18%).

Calculated dose: The calculated mean daily dose (range) was

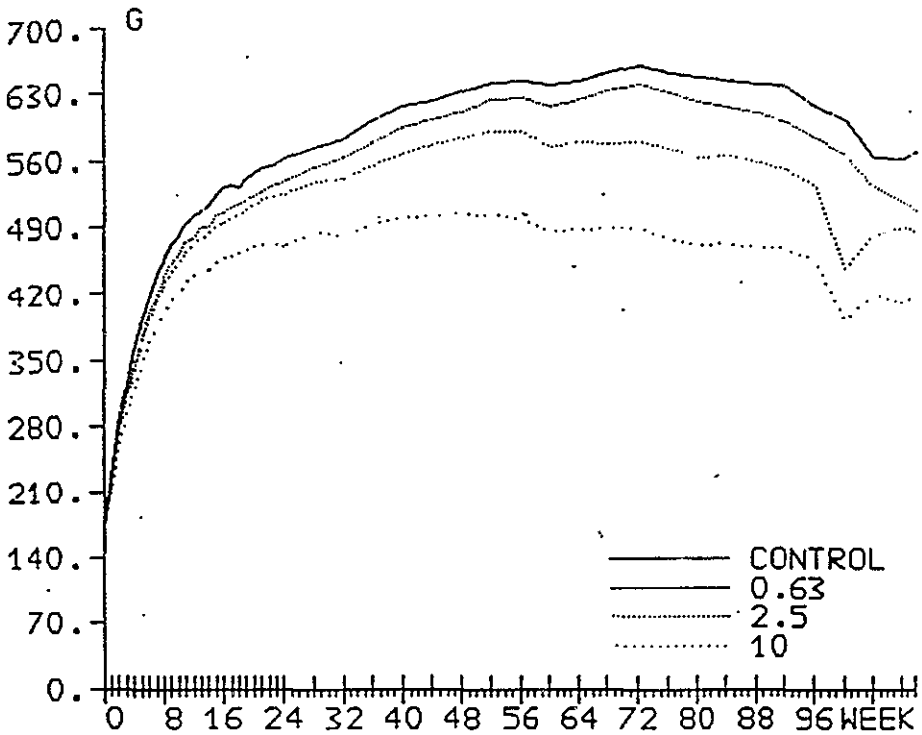
	Males	Females
LD	0.6 (0.479-0.775)	0.6 (0.514-0.806)
MD	2.5 (1.97-3.08)	2.4 (2.01-3.25)
HD	10.1 (7.65-12.3)	9.7 (7.67-12.4)

Department of Toxicology

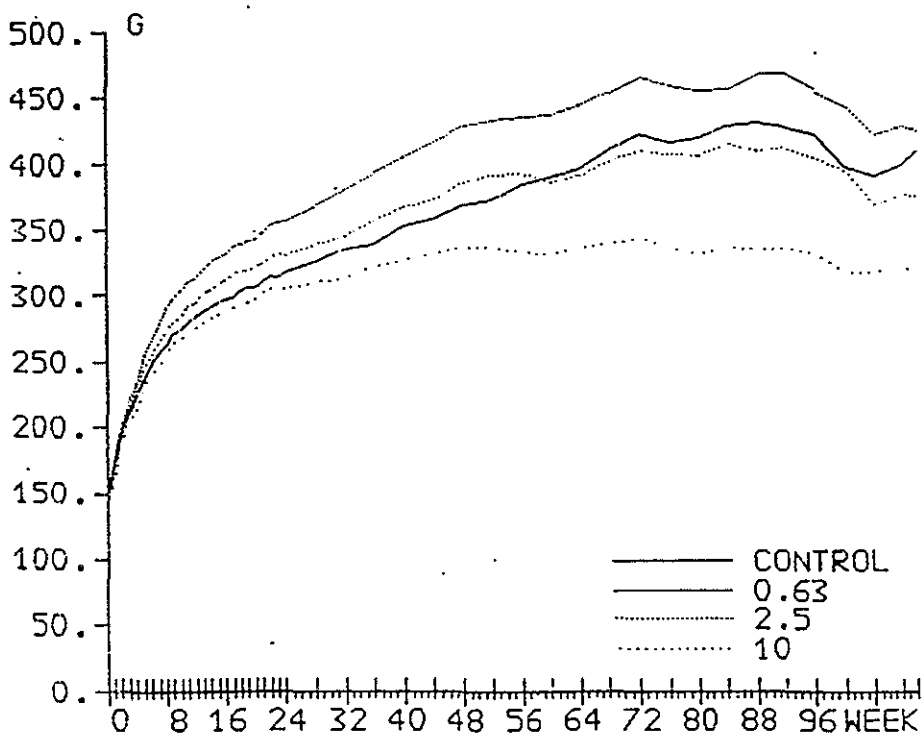
EXPERIMENT: 1928
Carcinogenicity study
R 64766 - FOOD - RAT - 24 MONTH

| BODY WEIGHT
| Mean values per dosage group in g

BODY WEIGHT MALES



BODY WEIGHT FEMALES



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Hematology: Hematology data were analyzed separately for terminally sacrificed (wks 54, 78, and 110) and animals sacrificed moribund.

Terminally sacrificed

Males: The only consistent changes were in MCV and MCH. Both parameters were increased at wk 54, 78, and 110. MCV was 2-6% and MCH was 2-7% higher in dosed than in control animals. Although there was some evidence of a dose-response effect at wk 54, by wk 110 the magnitude of the increase was similar for LD, MD, and HDM. Other significant findings were: (1) 2% increase in hct in MDM and HDM at wk 54, (2) 2-3% increase in hgb in MDM and HDM at wk 54, (3) decreased rbc at HD (5%) at wk 54, and at all doses (4% LD, 4% MD, 8% HD) at wk 78, (4) 8% decrease in wbc in HDM at wk 54, and (5) 13% increase in thrombocytes in MDM at wk 78.
Females: No consistent, dose-related changes were observed. Hct and hgb were reduced at all doses at wks 54 and 78 (2-5% for hct, 3-7% for hgb). Rbcs were reduced at wk 54 at all doses (3-6%), and at LD (3%) and HD (4%) at wk 78. Thrombocytes were elevated at all doses at wks 54 and 78 (4-8%). MCH and MCHC were slightly, but significantly, reduced at wk 54 in LDF and HDF (1-3%). MCV and MCHC were reduced in MDF at wk 78 by 1-2%. At wk 110, all values had normalized except for reduced hct in LDF (4%).

One female (sacrificed moribund at mo 19) had leucocytosis (wbc 33,500/mm^3) at wk 54. Recalculation of mean wbcs without the data for this female, did not change the results.
Sacrificed moribund

There were no differences among groups on any of the hematological parameters measured.
Clinical chemistry

Males: The following observations were made:

K: 12% decrease in MDM, HDM.
Cl: 2% decrease in LDM, 4% decrease in MDM.
Ca: 8% increase in LDM.
total protein: 7-9% increase at all doses.
albumin: 9% increase in HDM.
glucose: 18% decrease in HDM.
cholesterol: 52-62% increase in LDM, MDM.
TG: 122% increase in MDM (a 84% increase was noted in LDM, but this was not statistically significant.)
PI: 50-66% increase in LDM, MDM.
BUN: 20% decrease in MDM (a 74% increase was noted in LDM, but was not statistically significant.)
creatinine: 54% increase in LDM.
bilirubin: 45% decrease in MDM.
alkphos: 32-22% decrease in LDM and MDM.
AST: 21% decrease in LDM.
cholinesterase: 140, 175, and 188% increase in LDM, MDM, and HDM, respectively.

Except for albumin, alkphos, and AST data, all values were either above or below historical control values. However, there were no clear dose-related findings except for cholinesterase data.

Females: The following observations were made:

Cl: 1% decrease in LDF.
total protein: 6-4% increase in MDF and HDF.
albumin: 6-4% increase in MDF and HDF.
PI: 16% decrease in HDF.
BUN: 15-21% decrease in LDF and HDF.
bilirubin: 72% decrease in LDF.
AST: 36% decrease in MDF.

All values were within the range of historical control except for bilirubin.

Organ weights (terminally sacrificed animals only)

Males: At the HD, the absolute weight of lung (22%), spleen (24%), liver (20%), heart (11%), pancreas (10%), kidney (16%), thyroid (33%) and gonads (23%) were reduced. The absolute weight of pancreas was also reduced in LDM (13%) and that of thymus was also reduced in MDM (23%).

The following changes were noted in relative organ/tissue weight: elevated in lung (7% MD, 8% HD), liver (16% LD, 18% MD, 11% HD), heart (11% LD and MD, 22% HD), pancreas (24% HD), kidneys (34% LD, 19% MD, 16% HD), brain (13% LD, 15% MD, 58% HD) and reduced in thymus (14% HD). Both absolute and relative weight of adrenals were elevated at all doses (absolute: 35% LD, 42% MD, 18% HD; relative: 60% LD, 72% MD, 63% HD).

Females: At the HD, the absolute weight of lung (16%), spleen (22%), liver (23%), pancreas (14%), thymus (25%), and thyroid (38%) was reduced. The absolute weight of lung, pancreas, and thyroid was also reduced in MDF (10, 16, 24%, respectively). The absolute weight of heart, brain, and gonads were only reduced in MDF (6, 3, 15%, respectively).

The following changes were noted in relative organ/tissue weight: elevated in heart (18% HD), pancreas (8% HD), kidneys (5% MD, 20% HD), brain (23% HD), adrenals (32% HD), and gonads (11% HD), and reduced in thyroid (26% HD).

Gross pathology

The following drug-related findings were noted (sponsor's table):

Observation	Dosage group (mg/kg) 0	0.63	2.5	10
Males	X/N	X/N	X/N	X/N
Cachexia	12/50	19/50	24/50*	23/49*
Kidney: changed surface (rough)	10/50	20/50*	12/50	5/49
Kidney: swollen	8/50	20/50*	15/50	4/49
Mammary gland: stimulation	2/50	11/50*	25/50***	28/49***
Mammary gland: tissue mass	0/50	2/50	9/50**	14/49***
Mammary gland: tissue mass(friable)	0/50	0/50	4/50	7/49*
Pituitary gland: swollen	2/50	7/50	23/50***	25/49***
Seminal vesicle: dilated	0/50	0/50	0/50	8/49**
Testis: small	12/50	19/50	15/50	23/49*
Thymus: involution	8/50	11/50	18/50*	20/49*
Females				
Mammary gland: stimulation	41/50	50/50**	50/50**	49/50*
Pituitary gland: swollen	6/50	25/50***	19/50**	12/50
Uterus: swollen	7/50	0/50*	1/50	2/50

Statistics: test: *p<0.05, **p<0.01, ***p<0.001
X: number of positive animals

Histopathology

Nontumerous (summary data are presented in sponsor's table):

Males: Histopathological changes were noted in adrenal gland, epididymis, kidney, liver, mammary gland, pancreas, pituitary gland, prostate, seminal vesicle, spleen, and testes. Increased incidence of mineralization of kidney, mammary gland stimulation, diffuse hyperplasia of the pituitary gland, and subacute inflammation of the prostate were noted at all doses. Increased incidence of hypertrophy of the kidney at the LD [14/50; also elevated, but not statistically significant, at MD (12/50)] as compared to control (4/50) is consistent with the increased relative weight of kidney.

There were apparent decreases in the incidence of clear cell plaques in adrenal gland and liver, cystic kidney, focal hyperplasia of pancreas and testes, and prostatic changes (at the HD).

Females: Histopathological changes were noted primarily in kidney, mammary gland, lymph node, and pituitary gland. Increased incidences of diffuse hyperplasia and ectasia were noted in pituitary gland at LD and MD. Stimulation of the mammary gland was evident at all doses, although the incidence of glandular development was relatively high in controls (42/49). Focal hyperplasia of the mammary gland was increased only in MDF. Chronic disease of the kidney was less in MDF and HDF compared to controls; however, mineralization of the kidney was increased at all doses, but was significant only for LDF and MDF (19/50 control, 30/50 LD, 34/50 MD, 29/50 HD).

There were apparent decreases in the incidence of clear cell plaques in adrenal gland, fibrosis of heart (only control and HD examined), proliferation of ducts of liver, Sertoli-like cells of ovary (dose-related), focal hyperplasia of the pancreas (dose-related), and glandular development and pigmentation of the uterus (at LD).

Tumerous:

Males: There was an increase in the incidence of mammary gland adenocarcinoma in HDM, and in that of total mammary gland neoplasms in MDM and HDM. Mammary carcinomas were detected only in 2 HDM. There was a positive dose-related trend in the incidence of pancreatic adenomas and soft tissue fatal, but not incidental, fibrosarcomas.

Females: The incidence of mammary gland adenocarcinomas was elevated at all doses, but there was no dose-related response. There was, however, no drug-related increase in the total incidence of mammary gland neoplasms. Neoplasms of the genital tract (cervix, uterus, vagina) were decreased at all doses, consistent with a prolactin-mediated effect. The incidence of non-fatal, but not fatal, tumors of the hematopoietic system was somewhat increased at all doses compared to concurrent controls (3-4/48-49 vs 0/48), and historical controls (0-1/50, classified only as "tumor")

NON-TUMUROUS CHANGES: ♂ MICE

Organ/Tissue	Observation	Dosage Group (mg/kg)			
		Control	LD	MD	HD
Coagulating gland	dilated lumen	1/40	2/4*	4/7*	18/38***
Lung	focal hyperplasia	13/50	13/50	7/50	4/50*
Lymph node(s), mesenteric	diffuse atrophy	9/46	1/44*	5/39	4/41
Pancreas	inflammatory cell infiltration large islets	3/50 12/50	12/50* 16/50	5/48 15/48	8/50 28/50**
Pituitary gland	diffuse hyperplasia ectasia	1/45 0/45	0/40 0/40	0/45 0/45	8/47* 6/47*
Seminal vesicle	accumulated content dilated lumen inspissated material	2/48 1/48 3/48	3/5* 2/5* 1/5*	4/14* 9/14* 4/14*	24/50*** 13/50** 14/50*
Spleen	hyperplasia of the red pulp myelopoiesis	7/50 10/50	11/50 8/50	16/48* 18/48	20/49** 20/49*
Urinary bladd	hyalinization	26/49	1/3*	0/2*	15/48*

Significance com, uted by test (two tailed probability): * p> =.05 ** p> =.01 *** p > =.001

* No statistical analysis conducted. Statistical analysis is considered to be misleading because of the low number of samples examined histologically and the biased sampling at this level (only when neoplasia was suspended upon gross examination).

NON-TUMUR[illegible]S CHANGES ♀ MICE

Organ/Tissue	Observation	Dosage Group (mg/kg)			
		Control	LD	MD	HD
Adrenal gland	extracapsular cortical tissue	11/49	3/49*	5/45	4/49
	pigmentation	16/49	26/49	24/45	28/49*
	spinal cell hyperplasia	46/49	43/49	29/45***	40/49
Brain	large vacuoles	12/50	--	--	2/49*
Kidney	chronic disease	2/50	6/50	13/50**	13/50**
Liver	Kupffer cell proliferation	5/50	9/50	15/50*	16/50*
	myelopoiesis	1/50	4/50	9/50*	9/50*
Lung	focal hyperplasia	17/50	11/50	6/50*	9/50*
Lymph node(s), mesenteric	erythronphagocytosis	4/47	12/45*	5/44	3/45
	histiocytosis	0/47	0/45	6/44*	0/45
	myelopoiesis	2/47	11/45*	9/44*	10/45*
	plasmocytosis	3/47	1/45	4/44	11/45*
Mammary gland	accumulated content	10/50	36/50***	44/47***	42/48***
	amyloidosis	11/50	5/50	2/47*	3/48
	fibrosis	2/50	28/50***	33/47***	35/48***
	focal hyperplasia	1/50	26/50***	32/47***	36/48***
	glandular development	20/50	47/50***	46/47***	47/48***
	inflammatory cell infiltration	8/50	31/50***	31/47***	38/48***
	inspissated material	1/50	22/50***	30/47***	21/48***
	metaplasia	1/50	13/50**	16/47***	25/48***
	secretion present	8/50	42/50***	43/47***	42/48***
Ovary	amyloidosis	17/49	7/50*	0/46***	1/49***
	diffuse atrophy	1/49	3/50	10/46**	6/49
Pituitary gland	diffuse hyperplasia	3/48	26/46***	39/45***	41/48***
	ectasia	2/48	9/46*	29/45***	30/48***
	focal hyperplasia	1/48	10/46**	19/45***	12/48**
Spleen	hyperplasia	9/50	17/50	26/50***	18/50
	myelopoiesis	8/50	13/50	25/50***	17/50
	polynuclear cells	5/50	13/50	23/50***	19/50**
Uterus	glandular development	41/50	14/50***	18/50***	18/50***
Vagina	anestrus	3/46	14/48**	20/45***	22/47***
	diestrus	7/46	17/48*	5/45	12/47
	estrus	6/46	0/48*	0/45*	0/47*
	metestrus	27/46	14/48**	18/45	12/47**
	mucified aspect	2/46	17/48***	6/45	14/47**

Significance computed by test (two tailed probability): * p > =.05 ** p > =.01 *** p > =.00

SUMMARY OF NEOPLASMS: ♀ MICE, 18 MONTH CARCINOGENICITY STUDY

ORGAN/TISSUE	OBSERVATION	C	LD	MD	HD
Mammary gland	adenocarcinoma	0/50	7/50**	18/47***	17/48***
	carcinosarcoma	0/50	0/50	1/47	0/48
	fibroadenoma	0/50	0/50	1/47	0/48
	sarcoma	0/50	0/50	1/47	0/48
	TOTAL	0/50	7/50**	18/47***	17/48***
Lung	Primary Tumor				
	Benign	2/50	5/50	4/50	6/50
	Malignant	1/50	1/50	3/50	1/50
	TOTAL	3/50	6/50	6/50	7/50
Pituitary gland	adenoma	1/48	2/46	13/45***	21/48***

(one-tailed): ** $p<0.01$, *** $p<0.001$

Peto's trend statistic (no correction for continuity), asymptotic p value: $p<0.05$ $p=0.0445$

NON-TUMUROUS CHANGES: ♂ RAT

Organ/Tissue	Observation	Dosage Group (mg/kg)			
		Control	LD	MD	HD
Adrenal gland	clear cell plaques	14/50	5/50*	2/50**	2/49**
	congestion	1/50	4/50	12/50**	10/49**
	ectasia	4/50	9/50	17/50**	21/49***
Epididymis	cellular debris	16/50	24/50	26/50	31/49**
Kidney	chronic disease	44/50	45/50	26/50	31/49**
	cystic	13/50	19/50	45/50	34/49*
	hypertrophy	4/50	14/50*	11/50	3/49*
	mineralization	4/50	18/50**	12/50	1/49
Liver	clear cell plaques	23/50	13/50	9/50**	3/49***
Mammary gland	accumulated content	2/50	8/48	13/50**	17/49***
	female aspect	5/50	16/48	31/50***	37/49***
Pancreas	focal hyperplasia	13/49	8/49	10/49	1/49**
	vasculopathy	1/49	10/49*	6/49	1/49
Pituitary gland	diffuse hyperplasia	1/50	12/50**	33/50***	38/49***
	ectasia	7/50	8/50	22/50**	23/49***
	focal hyperplasia	18/50	20/50	31/50*	28/49
Prostate	focal hyperplasia	8/50	3/49	3/50	1/49*
	inspissated material	7/50	1/49	1/50	0/49*
	mineralization	10/50	5/49	3/50	1/49*
	subacute inflammation	16/50	34/49***	38/50***	41/49***
Seminal vesicle	accumulated content	0/48	2/47	1/49	15/48***
	infiltrating granulocytes	0/48	2/47	2/49	6/48*
	inspissated material	0/48	6/47*	5/49	23/48***
Spleen	pigmentation	3/50	15/50**	14/50**	10/49
Testis	accumulated content	13/50	4/50*	8/50	14/49
	degenertion	28/50	32/50	31/50	44/49***
	endocrine hyperplasia	6/50	0/50*	2/50	3/49
	mineralization	14/50	10/50	20/50	32/49***
	vasculopathy	5/50	19/50**	17/50**	12/49

Significance computed by test (two tailed probability): * $p < .05$ ** $p < .01$ *** $p < .001$

NON-TUMUROUS CHANGES: ♀ RAT

Organ/Tissue	Observation	Dosage Group (mg/kg)			
		Control	LD	MD	HD
Adrenal gland	clear cell plaques	9/50	4/50	1/50*	0/50**
Heart	fibrosis	17/44	-	-	6/47**
Kidney	chronic disease mineralization	27/50 19/50	32/50 30/50*	16/50* 34/50**	13/50** 29/50
Liver	proliferation of ducts	31/50	23/50	21/50	16/50**
Lymph node(s), mesenteric	diffuse atrophy	1/50	4/49	10/50*	9/50*
Mammary gland	focal hyperplasia glandular development	7/47 42/49	11/50 50/50*	18/50* 50/50*	9/50 50/50*
Ovary	Sertoli-like cells	28/50	13/50**	8/50***	7/50***
Pancreas	focal hyperplasia	6/50	5/50	0/50*	0/50*
Pituitary gland	diffuse hyperplasia ectasia	13/49 17/49	38/50*** 32/50**	29/50** 30/50*	21/50 18/50
Salivary gland, subli[illegible]gland	chronic inflammation	1/50	0/45	3/44	7/44*
Thymus	cystic	18/37	13/42	9/42*	11/35
Uterus	cyst glandular development pigmentation	6/49 46/49 6/49	1/50 39/50* 0/50*	1/50 41/50 2/50	0/50* 41/50 1/50
Vagina	mucified aspect	18/49	29/49*	25/50	18/50

Significance computed by test (two tailed probability): * $p < .05$ ** $p < .01$ *** $p < .001$

SUMMARY OF NEOPLASMS: 2 YEAR RAT CARCINOGENICITY STUDY

ORGAN/TISSUES	NEOPLASMS	MALES				FEMALES			
		C	LD	MD	HD	C	LD	MD	HD
Mammary gland	adenocarcinoma	0/50	0/48	3/50	13/49***	3/49	14/50**	16/50**	13/50**
	adenoma, adenofibroma, fibroadenoma	0/50	3/48	4/50	3/49	20/49	21/50	27/50	15/50
	carcinoma	0/50	0/48	0/50	2/49	-- No Data--			
	fibroma	0/50	1/48	0/50	1/49	4/49	3/50	0/50	0/50
	TOTAL	0/50	3/48	6/50*	17/49***	25/49	32/50	33/50	23/50
Pancreas endocrine	adenoma incidental	9/49	9/49	14/49	14/49$^{\#}$	3/50	4/50	4/50	3/50
Soft tissue	fibrosarcoma, fatal	0/50	0/50	2/50	2/50$^{\#}$	0/50	0/50	0/50	1/50
Hematopoietic system	tumor, fatal	2/50	1/50	3/50	0/49	2/50	1/50	1/50	2/50
	tumor, incidental	2/48	2/49	2/47	1/49	0/48	4/49	3/49	4/48
	TOTAL	4/50	3/50	5/50	1/49	2/48	5/50	4/50	6/50
Cervix	adenocarcinoma					1/50	0/50	0/50	0/50
	sarcoma					2/50	1/50	0/50	1/50
Uterus	adenocarcinoma					2/50	0/50	0/50	0/50
	polyp					4/50	3/50	0/50	0/50
Vagina	sarcoma					2/50	0/50	1/50	0/50
	TOTAL (genital)					11/50	4/50*	1/50**	1/50**

test (one-talled): * p<0.05, ** p<0.01, *** p<0.001
Peto's trend statistic (no correction for continuity), asymptotic p-value: $^{\#}$p<0.02

Table 2 : Cumulative mortality for control animals (50 animals at start of experiment) in cancer studies.

MEL

	Experiment no.						FEMALES					
Time (weeks)	1308	1548	1580 a	1580 b	1580 c	1580 d	1594	1649	1694	1987	1881	Comb.
												%
12	0	0	1	0	0	0	0	1	0	1	0	0.5
16	0	1	1	0	0	0	0	1	0	2	0	0.9
20	0	1	1	0	0	0	0	1	0	3	0	1.1
24	0	1	1	0	0	0	0	1	0	3	0	1.1
28	0	1	1	0	1	0	0	1	0	4	0	1.5
32	0	2	3	0	2	0	0	1	0	5	0	2.4
36	1	2	3	0	2	0	0	1	1	6	0	2.9
40	2	2	3	0	2	0	0	1	1	6	0	3.1
44	2	2	3	0	2	0	0	1	1	7	0	3.3
48	2	2	3	0	2	0	0	2	2	7	0	3.6
52	3	2	5	1	3	1	0	2	2	9	2	5.5
56	3	4	5	1	3	1	1	2	3	9	2	6.2
60	4	5	5	4	4	1	1	4	3	12	7	9.1
64	4	7	6	4	7	3	2	5	5	15	8	12.0
68	6	8	8	6	10	3	4	8	6	17	9	15.5
72	8	8	10	7	12	5	6	10	7	19	10	18.5
76	9	12	11	9	14	11	11	13	11	23	16	25.5
80	12	12	13	15	16	14	18	19	13	25	17	31.6
84	14	14	14	17	17	14	20	21	15	30	20	35.6
88	18	17	17	22	20	18	23	23	18	30	20	41.1
92	20	21	19	25	26	23	30	25	21			46.7
96	22	30	21	28	28	25	30	28	26			52.9
100	27	31	24	32	31	33		30	30			59.5
104	27				35	35		33				65.0
108					37	38		34				72.7
112					38	41						79.0

000-00160

Table 3 : Incidence of tumor types per tissue in male control mice per experiment and the total procentual occurrence

MALES

Experiment no.	1306	1548	1649	1580c	1580d	1987	1881
Adrenal gland							
Spindle cell tumor, benign	0/48	1/45	0/47	0/47	0/50	0/49	0/50
Bone, Skull (*)							
Osteoma	0/50	0/50	0/50	0/50	1/50	0/50	0/50
Epididymis							
Sarcoma	0/49	0/49	0/47	0/48	0/50	1/50	1/50
Glandular stomach							
Adenocarcinoma			0/49	1/45	0/49	0/49	0/50
Adenoma			0/49	1/45	0/49	0/49	0/50
Harderian gland (*)							
Adenoma	0/50	0/50	1/50	0/50	0/50	0/50	0/50
Hematopoietic system (*)							
Tumor	4/50	4/50	5/50	12/50	2/50	2/50	3/50
- lymphoma	1/50	0/50	0/50	0/50	0/50	0/50	0/50
- lymphosarcoma	0/50	1/50	0/50	6/50	0/50	1/50	0/50
- lymphoid leukemia	3/50	2/50	3/50	5/50	1/50	1/50	3/50
- myeloid leukemia	0/50	0/50	1/50	0/50	0/50	0/50	0/50
- histiocytic tumor	0/50	1/50	1/50	2/50	1/50	0/50	0/50
Lacrimal gland(s) (*)							
Adenoma	0/50	0/50	0/50	0/50	0/50	0/50	1/50
Kidney							
Adenoma	1/50	0/50	0/50	0/50	1/50	0/50	0/50
Adenocarcinoma	0/50	0/50	1/50	0/50	0/50	0/50	0/50
Lip (*)							
Papilloma	0/50	0/50	1/50	0/50	0/50	0/50	0/50
Liver							
Hepatic neoplastic nodule	10/50	9/50	10/50	9/49	14/50	9/49	7/50
Hepatocellular carcinoma	4/50	6/50	6/50	1/49	3/50	3/49	6/50
— Hepatocellular neoplasia	14/50	12/50	14/50	10/49	16/50	11/49	11/50
Hemangioendothelioma	0/50	1/50	1/50	3/49	4/50	1/49	1/50
Lung							
Primary lung tumor, benign	15/50	11/50	13/50	10/50	13/50	6/50	12/50
Primary lung tumor, malignant	6/50	4/50	9/50	10/50	16/50	6/50	5/50
— Primary lung tumor	19/50	15/50	21/50	17/50	25/50	9/50	16/50

Table 3 : Incidence of tumor types per tissue in male control mice per experiment and the total procentual occurrence

MALES

Experiment no.	1308	1548	1649	1580c	1580d	1987	1881
Mammary gland							
Carcinoma	0/47	0/50	0/49	0/47	0/49	1/47	0/48
Carcinosarcoma	0/47	0/50	1/49	0/47	0/49	0/47	0/48
Pituitary gland							
Adenoma	0/42	0/45	1/38	0/40	0/39	0/46	0/46
Scrotum (*)							
Hemangioma	1/50	0/50	0/50	0/50	0/50	0/50	0/50
Small intestine (*)			ileum				
Adenocarcinoma	0/50	0/50	1/44	0/50	1/50	0/50	0/50
Soft tissue							
Hemangiosarcoma	1/50	1/50	0/50	0/50	0/50	1/50	0/50
Sarcoma	0/50	0/50	0/50	0/50	1/50	0/50	0/50
Stomach (*)			forestomach				
Carcinoma, squamous cell	0/50	0/50	1/41	0/45	0/49	0/50	0/50
Spleen							
Hemangioendothelial sarcoma	0/49	0/49	0/50	1/49	0/47	0/49	1/50
Hemangioendothelioma	0/49	0/49	0/50	1/49	1/47	1/49	0/50
Testis							
Adenoma	0/49	0/50	0/50	0/47	1/50	0/50	0/50
Hemangioma	1/49	0/50	0/50	0/47	0/50	0/50	0/50
Hemangioendothelioma	0/49	1/50	0/50	0/47	1/50	0/50	0/50
Leydig cell tumor, benign	0/49	0/50	1/50	3/47	1/50	1/50	2/50
Leydig cell tumor, malignant	0/49	1/50	1/50	0/47	1/50	0/50	0/50
—Leydig cell tumor	0/49	1/50	2/50	3/47	2/50	1/50	2/50
Thyroid gland							
Adenoma	0/27	0/38	0/35	1/29	1/43	0/45	0/50
Trigeminal nerve (*)							
Schwannoma, benign	0/50	0/50	0/50	0/50	0/50	1/50	1/50

(*) denominator = number of autopsied animals

Table 4 : Incidence of tumor types per tissue in female control mice per experiment and the total procentual occurrence

FEMALES

Experiment no.	1308	1546	1649	1580c	1580d	1987	1881
Adrenal gland							
Adenoma	0/48	0/50	1/50	1/48	0/48	0/49	0/50
Phaechromocytoma	0/48	0/50	0/50	1/48	0/48	0/49	0/50
Spindle cell tumor, benign	0/48	0/50	0/50	0/48	0/48	0/49	0/50
Bone (*)							
Osteoma	0/50	0/50	0/50	1/50	0/50	0/50	0/50
Cardiaal system (*)							
Sarcoma	0/50	0/50	0/50	0/50	1/50	0/50	0/50
Cervix (*)							
Hemangioendothelial sarcoma	0/50	0/50	0/50	1/50	0/50	0/49	0/50
Hemangioendothelioma	0/50	0/50	0/50	0/50	1/50	0/49	0/50
Fibroleiomyosarcoma	0/50	0/50	0/50	1/50	0/50	0/49	0/50
Leiomyosarcoma	0/50	0/50	0/50	0/50	0/50	0/49	1/50
Sarcoma	1/50	0/50	2/50	1/50	0/50	1/49	0/50
Harderian gland (*)							
Adenoma	0/50	0/50	0/50	0/50	1/50	0/50	1/50
Hematopoietic system (*)							
Tumor	5/50	8/50	14/50	12/50	14/50	11/49	11/50
- lymphoma	0/50	0/50	0/50	0/50	0/50	0/49	0/50
- lymphosarcoma	2/50	4/50	3/50	4/50	4/50	6/49	6/50
- lymphoid leukemia	2/50	3/50	6/50	8/50	4/50	3/49	1/50
- myeloid leukemia	1/50	0/50	1/50	0/50	0/50	0/49	0/50
- hystiocytic tumor	0/50	0/50	4/50	0/50	4/50	1/49	3/50
- thymoma	0/50	1/50	0/50	0/50	0/50	1/49	0/50
Liver							
Hepatic neoplastic nodule	2/50	3/50	0/50	0/49	0/50	1/49	1/50
Hepatocellular carcinoma	0/50	0/50	0/50	0/49	0/50	0/49	0/50
--- Hepatocellular neoplasia	2/50	3/50	0/50	0/49	0/50	0/49	1/50
Hemangioendothelial sarcoma	0/50	0/50	0/50	0/49	1/50	0/49	0/50
Hemangioendothelioma	0/50	1/50	1/50	1/49	1/50	1/49	0/50
Hepatocytic carcinoma	0/50	0/.50	0/50	0/49	0/50	0/49	0/50
Lung							
Primary lung tumor, benign	7/50	4/50	12/50	9/50	6/50	4/49	8/50
Primary lung tumor, malignant	5/50	3/50	4/50	3/50	7/50	1/49	3/50
--- Primary lung tumor	12/50	6/50	16/50	11/50	11/50	5/49	11/50
Mammary gland							
Adenocarcinoma	3/50	1/47	3/49	1/47	5/48	1/49	2/50
Carcinoma	3/50	0/47	0/49	0/47	0/48	0/49	0/50

Table 4 : Incidence of tumor types per tissue in female control mice per experiment and the total procentual occurrence

FEMALES

Experiment no.	1308	1548	1649	1580c	1580d	1987	1981
Ovary							
Adenoma	0/50	1/50	1/50	1/49	0/49	0/49	0/50
Carcinoma	0/50	1/50	0/50	0/49	0/49	0/49	0/50
Granulosa-theca cell tumor, benign	0/50	0/50	0/50	1/49	0/49	0/49	0/50
Hemangioendothelial sarcoma	0/50	0/50	0/50	1/49	1/49	0/49	0/50
Hemangioendothelioma	0/50	0/50	2/50	0/49	0/49	1/49	0/50
Luteal-cell tumor, benign	1/50	0/50	2/50	1/49	1/49	1/49	0/50
Pancreas							
Endocrine adenoma	0/47	0/49	1/50	0/49	0/47	0/48	0/50
Pituitary gland							
Adenoma	1/45	2/44	1/46	0/40	3/44	2/48	0/49
Carcinoma	0/45	0/44	1/46	0/40	0/44	0/48	0/49
Skin (*)							
Carcinoma, squamous cell	0/50	0/50	0/50	0/50	1/50	0/50	0/50
Soft tissue (*)							
Fibroma	0/50	1/50	0/50	0/50	0/50	0/49	0/50
Fibrosarcoma	0/50	0/50	1/50	0/50	0/50	0/49	0/50
Hemangioendothelial sarcoma	0/50	0/50	0/50	0/50	0/50	1/49	0/50
Hemangioendothelioma	0/50	1/50	0/50	0/50	0/50	0/49	0/50
Sarcoma	1/50	0/50	0/50	0/50	0/50	0/49	1/50
Spleen							
Hemangioendothelial sarcoma	0/50	0/49	0/50	0/49	0/48	1/49	0/50
Hemangioendothelioma	0/50	2/49	1/50	0/49	0/48	1/49	2/50
Thyroid gland							
Adenoma	0/29	0/25	1/33	0/37	1/42	0/49	0/49
Urinary bladder (*)							
Fibroleiomyoma	0/50	1/50	0/50	0/41	0/46	0/40	0/46
Hemangioendothelioma	0/50	1/50	0/50	0/41	0/46	0/40	0/46
Uterus							
Adenocarcinoma	0/50	1/49	2/50	0/50	1/49	0/49	0/50
Adenoma	2/50	2/49	1/50	0/50	1/49	0/49	0/50
Adenoma, polypous	0/50	0/49	0/50	0/50	0/49	2/49	2/50
Carcinoma	0/50	0/49	2/50	0/50	0/49	0/49	0/50
Fibroleiomyoma	0/50	1/49	0/50	0/50	1/49	0/49	0/50
Fibroleiomyosarcoma	0/50	0/49	0/50	2/50	1/49	0/49	0/50
Hemangioendothelioma	0/50	0/49	0/50	2/50	2/49	2/49	0/50
Hemangioma	2/50	0/49	0/50	0/50	0/49	0/49	0/50
Leiomyosarcoma	0/50	0/49	0/50	0/50	0/49	1/49	1/50
Sarcoma	0/50	0/49	2/50	0/50	0/49	1/49	0/50
Vagina							
Carcinoma			1/42				0/43

(*) denominator = number of autopsied animals

000-00164

Table 1: Historical control data of cumulative mortality (50 animals at start of experiment) in carcinogenicity studies in male rats

Time (weeks)	Experiment No.											
	1155	1214	1230	1307	1317	1335	1450	1309	1650	1882	1952	2031
16	0	0	0	0	0	0	0	0	0	0	0	1
20	0	0	0	0	0	0	0	0	0	0	0	1
24	0	0	0	0	0	0	0	0	0	0	0	1
28	0	0	0	0	0	0	0	0	0	0	0	1
32	1	0	0	0	0	0	0	0	0	0	0	1
36	1	0	0	2	0	0	0	0	0	0	0	3
40	1	0	0	2	0	0	0	0	0	0	0	3
44	1	0	0	2	0	0	0	0	0	0	0	4
48	1	0	0	3	0	0	0	0	0	1	0	4
52	1	0	0	4	0	0	0	0	0	1	0	4
56	1	0	0	4	0	0	0	0	0	1	0	5
60	1	0	0	4	0	0	0	1	0	1	0	5
64	1	0	1	5	0	0	0	1	0	2	1	5
68	1	0	1	5	3	1	1	1	0	4	1	5
72	3	1	2	7	4	2	2	2	1	4	2	5
76	5	3	3	8	5	2	2	3	3	5	4	6
80	5	6	4	10	5	4	3	5	4	6	5	6
84	8	6	4	12	5	6	6	8	4	6	5	7
88	10	8	9	15	7	9	12	9	6	6	8	8
92	16	10	13	18	8	9	12	11	7	10	9	8
96	19	10	14	20	14	12	15	12	10	12	13	11
100	20	11	18	14	16	15	19	16	14	16	14	11
104	25	16	21	27	18	16	24	18	18	16	17	15
108	25	16	24	30	18	18	24	18	22	19	19	17
112									30	26		17
116									34	26		
120									36			
124									39			

Table 2: Historical control data of cumulative mortality (50 animals at start of experiment) in carcinogenicity studies in female rats

Time (weeks)	Experiment No.											
	1155	1214	1230	1307	1317	1335	1450	1309	1650	1882	1952	2031
12	0	0	0	0	1	0	0	0	0	0	0	0
16	0	0	0	0	1	0	0	0	0	0	0	0
20	0	0	0	0	1	0	0	0	0	0	0	1
24	0	0	0	0	1	0	0	0	0	0	0	1
28	0	0	0	0	1	0	0	0	0	0	0	1
32	0	0	0	0	1	0	0	0	0	0	0	1
36	0	0	0	0	1	0	0	1	0	0	0	1
40	0	0	0	0	1	0	0	1	0	0	0	1
44	0	0	0	0	1	0	0	2	1	0	0	2
48	0	0	0	0	1	0	0	2	1	0	2	2
52	1	0	0	0	1	0	1	2	1	1	2	2
56	1	0	0	0	1	0	2	4	1	1	3	3
60	2	0	2	0	1	0	3	4	1	1	3	3
64	2	1	2	0	1	1	4	4	1	1	3	3
68	3	2	2	0	1	1	5	6	1	1	3	4
72	3	3	3	2	1	2	6	7	4	1	3	7
76	4	3	6	3	2	3	7	9	5	4	3	7
80	5	5	7	5	4	4	8	9	6	7	6	8
84	6	13	12	5	7	5	8	11	7	7	7	8
88	10	16	13	6	10	7	9	15	8	12	10	9
92	12	17	16	7	15	8	10	15	11	15	10	11
96	17	21	20	7	18	11	12	20	13	17	12	14
100	18	21	22	10	21	16	12	22	18	17	15	16
104	20	24	24	13	23	18	16	23	21	19	23	18
108	20	25	26	16	23	19	16	23	21	22	23	19
112									24	26		19
116									31	26		
120									34			
124									39			

Table 3. Incidence of tumor types per tissue in male control rats per experiment

MALES

Experiment number	1155	1214	1230	1307	1317	1335	1450	1309	1650
Abdominal mesothelia (@)									
Sarcoma	0/50	1/50	0/50	0/50	0/50	0/50	0/50	0/50	0/50
Adrenal gland									
Ganglioneuroma	0/49	0/50	0/50	1/49	2/50	0/50	0/50	0/50	0/50
Phaeochromocytoma	4/49	4/50	13/50	4/49	5/50	6/50	5/50	6/50	8/50
Anus (@)									
Leiomyosarcoma	0/50	0/50	1/50	0/50	0/50	0/50	0/50	0/50	0/50
Auditory subaceous gland (@)									
Carcinoma	1/50	0/50	0/50	0/50	0/50	0/50	0/50	0/50	0/50
Bone									
Osteosarcoma	0/50	1/50	0/50	0/50	0/50	0/50	0/50	0/50	1/47
Brain									
Tumor of glia - glioma	1/48	1/49	0/50	0/50	0/50	0/50	0/50	0/50	0/50
Granular cell tumor	0/48	0/49	0/50	1/50	0/50	0/50	0/50	0/50	1/50
Epididymis									
Mesothelioma	0/50 @	0/50	0/50	0/50	0/50	0/50	0/50	0/50	1/50
Heart									
Sarcoma	1/50	0/50	0/50	0/50	0/50	0/49	0/50	0/50	0/50
Hematopoietic system (@)									
Tumor	0/50	0/50	0/50	1/50	2/50	2/50	4/50	1/50	2/50
Jaw(@)									
Squamous cell carcinoma	3/50	0/50	0/50	1/50	0/50	0/50	2/50	0/50	1/50
Schwannoma, benign	0/50	0/50	0/50	0/50	0/50	0/50	1/50	0/50	0/50
Kidney									
Adenoma	0/50	0/50	0/50	0/50	0/50	1/50	1/50	0/50	0/50
Adenocarcinoma	0/50	1/50	0/50	0/50	0/50	0/50	0/50	0/50	0/50
Carcinoma, transitional cell	0/50	1/50	0/50	0/50	0/50	0/50	0/50	0/50	1/50
Lipoma	0/50	0/50	0/50	0/50	0/50	0/50	0/50	0/50	1/50
Large intestine									
Adenocarcinoma	0/42	0/50	0/50	0/50	0/50	0/50	1/50	0/50	0/50
Liver									
Cholangioma	0/50	0/50	1/50	0/50	0/50	0/50	0/50	0/50	1/50
Hepatic neoplastic nodule	5/50	4/50	2/50	3/50	10/50	5/50	1/50	5/50	2/50
Hepatocellular carcinoma	0/50	0/50	0/50	1/50	0/50	1/50	0/50	1/50	1/50
Hepatocellular neoplasia	5/50	4/50	2/50	4/50	10/50	6/50	1/50	6/50	3/50
Lung									
Carcinoma, squamous cell	0/50	0/50	0/50	0/50	0/50	0/50	0/50	1/50	0/50
Lymph nodes									
Fibrosarcoma	1/36	0/36	0/44	0/35	0/43	0/43	0/42	0/50	0/50
Hemangioendothelial sarcoma	0/36	0/36	0/44	0/35	0/43	0/43	0/42	0/50	4/50
Hemangio(endothelio)ma	1/36	3/36	5/44	1/35	1/43	6/43	0/42	11/50	2/50
Mammary gland									
Adenoma-fibroadenoma	0/49	2/49	1/50	1/50	0/50	0/50	0/50	0/50	0/49
Fibroma	0/49	0/49	0/50	0/50	1/50	0/50	2/50	0/50	0/49

Table 3: Incidence of tumor types per tissue in male control rats per experiment

MALES

Experiment number	1155	1214	1230	1307	1317	1335	1450	1309	1650
Meninges (@)									
Meningioma	0/50	0/50	0/50	0/50	0/50	0/50	0/50	0/50	1/50
Sarcoma	0/50	0/50	0/50	0/50	0/50	1/50	0/50	0/50	0/50
Pancreas									
Adenocarcinoma, endocrine	0/49	0/49	0/50	0/48	0/50	0/50	0/48	1/50	0/49
Adenocarcinoma, exocrine	0/49	0/49	0/50	0/48	0/50	0/50	2/48	2/50	0/49
Adenoma, endocrine	5/49	6/49	9/50	7/48	9/50	9/50	5/48	6/50	7/49
Adenoma, exocrine	6/49	13/49	8/50	11/48	12/50	13/50	15/48	13/50	9/49
Sarcoma	0/49	0/49	0/50	0/48	0/50	0/50	0/48	0/50	1/49
Parathyroid gland									
Adenoma	0/32	0/50	0/50	0/50	1/36	0/50	0/50	0/50	0/50
Pituitary gland									
Adenoma	19/47	15/49	9/48	13/49	11/50	12/50	10/49	4/48	13/50
(adeno)carcinoma	0/47	2/49	0/48	0/49	1/50	1/50	0/49	0/48	3/50
Prostate									
Carcinoma	0/46	0/49	0/50	1/50	0/50	0/49	0/50	0/50	1/49
Sarcoma	0/46	0/49	0/50	0/50	0/50	0/49	0/50	0/50	1/49
Seminal vesicle									
Adenocarcinoma	0/45	0/49	1/50	0/48	0/50	0/49	0/50	0/50	0/49
Carcinoma	0/45	0/49	0/50	0/48	0/50	0/49	0/50	0/50	1/49
Skin (@)									
Adenoma	0/50	0/50	0/50	0/50	0/50	0/50	0/50	0/50	1/50
Carcinoma	1/50	0/50	1/50	0/50	0/50	0/50	0/50	0/50	2/50
Kerato-acanthoma	0/50	1/50	0/50	0/50	0/50	0/50	0/50	0/50	1/50
Papilloma	0/50	1/50	2/50	3/50	1/50	1/50	1/50	5/50	4/50
Small intestine									
Adenocarcinoma	1/46	1/47	0/50	1/47	1/50	1/50	0/50	0/50	0/49
Soft tissue (@)									
(Myxo)fibroma	1/50	3/50	1/50	1/50	3/50	3/50	0/50	1/50	3/50
Fibrosarcoma	1/50	1/50	1/50	0/50	0/50	0/50	0/50	0/50	0/50
Hemangioendothelioma	0/50	0/50	0/50	0/50	0/50	0/50	0/50	0/50	2/50
Hemangioma	0/50	0/50	1/50	0/50	0/50	1/50	0/50	0/50	0/50
Hemangiosarcoma	0/50	0/50	0/50	0/50	0/50	0/50	0/50	1/50	0/50
Histiocytoma	0/50	0/50	0/50	0/50	1/50	0/50	0/50	0/50	0/50
Lipoma	0/50	0/50	0/50	0/50	0/50	0/50	0/50	0/50	1/50
Phaeochromocytoma, malignant	0/50	0/50	0/50	0/50	0/50	0/50	0/50	0/50	1/50
Sarcoma	1/50	0/50	0/50	0/50	0/50	0/50	1/50	1/50	3/50
Spleen									
Fibroma	1/50	0/50	0/50	0/49	0/50	1/49	0/50	0/50	0/50
Glandular stomach (@)									
Adenocarcinoma	0/50	0/50	0/50	0/50	1/50	0/50	0/50	0/50	0/50
Testis									
Leydig cell tumor (benign)	8/50	13/50	15/50	16/50	15/50	17/50	15/50	6/50	5/50
Thyroid gland									
Adenoma (follicular)	4/48	8/49	8/50	10/50	8/50	9/50	8/50	4/50	4/50
(Adeno)carcinoma (follicular)	2/48	5/49	0/50	1/50	0/50	2/50	0/50	1/50	5/50
Adenoma "light cell" solid	2/48	3/49	4/50	3/50	2/50	2/50	1/50	3/50	3/50

Table 3: Incidence of tumor types per tissue in male control rats per experiment

MALES

Experiment number	1155	1214	1230	1307	1317	1335	1450	1309	1650
Tongue (@)									
Papilloma	0/50	0/50	0/50	1/50	0/50	0/50	0/50	0/50	0/50
Urinary bladder									
Carcinoma	0/48	0/50	1/48	0/47	0/50	0/46	0/50	0/50	0/50
Papilloma, transitional cell	0/48	0/50	0/48	0/47	0/50	0/46	0/50	0/50	0/50

(@) denominator = number of autopsied animals

Table 4: Incidence of tumor types per tissue in female control rats per experiment

FEMALES

Experiment number	1155	1214	1230	1307	1317	1335	1450	1309	1650
Abdominal mesothelia (@)									
Lipoma	0/50	0/50	0/50	0/50	1/50	0/50	0/50	0/50	0/50
Adrenal gland									
Adenoma	0/50	0/50	0/50	0/50	0/50	0/50	0/50	0/50	1/50
Phaeochromocytoma	2/50	1/50	1/50	5/50	2/50	2/50	0/50	3/50	0/50
Auditory sebaceous gland (@)									
Carcinoma	0/50	0/50	0/50	0/50	0/50	0/50	1/50	0/50	0/50
Bone									
Osteosarcoma	0/49	0/50	0/50	0/50	0/50	0/50	0/50	1/50	1/50
Cervix (@)									
Carcinoma, scirrhous	0/50	0/50	0/50	0/50	0/50	0/50	0/50	1/50	0/50
Fibroleiomyosarcoma	0/50	0/50	0/50	0/50	0/50	0/50	0/50	0/50	1/50
Leiomyoma	0/50	0/50	1/50	0/50	0/50	0/50	0/50	0/50	0/50
Sarcoma	0/50	5/50	0/50	3/50	1/50	0/50	2/50	2/50	2/50
Harderian gland (@)									
Adenocarcinoma	0/50	0/50	1/50	0/50	0/50	0/50	0/50	0/50	0/50
Heart									
Hemangioendothelioma	0/50	0/49	0/46	0/50	0/50	1/50	0/50	0/50	0/50
Hematopoietic sytem									
Tumor	1/50	3/50	1/50	0/50	3/50	1/50	0/50	3/50	1/50
Jaw (@)									
Kerato-acanthoma	0/50	0/50	2/50	0/50	0/50	0/50	0/50	0/50	0/50
Carcinoma, squamous cell	0/50	0/50	0/50	0/50	1/50	0/50	1/50	0/50	0/50
Schwannoma, benign	0/50	0/50	0/50	0/50	0/50	0/50	0/50	0/50	0/50
Kidney									
Adenocarcinoma	0/50	0/50	0/50	0/50	1/50	0/50	0/50	0/50	0/50
Adenoma	1/50	0/50	1/50	0/50	0/50	1/50	0/50	0/50	0/50
Lipoma	1/50	0/50	0/50	0/50	0/50	0/50	1/50	0/50	0/50
Liver									
Cholangioma	0/50	0/50	0/50	0/50	0/50	1/50	0/50	0/50	0/50
Hepatic neoplastic nodule	8/50	6/50	1/50	3/50	5/50	8/50	2/50	4/50	8/50
Lung									
Carcinoma	0/50	1/50	0/50	0/50	0/50	0/50	0/50	0/50	0/50
Lymph node									
Hemangio(endothelio)ma	0/40	1/27	1/38	2/39	0/34	0/37	0/43	1/49	0/48
Mammary gland									
Adenoma, fibroadenoma	18/50	22/50	18/50	20/50	16/50	27/50	13/50	19/50	19/50
Carcinoma	0/50	0/50	0/50	0/50	1/50	0/50	0/50	1/50	0/50
Fibroma	1/50	2/50	0/50	0/50	1/50	1/50	2/50	1/50	0/50
Adenocarcinoma	9/50	5/50	5/50	5/50	6/50	3/50	4/50	5/50	7/50
Mouth (@)									
Carcinoma, squamous cell	1/50								

Table 4: Incidence of tumor types per tissue in female control rats per experiment

FEMALES

Experiment number	1155	1214	1230	1307	1317	1335	1309	1450	1650
Ovary									
Sertoli cell tumor, benign	0/49	0/49	0/49	0/50	0/50	0/50	0/49	1/50	0/48
Sertoli cell tumor, malignant	0/49	0/49	0/49	0/50	0/50	0/50	0/49	1/50	0/48
Sertoli cell tumor	0/49	0/49	0/49	0/50	0/50	0/50	0/49	2/50	0/48
Granulosa-theca cell tumor	0/49	1/49	0/49	0/50	0/50	0/50	0/49	2/50	2/48
Carcinoma	0/49	0/49	0/49	1/50	0/50	0/50	0/49	0/50	0/48
Sarcoma	0/49	0/49	0/49	0/50	0/50	1/50	0/49	0/50	0/48
Meninges (@)									
Meningioma	0/50	0/50	0/50	0/50	0/50	0/50	0/50	0/50	1/50
Pancreas									
Adenocarcinoma, exocrine	0/50	0/50	0/50	0/50	1/50	0/50	0/49	0/49	0/49
Adenoma, endocrine	2/50	2/50	3/50	3/50	2/50	1/50	3/49	1/49	5/49
Adenoma, exocrine	0/50	1/50	2/50	2/50	3/50	3/50	1/49	1/49	0/49
Carcinoma, exocrine	0/50	1/50	0/50	0/50	0/50	0/50	0/49	0/49	0/49
Parathyroid gland									
Adenocarcinoma	0/29	0/50	0/50	0/50	0/50	0/50	0/50	0/50	1/34
Pituitary gland									
Adenoma	35/50	29/48	30/48	24/50	27/50	26/49	22/49	25/50	35/50
Adenocarcinoma	0/50	0/48	0/48	1/50	2/50	1/49	0/49	0/50	1/50
Salivary gland(s)									
Adenoma	0/50	1/50	0/50	0/50	0/50	0/50	0/50	0/50	0/50
Skin (@)									
Basal cell carcinoma	0/50	0/50	0/50	0/50	1/50	0/50	0/50	0/50	0/50
Papilloma	0/50	0/50	0/50	0/50	0/50	0/50	1/50	0/50	0/50
Small intestine									
Adenocarcinoma	0/50	0/50	0/47	0/50	1/50	0/50	0/50	0/50	0/48
Fibroleiomyoma	0/50	1/50	0/47	0/50	0/50	0/50	0/50	0/50	0/48
Fibroleiomyosarcoma	0/50	0/50	0/47	0/50	0/50	0/50	0/50	0/50	1/48
Soft tissue (@)									
Lipoma	0/50	0/50	1/50	0/50	0/50	0/50	0/50	0/50	0/50
Hemangioma	1/50	0/50	0/50	0/50	0/50	1/50	0/50	0/50	0/50
Hemangiosarcoma	1/50								
Fibrosarcoma	0/50	0/50	1/50	2/50	0/50	0/50	0/50	0/50	0/50
Sarcoma	0/50	0/50	0/50	0/50	0/50	0/50	0/50	0/50	1/50
Spleen									
Hemangioma	0/50	0/50	0/50	1/50	0/50	0/50	0/50	0/50	0/50
Stomach									
Fibrosarcoma	0/50	0/50	0/50	0/50	0/50	0/50	1/50	0/50	0/50
Thyroid gland									
Adenoma (follicular)	2/49	2/48	4/48	1/49	0/50	1/49	0/50	1/50	2/49
Adenoma, "light cell" solid	4/49	1/48	5/48	0/49	7/50	4/49	1/50	1/50	2/49
Urinary bladder									
Carcinoma	0/48	0/48	0/48	1/49	0/50	0/48	0/50	0/50	0/47
Uterus									
Adenoma, polypous	2/50	4/50	1/50	1/50	6/50	4/50	9/50	4/49	0/50
Adenocarcinoma	4/50	2/50	2/50	4/50	1/50	1/50	0/50	2/49	1/50
Carcinoma	0/50	0/50	0/50	0/50	1/50	0/50	1/50	1/49	1/50
Hemangioendothelioma	0/50	1/50	0/50	0/50	0/50	0/50	0/50	0/49	1/50
Polyp	0/50	0/50	0/50	0/50	0/50	0/50	0/50	0/49	7/50
Sarcoma	1/50	0/50	0/50	0/50	0/50	1/50	1/50	0/49	2/50

Table 4: Incidence of tumor types per tissue in female control rats per experiment

FEMALES

Experiment number	1155	1214	1230	1307	1317	1335	1339	1450	1650
Vagina (@)									
Adenocarcinoma	0/50	0/50	0/50	0/50	0/50	0/50	0/50	0/50	1/48
Leiomyoma	0/50	0/50	1/50	0/50	0/50	0/50	0/50	0/50	0/48
Sarcoma	0/50	0/50	2/50	1/50	1/50	2/50	1/50	0/50	0/48

(@) denominator = number of autopsied animals

SUMMARY AND EVALUATION

PHARMACOLOGY

Receptor studies and behavioral pharmacology: In vitro studies demonstrated that risperidone has high (i.e., subnanomolar) affinity for the $5HT_2$, α_1 and α_2 adrenergic, D_2, and H_1 receptors. Of these, risperidone has the highest affinity for the $5HT_2$ receptor. In this way, risperidone is like clozapine which has high affinity for $5HT_2$ and $5HT_{1C}$ receptors. Risperidone has weak/no affinity for the D_1, H_2, β-adrenergic, or $5HT_{1a, 1b}$ receptors. Compared to haloperidol, risperidone is 2-fold less potent at the D_2 receptor.

In vivo studies indicate that risperidone is 40-fold more potent than haloperidol and 100-fold more potent than clozapine at the $5HT_2$ receptor. At the D_2 receptor, risperidone is 7-fold less potent than haloperidol, but 3-5 fold more potent than clozapine.

The propensity to cause extrapyramidal side effects is attributed to the binding affinity of typical neuroleptics for the D_2 receptor. Risperidone has a lower affinity for the D_2 receptor and induces catalepsy at 2-5 fold higher doses compared to haloperidol. These observations suggest that risperidone may act more like an atypical antipsychotic drug, e.g., clozapine, in reduced incidence of extrapyramidal side effects. In addition, risperidone is similar to clozapine in that it has high affinity for the $5HT_2$ receptor. However, unlike clozapine, risperidone has no affinity for the muscarinic cholinergic receptor. Muscarinic cholinergic antagonists (e.g., Cogentin) have been shown to control, to some extent, the incidence of extrapyramidal side effects by antagonizing the inhibitory effect of acetylcholine on dopamine in the substantial nigra. The exact mechanism by which clozapine is associated with a reduced incidence of extrapyramidal effects is unknown.

Behavioral pharmacology tests indicate that risperidone has antidopaminergic activity, as exhibited by antagonism of apomorphine, amphetamime, and cocaine-induced hyperactivity and/or stereotypy. ED_{50} (s.c.) for these behaviors were similar to the proposed maximum therapeutic oral dose in humans. Risperidone also antagonized apomorphine-induced emesis in dog at doses 10-fold lower than the proposed maximum human dose. Risperidone also exhibited antiserotonin activity, blocking 5HT-and mescaline-induced head twitching ($5HT_2$) at doses (s.c.) 1.5-70 fold lower than the proposed human oral dose. The pharmacology of the major metabolite, 9-hydroxy-risperidone, was similar to that of risperidone. 9-hydroxy-risperidone was found to act as an antagonist at α- and dopamine receptors. It is not expected that 9-hydroxy-risperidone would have an pharmacological action not seen with risperidone. There do appear to be differences, however, since in behavioral tests, only risperidone was found to produce ataxia and tremors.

In other in vivo studies, risperidone reduced lethality after mast cell activation (ED_{50} of 0.028 mg/kg s.c.) and protected against noradrenaline and physostigmine-induced lethality. Risperidone had no effect on gastrointestinal motility (≤10 mg/kg s.c.) and did not induce hepatic drug-metabolizing enzymes at doses up to 10 mg/kg (p.o).

Endocrine studies

The effects of risperidone on serum prolactin, testosterone, and LH were tested.

Serum testosterone, LH: Risperidone had no effect on testosterone in either rats (6 wk, 0.63-10 mg/kg in diet) or humans (acute dose ≤2 mg; repeat dosing of 1 mg for 7 doses). In dogs,

however, risperidone at doses of 0.31-5.0 mg/kg for 3 mo resulted in dose-related decreases (31-75%) in testosterone. In humans, no changes in LH, FSH, or progesterone were noted after similar doses. In rats, changes in LH were inconsistent, but tended to be reduced after dosing for 1 mo (0.63-10 mg/kg in diet).

Serum prolactin: Risperidone was found to increase serum prolactin levels (2.5-22 fold, depending on dose and duration) after both acute and chronic (6 wk) administration at doses of 0.63-10 mg/kg p.o. (gavage and in diet) in rats and mice. The major active metabolite of risperidone, 9-hydroxy-risperidone (R 76477), was shown to have effects on serum prolactin similar to those of risperidone at doses of 0.01-5 mg/kg p.o. (gavage). Risperidone was also found to increase serum prolacin in humans (healthy male volunteers). At doses of ≤4 mg/kg p.o. and 1 mg i.m., serum prolactin was elevated 5-10 fold at 1-4 hr postdosing. Levels returned to normal 5-24 hr postdosing.

In initial studies, a comparison of risperidone's effect of serum prolactin with that of haloperidol suggested that risperidone was more potent in terms of elevating serum prolactin. This contradicted in vitro studies indicating that risperidone is 2-fold less potent at the D_2 receptor than is haloperidol. Further studies demonstrated that this apparent discrepancy was due to the presence of the active metabolite of risperidone, 9-hydroxy-risperidone, which had an effect similar to risperidone on serum prolactin. A comparison of plasma levels indicated that haloperidol was more potent than risperidone based on serum levels, but not on dose.

Cardiovascular studies: Cardiovascular effects of risperidone were tested in conscious dogs treated acutely (0.08, 0.31 mg/kg p.o.; 0.005-1.25 mg/kg i.v.) and chronically (6 days; 0.08 mg/kg i.p.) with risperidone. In acute studies, the main effect was hypotension; decreases were noted in systolic and diastolic blood pressure even at the lowest doses. Heart rate was decreased at a low dose (0.08 mg/kg p.o.); however, at a higher dose p.o. (0.32 mg/kg p.o.) or after i.v. dosing (0.005-1.25 mg/kg i.v.), heart rate was increased. ECG analyses indicated a prolonged QT interval after p.o. dosing (0.08-0.31 mg/kg, but frequency-related decreases in PQ and QT in another study after i.v. dosing (0.005-1.25 mg/kg).

After 6 days of dosing at 0.08 mg/kg i.p. in dogs, blood pressure was decreased. However, no significant changes were noted on ECG. No effects of risperidone on cardiac parameters were assessed after the initial dose in this study.

Effects on blood pressure are consistent with risperidone's affinity for the α-receptors.

PHARMACOKINETIC, ADME STUDIES

ADME studies were conducted in rat, mice, dog, rabbit, and human. Unfortunately, data from some of the oral (dietary) PK studies are of limited value because the time interval between removal of diet (i.e., removal of drug) and blood collection was not controlled. Considering the fairly short $t_{1/2}$ of risperidone, at least in rat and dog [0.6-1.4 (2.8) hr] (not measured in mice), small differences in the interval could have a substantial effect on the plasma levels of risperidone and its metabolite(s).

In rat, oral absorption of risperidone is rapid but incomplete, due to significant first-pass metabolism. Oral bioavailability in rat is lower than in dog or human (41, 76, and 69%, respectively). The major plasma metabolite is 9-hydroxy-risperidone which accounts for 26-63 and 15-46% of plasma radioactivity in males and females, respectively. Following a dose of ^{14}C or ^{3}H-risperidone, radioactivity is widely distributed, the pattern depending somewhat on the route of administration. Tissue/organs which tend to have higher levels of radioactivity include liver, kidney, pancreas, lung, adrenal, and stomach and GI (after oral dosing). In pigmented rats, radioactivity is detected in retinal pigment epithelium, iris, and skin. Brain levels of radioactivity are low (3-7 fold lower than plasma), but tend to be higher after i.v. than after p.o. dosing. After s.c. dosing with ^{3}H-risperidone, highest levels of radioactivity were detected in frontal cortex and

striatum; higher levels and a longer $t_{1/2}$ in frontal cortex reflect the higher affinity of risperidone for $5HT_2$ than for D_2 receptors. The $t_{1/2}$ in these brain areas were longe. than that in plasma (2.5-3.9 and 1 hr, respectively). In pregnant rats, radioactivity was widely distributed in fetal and fetal-associated tissue (placenta, fetal blood, ovaries, mammary gland), being particularly high in fetal membranes. In the lactating rat, risperidone and its metabolite, 9-hydroxyrisperidone, were rapidly secreted into milk, with levels of 9-hydroxy-risperidone (but not risperidone) being higher in milk than in plasma (2.6 fold). Excretion is primarily fecal (70%), with urinary excretion accounting for 25% of dose radioactivity. By 96 hr after dosing, 96-98% of dose radioactivity had been eliminated.

The $t_{1/2}\beta$ is longer for plasma total radioactivity is markedly longer than for risperidone (8 vs 0.6-1.4 hr, respectively). The longer $t_{1/2}\beta$ is not due to elimination of the major metabolite, 9-hydroxy-risperidone, since its $t_{1/2}\beta$ is only <3x longer (1.4-3.6 hr) than that of risperidone.

In dog, oral absorption of risperidone is rapid, with peak risperidone levels being reached within 1 hr of dosing. Absolute bioavailability is greater in dog than in rat, but exhibits wide interanimal variability (76±28%; range: 39-98%). The elimination rate is markedly longer for 9-hydroxy-risperidone than for risperidone ($t_{1/2}\beta$ is 0.8-1.4 and 15-21 hr for risperidone and 9-hydroxy risperidone, respectively). After an oral dose of radioactive risperidone, radioactivity is excreted equally in urine and feces (43 and 46%, respectively). This is in contrast to a mainly fecal route in rat.

In rabbit, pharmacokinetics of risperidone was conducted in only 4 males. The summary data, however, are based on the data from only 3 males, since the data from 1 male were significantly different from the others. Oral absorption of risperidone was within 2 hr of dosing with $T_{max} \approx 2$ hr. Bioavailability was not evaluated in rabbits, however, a comparison of AUC for total radioactivity and for risperidone suggests a substantial first-pass effect (1.27 vs 2.01 ng*hr/ml; ratio=0.63). The $t_{1/2}\beta$ for risperidone is longer in rabbit than the other species studied (5.1 hr).

Pharmacokinetic studies **in mice** were analyzed at the end of a 3-mo oral (dietary) toxicity and the 18-mo carcinogenicity studies. The data are compromised, however, because of the failure to control the time interval between removal of diet (i.e., drug) and collection of blood for analysis of plasma drug levels in these studies.

Pharmacokinetics studies **in humans** (based on sponsor's summary) were conducted in normal volunteers (phenotyped using debrisoquine or dextromethorphan) and psychotic patients. As with other neuroleptics, risperidone was not well tolerated in normals; therefore, the doses had to be confined to 1 and 2 mg. In normal volunteers, risperidone was rapidly (T_{max}=0.5-1 hr) and completely absorbed. Oral bioavailability was 69% for risperidone, suggesting some first-pass metabolism. The major metabolite in humans is 9-hydroxy-risperidone (as in the other species studied) and the plasma levels account for 100% of risperidone metabolism (the sum of plasma risperidone and 9-hydroxy-risperidone was 107%). The $t_{1/2}\beta$ for risperidone ranged from ≈3 hr in extensive metabolizers to 10-20 hr in intermediate and slow metabolizers. Kinetics were linear in normals up to 4 mg (limited data). In psychotic patients, plasma levels of risperidone and 9-hydro..y-risperidone were linear up to 10 mg. Linearity has not been demonstrated up to the maximum recommended human dose of 16 mg/day. An analysis of mean plasma levels "at endpoint" indicated that plasma risperidone levels did not increase, whereas, those of 9-hydroxy-risperidone and total did increase, with an increase in dose from 10 to 16 mg/day. This would suggest an induction in hepatic metabolism of risperidone to its major metabolite at doses above 10 mg/day.

TOXICITY STUDIES

Acute studies: Acute toxicity studies were performed in Wistar rat (i.v., p.o., s.c.), Swiss mice (i.v., p.o.), and mongrel and Beagle dog (i.v., p.o.). Risperidone was most acutely toxic in dog. The LD_{50} was similar after i.v. and p.o. administration and ranged from 70 to130 times the proposed maximum therapeutic dose in humans. In rats and mice, the LD_{50} was higher following p.o. than i.v. administration (134-250 and 280-800 fold higher than the proposed maximum human dose, respectively). In rats, toxicity was less following s.c. than after p.o. administration. In rodents, risperidone tended to be more toxic to females than males when administered orally, suggesting greater absorption or less of a first-pass effect in females. The most common clinical signs in rodents included ptosis, prostration, sedation, tremors, catalepsy, hypothermia, and hypotonia. At near-lethal doses, convulsions, ataxia, and GI erosion and bleeding were also noted. Diarrhea, salivation, and loss of righting reflex were also observed in dogs. In dogs, death was preceeded by clonic convulsions, loss of righting reflex, salivation, and sedation (females). The occurrence of salivation is consistent with cholinergic activation at higher doses of risperidone.

The acute toxicity of the major risperidone plasma metabolite, 9-hydroxy-risperidone, was studied at doses of 20-320 mg/kg p.o. 9-hydroxy-risperidone was more toxic in females than males; the LD_{50} was 148 mg/kg in males and 65 mg/kg in females. The main clinical signs were similar to those noted with risperidone: catalepsy, tremor, ptosis, prostration, sedation, hypothermia, and ataxia. At the HD, all animals exhibited convulsions. The main gross pathology findings were petechia and hemorrhagic areas in the stomach.

Subchronic and chronic studies (see summary table): Subchronic (1 (pilot), 3 mo, and 3 mo + recovery) and chronic (1 yr) studies were conducted in Wistar rat and Beagle dog.

Rats were treated with risperidone at doses of 0.16, 0.63, 0.63, 2.5, and 10 mg/kg or 0.63, 2.5, and 10 mg/kg, depending upon the study. Risperidone was presented in the diet, except in the 3-mo + 1 mo recovery study in which dosing was by gavage. No **clinical signs** were observed in any of the toxicity studies. Drug-related changes in **body weight** (and/or body weight gain) were fairly consistent among studies. In males, body weight/body weight gain was decreased at all but the lowest dose (0.16 mg/kg), with the maximum decrease at the HD (5-26%). In females, body weight was decreased at the HD (5-26%), but was increased at the lower doses (5-25%). Changes in **food consumption** tended to be consistent with changes in body weight. No **ophthalmic** findings were noted in the 3-mo or 1-yr toxicity studies. Changes were noted in various **hematology** parameters. In all but the 3-mo + recovery study, platelets were reduced in HDM (15-18%). In the 3-mo study, reductions in platelets were noted in all treated groups (not dose-dependent, 11-13%). At 3 mo, clotting time did not seem to be affected; however, clotting time was not assessed in the 1 yr study. In the 1-yr study, there was a 9-21% reduction in wbc in HD animals. In the 3 -mo and 1-yr studies, small (5-8%), non-dose-related, increases were noted in rbc, hct, hgb, MCH, and/or MCV, suggestive of dehydration.

Drug-related changes in **clinical chemistry** parameters included decreases in serum total protein (7-12% in MDM, HDM, 8% in HDF in 3 mo + recovery study and ≤10% in HDF in the 1 yr study), serum albumin (8% in HDM in the 3 mo + recovery and ≤10% in HDF in the 1 yr study), alkphos (34-47% in males, 45% in HDF in 1 mo study and 20% in HDM and HDF in 3 mo study), LDH (30-40% in HD animals in 3 mo study). In the 3 mo + recovery study, decreases were noted in serum glucose (15%) in HDF, serum Ca (5% in HDM), and TG (63% in HDM). Increases were noted in BUN (MDM: 22%, HDM: 51%, HDF: 21%). These effects were reversible, except for the changes in BUN in HDF. In the 1 yr study, serum K was decreased by 4-12% in HDM.

No drug-related changes in **urinalysis** parameters were noted in the 1 and 3-mo studies. Decreased urinary creatinine was observed in the 3 mo + recovery (MDM: 23%, HDM: 34%; in females, 33, 49, and 55 at 0.16, 2.5, and 10 mg/kg, respectively) and the 1-yr studies (30% in HDM). In the 3-mo +

SUBCHRONIC AND CHRONIC TOXICITY STUDIES

STUDY	SPECIES/STRAIN	N	DOSE (mg/kg)	ROUTE	DRUG BATCH #
Pilot, 1 month	rat, Wistar	5/sex/group	0, 0.63, 2.5, 10	diet	A0301
3 month toxicity	rat, Wistar	20/sex/group	0, 0.63, 2.5, 10	diet	A0101
3 month toxicity, 1 month recovery	rat, Wistar	10/sex/group (main) 5/sex/group (recovery)	0, 0.16, 0.63, 2.5, 10	gavage	PFA151
12 month toxicity	rat, Wistar	20/sex/group	0, 0.63, 2.5, 10	diet	PFA021
pilot, 1 month	dog, Beagle	2/sex/group	0.0.16, 0.63, 2.5	p.o.	A0301
3 month toxicity	dog, Beagle	4/sex/group	0, 0.31, 1.25, 5.0	gelatin capsules	A0301
3 month toxicity, 2 month recovery	dog, Beagle (males)	6/group of these, 2/group for recovery	0, 0.31, 1.25, 5.0	gelatin capsules	PFA221
12 month toxicity	dog, Beagle	4/sex/group	0, 0.31, 1.25, 5.0	capsules	PFA021

recovery study, urinary pH was increased 7-11% in HD animals and protein was decreased in males and females (males: 67-56% at 2.5-10 mg/kg; females: 59, 30, and 54% at 0.16, 2.5, and 20 mg/kg, respectively). Effects were reversible except for decreases in specific gravity (2%) and protein (45%) noted in HDM

Drug-related changes were noted in the **weights** of various **organs/tissues;** however, the only organ/tissue consistently affected was the liver. In males, absolute liver weight was consistently decreased at the HD (10-23%); relative liver weight was decreased (7-20%) in all dosed males only in the 1 mo pilot study. In females, no changes were noted in liver weight at 1 yr, although, in the shorter studies decreases were observed in absolute (4-50%) and relative (7-24%) liver weight. Changes in adrenal weigh, although not consistent, were observed in all but the 3-mo (no recovery) study. In the 1-mo pilot study, absolute and relative adrenal weights were decreased in females at all doses (16-31%), but were increased in MDM. In the 3-mo + recovery study, relative adrenal weight was increased in MDM (27%) and HDM (38%), but decreased in HDF (18%); relative adrenal weight was increased by 18% in HDF. At 1-yr, relative and absolute adrenal weight were increased in HDM (24-55%), but decreased in HDF (10-20%). In general, adrenal weight tended to be increased in males and decreased in females. Changes in weight of spleen, kidney, and lung were noted in one or more studies, but not in the 1-yr study. In addition to the changes in liver and adrenal weight observed in the 1-yr study, decreases in thymus weight (10-20%) were noted in MDF and HDF.

Histopathology findings were consistent and primarily involved effects in males and females consistent with hyperprolactinemia. Stimulation of the mammary gland development and secretion was consistently observed in females at all doses. In males, longer exposure and higher doses, in general, were required for risperidone to exert changes in mammary gland. No changes were noted at 1 mo. At 3 mo, "feminization" of mammary gland tissue was evident (often including secretion) in some males at all doses, but was more evident at the MD and HD. At 1-yr, mammary gland development and secretion were noted in all HDM. Other findings noted in females were decreased corpora lutea, decreased uterine gland development, and decreased vaginal cornification and epithelial thickening. At 1 mo, these changes were noted only HDF; with longer duration of treatment, uterine and vaginal changes were noted in females at all doses. In males, inflamation of the prostate (neutrophilic infiltration, inflamation of prostatic tubules, increased prostatic granulocytes) was noted in 3-mo and 1-yr studies primarily at the HD, but also noted at the MD in one 3-mo study. Swelling and diffuse hyperplasia of the pituitary was noted only in males and only in the 1-yr study.

In the 3 mo + recovery study, most histopathology findings (excluding neoplasms) were reversible; however, mammary gland and uterine changes were still evident in HDF at the end of the recovery period.

A number of neoplasms were detected at the end of the 1-yr study. Mammary gland masses were noted in 1 LDF and 3 HD animals (1 fibroadenoma in a HDM, 3 adenocarcinomas (1 LDF, 2 HDF). Other findings include lymphocytic-lymphoblastic leukemia (1 LDM), renal adenocarcinoma (1 MDF), squamous carcinoma (1 LDM, 1 HDF) and lymphocytic leukemia, a menigioma, and a thyroid adenoma (in controls).

Dogs were treated with risperidone at doses of 0, 0.31, 1.25, and 5.0 mg/kg except in the 1-mo pilot study in which doses were 0, 0.16, 0.63, and 2.5 mg/kg. Risperidone was given in a gelatin capsule in the two 3-mo studies and 1-yr study. The formulation used in the 1-mo pilot study was not specified. The 3-mo + recovery study only included male dogs; therefore, there was no attempt to study the reversibility of drug-related effects in female dogs. The most common **clinical sign** was sedation. As observed in the 3 mo studies and the 1yr study, sedation was slight in all LD, moderate in MD and severe in all HD. Slight catalepsy was noted in HD animals in the 1-mo pilot study and tremor and decubitus was observed in some HD animals in the 3-mo (no recovery) study. In the 1-yr study, the only clinical sign was sedation. The initial effect of risperidone on **body weight** was to reduce body weight gain at the HD. In the 1-mo pilot study, body weight was increased except at the HD at which there was a slight weight loss during Wk 2-3. In the 3-mo studies, body weight gain was decreased for the first 1-9 wks in the HD animals, but by the end of the study body weight gain was comparable among groups. In the 1-yr study,

initial decreased body weight gain was followed after about 6 wks with accelerated weight gain. By the end of the study, the body weight gain of treated animals were up to 100% higher than that of control, with MD and HD being similar. There were no drug-related **ophthalmic** findings.

Drug-related effects were noted on several **hematology** parameters. Decreases (5-15%) in hct, hgb, and rbc were observed in all but the 1-mo pilot study. In the 1-yr study, these parameters were decreased in MD and HD dogs during the first 12 wk, but returned to normal after this period. Haptoglobin was increased in a dose-related manner in the 1-mo pilot (MD, HD: 43-82%), 3-mo (no recovery; 56-115%) and 1-yr (50-70%) studies. Decreased thrombocytes (72-92%) at all doses and decreased monocytes (38%) at the HD were observed in the 3-mo + recovery study. Changes were also noted in a number of **clinical chemistry** parameters. Serum K+ was decreased 4-10% at all doses in the 3-mo (no recovery) study, but only in the HD in the 1-yr study. Increases in serum cholesterol (30-70%) and phospholipid (20-40%) were observed in MD and HD animals at 3 mo, but at all doses (dose-related) at 1-yr. Findings observed only in one study include a 12-27% increase in serum glucose in all groups (3-mo) and a consistent elevation (10-20%) in serum Ca (1-yr). In the 3-mo + recovery study, all drug-related effects on hematology and clinical chemistry parameters were reversible.

The only consistent drug-related findings on **urinalysis** parameters were decreased pH (3-16%) at all doses in the 3-mo + recovery study and an increase in urinary creatinine (70%) at all doses in the 1-yr study. The latter finding may reflect the increased body weight gain and food consumption in that study.

ECG analysis revealed no effects of risperidone on heart rate or ECG; however, it is unclear when the examination was performed in relation to dose, making the result difficult to interpret.

Analysis of **serum testosterone and LH** (in the 3 mo + 2 mo recovery study) indicated that risperidone had no effect on serum LH; however, there was a dose-related decreased in serum testosterone (C: 9.1, LD: 6.3, MD: 3.4, HD: 2.3 nmol/L). The effect on serum testosterone was reversed at the end of the recovery period in both LD dogs, but in only 1 MD and 1 HD dog. In the other MD and HD dogs, serum testosterone levels continued to decrease (MD: from 4.8 to 2.7, HD: from 3.2 to 0.9) during the recovery period. Collection of sperm was very difficult in risperidone-treated dogs. At the LD, sperm could be collected in 2/6 dogs; in MD and HD dogs, sperm could not be collected at the end of the main study . At the end of the recovery period, sperm could only be collected in 1 MD and 1HD dog. Sperm collected from MD dog appeared normal, whereas, that from the HD dog had reduced motility and low concentration. Therefore, risperidone clearly had an adverse effect on sperm quality which was still evident at the end of the 2-mo recovery period. There was no NOEL since sperm volume was reduced or nonexistent in LD animals. The LD is similar to 35% higher than the proposed maximum therapeutic dose in humans.

A number of drug-related changes in **organ/tissue** weight were observed (gross pathology and histopathology were not performed in the 1-mo pilot study). Absolute and relative spleen weight was increased in a dose-related manner in the 3-mo and 1-yr studies. In the 3-mo study (no recovery) spleen weight was increased by 16-25% and 8-23% for absolute and relative weight, respectively. In the 1-yr study, spleen weight was 2-fold higher in drug-treated than in control. Gonad weight was consistently reduced in males and females. Decreases ranged from 18 up to 58% and were dose-dependent in males at 3-mo and 1-yr and in females at 1 yr. Absolute and relative prostate weight was consistently reduced: $\geq$50% in MDM and HDM in the 3-mo study, 15-59% (dose-related) in the 3-mo + recovery (still reduced by 59-62 and 32-34% in MDM and HDM, respectively, at the end of the recovery period, and $\leq$58% (dose-related) in the 1-yr study. Small increase in liver weight were noted in the 3-mo and 1-yr studies (5-35%).

Histopathology findings primarily involved prolactin-responsive tissues. In males, incomplete spermatogenesis was observed at 3-mo (1 control, 0/4 LD, 3/4 MD, and 3/4 HD) and an increased incidence of degeneration of testicular tubules (1-yr) and fibrotic prostate were noted at all doses at 1-yr. At 3-mo, the incidence of fibrotic, immature prostate was increased only at the MD and HD. In addition, there was a dose-related decreased in prostate development at 3-mo, although the effect was significant only at the HD. In females, there were decreases evident in uterine development, in vaginal epithelial thickness, and an absence of corpora lutea (in all MD and HD at 1 yr, and in 15/16 risperidone-treated females in the 3-mo study). The data were inconsistent in terms of the effect of risperidone on mammary

gland development. In the 3-mo study, stimulation of mammary gland development was noted in LDF and MDF, however, in the 1-yr study, mammary gland development was decreased in MDF and HDF. A decrease in mammary gland development is inconsistent with the known actions of prolactin and data obtained in rat. (Prolactin levels were not monitored in the dog.) Increases in rbc content of spleen (red pulp) were observed in at all doses at 1-yr and in MD and HD or HD only at 3 mo. This finding was reversible in males.

Plasma levels of risperidone and 9-hydroxy-risperidone were measured in the 3 mo (no recovery) and 12 mo oral toxicity studies. In the 3 mo study, plasma levels of both compounds tended to be lower on Day 93 than on Day 1; however, in the 12-mo study, a similar trend was not observed. In the 12-mo study, plasma levels of risperidone and 9-hydroxy-risperidone were slightly higher at the end of the study than on Day 1. Overall, plasma levels of 9-hydroxy-risperidone were ≈2-fold higher than those of risperidone. In the 3 mo study, the plasma levels of risperidone and 9-hydroxy-risperidone were 50-76 and 156-188 ng/ml at the LD (0.31 mg/kg), 101-243 and 765-946 ng/ml at the MD (1.25 mg/kg), and 530-815 and 1248-1588 ng/ml at the HD (5 mg/kg). In the 12-mo study, the values were 105-117 and 160-251 at the LD, 245-375 and 587-766 at the MD, and 503-726 and 1576-2236 ng/ml at the HD. The doses in the 12-mo study were the same as in the 3 mo study.
In summary, the following observations were made:

Rat (doses are compared to the proposed maximum human dose of 10-16 mg/day, i.e., 0.2-0.3 mg/kg)

(1) The lowest doses of risperidone associated with mortality in acute toxicity studies were:

males: 28.3, 160, and 80 mg/kg for i.v., s.c., and p.o. dosing, respectively.
females: 28.3, 40, and 40 mg/kg for i.v., s.c., and p.o. dosing, respectively.

The lowest dose of 9-hydroxy-risperidone associated with mortality in an acute oral toxicity study were 80 mg/kg and 40 mg/kg for males and females, respectively. Thus, both risperidone and 9-hydroxyrisperidone were more acutely toxic in females than in males. For risperidone, this is consistent with higher plasma levels of risperidone in females than males after doses of 0.16-10 mg/kg (based on 2/sex/grp).

(2) In acute toxicity studies, the most common clinical signs were CNS effects such as sedation, ataxia, catalepsy, prostration, and convulsions (at high doses). There was no NOEL; convulsions were observed at ≥160 mg/kg p.o. and ≥28.6 mg/kg i.v. in males and ≥320 mg/kg p.o. and ≥23.8 mg/kg i.v. in females. No convulsions were noted after s.c. dosing. Although plasma exposure to risperidone tends to be higher in females per dose than males, males exhibited convulsions at lower doses than females. This suggests that either males are more susceptible to the convulsant effects of risperidone or that 9-hydroxy-risperidone may affect seizure threshold to a greater extent than risperidone. Per dose, plasma exposure to 9-hydroxy-risperidone tended to similar or higher in males than females. In addition, convulsions were noted at lower doses of 9-hydroxy-risperidone in males than females (80 vs 320 mg/kg, respectively).

There were no drug-related clinical signs associated with doses of risperidone of up to 10 mg/kg in subchronic and chronic toxicity studies. This suggests that the HD could, and, perhaps, should have been increased for these studies. The HD used is 30-50 fold higher than the proposed maximum therapeutic dose in humans.

(3) In males, body weight was decreased compared to controls primarily at the HD. In females, body weight was elevated at lower doses (0.16-2.5 mg/kg; the low dose being similar to the proposed human dose) and decreased compared to controls at the HD.

(4) No drug-related ophthalmic findings were noted.

(5) Drug-related changes were observed in several hematology and clinical chemistry parameters, primarily at the HD: (a) small decreases in platelets and wbcs at the HD, (b) small, non-dose-related increases in rbc, hct, hgb, MCH, and/or MCV, (c) decreased serum total protein and albumin at the HD, and (d) increased BUN at the MD and HD in males and at the HD in females.

The slight increase in rbc indices is suggestive of slight dehydration. The decrease in serum proteins (primarily albumin) suggests a slightly reduced synthetic capacity in liver, and may contribute to the slight hemoconcentration. Increases in BUN are also consistent with mild dehydration in the absence of elevated plasma creatinine levels.

(6) Although change in the weight of various organs/tissues were noted in risperidone-treated rats (e.g., liver, adrenal, spleen, kidney, lung, and thymus), histopathological findings were noted only in prolactin-responsive organs/tissues. Stimulation of mammary gland development and secretion were consistently observed in males and females. The effect in males, in general, was noted after longer duration of treatment (≥1 mo) and at higher doses (some changes were noted at LD, but secretion noted primarily at the HD) than in females. Other histopathological changes noted in females at all doses after 1 mo. include decreases in corpora lutea, uterine gland development, and vaginal cornification and epithelial thickening. This would suggest that risperidone would have significant effects on female reproductive fertility.

In males, inflammation of the prostate and prostatic tubules (neutrophilic infiltration, increased prostatic granulocytes) was noted primarily at the HD, but also at the MD in one study. Swelling and diffuse hyperplasia of the pituitary gland was noted in HDM at 1 yr.

At the end of the 1-yr study, neoplasms were detected in risperidone-treated and control animals. Mammary gland masses were noted in 1 LDF (adenocarcinoma) and 3 HD animals (fibroadenoma, adenocarcinoma).

Dog (doses are compared to the proposed maximum human dose of 10-16 mg/day, i.e., 0.2-0.3 mg/kg)

(1) The lowest dose of risperidone associated with mortality in acute toxicity studies was 20 mg/kg for p.o. and i.v. dosing. No mortality occurred at 10 mg/kg, but 3/4 to 4/4 dogs died at 20 mg/kg. This dose is 70-100 fold higher than the proposed human dose The data were similar for males and females.

(2) In acute toxicity studies, the most common clinical signs indicated CNS effects and were similar to those observed in the acute toxicity studies in rats (i.e., ataxia, prostration, sedation, and tremors). In addition, diarrhea, defecation, salivation and loss of righting reflex were also observed in dogs. Catalepsy was exhibted by a few animals. Clonic convulsions, salivation, loss of righting reflex, and tremors were observed primarily at the HD and, except for tremors, were associated with mortality. There was no NOEL. The LD was 8-12 fold higher than the proposed human dose.

In the subchronic and chronic studies, the main clinical sign was a dose-related increase in the severity of sedation. Slight catalepsy , tremors, and decubitus was observed at the HD in subchronic studies; however, in the 1-yr study, only sedation was observed.

(3) The initial effect (1-9 wks) on risperiodone on body weight was to decrease body weight gain. Thereafter, in the 3-mo study, body weight gain was comparable among groups. In the 1-yr study, body weight gain in risperidone-treated animals increased up to 100% above control values, with weight gain being similar at MD and HD.

(4) As in rats, there were no ophthalmic findings. No changes in ECG parameters were noted; however, the interval between dosing and measurement was not specified, making interpretation difficult.

(5) A number of drug-related findings were noted on hematology and clinical chemistry parameters. The most consistent finding was a dose-dependent increase in serum haptoglobin which was observed in the 3-mo (no recovery) and 1-yr studies. Increases of haptoglobin occur in acute phase reactions, i.e., in reaction to a variety of conditions including inflammation and stress. The implications for the increased levels noted in the toxicity studies is unclear. Other observations include increases in serum cholesterol and phospholipid (at MD and HD at 3 mo, and at all doses at 1 yr) and small decreases in serum K^+ at all doses at 3-mo, but only in HD at 1 yr.

(6) Analysis of serum testosterone and LH levels revealed no effect of risperidone on LH; however, risperidone had a marked dose-related effect on serum testosterone. Serum testosterone levels in risperidone-treated dogs (3 mo duration) were reduced 30-75% during dosing. This effect was reversible in 2/2 LD, but only in 1/2 MD and 1/2 HD dogs at the end of a 2-mo recovery period. Collection and analysis of sperm indicated reduced quality and quantity of sperm at all doses, but expecially at the MD and HD. In fact, sperm could not be collected from MD and HD dogs (6/grp) during the main study , and could be collected from only 1/2 MD and 1/2 HD dogs at the end of the recovery period. At the LD, sperm could only be collected from 2/6 dogs. Therefore, there was no NOEL for the risperidone effect on serum testosterone. The LD is $\leq$1.4 fold higher than the proposed maximum therapeutic dose in humans. Plasma drug levels were not analyzed in the 3 mo + 2 mo recovery study. However, based on a comparison of C_{max} (dog) obtained in the 3-mo and 12-mo dog studies and steady state (human) levels, the plasma exposure for risperidone and 9-hydroxy-risperidone was $\approx$8-9 fold and $\approx$1 5-2.5 fold higher, respectively, at the LD in dogs than at the maximum proposed therapeutic dose in humans.

(7) The primary changes (dose-related) in the organ/tissue weight were noted in spleen (increased in absolute and relative weight at 3 mo and 1 yr), gonads (reductions in males and females, especially at 1 yr), and prostate (decreased, even after recovery period at MD and HD). Histopathological findings were consistent with organ/tissue weight changes. In males, incomplete spermatogenisis (at 3 mo in MD and HD dogs), and an increase in degeneration of testicular tubules and fibrotic prostate were noted at all doses at 1 yr. In females, there was evidence of decreased uterine development, in vaginal epithelial thickness, and an absence of corpora lutea (at MD and HD in 1-yr study, but at all doses in 3-mo study). These data suggest a deleterrious effect of risperidone on male and female reproductive fertility, and are consistent with findings in rat. The data on mammary gland development were inconsistent. Stimulation of mammary gland development was noted in LD and MD females in the 3-mo study; however, decreased mammary gland development was observed at similar doses in the 1-yr study. No effect was noted in males. Considering that other histopathological changes noted in dog are consistent with hyperprolactinemia (e.g., reduced uterine development), the lack of a consistent effect on mammary gland development make the data difficult to interpret.

One other consistent histopathology finding was an increase in the rbc (red pulp) content of spleen . This finding was observed at MD and HD or HD only at 3-mo, but at all doses at 1-yr.

REPRODUCTIVE STUDIES

Segment I studies: Three Segment I studies were conducted, one in which both males and females were treated with resperidone, one in which males only were treated, and one in which females

only were treated. In the first study, male and female Wistar rats (24/sex/grp) were dosed with 0, 0.31, 1.25, or 5 mg/kg risperidone (orally, in diet). Females were dosed daily from 2 wks prior to mating to Day 8 of gestation. Males were dosed daily from 60 days prior to mating through the mating period. The only clinical sign was food wastage in HDF group. Dose-dependent reductions in body weight gain were observed in males (5-21%). Body weight was reduced by 50% in HDF compared to controls prior to mating. During pregnancy, body weight gain in HDF was reduced by 10%, but normalized after dosing was terminated (Day 10-22 of gestation). Dose-dependent decreases were noted in the number of animals that mated (controls: 24/24, LD: 17/24, MD: 12/24, and HD: 6/24). The % fertility was, however, only reduced at the HD (control: 22/24, LD: 16/17, MD: 12/12, and HD: 5/6). Time to mate was increased at the LD and HD (control: 2, LD: 5, MD: 3, HD: 9.5 days). Skeletal analysis of fetuses revealed no drug-effect, except for possibly an increase in wavy ribs (considered to be a minor variation). The incidence of wavy ribs was increased in treated animals, both in terms of % of total fetuses and % of total litters/grp: expressed as % of total fetuses/grp, 2.6% for control, 3.3% for LD, 5% for MD, and 13% for HD; expressed as % of total litters/grp, 9% for control and 33-40% for drug-treated rats.

In the second Segment I study, male Wistar rats (24/grp) were adminstered risperidone (by gavage) at doses of 0, 0.16, 0.63, and 2.5 mg/kg for ≥60 days prior to mating and throughout the mating period. Females were not treated. No clinical signs were observed at any dose. One male died during the premating period, but the cause of death was not determined. There was evidence of pneumonia at necropsy. Body weight was reduced only in the HD group as compared to controls (9%). No drug related effects were noted on any fertility or reproductive performance parameter. There were also no drug-related effects on skeletal examinations in fetuses. The % of total fetuses/grp with wavy ribs was increased at MD and HD (control: 4.8%, LD: 4.6%, MD: 5.8%, and HD: 9.2%); however, the % of affected litters/grp was similar among groups.

In the third Segment I study, female Wistar rats (24/grp) received risperidone daily by gavage at doses of 0, 0.16, 0.63, and 2.5 mg/kg. Dosing was continued from 14 days prior to mating through Day 8 of gestation. Males were not treated. The primary clinical sign was sedation, and was observed in MDF and HDF. Body weight was reduced by 5% in HDF, but only during the pre-cohabitation period. At other doses, body weights were similar to control. The only drug-related effect was an increase in cohabitation-mating interval evident at all doses (control: 2, LD: 5, MD: 4.5, HD: 11 days). In addition, the number of animals with a mating interval greater than two normal estrus cycles (i.e., ≥8 days) was increased at all doses (control: 10.5, LD: 44, MD: 44, HD: 70.6%). All other parameters exhibited no drug-related effects. Skeletal examination of fetuses revealed no drug-related effects.

From these Segment I studies, it is evident that risperidone affects mating behavior at the doses tested, primarily in females. The doses used were similar (0.8 fold) to 45 fold higher than the proposed human dose (8-10 mg/day and up to 16-fold higher than the maximum proposed human dose. The only consistent effect of risperidone was a dose-related increase in the mating interval during cohabitation (i.e., time to mate). This effect was observed in the study in which males and females were treated and in the study in which only females were treated. Drug-related changes in the number mated and % fertility were observed only in the study in which both males and females were treated. The HD (5 mg/kg) used in this study was higher than that (2.5 mg/kg) in the male-treated or female-treated studies. Treatment at 5 mg/kg resulted in toxicity in both males and females, evidenced primarily as reduced body weight gain. Fertility was reduced only at the HD and, therefore, may be the result of toxicity in males and/or females. The reduction in the number mated, however, was dose-related, and was evident at the LD (0.31 mg/kg). This finding was not replicated in the other Segment I studies. For this reason, effects of risperidone on male reproductive behavior cannot be ruled out. The reason for the discrepancy is unclear, but may be related to procedural differences among the studies, such as route of administration.

Segment II studies: four Segment II studies were conducted, 3 in rats and 1 in rabbits. In the first two Segment II studies in rats, risperidone was administered to females (24/grp) by gavage on Day 6 through Day 16 of gestation at doses of 0, 0.63, 2.5, and 10.0 mg/kg. Dams were sacrificed on Day 22. In the first Segment II study, palpebral ptosis was noted in dams at the HD and maternal gestational body

weight gain was reduced at MD and HD (by 2 and 13%, respectively). The only drug-related finding was reduced body weight (6%) at the HD. There were no drug-related findings upon gross examination of fetuses. Skeletal examination was performed by radiography on all fetuses. Apparently, no fetuses were examined using the Alizarin red staining technique. No drug-related skeletal abnormalities/variations were noted. In the second Segment II study in rats, palpebral ptosis was noted at all doses (in 1 female only at LD) and maternal body weight gain was reduced by 28% in HDF. Skeletal examination was performed by radiography on all fetuses and with Alizarin red stain in 1/2 of the fetuses in each litter. The only drug-related finding noted was a dose-related increase in the number of skeletal variations, particularly missing phalanges. The % of affected litters (i.e., at least 1 affected fetus per litter) for missing phalanges was 2.7, 3.2, 5.1, and 7.6% for control, LD, MD, and HD, respectively.

In the third Segment II study in rats, risperidone was administered to females (F_0; 36/grp) by gavage on Day 8 through Day 18 of gestation at doses of 0, 0.63, 2.5, and 10 mg/kg. Twenty-four dams/grp were sacrificed on Day 22 of pregnancy. Twelve dams/grp were allowed to deliver naturally and followed through lactation and weaning. Pups (F_1) were evaluated for behavioral and physical development. One male and one female per litter (a total of 10/sex/grp) were selected at random for mating; the remaining were sacrificed. At 3 mo of age, the F_1 generation "pups" were mated. On Day 22 of gestation, dams were sacrificed and adults and fetuses were examined. The primary clinical sign noted in all drug-treated F_0 generation dams was sedation. The degree of sedation increased with dose (slight in 24/24 LDF, moderate in 24/24 MDF, and severe in 24/24 HDF). Body weight was affected by risperidone, but only in HDF (reduced by 5-7%). The number of corpora lutea was 6.8% higher in treated dams than in controls. The number of resorptions was elevated at the LD compared to controls (1.05 and 0.55/litter, respectively). Although there was no increase in the number of resorptions at the HD, there was a high number of resorptions in 2 HD litters (12/12 and 8/13). Examination of fetal visera revealed no drug-related effects. Skeletal examination of fetuses (data on examination of 1/2 of each litter) revealed an increased incidence of some skeletal variations/abnormalities at the MD and HD, such as one rudimentary 14th rib, rudimentary 14th pair of ribs, and asymetric sternum bone(s). The incidence of reduced number of metatarsal bones was increased only in the HD fetuses. In the F_1 pups, body weight was elevated in all drug-treated males and LD females by the end of lactation as compared to controls. Physical and behavioral development of F_1 pups was similar among groups except for a possibly drug-related increase in horizontal activity at 5 wk postpartum. Mating and fertility of F_1 rats were comparable among groups and examination of F_2 pups revealed no clear drug-related findings.

In the Segment II study conducted in white rabbits, risperidone was administered by gavage to 15 rabbits/grp on Day 6 through Day 18 of gestation at doses of 0, 0.31, 1.25, and 5.0 mg/kg. Does were sacrificed on Day 28 of gestation. Three HD does died during the study; deaths were presumed to be drug-related by the sponsor. The pregnancy rate was similar for all groups (73-80%); therefore, there were fewer pregnant does/grp than recommended in the guidelines (i.e., 12 pregnant does/grp), especially for the HD group in which there were only 9 pregnant does. HD does lost body weight (mean loss of 100 g) during dosing, whereas other groups gained (117-169 g). There were no drug-related effects on any of the reproductive parameters analyzed (e.g., litter size, resorptions, survival rate, fetal body weight). The primary drug-related observation upon skeletal examination was the incidence of extra ribs on the 13th thoracic vertebra: 21/85 (25%) in control, 14/65 (21%) at LD, 40/102 (39%) at MD, and 44/73 (60%) at HD.

The first Segment II study was inadequate in terms of skeletal analysis; a radiographic technique was used instead of the more sensitive Alizarin red stain. This is the only Segment II study in which a drug-related increase in skeletal abnormalities/variants was not noted. In the other Segment II studies in rats, dose-related increases in a number of skeletal variants/abnormalities were noted, including missing phalanges, rudimentary 14th pair of ribs, one rudimentary 14th rib, and asymmetric sternum bones. The doses associated with these observations range from 3-90 fold higher than the proposed therapeutic dose in humans (8-10 mg/day). In the rabbit Segment II study, there was an increase in extra ribs on the

13th thoracic vertebra at the MD and HD. These doses are 6-11 and 25-45 fold higher than the proposed human dose. No visceral abnormalities were noted in any of the Segment II studies. The study of F_1 and F_2 rats indicated no drug-related effects on behavior, mating or fertility. The only possibly drug-related finding was elevated body weight in F_1 male pups of all drug-treated dams and in F_1 female pups of LD dams.

Segment III studies: Two Segment III studies were conducted in rats. In the first study, female Wistar rats (24/grp) were adminstered risperidone in the diet at doses of 0, 0.31, 1.25, and 5.0 mg/kg from Day 16 of gestation through Day 21 of lactation. Body weight **gain** was reduced by 43% in the HD group on Days 16-21 of gestation, whereas, there was a dose-dependent reduction in body weight (by 6-19% compared to controls) during lactation. Drug effects were noted on pup survival and pup weight on Day 4. Pup survival on Day 4 was only 34.7% in the HD grp compared to 83.1-86.5% for the LD, MD and control grps. Pup body weight in the HD grp was also reduced compared to that in the LD, MD and control grps (8.0 g vs 9.8-10.2 g). Survival was not further affected after Day 4 and pup body weights were comparable among groups on Day 21 of lactation (weaning).

In the second Segment III study, risperidone was adminstered to female Wistar rats (24/grp) by gavage at doses of 0, 0.16, 0.63, and 2.5 mg/kg from Day 18 of gestation through Day 21 of lactation. After weaning, 1 male and 1 female pup was randomly chosen from each litter for subsequent mating (at 3 mo of age). There was an increase in the number of dead pups at birth in the HD grp (mean of 1.27 vs 0.08 pups/litter for HD and control, respectively). There were no consistent drug effects on pup body weight. Survival rate was reduced at all doses, being lowest at the HD (control: 80.8, LD: 55.1, MD: 56.0, HD: 34.7%). After Day 4, survival tended to be similar among all groups. The sponsor attributed the reduced survival rate in treated groups to impaired lactation performance due to risperidone. However, the observation that the survival rate in control litters of dams with poor lactation performance was greater than that in litters of drug-treated dams suggests the possibility of a deleterious effect of risperidone on the pups. In the F_1 generation, there were no drug-related effects on body weight or fertility in adults. There was an increase in resorptions in offspring of HD dams; this was attributed to the increased number of corpora lutea in the HD group by the sponsor. The number of corpora lutea were, however, fairly comparable among groups (control: 16.8, HD: 17.3/dam). The only finding in F_2 fetuses was in increase in the incidence of rudimentary 13th pair of ribs in the HD group (10/114 in HD vs 1/109-1/142 in other groups).

The one consistent drug-related effect in the two Segment III studies was reduced pup survival rate during the first 4 days postpartum. In one study, this effect was noted only at the HD (5.0 mg/kg). The doses in the second study were lower, but reduced pup survival rate (Day 4) was noted at all doses (0.16-2.5 mg/kg). The reason(s) for the discrepancy is unclear, but may be due to differences in procedure (e.g., route of administration) between the two studies. The LD and MD used in the second study are similar to, whereas the HD is 8-11 fold higher than, the proposed human dose (0.22-0.32 mg/kg/day). It is difficult to determine if the reduced survival rate is due to an effect of risperidone on the dam or pup, or both. There was a dose-dependent increase in the incidence of impaired lactation behavior (no detailed description was given). However, lactation behavior is affected by a variety of factors, and altered pup behavior (e.g., reduced auditory signals) may also result in altered maternal behavior.

Reproductive capacity study in Wistar rats (2-generation reproductive study with 1 litter per generation): This study was a combined Segment I, II, and III in rats. Risperidone was administered only to the F_0 generation (24/sex/grp) in the diet at intended doses of 0, 0.16, 0.63, and 2.5 mg/kg. F_0 males were treated for 60 days prior to a during mating (maximum of 14 days). F_0 females were treated for 14 days prior to and during mating, and throughout pregnancy and lactation. The main clinical sign noted in both males and females was food wastage, especially at MD and HD. This prevented accurate calculation of actual dose. Risperidone had no effect on body weight during the cohabitation period in either males or females. During pregnancy, body weight was reduced in HD dams by 9%

compared to controls. Risperidone markedly affected pregnancy and copulation indexes at the HD (37.5% vs 95.7% for HD and control, respectively, for both indexes). There was also a dose-dependent increase in the cohabitation mating interval (i.e., time to mate) (control: 2.4, LD: 6.3, MD: 9.4, HD: 11.6 days). Fertility was not affected.

In F_1 generation pups, birth weight was slightly reduced only at the HD. During lactation, body weight in LD and MD pups tended to be somewhat elevated (15 and 24%, respectively), but was comparable among groups by the end of lactation. Survival rate was reduced on Day 4 postpartum in LD and HD groups (control: 81.9, LD: 70.8, MD: 75.1, HD: 72.2%), but was comparable among groups, although still slightly lower at the HD, by Day 14 of lactation (on Day 21, control: 60.9, LD: 59.2, MD: 62.9, HD: 50.0%). The sponsor attributed the reduced survival rate to impaired nursing behavior in drug-treated dams. However, the data indicate that only 1 LD dam was observed to exhibit such behavior during the first few days of lactation. External examination of pups revealed no drug-related abnormalities. Physical and behavior development (including horizontal activity) appeared normal in all groups, except for a delay in vaginal opening in HD female pups.

In F_1 generation rats during pregnancy, food wastage was increased only in females of HD dams, and body weight was elevated in females of LD and MD dams. There were no differences in mating or fertility parameters among groups. The only possibly drug-related finding was an increase in a number of skeletal abnormalities in MD F_2 fetuses. These include incomplete ossification of frontal bone and supraoccipital bone, one rudimentary 13th rib, and a reduced number of metatarsal bones.

Skeletal examinations (methods summary): The sponsor was asked to summarize the method(s) used for skeletal analysis in the reproductive studies since the descriptions varied among studies and the exact methods and the number of fetuses examined per method per study were unclear. A summary was provided in the sponsor's submission dated 3/29/93 (attached). All fetal skeletons were examined radiographically and 50% of fetuses (selected randomly) were examined with Alizarin red staining in the male-treated only and female-treated only Segment I studies, in 3 Segment II studies in rat (one with 2nd generation analysis), in the Segment III study, and in the multigeneration (combined Segment I, II, and II) study. Only radiographic analysis was performed on rabbit fetal skeletons in the Segment II study. Although Alizarin red staining is the preferred method for skeletal analysis, radiographic analysis is generally acceptable in rabbit studies.

Plasma drug levels: Plasma drug levels were not analyzed in any of the reproductive studies. Although plasma levels were measured in other studies, including the 3-mo and 12 mo oral toxicity studies in rats, the data are inconsistent and incomplete. In some studies, risperidone levels only were measured (i.e., plasma levels the major (active) metabolite, 9-hydroxy-risperidone, were not measured). In addition, in dietary studies the time interval between removal of the diet and collection of blood for plasma drug analysis was not controlled; therefore, in these cases the plasma data are of little or no value. In gavage studies, plasma risperidone levels varied widely between studies (e.g., following a single dose of 1.25 mg/kg, C_{max}=416 ng/ml; following dosing at 0.63, 2.5, and 10 mg/kg, 1 hr plasma levels were 10.5-69.9, 94-117, and 370-990 ng/ml). Plasma risperidone levels reported at the end of a 3-mo dietary toxicity study (no indication of diet removal-plasma collection time interval) were 5.3-15.5 and 21.6-71.2 mg/kg at 2.5 and 10 mg/kg, respectively. It is very difficult, then, to estimate plasma exposure to either risperidone or 9-hydroxy-risperidone during the reproductive, as well as other, studies. Comparisons, therefore, are between animal doses and proposed human doses estimated in mg/m^2.

(1) the doses associated with adverse effects on mating in rats range from 8-fold lower to 4-fold higher than the maximum recommended human dose (MRHD; 16 mg/day; 10.9 mg/m^2).

Risperidone Preclinical Reproduction Studies Fetal Skeletal Evaluation Summary			
Study Description	Total number of fetuses examined by;		Methods Reference
	Radiographic methods	Alizarin staining methods	
Segment I (♀ & ♂) Wistar rat N 64502 / Exp. 1829 Report date: November 1988, Belgium	Control: 268 0.31 mg: 210 1.25 mg: 156 5.00 mg: 61 TOTAL 695	None examined	1
Segment I (♂) Wistar rat N 84191 / Exp. 2327a Report date: December 1991, Belgium	Control: 227 0.16 mg: 240 0.63 mg: 224 2.50 mg: 282 TOTAL 973	Control: 117 0.16 mg: 126 0.63 mg: 117 2.50 mg: 146 TOTAL 506	2
Segment I (♀) Wistar rat N 84192 / Exp. 2327b Report date: December 1991, Belgium	Control: 236 0.16 mg: 242 0.63 mg: 229 2.50 mg: 212 TOTAL 919	Control: 122 0.16 mg: 124 0.63 mg: 120 2.50 mg: 110 TOTAL 476	2
Segment II Sprague-Dawley rat N 51864 / Exp. -788/86-05 Report date: July 1986, France	Control: 249 0.63 mg: 250 2.50 mg: 262 10.0 mg: 230 TOTAL 991	None examined	1
Segment II Sprague-Dawley rat N 71471 / Exp. 2077/89-08 Report date: January 1990, France	Control: 225 0.63 mg: 247 2.50 mg: 254 10.0 mg: 225 TOTAL 951	Control: 116 0.63 mg: 128 2.50 mg: 132 10.0 mg: 116 TOTAL 492	2a

Fetal Skeletal Evaluation Summary (continued)

Segment II Wistar rat w/ 2nd generation N 84095 / Exp. 2328 Report date: November 1991, Belgium	F_1 Generation		2
	Control: 250 0.63 mg: 236 2.50 mg: 266 10.0 mg: 258 TOTAL 1010	Control: 125 0.63 mg: 122 2.50 mg: 137 10.0 mg: 134 TOTAL 518	
	F_2 Generation		
	Control: 132 0.63 mg: 120 2.50 mg: 132 10.0 mg: 142 TOTAL 526	Control: 60 0.63 mg: 62 2.50 mg: 69 10.0 mg: 73 TOTAL 264	
Segment II New Zealand white rabbits N 56347 / Exp. -804/86-13 Report date: December 1986, France	Control: 85 0.31 mg: 65 1.25 mg: 102 5.00 mg: 73 TOTAL 325	None examined	3
Segment III Wistar rat w/ 2nd Generation N 84093 / Exp. 2078 Report date: November 1991, Belgium	F_2 Generation		2
	Control: 128 0.16 mg: 142 0.63 mg: 109 2.50 mg: 114 TOTAL 493	Control: 66 0.16 mg: 74 0.63 mg: 54 2.50 mg: 59 TOTAL 253	

Fetal Skeletal Evaluation Summary (continued)			
Two generation Wistar rat reproduction N 84094 / Exp. 2180 Report date: November 1991, Belgium	F_2 Generation		2
	Control: 277 0.16 mg: 288 0.63 mg: 277 2.50 mg: 217 TOTAL 1059	Control: 143 0.16 mg: 149 0.63 mg: 145 2.50 mg: 113 TOTAL 550	

1) Radiographic examinations are carried out for all fetuses of all groups. Rat fetuses of each litter are randomized for dissection (one-third) and if indicated, by the results of the radiographic examination, for clearing and bone staining with alizarin.

2) Radiographic examinations were carried out for all fetuses of all groups and one-half of the rat fetuses of each litter were randomized for dissection, whereas the other half was examined using the Alizarin stain.

2a) This study was conducted to supply further support to the conclusions of experiment -788/86-05, report number N 51864, particularly in regard to the low number of skeletal abnormalities present in that study. For this study, radiographic examinations were carried out for all fetuses of all groups and one-half of the rat fetuses of each litter were randomized for dissection, whereas the other half was examined using the Alizarin stain.

3) Radiographic examinations are carried out for all fetuses of all groups. All rabbit fetuses of each litter are dissected for organ examination and if indicated by the results of the radiographic examination for clearing and bone staining with alizarin.

(2) the doses associated with reduced pup survival during the first 4 days postpartum are similar to and up to 4 fold higher than the MRHD.

In summary, the following observations were made:

1. Risperidone adversely affected mating behavior as evidenced by an increase in the mating interval (i.e., time to mate) and, possibly, by a decrease in the number mated at doses of 0.16-5 mg/kg. At the higher dose (5 mg/kg), fertility was also impaired. However, since body weight in males and females was also reduced at this dose compared to controls, reduced fertility may have resulted from drug-induced toxicity. Although the evidence suggests that risperidone primarily affects female mating behavior, an effect on male mating behavior cannot be ruled out.

Decreases in serum testosterone, sperm volume and quality, and degeneration of testicular tubules were observed in dogs treated orally with risperidone for 3 mo. These findings were noted at doses similar to 35% higher than the proposed maximum therapeutic dose in humans.

2. Risperidone treatment was associated with a small increase in the incidence of a number of skeletal variations/abnormalities, including wavy ribs (minor variation), missing phalanges (delayed ossification), one rudimentary 14th rib, rudimentary 14th pair of ribs, asymmetric sternum bone, and extra ribs on the 13th thoracic verterbra. These findings were noted at doses of 0.63-10 mg/kg. Several factors suggest that these observations (made in consultation with Dr. Ann Wilk) do not indicate teratogenicity of risperidone (in consultation with Dr. Ann Wilk):

(a) the findings are common skeletal variations in rats and are often related to maternal stress, which was evident in HD animals in these studies. Selected historical control data are presented in attached table.
(b) metatarsal, not metacarpal, bones were reduced in number. This is significant in that metatarsal bones are the last to ossify and may be affected by a drug-induced delay in ossification. Metacarpal bones, on the other hand, ossify earlier and should not be affected by such a drug effect. This suggests that risperidone <u>may</u> delay ossification rather than be teratogenic.
(c) In studies in which an increase in skeletal variations were noted in F_2 pups, F_1 pups were not affected. This suggests the absence of a drug effect since it would be highly unlikely that a drug effect would skip a generation.

3. Risperidone treatment, at doses of 0.16-2.5 mg/kg, was associated with a decrease in pup survival during the first four days postpartum. Although the sponsor suggested that decreased pup survival was due to poor lactation performance in the dams, an effect of risperidone on the pups cannot be ruled out.

MUTAGENICITY STUDIES

The mutagenic potential of risperidone was evaluated in the following <u>in vitro</u> and <u>in vivo</u> assay systems (all tests included positive controls):

Ames reverse mutation test using Salmonella and Escherichia coli with and without metabolic activation (S9) at risperidone concentrations of 50-5000 µg/plate (Salmonella) or 25-2500 µg/plate,

chromosome aberration in cultured peripheral human lymphocytes) at risperidone concentrations of 1-100 µg/plate and in Chinese hamster lung fibroblasts at risperidone concentrations of 0.09-0.49 mM with and without metabolic activator (S9),

mammalian gene mutation test with L5178Y mouse lymphoma cells (with independent repeat) at risperidone concentrations of 25-250 µg/mL with and without metabolic activator (S9),

DNA repair in primary culture of rat hepatocytes (with independent repeat) at risperidone concentrations of 0.003-128 µg/mL,

micronucleus test in male and female mice dosed with 2.5-40 mg/kg i.g. risperidone. Structural chromosome aberrations in bone marrow erythrocytes were evaluated 30 hr after dosing,

sex-linked recessive lethal test in Drosophila Melanogaster. Males were fed risperidone (250 and 750 ppm) for 3 days and then mated. F_2 progeny were examined for recessive lethal mutations.

There was no evidence of mutagenic potential in any of the studies. Stability data were provided for risperidone in DMSO (24 hr) and in ethanol (72 hr); temperature was not specified.

CARCINOGENICITY STUDIES

Carcinogenicity studies were conducted in albino Swiss mice and Wistar rats.

Albino Swiss mice, 3-mo dose-range finding study.

The doses used in the 18-mo carcinogenicity study in mice were based on data collected in a 3-mo oral dose-range finding study in albino Swiss mice. Risperidone was presented in the diet at intended doses of 0, 1.25, 5, and 20 mg/kg. The only clinical sign was food wastage which was noted in control, LD and MD males and in females in control and all dosage groups. This precluded accurate quantitation of food consumption, and, therefore, calculation of actual doses. There was no unscheduled mortality. Body weight gain tended to be elevated in females (10-57%) in all dose groups; body weight was 10-16% higher in dosed than in control groups. In males, body weight gain changes were transient and tended to be reduced at the HD (50-100% during Wk 1) but elevated at the MD (27-30%). No marked drug effects were noted on any hematology or clinical chemistry parameters in males. In females, there was a dose-related reduction in glucose (15-25%), and increases in cholesterol and phospholipid at all doses (34-43 and 24-29%, respectively). Organ/tissue weights were affected in both males and females. In HD males, increases in relative and absolute weight of spleen and absolute weight of pancreas were noted. In HD females, increases in absolute and relative weight of pancreas and thymus were noted. Changes in weight of other organs/tissues were noted, but values were within those of historical control. No drug-related gross pathology findings were noted in males. In females, swollen pituitary gland was noted in 2-3/10 in each dose group and there was a dose-related stimulation of the mammary gland. No histopathology nor analysis of plasma drug levels were performed.

The following observations were the basis of dose selection for the carcinogenicity study in mice:

Males

(1) increased weight of kidneys and adrenals in all groups,
(2) "slight" changes in some parameters of blood and serum analysis (only at 20 mg/kg),

Females

(1) increased body weight at all doses,
(2) decreased serum glucose (all doses) and alkaline phosphatase (only MDF were below historical control values),
(3) increased serum cholesterol and phospholipids at all doses,
(4) increased incidence of mammary gland stimulation at all doses,
(5) decreased weight of ovaries at MD and HD.

Albino Swiss mice, 18-mo carcinogenicity study.

Albino Swiss mice (50/sex/grp) were administered risperidone orally (in diet) at intended doses of 0, 0.63, 2.5, and 10 mg/kg for 18 months. Calculation of actual dose was compromised by food wastage and possible analytical problems. The sponsor calculated actual doses as 0.673-0.697, 2.68-2.83, and 10.5-10.7 mg/kg in LD, MD, and HD groups, respectively. There were no significant drug-related effects on mortality, although the mortality rate tended to be higher at the MD and HD in females. The mortality rates in MDF and HDF was somewhat higher (64-66%), whereas in the other groups (including control) the mortality rate ranged from 32-52%. The mortality rates for historical controls was 21.2-22.2% for males and 28.6-30.1% for females. The higher rates in this study make comparisons to historical controls difficult. Spontaneous tumor incidences in the historical controls may be higher as a result of the reduced mortality.

There was no marked effect of risperidone on body weight in males. During the first few weeks, a small decrease in body weight was noted at all doses (3-6%); however, body weight was similar among groups by the end of the study. In females, body weight was similar among dosed groups, but was elevated in all dosed groups (4-18%) compared to controls.

Changes were noted in a number of hematological (females only) and clinical chemistry parameters, including decreases in hct (6-16%) and rbcs (9-15%) at all doses and in hbg (13-14%) at MD and HD in females, and dose-related decreases in glucose in both males (MD: 13%, HD: 26%) and females (10-21%).

Non-tumorous change

Organ/tissue weights: In males, observations included an increase in the absolute and relative weight of spleen (MD: 12-13%, HD: 30-33%), liver (HD: 22-24%), heart (absolute: 7% LD, 12% MD, 18% HD; relative: 12% MD, 15% HD), and kidney (absolute: 8% LD, 16% HD; relative: 6% LD, 7% MD, 13% HD), and a decrease in the relative weight of testes (9% MD, 12% HD). In females, observations included an increase (not dose-related) in absolute (31-42%) and relative (14-26%) liver weight, and a decrease in absolute (28% MD, 33% HD) and relative (19% LD, 38% MD, 38% HD) ovary weight.

Histopathology (see summary tables): In males, the major changes were noted in pituitary (hyperplasia, ectasia), pancreas (inflammatory cell infiltration, "large islets"), seminal vesicles (dilated lumen, accumulated content, inspissated material), and spleen (hyperplasia of red pulp, myelopoiesis) An increase in the incidence of these observations occurred primarily at the HD.

In females, the major changes were noted, at all doses, in mammary gland, pituitary gland, uterus and vagina. Mammary gland changes included increased incidence of fibrosis, hyperplasia, glandular development, inflammatory cell infiltration, and secretion. An increased incidence of hyperplasia was also noted in pituitary gland. Changes in uterus and vagina were indicative of a more restive state.

Tumorous changes

There were no drug-related increases in tumors in males. The incidence of some tumors (e.g., hepatic neoplastic nodule, neoplasia, and carcinomas, and malignant primary lung tumors) were lower in drug-treated males; this decrease may be due, in part, to the higher mortality rate in the current study as compared to that of the historical controls. There is also the question of whether or not the HD approximated the MTD in males.

In females, there was an increased incidence in mammary neoplasms (adenocarcinomas: 0/50 C, 7/50 LD, 18/47 MD, 17/48 HD) and pituitary adenomas (1/48 C, 2/46 LD, 13/45 MD, 21/48 HD). These neoplasms are consistent with hyperprolactinemia resulting from chronic risperidone treatment. There was also a dose-related trend in the incidence of primary lung tumor; however, incidences were within historical control values.

Plasma drug levels

Plasma levels of risperidone and 9-hydroxy-risperidone were analyzed on blood samples collected at autopsy. The interval of time between removal of medicated diet and autopsy ranged from 1 to 8 hrs; therefore, the plasma data are of limited value. The problem was compounded by the need to pool blood samples (n=3-6) of mice sacrificed at different times. The sponsor did analyze the plasma data in terms of time after diet removal and concluded that the plasma concentrations of risperidone and its metabolite "remained fairly constant as a function of time after withdrawal of the medicated food in both male and female mice." The validity, however, of comparing such data among samples is questionable, especially since the samples were pooled samples of up to 6 animals.

With these issues in mind, the data indicated that the levels of risperidone were below the limits of detection in LDM, LDF, and MDF, and the levels of 9-hydroxy-risperidone were undetectable in LDM and LDF. At the HD, mean plasma levels of risperidone were 14.3-14.5 ng/ml in males and females, and of 9-hydroxy-risperidone were 40.9 and 50.6 ng/ml in females and males, respectively. Plasma data were corrected to theoretical doses.

Carcinogenicity study in Wistar rats.

Risperidone was administered orally in the diet to SPF Wistar rats (50/sex/grp) at doses of 0, 0.63, 2.5, and 10 mg/kg. Dosage selection was based on the cumulative toxicological information in rats. [Subchronic and chronic toxicity and Segment I, II, and III studies were conducted in Wistar rats.] The dietary concentration of risperidone was adjusted to changes in body weight and food consumption. There was no description of the assay methods for determination of drug in diet in this study. According to the sponsor, risperidone concentration in diet and stability were verified Calculated doses were 0.6, 2.4-2.5, 9.7-10.1 for LD, MD, and HD, respectively.

Treatment duration was originally scheduled for 24 mo; however, due to a low mortality rate in controls at 24 mo. (28%), the treatment was extended to 25 mo. At 25 mo, the mortality rate for control and LD animals was ≈50%. The decision to extend the study was of questionable value. The mortality rates at 23-24 mo in MDM and HDM were 74 and 66%, respectively. At the end of the study the mortality rate in MDM and HDM increased to 78 and 74%, respectively. In the other groups, the mortality rates were 48 (control male) and 58% (LDM). Overall, in males there was a dose-related increase in mortality rate. In females, there was no statistically significant dose-related trend in mortality rate. At 24 mo, the mortality rates were 28, 36, 38, and 54% for control, LDF, MDF, and HDF, respectively. At the end of the study (25 mo.), the mortality rates had increased to 50, 42, 54, and 60%. Mortality rates in the historical controls (at Wk 108, M: 16-30% and F: 16-25%) were lower than in the current study in both males and females.

There were no dose-related clinical signs. Body weight was reduced (compared to controls) in a dose-related manner throughout the study in males. At the end of the study, body weight was 11, 14, and 27% (LDM, MDM, and HDM, respectively) lower than control males. In females, body weight was elevated in LDF compared to controls. In MDF, body weight was elevated up to Wk 56, but was reduced after Wk 76 to 12-14% below control. Body weight was reduced in HDF by 35% as compared to controls.

There were no consistent, dose-related changes in hematological or clinical chemistry parameters in males or females terminally sacrificed or sacrificed moribund. One exception was a dose related increase (140-188%) in cholinesterase in males. Serum cholinesterase levels are considered to reflect liver function (especially hepatic synthetic capacity); however, slight elevations, in lieu of a decrease in serum albumin, are of questionable significance.

Non-tumerous changes

Organ/tissue weights: In general, changes in absolute and relative organ/tissue weights in drug-treated animals were reflective of changes in body weight (absolute weight) or of sparing of organ weight in the face of body weight changes (relative weight). In males, there was an increase (non-dose related) in absolute and relative adrenal weight (18-35 and 60-72%, respectively). In females, absolute and relative thyroid weight was reduced at the HD (38 and 26%, respectively).

Histopathology (see summary tables): In males, histopathological changes were noted in a variety of organs. Mineralization of the kidney, mammary gland stimulation, hyperplasia of the pituitary gland, and subacute inflammation of the prostate were noted at all doses. The incidence of focal hyperplasia of the pancreas was reduced in HDM. In adrenal gland, the incidence of clear cell plaques were reduced at all doses, whereas congestion and ectasia were increased in MDM and HDM.

In females, stimulation of the mammary gland and mineralization of the kidney were increased at all doses. Diffuse hyperplasia and ectasia of the pituitary gland were noted at LD and MD only. Decreases were noted in the incidence of several findings, including clear cell plaques in adrenal gland and focal hyperplasia of the pancreas.

Tumerous changes (see summary tables)

In males, there was an increase in the incidence of mammary gland neoplasms, primarily due to fatal and incidental adenocarcinomas at the HD. The total incidence of mammary gland neoplasms was increased at MD and HD. There were also significant dose-related trends in the incidence of pancreatic adenoma (incidental) and soft tissue fibrosarcoma (fatal). The sponsor attributes these findings to the effects of hyprolactinemia; however, this reviewer has not been able to document the presence of prolactin receptors in pancreas ("soft tissue"???).

In females, drug-related changes in neoplasms were primarily in mammary gland adenocarcinomas (increased at all doses, non-dose related) and reproductive organs/tissue (i.e., cervix, uterus, vagina; significant decrease in total genital neoplasms). Non-fatal (incidental) tumors of the hematopoietic system occurred only in dosed females; however, there was no significant dose-related trend in non-fatal or total tumors of the hematopoietic system.

Plasma drug levels

The issues raised concerning plasma drug levels in the 18 mo mice carcinogenicity study apply to this study. Blood samples were collected at autopsy; autopsy was performed 1-6.5 hr after removal of medicated diet. In addition, plasma data were based on individual and pooled samples (n=2-6). The

plasma data were analyzed according to time from diet removal to blood sampling and summarized using the highest plasma value analyzed per group.

The highest plasma levels reported for risperidone were 4.1-5.0 (LD), 10.1-15.1 (MD), and 40.5-46.9 (HD) ng/ml and for 9-hydroxy-risperidone were 9.0-10.5 (LD), 24.3-41.1 (MD), and 104-126 (HD) ng/ml. Plasma data were corrected to theoretical dose.

Conclusions from the 18-mo carcinogenicity study in mice and the 2-yr carcinogenicity study in rats:

18-mo mice carcinogenicity study

1) The theoretical HD used in the study was 30-45 fold higher than the proposed maximum therapeutic dose in humans (16 mg/day).

2) It was not possible to confirm levels of plasma exposure for risperidone or 9-hydroxy-risperidone because of:

   (a) food wastage in nearly all groups which made calculation of food consumption, and thereby, actual dose difficult.
   (b) the possible lack of a sufficiently reliable assay system to confirm diet risperidone concentrations or stability.
   (c) the failure to control the interval between removal of the medicated diet and blood collection for plasma drug analysis.

   Comparing plasma drug levels obtained in humans with those measured in mice would give a conservative estimate of relative risk since, in all probability, peak plasma levels mice were higher than reported. In mice, plasma drug levels were undetectable at the LD (0.63 mg/kg). At the MD (2.5 mg/kg), risperidone was detectable in males only. Plasma levels of risperidone in mice at the MD (males only) were 2.5 fold lower than plasma risperidone levels in humans at 10-16 mg/day. At the HD (10 mg/kg) in mice, plasma risperidone levels were only slightly higher (15%) than in humans at 10-16 mg/day. Compared to MD mice,plasma 9-hydroxy-risperidone levels were 4-6 fold and 7-10 fold higher in humans at 10 and 16 mg/day, respectively. Compared to HD mice, plasma 9-hydroxy-risperidone levels were 1.2-1.5 fold and 2-2.5 fold higher in humans at 10 and 16 mg/day.

3) It does not appear that the MTD was achieved in male mice. Doses were selected on the basis of data collected during a 3-mo dose-range finding study. In that study, no consistent effects were noted on body weight at the HD (20 mg/kg), nor were there any marked drug-related effects on hematology or clinical chemistry parameters. Changes in organ/tissue weights were noted; however, no histopathology was performed in order to verify toxicity. No analysis of plasma drug levels were conducted in order to document plasma drug exposure. In the 18-mo carcinogenicity study, the HD was lowered to 10 mg/kg. No drug-related effects were noted on mortality, body weight, or hematological parameters. Serum glucose was reduced at the MD (13%) and HD (26%). [This was not a consistent finding; during the dose-range finding study, serum glucose was not affected in males at 20 mg/kg.] At the HD, changes were noted in the weight of various organs (10-27%; e.g., spleen liver, heart) and histopathological changes were noted in various organs/tissues, particularly at the HD. However, there were no drug-related increases in tumors in males.

3) It is not clear that the MTD was achieved in female mice. Although not statistically significant, there was a trend for mortality rate to be higher in MDF and HDF than in the other groups (64-68 vs 50-52%). Body weight was elevated in a non-dose-related fashion at all doses (4-18%). [In the dose-range finding study, the elevation in body weight at the HD (20 mg/kg) was 6-13% compared to control.] Dose-related changes were noted in serum glucose (10-21%, compared to 25% at the HD in the dose-range finding study), consistent with findings in males. The increase in serum cholesterol and phospholipid noted in the dose-range finding study was not observed in the carcinogenicity study; however, the changes in the dose-range finding study were not dose-related. Changes were noted in weight of liver (non-dose related increase) and ovary (decrease; 38% for relative weight at MD and HD). Primary changes noted in histopathology were increased incidence of mammary gland development (hyperplasia, secretion, inflammatory cell infiltration), pituitary gland (hyperplasia), and uterus and vagina (changes indicative of restive state). No histopathology was performed in the dose-range finding study. These data suggest that the HD in the carcinogenicity should have been at least equal to the HD used in the dose-range finding study; however, if the trend for mortality rate to be higher in MDF and HDF is real, then the HD used may be justified.

4) There was an increase in the incidence of mammary gland neoplasms (specifically, adenocarcinomas) and pituitary gland adenomas in risperidone treated females, with greatest response at MD and HD (doses 12-18 and 50-70 fold higher than the maxmimum proposed human dose). These neoplasms are consistent with chronic hyperprolactinemia, which has been demonstrated in mice after both acute and chronic dosing (0.63-10 mg/kg, p.o.). A dose-related trend in primary lung tumors (primarily benign) was noted in females; however, incidences were well within historical control values.

2-yr rat carcinogenicity study

1) The theoretical HD used in the study was 30-45 fold higher than the proposed maximum therapeutic dose in humans (16 mg/day).

2) The mortality rates in MDM and HDM (78 and 74%, respectively) were close to the maximum recommended rate.

3) It was not possible to confirm plasma drug exposure because the interval between removal of the medicated diet and blood collection was not controlled. Data from a previous study, in which doses of 0.16-10 mg/kg were administered to Wistar rats (satellite group, n=2) by gavage for 3 mo, could not be used for comparison because plasma levels of risperidone and 9-hydroxy-risperidone were up to 30-fold higher than levels reported in dietary studies at comparable doses.

Comparing plasma drug levels obtained in humans with those measured in rats would give a conservative estimate of relative risk since, in all probability, peak plasma levels in rats were higher than reported. Plasma risperidone levels in humans (10-16 mg/day) were 2.5-3 fold higher than in LD rats, similar to those in MD rats, and 3-4 fold lower than those in HD rats. At 10 mg/day, plasma levels of 9-hydroxy-risperidone in humans were 6-7 fold higher than in LD rats, 2-4 fold higher than in MD rats, and slightly lower (6-28%) than in HD rats.

4) The HD exceeded the MTD in both males and females based on the reduced body weight in males (LD: 11%, MD: 14%, HD: 27%) and in females (23% at HD).

5) Drug-related changes in the incidence of certain neoplasms were noted in both males and females:

a) In males, the incidence of mammary gland adenocarcinomas was increased in MDM and HDM, but signficantly only in HDM. The incidence of mammary gland neoplasms in total was increased in MDM and HDM. There were dose-related trends in the incidence of pancreatic (endocrine) adenomas and soft tissue fibrosarcoma (fatal).

b) In females, the incidence of mammary gland adenocarcinomas was increased in MDF and HDF. However , there was no drug-related increase in overall number of mammary gland neoplasms. The incidence of total neoplasms of the cervix, uterus, and vagina was reduced at all doses.

c) The incidences of pancreatic adenomas and soft tissue fibrosarcomas in MDM and HDM are above the level of historical control. The incidence of soft tissue fibrosarcoma was only 2/50 for both dose groups versus 0-1/50 for historical control. This small increase may or may not have any real significance.

6) Increases in various mammary gland and pituitary neoplasms, benign and malignant, are consistent with chronic hyperprolactinemia. Hyperprolactinemia commonly results from chronic neuroleptic administration and was demonstrated in rats after acute and chronic dosing and in humans after acute dosing with risperidone. The sponsor indicated that the observed dose-related trend in pancreatic adenomas in male rats was also prolactin related. To the reviewer's knowledge, prolactin receptors have been identified in a number of organs/tissues (e.g., choroid plexus, liver, kidney, mammary gland, mammary tumor, adrenal, ovary, testis, prostate, seminal vesicles and uterus), but not in endocrine pancreas. The sponsor, at the Agency's request, submitted documentation (4/13/93, Vol 1-2).

Of the 35 articles submitted, 4 contained data relevant to the relationship between pancreatic adenoma and hyperprolactinemia. Meuris et al.,(Endocrinology, 112(6):2221-2223, 1983) reported the presence of prolactin-like immunoreactivity in rat pancreatic islet cells. Immunoreactivity was specific (no immunostaining in response to anti-GH and -hPL sera) and was detected in the cytoplasm, but not in nucleus, of all islet cells examined. In a study by Mori et. al (JNCI 76(6), 1986), serum prolactin was increased 2-fold (140±33 vs 64±11 mg/ml) in mice by placing transplants of single anterior pituitary glands in lumina of right uterine horn, pancreatic tissue, or under kidney. In mice receiving pituitary gland transplants, there was histological evidence of inflammation, hypertrophy, and hyperplasia (resembling adenoma) of the islet cells. Pancreatic carcinoma was noted in one mouse. The authors concluded that the pancreatic islet cell changes resulted from hyperprolactinemia since GH secretion from a single pituitary gland transplant would be insufficient to exert any biological effect. Serum GH was not, however, quantitated. In MtTW15 mammosomatotropic tumor-bearing rats, increases in serum levels of GH (8-60 fold) and PRL (2-3 orders of magnitude) were associated with increased pancreatic weight and islet cell size (Diabetes 32:67-74, 1983). Richardson (Diabetologia 10:479-483, 1974) studied the effects of hypophysectomy on cyproheptadine-induced pancreatic ß-cell lesions in rats. Alone, cyproheptadine (a potent serotonin and histamine antagonist) has been shown to produce increases in pancreatic islet diameter and formation of electron-dense vesicles and marked dilation of rER in islet cells. Hypophysectomy prevented these types of pancreatic islet changes, suggesting a role for drug-induced increases in pituitary secretions in such changes. Together, these studies suggest, but do not directly demonstrate, pancreatic islet cell responsiveness (e.g., altered morphology) to increased serum prolactin.

Another issue is the relevance of these preclinical findings to humans. Epidemological studies have suggested that the observation of mammary gland changes in animals treated chronically with neuroleptics is not relevant to humans. This conclusion is based on the lack of an observed increase in breast neoplasms in a large number of patients treated chronically with neuroleptics. Also, unlike rodents in which a relationship between hyperprolactinemia and mammary gland neoplasms has been clearly demonstrated, a role for PRL in human breast cancer has not been established. The possibility, however, that differences between rodents and humans may be explained, at least in part, by differences in serum prolactin levels has not been systematically explored. That is, are serum prolactin levels elevated in humans to the extent and duration associated with increased mammary gland neoplasms in rodent studies. The relevance of observed pituitary gland and pancreatic neoplasms in animals treated with neuroleptics (e.g., risperidone) to humans has not been determined. Conclusions about hyperprolactinemia and breast cancer are not necessarily generalizable to neoplasms in other organ/tissues.

Analysis of serum prolactin levels indicated that there was a dose-related increase in the % of patients with increased serum prolactin (20-50%2). There was also an increase in absolute serum prolactin levels (58-100%) in these patients. By comparison, a 20% increase in serum prolactin levels were noted in haloperidol-treated patients, and 14% of haloperidol-treated patients were affected.

Although limited carcinogenicity data are available for neuroleptics, 2-yr studies have been conducted in rats using, among others, sulpiride, chlorpromazine, and penfluridol [cf "IND Review of toxicological data (submission of 1/13/82)", Barry N Rosloff, Ph.D (3/4/82); "Pharmacologist review of two year rat carcinogeni city studies", Joseph F. Contrera, Ph.D. (4/6/81)]. The incidence of pancreatic (endocrine) adenoma was increased after dosing with all three of these neuroleptics. Except for one study of penfluridol in which no increase was observed, the increased incidence (%) of pancreatic islet adenoma was greater with sulpiride, chlorpromazine, and penfluridol (total pancreatic tumors) than with risperidone (12-, 7-, 3 to 12-, and 1.6-fold, respectively, at the HD). At least in the case of penfluridol, this observation prevented further development in the U.S. Increases in pituitary gland neoplasia were noted in rodents treated with haloperidol (mice only), sulpiride (rat), and risperidone (mice). No consistent effect was noted with chlorpromazine.

In summary, it is clear that both pancreatic islet adenoma and pituitary gland neoplasia are observed with other neuroleptics and that the magnitude of the effect is no greater with risperidone than with other neuroleptics (based on limited data). In addition, data from published studies suggest that these types of neoplasia are related to hyperprolactinemia.

RECOMMENDATIONS

The preclinical studies submitted in support of the NDA for risperidone are sufficient to recommend approval of the application from a pharmacology/toxicology standpoint. However, the mouse carcinogenicity study is inadequate, based on the lack of an MTD in males. It is recommended that the study be repeated using higher doses during Phase 4.

Lois M Freed

Lois M. Freed, Ph.D.

cc
NDA ORIG (#20,272)
Div File
HFD-120
/G.Fitzgerald/L.M.Freed/S.Hardeman

CAC PACKAGE FOR NDA# 20,272 (RISPERIDONE)

Date: 4/21/93
Reviewer: Lois M. Freed, Ph.D.
HFD-120

Carcinogenicity studies

Carcinogenicity studies were performed in abino Swiss mice (18-mo) and Wistar rat (2-yr). A 3-mo dose range finding study was conducted in albino Swiss mice. For the rat carcinogenicity study, doses were based on cumulative toxicological data.

Mutagenicity studies

Nine mutagenicity studies (including Ames, chromosomal aberration/ human lymphocytes, mouse lymphoma, DNA-repair/rat hepatocyte tests, and micronucleus test in mice) were conducted and no evidence of mutagenic potential was obtained in any test.

Findings

Mice. No drug-related neoplasms were observed in males; however, according to the statistical review (attached) there was a marginally significant positive linear trend in malignant primary lung tumors. In resperidone-treated females, there were increases in the incidence of mammary gland neoplasms (specifically, adenocarcinomas) and pituitary gland adenomas. A dose-related trend in primary lung tumors (benign) was noted in females. For both males and females, the incidence of primary lung tumor was within historical control rates.

It does not appear that the MTD was achieved in male or female mice. In addition, the data (although of limited value) suggest that plasma levels of risperidone and 9-hydroxy-risperidone (the major plasma metabolite), even in HD mice, were similar or lower than those measured in humans at therapeutic doses (10-16 mg/day).

Rat. Drug-related neoplasms were noted in both males and females. In males, the incidences of mammary gland adenocarcinomas and total mammary gland neoplasms were increased. There were also significant dose-related trends in the incidence of pancreatic (endocrine) adenomas and soft tissue fibrosarcomas (fatal). In females, the incidence of mammary gland adenocarcinomas was increased, but there was no increase in total mammary gland neoplasms. The incidence of total neoplasms of the cervix, uterus, and vagina was reduced at all doses.

It appears that the MTD was reached (or exceeded) in males and females based primarily on body weight changes. In males, body weight was reduced compared to controls at all doses, thereby raising the possibility that tumor formation may have been inhibited (as a result of dietary restriction) in these animals.

Issues raised

The inadequacy of the mice carcinogenicity study due to lack of MTD (especially in males).

The relationship between hyperprolactinemia and pancreatic adenomas, and relevance of an observed positive trend in pancreatic adenomas in male rats to human risk.

Relevance of observed positive trends in incidence of primary lung tumors (mice) and soft tissue fibrosacromas (fatal; male rats) to human risk.

CARCINOGENICITY

1. **Oral toxicity study in Swiss mice.**

This study was the dose-ranging study for the mouse 18-mo carcinogenicity study.

SPF albino Swiss mice (10/sex/grp) were dosed orally (in diet) for 3 mo at intended doses of 1.25, 5, and 20 mg/kg (corresponding to 0.63, 2.5, and 10 mg/100 g diet). Clinical observations were made daily. Body weight and food consumption were measured weekly. Ophthalmoscopy, hematology, and clinical chemistry parameters were tested at the end of the study. At necropsy, organ weights (relative and absolute) were recorded and gross pathology was assessed.

Results

Mortality: There were no **unscheduled deaths.**

Clinical observations: The only **clinical sign** observed was food wastage. In males, food wastage was noted in control (1/10) and in LD and MD groups (3/10 in each group). In females, food wastage was noted in all groups (3/10 control, 5/10 LD, 6/10 MD, and 1/10 HD).

Ophthalmology: There were no drug-related **ocular abnormalities** according to the sponsor (no data presented)

Body weight and food consumption: **Body weight** was only affected in females. In males, there was a transient decrease in body weight (compared to control) at wk 1 in HDM. In females, body weight was elevated above control levels at all doses. At the LD, body weight was increased by ≈10% above controls at Wk 10 and 12. At the MD, increased body weight was evident from Wk 8 on (7-16% above controls). At the HD, body weight was 6-13% higher than control at Wks 9, 11, and 13. **Body weight gain** was reduced at Wks 1 and 2 in HDM (50-100%), but increased at Wks 6, 11, and 13 in MDM (27-30%). In females, body weight gain was elevated (17-57%) from Wk 6-7 on at MD and HD and at Wks 6, 8-10, and 12-13 at the LD.

Food consumption could not accurately be measured because of food wastage in most groups.

Actual dose could not be determined because of food wastage. However, the sponsor stated that actual doses must have been close to the intended doses, and perhaps somewhat higher in females. Since no food wastage was noted in HDM, the actual dose may have been close to the intended dose for that group (calculated dose = 20.1 mg/kg in this group).

Hematology: There were no drug-related effects on **hematology** paramenters in females. In males, there was a small, but non-dose related increase in MCV (2.3-4.8%). In HDM, there were increases in MCHgb (4%) and segmented neutrophils (80%), and a decrease in lymphocytes (8%). The values for segmented neutrophils and lymphocytes were outside the range of historical controls.

Clinical chemistry: For **clinical chemistry** parameters in males, decreases noted in LDM [ALT (20%)], MDM [K (16%), BUN (18%), AST (32%)], and HDM [inorganic phosphate (16%), albumin (7%), and creatinine (20%)] were within the range of historical control. In HDM, decreases in total protein (6%) and phospholipids (14%) were outside the range of historical controls. There were no clear dose-related findings in males, although some effects were observed only in HDM.

In females, there was a dose-related *reduction* in glucose (LD: 15%, MD: 20%, HD: 25%), all values falling below historical control levels. Non-dose related findings included elevated

cholesterol and phospholipid at all doses (34-43% and 24-29%, respectively), and decreased AlkPhos in HDF (35%); however, levels fell within the range of historical control. In MDF, AlkPhos was reduced by 46%, which fell below the level of historical control.

Organ/tissue weights: Organ weights were affected in both males and females. In HDM, there was an increase in relative and absolute spleen weight (18-19%) and an increase in absolute weight of pancreas (15%). Increased kidney weight (relative and absolute) was elevated at all doses (15-23%). Absolute and relative adrenal weight was elevated at all doses (50-75% and 27-45%, respectively), although, values fell within the range of historical control. There were no clear dose-related findings.

In females, absolute liver weight was increased at all doses (12-23%). Relative liver weight was elevated only at the LD (11%). Relative heart weight was decreased at the MD (9%), while elevated pancreas [absolute (22%) and relative (10%)] and thymus weight [absolute (27%)] was noted at the HD. Relative brain weight was decreased (12-13%) at the MD and HD, but absolute brain weight remained unchanged. Altered weight of spleen [relative (9%), HD], adrenals [absolute (9%, MD) and relative (19-24%, all doses)], kidney [absolute (12-14%) at all doses], and gonads [absolute (24-29%) and relative (32-35%) at all doses] were within historical control values.

Gross pathology: There were no drug-related **gross pathology** findings in males. In females, there was a dose-related stimulation of the mammary gland (1/10 control, 6/10 LD, 7/10 MD, 10/10 HD). Swollen pituitary gland was noted in 0/10 control, 2/10 LDF, 3/10 MDF, and 3/10 HDF. Pale liver was detected in 0/10 control, 2/10 LDF, 1/10 MDF, and 1/10 HDF.

Histopathology: No histopathology was performed. Also, there was no analysis of plasma drug levels to confirm dosing.

2. Mouse carcinogenicity study report

Methods

Animals: SPF Swiss mice were obtained from Charles River Labs (France). All mice (50/sex/grp) were <6 wks old at start of study.

Drug Preparation and Dose: Risperidone was administered orally in the diet at doses of **0, 0.63, 2.5, and 10 mg/kg**. Doses were based primarily upon the results of the dose range-finding study (No. 1926). Fresh diet was mixed at least each month.

Stability analysis was conducted using two separate extraction techniques followed by uv spectroscopy and/or HPLC. Originally, diet mix samples were assayed for risperidone after initial extraction using dichloromethane followed by uv specroscopy. Data indicated a risperidone concentration of 71-95% of the intended concentration. Data from the mice dose range-finding study, using the same extraction and detection procedure, indicated a recovery of 92-100%. The method was then changed to detection with HPLC to increase the specificity of analysis. Following this change, recovery fell to 51.9-80.4%. According to the sponsor, modification of the extraction procedure (substitution of 0.1% N HCl for dichloromethane) increased recovery to 97.5-102.9% in one test and to 91.1-116.7% in another (during a different study). The sponsor concluded that the low recovery noted previously with the old extraction technique and uv spectroscopy was due, not to a low concentration of drug in the diet, but to incomplete recovery. This does not, however, explain why recovery was close to 100% using the old extraction procedure and uv spectroscopy. It is also troublesome that the new extraction procedure and HPLC detection results in recovery >100%. These stability data do not, therefore, provide a confident estimate of drug concentration in the diet mixtures.

Observations:

Behavior and appearance: at least once per day.
Record of palpable masses: conducted weekly. Time of appearance, location of mass, and dimensions of the mass were recorded.
Body weight: recorded weekly for the first 12 mo, then monthly (4 wks) thereafter.
Food consumption: recorded weekly for the first 12 mo, then monthly (4 wks) thereafter.
Water consumption: not accurately monitored.
Hematology: analyzed at 12 mo and at terminal sacrifice. Tests included hct, hgb, rbc, wbc, thrombocyte count, MCV, MCH, MChgb.
Clinical chemistry: analyzed at terminal sacrifice. Tests included: Na, K, Cl, Ca, Pi, total protein, albumin, haptoglobin, glucose, cholesterol, triglycerides, phospholipids, BUN creatinine, total bilirubin, AlkPhos, AST, ALT, cholinesterase.
Postmortum studies: organ weights (adrenals, brain, heart, kidneys, liver, lungs, pancreas, ovaries, spleen, testes, thymus) for terminal sacrifices and gross pathology for all animals. Histopathology for all animals for the following organs: adrenals, kidneys, liver and gall bladder, lungs, mammary gland, overies, pancreas, pituitary gland, mesenteric lymph nodes, salivary glands, spleen, testes with epididymes, thymus, uterus, vagina, and any organ suspect for neoplasm. Histopathology for all controls and HD animals: bone with bone marrow, brain, esophagus, heart, seminal vesicles, stomach, thyroids, trachea, urinary bladder.

Results

Mortality: There were no drug-related effects on mortality (or moribund sacrifice).

Mortality rates (%)

Dose (mg/kg)	Males	Females
0	46%	52%
0.63	32%	50%
2.5	48%	64%
10	50%	66%

Mortality for historical controls was 21.2-22.2% for males and 28.6-30.1% for females (percentages interpolated from tables provided by sponsor), considerably less than the percentages in the current study for both males and females. Therefore, spontaneous tumor incidences in the historical controls may be higher by virtue of decreased mortality.

Clinical observations: The most common clinical signs in both males and females were "bad" condition and food wastage. In males, there were no clear drug-related findings. Food wastage was increased in the LD group (43/50 vs 25/50 in LD and control, respectively) in males. In females, there was a high incidence of food wastage in all groups (27-37/50). An increased incidence of abdominal distension was noted in HDM (13/50 vs 3/50 in HD and control, respectively). There was a non-significant increase in the incidence of subcutaneous mass at the HD (4/50 control, 3/50 LD, 3/50 MD, and 9/50 HD). In females, there was an increased incidence of subcutaneous mass at all doses (1/50 control, 8/50 LD, 17/50 MD, and 16/50 HD).

Body weight: In males, body weight was decreased compared to controls during the first 4-5 wks of the study at all doses (3-6%). There was a tendency for body weight to be elevated (5-7%) at the LD and MD during weeks 41-60; however, body weight was similar among groups at the end of the study.

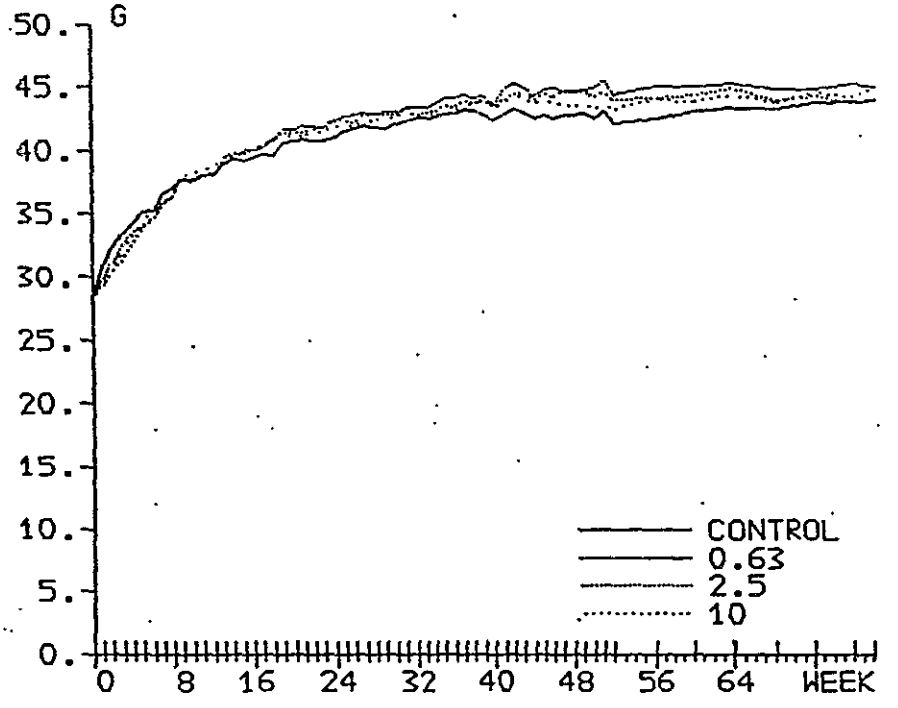
In females, body weight was 4-18% higher than control at all doses throughout the study.

JANSSEN PHARMACEUTICA NV
Department of toxicology

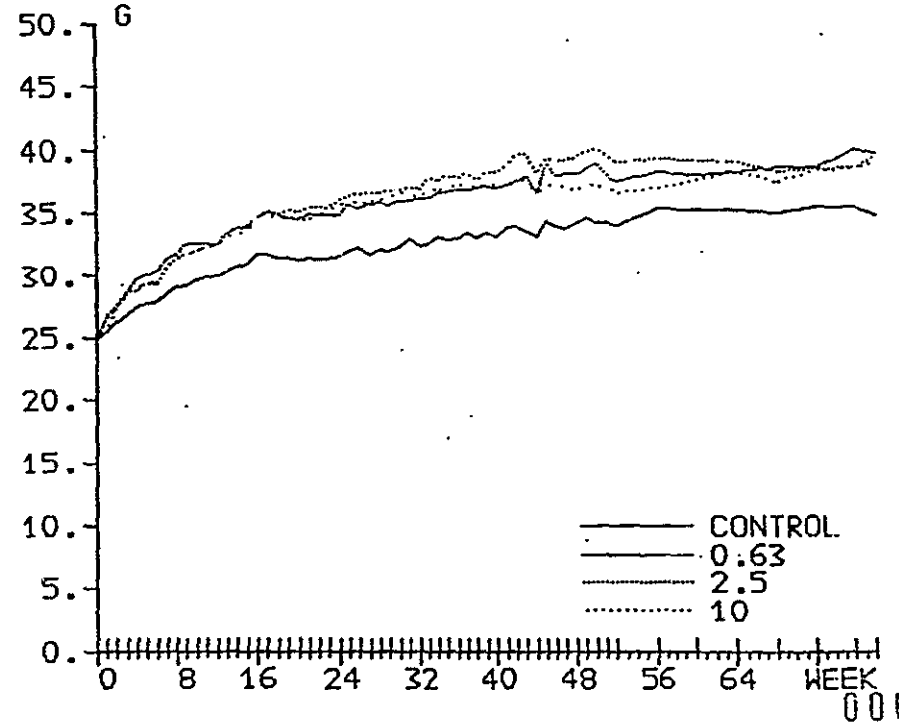
EXPERIMENT: 1927
Carcinogenicity study
R 64766 - FOOD - MICE - 18 MONTH

| BODY WEIGHT |
| Mean values per dosage group in g |

BODY WEIGHT MALES



BODY WEIGHT FEMALES



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Food consumption: Food wastage precluded accurate analysis of food consumption. Overall, however, the data suggest that food consumption was increased (4-15%) in dosed males and females compared to control throughout most of the study; therefore, food consumption was probably similar or slightly higher (especially in females) in dosed animals as compared to control.

Test article intake: Accuracy of calculated dose data are compromised by food wastage and problems of quantitation of risperidone in the diet mixture. Overall, the doses calculated from body weight and food consumption data, were 0.697, 2.83, and 10.5 mg/kg for males, and 0.673, 2.68, and 10.7 mg/kg for females.

Hematology: There were no clear drug-related findings in males. At 1 yr, there was a decrease in wbc at the MD and HD (16 and 25%, respectively) and a small, but significant, increase in MCHgb (pg) of 1-3% at all doses. Leucocytosis was noted in 6 control, 7 LD, 3 MD, and 3 HD males. Of these, 1 LDM had a confirmed tumor of the hematopoietic system. At the end of the study, rbcs were decreased by 2% at the LD and small, but significant, increases in MCV (2% at all doses) and HCHgb (pg) (<1% at LD). Hematology results were similar among non-terminal deaths.

In females, the following were noted at 1 yr: decreased Hct (9%) at HD, decreased Hgb at MD (5%) and HD (9%), decreased rbc at MD (7%) and HD (11%), increased thrombocytes (9) at MD, and increased MCV and MCHgb (2.3%) at HD. Leucocytosis was noted in 2 control, 5 LD, 1 MD, and 3 HD females. Of these, 2 had confirmed tumors of the hematopoietic system. At the end of the study, Hct was decreased at all doses (6% LD, 16% MD, 16% HD), Hgb was decreased at MD (14%) and HD (13%), rbc was decreased at all doses (9% LD, 18% MD, 15% HD), thrombocytes were increased by 40-41% at LD and MD, and MCHgb was increased by 3% at LD and MD. Hematology results were similar among non-terminal deaths.

Clinical chemistry: In males, the following were noted: increased Na (1%) at MD and HD, decreased glucose at MD (13%) and HD (26%), a dose-related increase in cholinesterase (10% LD, 28% MD, 48% HD), tendency for haptoglobin to be increased (6% LD, 75% MD, 194% HD).

In females, the following were noted: increased Ca at MD (7%) and HD (10%), increased total protein at MD (6%) and HD (20%), increased albumin at HD (9%), increased haptoglobin at MD (6.8 fold) and HD (14-fold), a dose-related decrease in glucose (10% LD, 18% MD, 21% HD), dose-related increase in cholesterol [23% LD, 41% MD (not sign.), 61% HD), decreased TG at HD (36%), a dose-related increase in phospholipids [21% LD, 22% MD (not sign.), 52% HD], decreased total bilirubin at the HD (9%), decreased alkphos at LD (51%), MD (74%), and HD (73%), increased cholinesterase at HD (24%).

Organ weights: In males, the following were noted: increase in absolute lung weight at HD (8%), increase in absolute and relative spleen weight at MD (12-13%) and HD (30-32%), increased absolute and relative liver weight at HD (22-24%), increased absolute (7% LD, 12% MD, and 18% HD) and relative (12% MD and 15% HD) weight of heart, increased absolute kidney weight at LD (8%) and HD (16%) and a dose-related increase in relative kidney weight (6% LD, 7% MD, and 13% HD), and a decrease in relative gonad weight at MD (9%) and HD (12%).

In females, the following were noted: increase in absolute lung weight at LD (10%) and MD (15%), increased absolute spleen weight at MD (27%) and HD (29%), increased absolute (31% LD, 42% MD, 31% HD) and relative (14% LD, 26% MD, 18% HD) liver weight, a dose-related increase in absolute heart weight (10% LD, 12% MD, 15% HD), increased absolute weight of pancreas at LD (17%) and of kidney at MD (12%), decreased relative weight of brain at LD (12%) and MD (13%), decreased absolute (10% MD, 20% HD) and a dose-related decrease in relative (18% LD, 22% MD, 25% HD) adrenal weight, decreased absolute gonad weight at MD (28%) and HD (33%), and

a dose-related decrease in relative gonad weight (19% LD, 38% MD, 40% HD). No data were presented for animals that died or that were sacrificed moribund.

Gross pathology: Drug-related macroscopic changes were noted in kidney (swollen), testis (small), mammary gland (stimulation, tissue mass), pituitary gland (swollen, tissue mass), spleen (swollen), and seminal vesicles (dilated) and are summarized in the following table (from sponsor's submission). In addition, there were drug-related decreases in incidence of ovarian (cyst), uterus (swollen, cystic), and mammary gland (edematous) changes. No drug-related macroscopic findings were noted in LDM.

Additional observations include a tendency for increased incidence of liver mass (0/50 control, 3/50 LD, 3/50 MD, 4/50 HD), brown seminal vesicles (0/50 control, 0/50 LD, 2/50 MD, 5/50 HD), swollen spleen (8/50 control, 9/50 LD, 10/50 MD, 12/50 HD), and stomach wall thickening (1/50 control, 7/50 LD, 3/50 MD, 5/50 HD) in males. In females, there was a tendency for increased anemia (10/50 control, 14/50 LD, 15/50 MD, 15/50 HD, eye and adnexal mass (0/50 control, 0/50 LD, 2/50 MD, 2/50 HD), jaw, tissue mass in 2/50 HD, and lung nodule (4/50 control, 10/50 LD, 7/50 MD, 6/50 HD). None of these observations were statistically significant or dose-related.

Histopathology:

Non-tumorous changes (summary data are presented in sponsor's table):

Males: Histopathological changes were noted in pancreas, pituitary gland, seminal vesicle, and spleen. Hyperplasia of the pituitary gland was noted at the HD (8/47) and hyperplasia of the spleen (red pulp) was noted at the MD (16/48) and HD (20/49). Incidence of "large islets" was increased at the HD (28/50). It is unclear whether this refers to hypertrophy of the islet cells or not. There appeared to be a dose-related impairment of seminal vesicles function (accumulated contents, dilated lumen, inspissated material).

Females: Histopathological changes were noted primarily in mammary gland and indicated marked stimulation of secretion and growth. Fibrosis, focal hyperplasia, secretion, glandular development, and metaplasia were noted at all doses. Reduced glandular development of the uterus and hyperplasia (diffuse and focal) of the pituitary gland were noted at all doses. Vaginal changes indicative of disruption of the estrus cycle were noted, e.g., increased anestrus and decreased estrus at all doses.

Tumorous changes:

Males: There were no drug-related increases in tumors in males. The incidence of some tumors in males was considerably lower than in historical controls, e.g., hepatic neoplastic nodule, neoplasia, and carcinomas. The incidence of malignant primary lung tumors was lower than in historical controls, whereas, the incidence of benign primary lung tumors was similar to that in historical controls. The differences may be due, in part, to the decreased mortality rate in the historical controls compared to the current study.

Females: There were drug-related increases in mammary gland neoplasms (specifically, adenocarcinomas) and pituitary gland adenomas.

Mammary gland neoplasms:

	Control	LD	MD	HD
adenocarcinoma	0/50	7/50*	18/47**	17/48**
carcinosarcoma	0/50	0/50	1/47	0/48
fibroadenoma	0/50	0/50	1/47	0/48
sarcoma	0/50	0/50	1/47	0/48
Total	0/50	7/50*	18/47**	17/48**

*p<0.01, **p<0.001,

Pituitary gland neoplasms:

	Control	LD	MD	HD
adenoma	1/48	2/46	13/45**	21/48**

**p<0.001

Primary lung tumors in female mice:

	Control	LD	MD	HD
Benign	2/50	5/50	4/50	6/50
Malignant	1/50	1/50	3/50	1/50
Total	3/50	6/50	7/50	7/50*

*asymptotic p-values, Peto's trend statistic (no correction for continuity)

Incidence of benign, malignant, and total primary lung tumors in the historical controls (7 studies):

	#1308	#1548	#1649	#1580c	#1580d	#1987	#1881
Benign	7/50	4/50	12/50	9/50	6/50	4/49	8/50
Malignant	5/50	3/50	4/50	3/50	7/50	1/49	3/50
Total	12/50	7/50	16/50	12/50	13/50	5/49	11/50

3. Carcinogenicity study in Wistar rats.

Methods

Animals: SPF Wistar rat were obtained from Charles River Germany. All rats (50/sex/grp) were <6 wks old at the start of the study.

Drug Preparation and Dose: Risperidone was administered orally in the diet at doses of 0, 0.63, 2.5, and 10 mg/kg. The doses were chosen on the basis of cumulative information on risperidone toxicity in rats. The dietary concentration of risperidone was adapted to changes in body weight and food consumption.

Study duration: The study duration was 25 mo. when the mortality rate for control and LD animals was ≈50%.

Observations:

Behavior and appearance: all animals were observed daily.
Records of palpable masses: all animals were palpated weekly. Time of appearance, location and dimensions of palpable masses were recorded.

Mortality: rats sacrificed moribund or found dead were examined macroscopically, and, if possible, complete tissue samples were preserved.

Body weight: individual body weights were recorded weekly during the first 6 wks, and monthly thereafter, and at sacrifice.

Food consumption: individual food consumption records were recorded weekly during the first 6 wks and monthly thereafter.

Water consumption: monitored daily, but no records kept.

Hematology: the following hematology parameters were assayed in all animals at 12 and 18 mo of dosing, in all terminally sacrificed animals, and if possible, in animals found dead: hct, hgb, rbc, wbc, thrombocyte count, differential count (only if wbcs are elevated), MCV, MCH, and MCHC. The methology was changed from "Ortho methodology" to "Sysmex methodology" at wk 55.

Clinical chemistry: the following clinical chemistry parameters were assayed in all terminally sacrificed animals: Na, K, Cl, Ca, Pi, total protein, albumin, haptoglobin, glucose, cholesterol, TG, PL, BUN, creatinine, total bilirubin, alkphos, AST, ALT, and cholinesterase.

Necropsy: terminal studies included organ/tissue weights (adrenals, brain, heart, kidneys, liver, lungs, pancreas, ovaries, spleen, testes, thymus, thyroid), gross pathology, and fixation of the following organs/tissues for histopathology:

for all animals: adrenals, kidneys, liver, lungs, mammary gland, ovaries, pancreas, pituitary gland, prostate, mesenteric lymph nodes, salivary glands, seminal vesicles (with coagulating gland), spleen, testes with epididymes, thymus, thyroids (with parathyroid), uterus, vagina, any organ/tissue suspect for neoplasm.

for controls and HD animals: bone (with bone marrow), brain, caecum, colon, duodenum, esophagus, eye, exorbital lacrimal gland, external ear (Zymbal gland), heart, ileum, jejunum, nasal turbinates, rectum, skeletal muscle, spinal cord, stomach, trachea, urinary bladder.

On occasion, autolysis precluded examination of some tissue. In only one animal was histopathology not performed because of extensive autolysis.

Results

Mortality: Mortality was assessed at 24 mo (26 lunar months) and was 28% in males and females. Because of this rate of mortality, the study was extended for an additional month (25 mo; 28 lunar months). Calculated for the last 3-4 mo, the mortality rate was significantly higher at the MD and HD than in controls in males and was somethat, but not significantly, higher at the HD than in controls in females.

Overall, mortality was 54-62% higher in LD and MD males and 20% higher in HD females than in corresponding controls.

Mortality at 25 mo:

Group	Males	Females
control	48%	50%
LD	58%	42%
MD	78%	54%
HD	74%	60%

Clinical observations: In males, the only drug-related clinical signs were increased incidence of "bad condition" (26/50 vs 15/50) and swollen paws (6/50 vs 0/50) at the MD compared to controls.

Subcutaneous mass was detected in 13/50 control, 19/50 LD, 20/50 MD, and 21/50 HD animals. A cutaneous mass was detected in 2/50 control, 6/50 LD, 4/50 MD, and 1/50 HD.

In females, the only findings were decreased incidence of alopecia (7/50 control, 2/50 LD, 1/50 MD, and 0/50 HD) and abdominal distension (6/50 control, 2/50 LD, 1/50 MD, and 0/50 HD) at all doses, but significant at the HD. Subcutaneous mass was detected in 20/50 control, 26/50 LD, 27/50 MD, and 21/50 HD. A cutaneous tissue mass was only detected in 1/50 HDF.

Body weight and food consumption:

Body weight

Males: In males, body weight was decreased at the MD and HD compared to controls throughout the study. In LDM, body weight was reduced by 4-5% compared to controls until wk 40 and by 4-11% from wk 80 to wk 111. At the end of the study, body weight was reduced by 11 (LDM), 14% (MDM), and 27% (HDM). Body weight gain data showed similar trends. Body weight gain was reduced by 16 (LDM), 20 (MDM), and 37% (HDM) at the end of the study.

Females: In females, body weight was elevated compared to controls by 5-15% in LDF throughout most of the study and by 2-6% in MDF until wk 56. From wk 76 on, body weight in MDF was reduced compared to controls by 12-14%. At the HD, body weight was reduced compared to controls, begining at wk 24 and continuing for the rest of the study. At the end of the study, body weight was similar to control levels at the LD and MD, but was 23% lower in HDF. Body weight gain data showed similar trends. Body weight gain was decreased only in HDF (35%) by the end of the study, that of the LDF and MDF being similar to control.

Food consumption

Males: In males, the only consistent observation was decreased food consumption in HDM through wk 76, and during wks 81-84 and 97-100.

Females: Food consumption was elevated in LDF through wk 49-52, and occasionally thereafter. There were sporadic changes in food consumption in MDF, but a consistent reduction in HDF throughout the study (5-18%).

Calculated dose: The calculated mean daily dose (range) was:

	Males	Females
LD	0.6 (0.479-0.775)	0.6 (0.514-0.806)
MD	2.5 (1.97-3.08)	2.4 (2.01-3.25)
HD	10.1 (7.65-12.3)	9.7 (7.67-12.4)

Hematology: Hematology data were analyzed separately for terminally sacrificed (wks 54, 78, and 110) and animals sacrificed moribund.

Terminally sacrificed

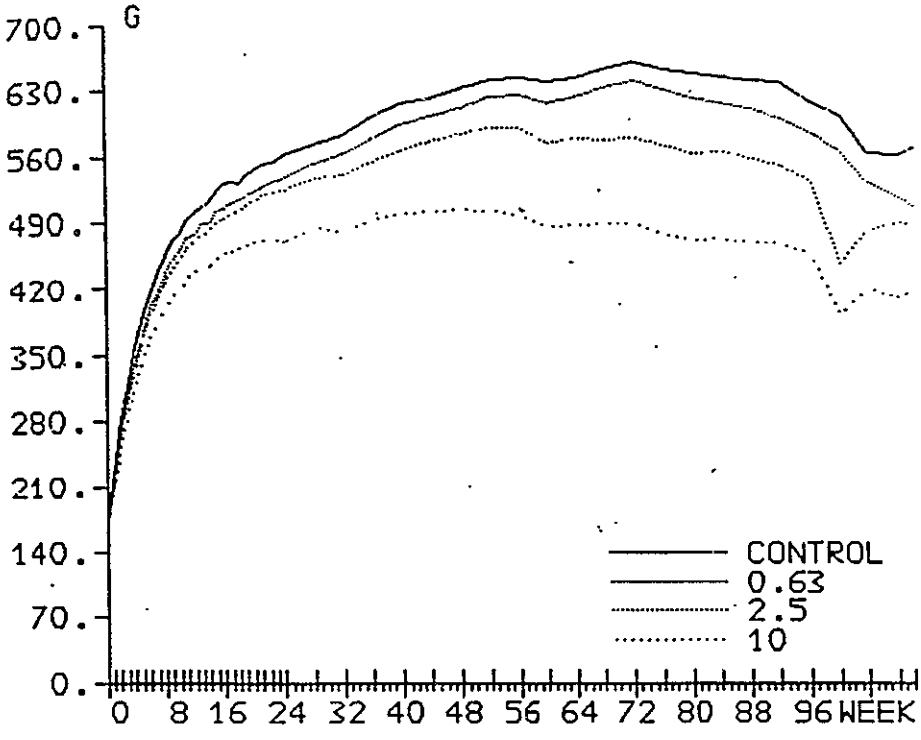
Males: The only consistent changes were in MCV and MCH. Both parameters were increased at wk 54, 78, and 110. MCV was 2-6% and MCH was 2-7% higher in dosed than in control animals. Although there was some evidence of a dose-response effect at wk 54, by wk 110 the magnitude of the increase was similar for LD, MD, and HDM. Other significant findings were: (1) 2% increase in hct in MDM and HDM at wk 54, (2) 2-3% increase in hgb in MDM and HDM at wk 54, (3) decreased rbc at HD (5%) at wk 54, and at all doses (4% LD, 4% MD, 8% HD) at wk 78, (4) 5% decrease in wbc in HDM at wk 54, and (5) 13% increase in thrombocytes in MDM at wk 78.

JANSSEN PHARMACEUTICA NV
Department of toxicology

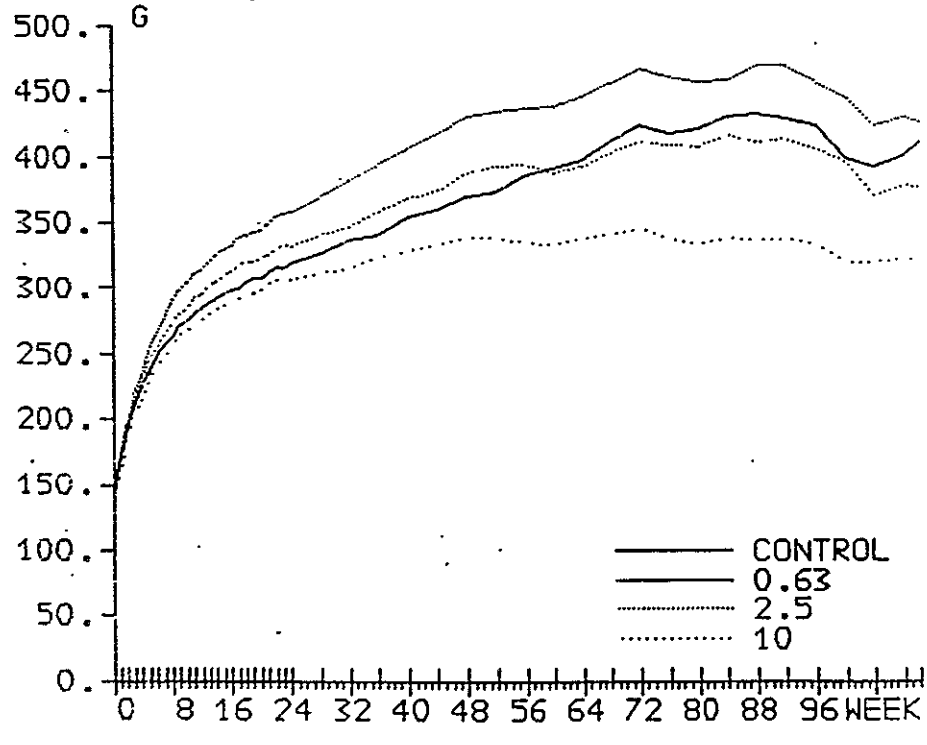
EXPERIMENT: 1928
Carcinogenicity study
R 64766 - FOOD - RAT - 24 MONTH

| BODY WEIGHT |
| Mean values per dosage group in g |

BODY WEIGHT MALES



BODY WEIGHT FEMALES



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Females: No consistent, dose-related changes were observed. Hct and hgb were reduced at all doses at wks 54 and 78 (2-5% for hct, 3-7% for hgb). Rbcs were reduced at wk 54 at all doses (3-6%), and at LD (3%) and HD (4%) at wk 78. Thrombocytes were elevated at all doses at wks 54 and 78 (4-8%). MCH and MCHC were slightly, but significantly, reduced at wk 54 in LDF and HDF (1-3%). MCV and MCHC were reduced in MDF at wk 78 by 1-2%. At wk 110, all values had normalized except for reduced hct in LDF (4%).

One female sacrificed moribund at mo 19) had leucocytosis (wbc 33,500/mm^3) at wk 54. Recalculation of mean wbcs without the data for this female, did not change the results.

Sacrificed moribund

There were no differences among groups on any of the hematological parameters measured.

Clinical chemistry

Males: The following observations were made:

K: 12% decrease in MDM, HDM.
Cl: 2% decrease in LDM, 4% decrease in MDM.
Ca: 8% increase in LDM.
total protein: 7-9% increase at all doses.
albumin: 9% increase in HDM.
glucose: 18% decrease in HDM.
cholesterol: 52-62% increase in LDM, MDM.
TG: 122% increase in MDM (a 84% increase was noted in LDM, but this was not statistically significant.)
Pl: 50-66% increase in LDM, MDM.
BUN: 20% decrease in MDM (a 74% increase was noted in LDM, but was not statistically significant.)
creatinine: 54% increase in LDM.
bilirubin: 45% decrease in MDM.
alkphos: 32-22% decrease in LDM and MDM.
AST: 21% decrease in LDM.
cholinesterase: 140, 175, and 188% increase in LDM, MDM, and HDM, respectively.

Except for albumin, alkphos, and AST data, all values were either above or below historical control values. However, there were no clear dose-related findings except for cholinesterase data.

Females: The following observations were made:

Cl: 1% decrease in LDF.
total protein: 6-4% increase in MDF and HDF.
albumin: 6-4% increase in MDF and HDF.
Pl: 16% decrease in HDF.
BUN: 15-21% decrease in LDF and HDF.
bilirubin: 72% decrease in LDF.
AST: 36% decrease in MDF.

All values were within the range of historical control except for bilirubin.

Organ weights (terminally sacrificed animals only)

Males: At the HD, the absolute weight of lung (22%), spleen (24%), liver (20%), heart (11%), pancreas (10%), kidney (16%), thyroid (33%) and gonads (23%) were reduced. The absolute weight of pancreas was also reduced in LDM (13%) and that of thymus was also reduced in MDM (23%).

The following changes were noted in relative organ/tissue weight: elevated in lung (7% MD, 8% HD), liver (16% LD, 18% MD, 11% HD), heart (11% LD and MD, 22% HD), pancreas (24% HD), kidneys (34% LD, 19% MD, 16% HD), brain (13% LD, 15% MD, 58% HD) and reduced in thymus (14% HD). Both absolute and relative weight of adrenals were elevated at all doses (absolute: 35% LD, 42% MD, 18% HD; relative: 60% LD, 72% MD, 63% HD).

Females: At the HD, the absolute weight of lung (16%), spleen (22%), liver (23%), pancreas (14%), thymus (25%), and thyroid (38%) was reduced. The absolute weight of lung, pancreas, and thyroid was also reduced in MDF (10, 16, 24%, respectively). The absolute weight of heart, brain, and gonads were only reduced in MDF (6, 3, 15%, respectively).

The following changes were noted in relative organ/tissue weight: elevated in heart (18% HD), pancreas (8% HD), kidneys (5% MD, 20% HD), brain (23% HD), adrenals (32% HD), and gonads (11% HD), and reduced in thyroid (26% HD).

Gross pathology

The following drug-related findings were noted (sponsor's table):

Observation	Dosage group (mg/kg) 0	0.63	2.5	10
Males	X/N	X/N	X/N	X/N
Cachexia	12/50	19/50	24/50*	23/49*
Kidney: changed surface (rough)	10/50	20/50*	12/50	5/49
Kidney: swollen	8/50	20/50*	15/50	4/49
Mammary gland: stimulation	2/50	11/50*	25/50***	28/49***
Mammary gland: tissue mass	0/50	2/50	9/50**	14/49***
Mammary gland: tissue mass(friable)	0/50	0/50	4/50	7/49*
Pituitary gland: swollen	2/50	7/50	23/50***	25/49***
Seminal vesicle: dilated	0/50	0/50	0/50	8/49**
Testis: small	12/50	19/50	15/50	23/49*
Thymus: involution	8/50	11/50	18/50*	20/49*
Females				
Mammary gland: stimulation	41/50	50/50**	50/50**	49/50*
Pituitary gland: swollen	6/50	25/50***	19/50**	12/50
Uterus: swollen	7/50	0/50*	1/50	2/50

Statistics: Chi-Square test: *p<0.05, **p<0.01, ***p<0.001
X: number of positive animals
N: total number of animals

Histopathology

Nonturnerous (summary data are presented in sponsor's table):

Males: Histopathological changes were noted in adrenal gland, epididymis, kidney, liver, mammary gland, pancreas, pituitary gland, prostate, seminal vesicle, spleen, and testes. Increased incidence of mineralization of kidney, mammary gland stimulation, diffuse hyperplasia of

the pituitary gland, and subacute inflammation of the prostate were noted at all doses. Increased incidence of hypertrophy of the kidney at the LD [14/50: also elevated, but not statistically significant, at MD (12/50)] as compared to control (4/50) is consistent with the increased relative weight of kidney.

There were apparent decreases in the incidence of clear cell plaques in adrenal gland and liver, cystic kidney, focal hyperplasia of pancreas and testes, and prostatic changes (at the HD).

Females: Histopathological changes were noted primarily in kidney, mammary gland, lymph node, and pituitary gland. Increased incidences of diffuse hyperplasia and ectasia were noted in pituitary gland at LD and MD. Stimulation of the mammary gland was evident at all doses, although the incidence of glandular development was relatively high in controls (42/49). Focal hyperplasia of the mammary gland was increased only in MDF. Chronic disease of the kidney was less in MDF and HDF compared to controls; however, mineralization of the kidney was increased at all doses, but was significant only for LDF and MDF (19/50 control, 30/50 LD, 34/50 MD, 29/50 HD).

There were apparent decreases in the incidence of clear cell plaques in adrenal gland, fibrosis of heart (only control and HD examined), proliferation of ducts of liver, Sertoli-like cells of ovary (dose-related), focal hyperplasia of the pancreas (dose-related), and glandular development and pigmentation of the uterus (at LD).

Tumerous:

Males: There was an increase in the incidence of mammary gland adenocarcinoma in HDM, and in that of total mammary gland neoplasms in MDM and HDM. Mammary carcinomas were detected only in 2 HDM. There was a positive dose-related trend in the incidence of pancreatic adenomas and soft tissue fatal, but not incidental, fibrosarcomas.

Females: The incidence of mammary gland adenocarcinomas was elevated at all doses, but there was no dose-related response. There was, however, no drug-related increase in the total incidence of mammary gland neoplasms. Neoplasms of the genital tract (cervix, uterus, vagina) were decreased at all doses, consistent with a prolactin-mediated effect. The incidence of non-fatal, but not fatal, tumors of the hematopoietic system was somewhat increased at all doses compared to concurrent controls (3-4/48-49 vs 0/48), and historical controls (0-1/50, classified only as "tumor")

Analysis of Plasma Drug levels in Carcinogenicity Studies

1. Plasma levels of risperidone and 9-hydroxy-risperidone (ng/ml) were measured at the end of an 18-mo carcinogenicity study conducted in SPF Albino Swiss mice (50/sex/grp). Risperidone was administered orally (in diet) at doses of 0.63, 2.5, and 10 mg/kg. Diet was corrected for body weight and food intake; actual doses were 0.499-0.736, 2.11-3.27, and 8.01-10.6 mg/kg. Blood samples were collected 1-8 hr after diet removal. Plasma levels of both risperidone and 9-hydroxy-risperidone following 0.63 mg/kg and 2.5 mg/kg (only in females) were undetectable; in males, plasma levels of risperidone were near the lower limit of detectability. Plasma 9-hydroxy-risperidone levels were higher than risperidone levels in both males and females. Plasma levels of 9-hydroxy-risperidone tended to be lower in females than in males and to increase somewhat linearly with increase in dose from 2.5-10 mg/kg.

Dose (mg/kg/day)	risperidone (male)	(female)	9-hydroxy-risperidone	(female)	ratio (R:9-OH-R)	(female)
0.63	n.d.	n.d	n.d.	n.d.	n.d.	n.d.
2.5	5.3	≤5	14.9	9.7	2.8	—
10	14.5	14.3	50.6	40.9	3.5	2.86

2. Plasma levels of risperidone and 9-hydroxy-risperidone (ng/ml) were measured at the end of the 24 mo carcinogenicity study conducted in Wistar rats (50/sex/grp). Risperidone was administered orally in the diet at doses of 0, 0.63, 2.5, and 10 mg/kg. Drug concentrations in the diet were changed as necessary to provide the appropriate doses of risperidone. Blood samples were collected at autopsy, i.e., 1-6.5 hr after removal of the medicated diet. Individual or pooled (2-6) serum samples were analyzed for drug levels by HPLC (limit of detection was 2.0 ng/ml for both compounds). Concentrations were corrected to theoretical doses. The data were analyzed according to the length of time between removal of medicated diet and blood collection (at autopsy) and according to the highest concentrations at each dose. Clearly the time interval between diet removal and blood sampling had a marked effect on plasma concentrations. Therefore, the data are of questionable value, especially since the analyzes were based partly on pooled samples, in which each sample potentially could have been collected at a different time after removal of the medicated diet. The highest plasma levels of risperidone and 9-hydroxy-risperidone are presented in the following table:

Dose (mg/kg)	risp male	9-OH male	sum male	risp female	9-OH female	sum female
0.63	4.1	9.0	13.1	5.0	10.5	15.5
2.5	10.1	24.3	34.4	15.1	41.1	56.2
10	40.5	104	145	46.9	126	173

SUMMARY OF CARCINOGENICITY STUDIES

Carcinogenicity studies were conducted in albino Swiss mice and Wistar rats.

Albino Swiss mice, 3-mo dose-range finding study.

The doses used in the 18-mo carcinogenicity study in mice were based on data collected in a 3-mo oral dose-range finding study in albino Swiss mice. Risperidone was presented in the diet at intended doses of 0, 1.25, 5, and 20 mg/kg. The only clinical sign was food wastage which was noted in control, LD and MD males and in females in control and all dosage groups. This precluded accurate quantitation of food consumption, and, therefore, calculation of actual doses. There was no unscheduled mortality. Body weight gain tended to be elevated in females (10-57%) in all dose groups; body weight was 10-16% higher in dosed than in control groups. In males, body weight gain changes were transient and tended to be reduced at the HD (50-100% during Wk 1) but elevated at the MD (27-30%). No marked drug effects were noted on any hematology or clinical chemistry parameters in males. In females, there was a dose-related reduction in glucose (15-25%), and increases in cholesterol and phospholipid at all doses (34-43 and 24-29%, respectively). Organ/tissue weights were affected in both males and females. In HD males, increases in relative and absolute weight of spleen and absolute weight of pancreas were noted. In HD females, increases in absolute and relative weight of pancreas and thymus were noted. Changes in weight of other organs/tissues were noted, but values were within those of historical control. No drug-related gross pathology findings were noted in males. In females, swollen pituitary gland was noted in 2-3/10 in each dose group and there was a dose-related stimulation of the mammary gland. No histopathology nor analysis of plasma drug levels were performed.

The following observations were the basis of dose selection for the carcinogenicity study in mice:

Males

(1) increased weight of kidneys and adrenals in all groups,
(2) "slight" changes in some parameters of blood and serum analysis (only at 20 mg/kg),

Females

(1) increased body weight at all doses,
(2) decreased serum glucose (all doses) and alkaline phosphatase (only MDF were below historical control values),
(3) increased serum cholesterol and phospholipids at all doses,
(4) increased incidence of mammary gland stimulation at all doses,
(5) decreased weight of ovaries at MD and HD.

Albino Swiss mice, 18-mo carcinogenicity study.

Albino Swiss mice (50/sex/grp) were administered risperidone orally (in diet) at intended doses of 0, 0.63, 2.5, and 10 mg/kg for 18 months. Calculation of actual dose was compromised by food wastage and possible analytical problems. The sponsor calculated actual doses as 0.673-0.697, 2.68-2.83, and 10.5-10.7 mg/kg in LD, MD, and HD groups, respectively. There were no significant drug-related effects on mortality, although the mortality rate tended to be higher at the MD and HD in females. The mortality rates in MDF and HDF was somewhat higher (64-66%), whereas in the other groups (including control) the mortality rate ranged from 32-52%. The mortality rates for historical controls was 21.2-22.2% for males and 28.6-30.1% for females. The higher rates in this study make comparisons to historical controls difficult. Spontaneous tumor incidences in the historical controls may be higher as a result of the reduced mortality.

There was no marked effect of risperidone on body weight in males. During the first few weeks, a small decrease in body weight was noted at all doses (3-6%); however, body weight was similar among

groups by the end of the study. In females, body weight was similar among dosed groups, but was elevated in all dosed groups (4-18%) compared to controls.

Changes were noted in a number of hematological (females only) and clinical chemistry parameters, including decreases in hct (6-16%) and rbcs (9-15%) at all doses and in hbg (13-14%) at MD and HD in females, and dose-related decreases in glucose in both males (MD: 13%, HD: 26%) and females (10-21%).

Non-tumorous change

Organ/tissue weights: In males, observations included an increase in the absolute and relative weight of spleen (MD: 12-13%, HD: 30-33%), liver (HD: 22-24%), heart (absolute: 7% LD, 12% MD, 18% HD; relative: 12% MD, 15% HD), and kidney (absolute: 8% LD, 16% HD; relative: 6% LD, 7% MD, 13% HD), and a decrease in the relative weight of testes (9% MD, 12% HD). In females, observations included an increase (not dose-related) in absolute (31-42%) and relative (14-26%) liver weight, and a decrease in absolute (28% MD, 33% HD) and relative (19% LD, 38% MD, 38% HD) ovary weight.

Histopathology (see summary tables): In males, the major changes were noted in pituitary (hyperplasia, ectasia), pancreas (inflammatory cell infiltration, "large islets"), seminal vesicles (dilated lumen, accumulated content, inspissated material), and spleen (hyperplasia of red pulp, myelopoiesis). An increase in the incidence of these observations occurred primarily at the HD.

In females, the major changes were noted, at all doses, in mammary gland, pituitary gland, uterus and vagina. Mammary gland changes included increased incidence of fibrosis, hyperplasia, glandular development, inflammatory cell infiltration, and secretion. An increased incidence of hyperplasia was also noted in pituitary gland. Changes in uterus and vagina were indicative of a more restive state.

Tumorous changes

There were no drug-related increases in tumors in males. The incidence of some tumors (e.g., hepatic neoplastic nodule, neoplasia, and carcinomas, and malignant primary lung tumors) were lower in drug-treated males; this decrease may be due, in part, to the higher mortality rate in the current study as compared to that of the historical controls. There is also the question of whether or not the HD approximated the MTD in males.

In females, there was an increased incidence in mammary neoplasms (adenocarcinomas: 0/50 C, 7/50 LD, 18/47 MD, 17/48 HD) and pituitary adenomas (1/48 C, 2/46 LD, 13/45 MD, 21/48 HD). These neoplasms are consistent with hyperprolactinemia resulting from chronic risperidone treatment. There was also a dose-related trend in the incidence of primary lung tumor; however, incidences were within historical control values.

Plasma drug levels

Plasma levels of risperidone and 9-hydroxy-risperidone were analyzed on blood samples collected at autopsy. The interval of time between removal of medicated diet and autopsy ranged from 1 to 8 hrs; therefore, the plasma data are of limited value. The problem was compounded by the need to pool blood samples (n=3-6) of mice sacrificed at different times. The sponsor did analyze the plasma data in terms of time after diet removal and concluded that the plasma concentrations of risperidone and its metabolite "remained fairly constant as a function of time after withdrawal of the medicated food in both male and female mice." The validity, however, of comparing such data among samples is questionable, especially since the samples were pooled samples of up to 6 animals.

With these issues in mind, the data indicated that the levels of risperidone were below the limits of detection in LDM, LDF, and MDF, and the levels of 9-hydroxy-risperidone were undetectable in LDM and LDF. At the HD, mean plasma levels of risperidone were 14.3-14.5 ng/ml in males and females, and of 9-hydroxy-risperidone were 40.9 and 50.6 ng/ml in females and males, respectively. Plasma data were corrected to theoretical doses.

Carcinogenicity study in Wistar rats.

Risperidone was administered orally in the diet to SPF Wistar rats (50/sex/grp) at doses of 0, 0.63, 2.5, and 10 mg/kg. Dosage selection was based on the cumulative toxicological information in rats. [Subchronic and chronic toxicity and Segment I, II, and III studies were conducted in Wistar rats.] The dietary concentration of risperidone was adjusted to changes in body weight and food consumption. There was no description of the assay methods for determination of drug in diet in this study. According to the sponsor, risperidone concentration in diet and stability were verified. Calculated doses were 0.6, 2.4-2.5, 9.7-10.1 for LD, MD, and HD, respectively.

Treatment duration was originally scheduled for 24 mo; however, due to a low mortality rate in controls at 24 mo. (28%), the treatment was extended to 25 mo. At 25 mo, the mortality rate for control and LD animals was ≈50%. The decision to extend the study was of questionable value. The mortality rates at 23-24 mo in MDM and HDM were 74 and 66%, respectively. At the end of the study the mortality rate in MDM and HDM increased to 78 and 74%, respectively. In the other groups, the mortality rates were 48 (control male) and 58% (LDM). Overall, in males there was a dose-related increase in mortality rate. In females, there was no statistically significant dose-related trend in mortality rate. At 24 mo, the mortality rates were 28, 36, 38, and 54% for control, LDF, MDF, and HDF, respectively. At the end of the study (25 mo.), the mortality rates had increased to 50, 42, 54, and 60%. Mortality rates in the historical controls (at Wk 108, M: 16-30% and F: 16-25%) were lower than in the current study in both males and females.

There were no dose-related clinical signs. Body weight was reduced (compared to controls) in a dose-related manner throughout the study in males. At the end of the study, body weight was 11, 14, and 27% (LDM, MDM, and HDM, respectively) lower than control males. In females, body weight was elevated in LDF compared to controls. In MDF, body weight was elevated up to Wk 56, but was reduced after Wk 76 to 12-14% below control. Body weight was reduced in HDF by 35% as compared to controls.

There were no consistent, dose-related changes in hematological or clinical chemistry parameters in males or females terminally sacrificed or sacrificed moribund. One exception was a dose related increase (140-188%) in cholinesterase in males. Serum cholinesterase levels are considered to reflect liver function (especially hepatic synthetic capacity); however, slight elevations, in lieu of a decrease in serum albumin, are of questionable significance.

Non-tumerous changes

Organ/tissue weights: In general, changes in absolute and relative organ/tissue weights in drug-treated animals were reflective of changes in body weight (absolute weight) or of sparing of organ weight in the face of body weight changes (relative weight). In males, there was an increase (non-dose related) in absolute and relative adrenal weight (18-35 and 60-72%, respectively). In females, absolute and relative thyroid weight was reduced at the HD (38 and 26%, respectively).

Histopathology (see summary tables): In males, histopathological changes were noted in a variety of organs. Mineralization of the kidney, mammary gland stimulation, hyperplasia of the pituitary gland, and subacute inflammation of the prostate were noted at all doses. The incidence of focal hyperplasia of the pancreas was reduced in HDM. In adrenal gland, the incidence of clear cell plaques were reduced at all doses, whereas congestion and ectasia were increased in MDM and HDM.

In females, stimulation of the mammary gland and mineralization of the kidney were increased at all doses. Diffuse hyperplasia and ectasia of the pituitary gland were noted at LD and MD only.

Decreases were noted in the incidence of several findings, including clear cell plaques in adrenal gland and focal hyperplasia of the pancreas.

Tumerous changes (see summary tables)

In males, there was an increase in the incidence of mammary gland neoplasms, primarily due to fatal and incidental adenocarcinomas at the HD. The total incidence of mammary gland neoplasms was increased at MD and HD. There were also significant dose-related trends in the incidence of pancreatic adenoma (incidental) and soft tissue fibrosarcoma (fatal). The sponsor attributes these findings to the effects of hyprolactinemia.

In females, drug-related changes in neoplasms were primarily in mammary gland adenocarcinomas (increased at all doses, non-dose related) and reproductive organs/tissue (i.e., cervix, uterus, vagina; significant decrease in total genital neoplasms). Non-fatal (incidental) tumors of the hematopoietic system occurred only in dosed females; however, there was no significant dose-related trend in non-fatal or total tumors of the hematopoietic system.

Plasma drug levels

The issues raised concerning plasma drug levels in the 18 mo mice carcinogenicity study apply to this study. Blood samples were collected at autopsy; autopsy was performed 1-6.5 hr after removal of medicated diet. In addition, plasma data were based on individual and pooled samples (n=2-6). The plasma data were analyzed according to time from diet removal to blood sampling and summarized using the highest plasma value analyzed per group.

The highest plasma levels reported for risperidone were 4.1-5.0 (LD), 10.1-15.1 (MD), and 40.5-46.9 (HD) ng/ml and for 9-hydroxy-risperidone were 9.0-10.5 (LD), 24.3-41.1 (MD), and 104-126 (HD) ng/ml. Plasma data were corrected to theoretical dose.

Conclusions from the 18-mo carcinogenicity study in mice and the 2-yr carcinogenicity study in rats:

18-mo mice carcinogenicity study

1) The theoretical HD used in the study was 30-45 fold higher than the proposed maximum therapeutic dose in humans (16 mg/day).

2) It was not possible to confirm levels of plasma exposure for risperidone or 9-hydroxy-risperidone because of:

   (a) food wastage in nearly all groups which made calculation of food consumption, and thereby, actual dose difficult.
   (b) the possible lack of a sufficiently reliable assay system to confirm diet risperidone concentrations or stability.
   (c) the failure to control the interval between removal of the medicated diet and blood collection for plasma drug analysis.

   Comparing plasma drug levels obtained in humans with those measured in mice would give a conservative estimate of relative risk since, in all probability, peak plasma levels mice were higher than reported. In mice, plasma drug levels were undetectable at the LD (0.63 mg/kg). At the MD (2.5 mg/kg), risperidone was detectable in males only. Plasma levels of risperidone in mice at the MD (males only) were 2.5 fold lower than plasma risperidone levels in humans at 10-16 mg/day. At the HD (10 mg/kg) in mice, plasma risperidone levels were only slightly higher (15%) than in humans at 10-16 mg/day. Compared to MD mice,plasma 9-hydroxy-risperidone levels were 4-6

fold and 7-10 fold higher in humans at 10 and 16 mg/day, respectively. Compared to HD mice, plasma 9-hydroxy-risperidone levels were 1.2-1.5 fold and 2-2.5 fold higher in humans at 10 and 16 mg/day.

3) It does not appear that the MTD was achieved in male mice. Doses were selected on the basis of data collected during a 3-mo dose-range finding study. In that study, no consistent effects were noted on body weight at the HD (20 mg/kg), nor were there any marked drug-related effects on hematology or clinical chemistry parameters. Changes in organ/tissue weights were noted; however, no histopathology was performed in order to verify toxicity. No analysis of plasma drug levels were conducted in order to document plasma drug exposure. In the 18-mo carcinogenicity study, the HD was lowered to 10 mg/kg. No drug-related effects were noted on mortality, body weight, or hematological parameters. Serum glucose was reduced at the MD (13%) and HD (26%). [This was not a consistent finding; during the dose-range finding study, serum glucose was not affected in males at 20 mg/kg.] At the HD, changes were noted in the weight of various organs (10-27%; e.g., spleen liver, heart) and histopathological changes were noted in various organs/tissues, particularly at the HD. However, there were no drug-related increases in tumors in males.

3) It is not clear that the MTD was achieved in female mice. Although not statistically significant, there was a trend for mortality rate to be higher in MDF and HDF than in the other groups (64-68 vs 50-52%). Body weight was elevated in a non-dose-related fashion at all doses (4-18%). [In the dose-range finding study, the elevation in body weight at the HD (20 mg/kg) was 6-13% compared to control.] Dose-related changes were noted in serum glucose (10-21%, compared to 25% at the HD in the dose-range finding study), consistent with findings in males. The increase in serum cholesterol and phospholipid noted in the dose-range finding study was not observed in the carcinogenicity study; however, the changes in the dose-range finding study were not dose-related. Changes were noted in weight of liver (non-dose related increase) and ovary (decrease; 38% for relative weight at MD and HD). Primary changes noted in histopathology were increased incidence of mammary gland development (hyperplasia, secretion, inflammatory cell infiltration), pituitary gland (hyperplasia), and uterus and vagina (changes indicative of restive state). No histopathology was performed in the dose-range finding study. These data suggest that the HD in the carcinogenicity should have been at least equal to the HD used in the dose-range finding study; however, if the trend for mortality rate to be higher in MDF and HDF is real, then the HD used may be justified.

4) There was an increase in the incidence of mammary gland neoplasms (specifically, adenocarcinomas) and pituitary gland adenomas in risperidone treated females, with greatest response at MD and HD (doses 12-18 and 50-70 fold higher than the maxmimum proposed human dose). These neoplasms are consistent with chronic hyperprolactinemia, which has been demonstrated in mice after both acute and chronic dosing (0.63-10 mg/kg, p.o.). A dose-related trend in primary lung tumors (primarily benign) was noted in females; however, incidences were well within historical control values.

2-yr rat carcinogenicity study

1) The theoretical HD used in the study was 30-45 fold higher than the proposed maximum therapeutic dose in humans (16 mg/day).

2) The mortality rates in MDM and HDM (78 and 74%, respectively) were close to the maximum recommended rate.

3) It was not possible to confirm plasma drug exposure because the interval between removal of the medicated diet and blood collection was not controlled. Data from a previous study, in which doses of 0.16-10 mg/kg were administered to Wistar rats (satellite group, n=2) by gavage for 3 mo, could not be used for comparison because plasma levels of risperidone and 9-hydroxy-risperidone were up to 30-fold higher than levels reported in dietary studies at comparable doses.

Comparing plasma drug levels obtained in humans with those measured in rats would give a conservative estimate of relative risk since, in all probability, peak plasma levels in rats were higher than reported. Plasma risperidone levels in humans (10-16 mg/day) were 2.5-3 fold higher than in LD rats, similar to those in MD rats, and 3-4 fold lower than those in HD rats. At 10 mg/day, plasma levels of 9-hydroxy-risperidone in humans were 6-7 fold higher than in LD rats, 2-4 fold higher than in MD rats, and slightly lower (6-28%) than in HD rats.

4) The HD exceeded the MTD in both males and females based on the reduced body weight in males (LD: 11%, MD: 14%, HD: 27%) and in females (23% at HD).

5) Drug-related changes in the incidence of certain neoplasms were noted in both males and females:

a) In males, the incidence of mammary gland adenocarcinomas was increased in MDM and HDM, but signficantly only in HDM. The incidence of mammary gland neoplasms in total was increased in MDM and HDM. There were dose-related trends in the incidence of pancreatic (endocrine) adenomas and soft tissue fibrosarcoma (fatal).

b) In females, the incidence of mammary gland adenocarcinomas was increased in MDF and HDF. However , there was no drug-related increase in overall number of mammary gland neoplasms. The incidence of total neoplasms of the cervix, uterus, and vagina was reduced at all doses.

c) The incidences of pancreatic adenomas and soft tissue fibrosarcomas in MDM and HDM are above the level of historical control. The incidence of soft tissue fibrosarcoma was only 2/50 for both dose groups versus 0-1/50 for historical control. This small increase may or may not have any real significance.

6) Increases in various mammary gland and pituitary neoplasms, benign and malignant, are consistent with chronic hyperprolactinemia. Hyperprolactinemia commonly results from chronic neuroleptic administration and was demonstrated in rats after acute and chronic dosing and in humans after acute dosing with risperidone. The sponsor indicated that the observed dose-related trend in pancreatic adenomas in male rats was also prolactin related. To the reviewer's knowledge, prolactin receptors have been identified in a number of organs/tissues (e.g., choroid plexus, liver, kidney, mammary gland, mammary tumor, adrenal, ovary, testis, prostate, seminal vesicles and uterus), but not in endocrine pancreas. The sponsor, at the Agency's request, submitted documentation (4/13/93, Vol 1-2).

Of the 35 articles submitted, 4 contained data relevant to the relationship between pancreatic adenoma and hyperprolactinemia. Meuris et al.,(Endocrinology, 112(6):2221-2223, 1983) reported the presence of prolactin-like immunoreactivity in rat pancreatic islet cells. Immunoreactivity was specific (no immunostaining in response to anti-GH and -hPL sera) and was detected in the cytoplasm, but not in nucleus, of all islet cells examined. In a study by Mori et. al (JNCI 76(6), 1986), serum prolactin was increased 2-fold (140±33 vs 64±11 mg/ml) in mice by placing transplants of single anterior pituitary glands in lumina of right uterine horn, pancreatic tissue, or under kidney. In mice receiving pituitary gland transplants, there was histological evidence of inflammation, hypertrophy, and hyperplasia (resembling adenoma) of the islet cells. Pancreatic carcinoma was noted in one mouse. The authors concluded that the pancreatic islet cell changes resulted from hyperprolactinemia since GH secretion from a single pituitary gland transplant would be insufficient to exert any biological effect. Serum GH was not, however,

quantitated. In MtTW15 mammosomatotropic tumor-bearing rats, increases in serum levels of GH (8-60 fold) and PRL (2-3 orders of magnitude) were associated with increased pancreatic weight and islet cell size (Diabetes 32:67-74, 1983). Richardson (Diabetologia 10:479-483. 1974) studied the effects of hypophysectomy on cyproheptadine-induced pancreatic ß-cell lesions in rats. Alone, cyproheptadine (a potent serotonin and histamine antagonist) has been shown to produce increases in pancreatic islet diameter and formation of electron-dense vesicles and marked dilation of rER in islet cells. Hypophysectomy prevented these types of pancreatic islet changes, suggesting a role for drug-induced increases in pituitary secretions in such changes. Together, these studies suggest, but do not directly demonstrate, pancreatic islet cell responsiveness (e.g., altered morphology) to increased serum prolactin.

Another issue is the relevance of these preclinical findings to humans. Epidemological studies have suggested that the observation of mammary gland changes in animals treated chronically with neuroleptics is not relevant to humans. This conclusion is based on the lack of an observed increase in breast neoplasms in a large number of patients treated chronically with neuroleptics. Also, unlike rodents in which a relationship between hyperprolactinemia and mammary gland neoplasms has been clearly demonstrated, a role for PRL in human breast cancer has not been established. The possibility, however, that differences between rodents and humans may be explained, at least in part, by differences in serum prolactin levels has not been systematically explored. That is, are serum prolactin levels elevated in humans to the extent and duration associated with increased mammary gland neoplasms in rodent studies. The relevance of observed pituitary gland and pancreatic neoplasms in animals treated with neuroleptics (e.g., risperidone) to humans has not been determined. Conclusions about hyperprolactinemia and breast cancer are not necessarily generalizable to neoplasms in other organ/tissues.

Analysis of serum prolactin levels indicated that there was a dose-related increase in the % of patients with increased serum prolactin (20-50%2). There was also an increase in absolute serum prolactin levels (58-100%) in these patients. By comparison, a 20% increase in serum prolactin levels were noted in haloperidol-treated patients, and 14% of haloperidol-treated patients were affected.

Although limited carcinogenicity data are available for neuroleptics, 2-yr studies have been conducted in rats using, among others, sulpiride, chlorpromazine, and penfluridol [cf "IND Review of toxicological data (submission of 1/13/82)", Barry N Rosloff, Ph.D (3/4/82); "Pharmacologist review of two year rat carcinogenicity studies", Joseph F. Contrera, Ph.D. (4/6/81)]. The incidence of pancreatic (endocrine) adenoma was increased after dosing with all three of these neuroleptics. Except for one study of penfluridol in which no increase was observed, the increased incidence (%) of pancreatic islet adenoma was greater with sulpiride, chlorpromazine, and penfluridol (total pancreatic tumors) than with risperidone (12-, 7-, 3 to 12-, and 1.6-fold, respectively, at the HD). At least in the case of penfluridol, this observation prevented further development in the U.S. Increases in pituitary gland neoplasia were noted in rodents treated with haloperidol (mice only), sulpiride (rat), and risperidone (mice). No consistent effect was noted with chlorpromazine.

In summary, it is clear that both pancreatic islet adenoma and pituitary gland neoplasia are observed with other neuroleptics and that the magnitude of the effect is no greater with risperidone than with other neuroleptics (based on limited data). In addition, data from published studies suggest that these types of neoplasia are related to hyperprolactinemia.

NON-TUMUROUS CHANGES: ♂ MICE

Organ/Tissue	Observation	Dosage Group (mg/kg)			
		Control	LD	MD	HD
Coagulating gland	dilated lumen	1/40	2/4*	4/7*	18/38***
Lung	focal hyperplasia	13/50	13/50	7/50	4/50*
Lymph node(s), mesenteric	diffuse atrophy	9/46	1/44*	5/39	4/41
Pancreas	inflammatory cell infiltration large islets	3/50 12/50	12/50* 16/50	5/48 15/48	8/50 28/50**
Pituitary gland	diffuse hyperplasia ectasia	1/45 0/45	0/40 0/40	0/45 0/45	8/47* 6/47*
Seminal vesicle	accumulated content dilated lumen inspissated material	2/48 1/48 3/48	3/5* 2/5* 1/5*	4/14* 9/14* 4/14*	24/50*** 13/50** 14/50*
Spleen	hyperplasia of the red pulp myelopoiesis	7/50 10/50	11/50 8/50	16/48* 18/48	20/49** 20/49*
Urinary bladder	hyalinization	26/49	1/3*	0/2*	15/48*

Significance computed by test (two tailed probability): * p>=.05 ** p>=.01 *** p >=.001

* No statistical analysis conducted. Statistical analysis is considered to be misleading because of the low number of samples examined histologically and the biased sampling at this level (only when neoplasia was suspended upon gross examination).

NON-TUMUROI HANGES ♀ MICE

Organ/Tissue	Observation	Dosage Group (mg/kg)			
		Control	LD	MD	HD
Adrenal gland	extracapsular cortical tissue	11/49	3/49*	5/45	4/49
	pigmentation	16/49	26/49	24/45	28/49*
	spinal cell hyperplasia	46/49	43/49	29/45***	40/49
Brain	large vacuoles	12/50	–	–	2/49*
Kidney	chronic disease	2/50	6/50	13/50**	13/50**
Liver	Kupffer cell proliferation	5/50	9/50	15/50*	16/50*
	myelopoiesis	1/50	4/50	9/50*	9/50*
Lung	focal hyperplasia	17/50	11/50	6/50*	9/50*
Lymph node(s), mesenteric	erythronphagocytosis	4/47	2/45*	5/44	3/45
	histiocytosis	0/47	0/45	6/44*	0/45
	myelopoiesis	2/47	11/45*	9/44*	10/45*
	plasmocytosis	3/47	1/45	4/44	11/45*
Mammary gland	accumulated content	10/50	36/50***	44/47***	42/48***
	amyloidosis	11/50	5/50	2/47*	3/48
	fibrosis	2/50	28/50***	33/47***	35/48***
	focal hyperplasia	1/50	26/50***	32/47***	36/48***
	glandular development	20/50	47/50***	46/47***	47/48***
	inflammatory cell infiltration	8/50	31/50***	31/47***	38/48***
	inspissated material	1/50	22/50***	30/47***	21/48***
	metaplasia	1/50	13/50**	16/47***	25/48***
	secretion present	8/50	42/50***	43/47***	42/48***
Ovary	amyloidosis	17/49	7/50*	0/46***	1/49***
	diffuse atrophy	1/49	3/50	10/46**	6/49
Pituitary gland	diffuse hyperplasia	3/48	26/46***	39/45***	41/48***
	ectasia	2/48	9/46*	29/45***	30/48***
	focal hyperplasia	1/48	10/46**	19/45***	12/48**
Spleen	hyperplasia	9/50	17/50	26/50***	18/50
	myelopoiesis	8/50	13/50	25/50***	17/50
	polynuclear cells	5/50	13/50	23/50***	19/50**
Uterus	glandular development	41/50	14/50***	18/50***	18/50***
Vagina	anestrus	3/46	14/48**	20/45***	22/47***
	diestrus	7/46	17/48*	5/45	12/47
	estrus	6/46	0/48*	0/45*	0/47*
	metestrus	27/46	14/48**	16/45	12/47**
	mucified aspect	2/46	17/48***	6/45	14/47**

Significance computed by test (two tailed probability): * p > =.05 ** p > =.01 *** p > =.00

SUMMARY OF NEOPLASMS: ♀ MICE, 18 MONTH CARCINOGENICITY STUDY

ORGAN/TISSUE	OBSERVATION	C	LD	MD	HD
Mammary gland	adenocarcinoma	0/50	7/50**	18/47***	17/48***
	carcinosarcoma	0/50	0/50	1/47	0/48
	fibroadenoma	0/50	0/50	1/47	0/48
	sarcoma	0/50	0/50	1/47	0/48
	TOTAL	0/50	7/50**	18/47***	17/48***
Lung	Primary Tumor				
	Benign	2/50	5/50	4/50	6/50
	Malignant	1/50	1/50	3/50	1/50
	TOTAL	3/50	6/50	6/50	7/50
Pituitary gland	adenoma	1/48	2/46	13/45***	21/48***

(one-tailed): ** p<0.01, *** p<0.001

Peto's trend statistic (no correction for continuity), asymptotic p value: p<0.05 p=0.0445

NON-TUMUROUS CHANGES: ♂ RAT

Organ/Tissue	Observation	Dosage Group (mg/kg)			
		Control	LD	MD	HD
Adrenal gland	clear cell plaques	14/50	5/50*	2/50**	2/49**
	congestion	1/50	4/50	12/50**	10/49**
	ectasia	4/50	9/50	17/50**	21/49***
Epididymis	cellular debris	16/50	24/50	26/50	31/49**
Kidney	chronic disease	44/50	45/50	26/50	31/49**
	cystic	13/50	19/50	45/50	34/49*
	hypertrophy	4/50	14/50*	11/50	3/49*
	mineralization	4/50	18/50**	12/50	1/49
Liver	clear cell plaques	23/50	16/50	9/50**	3/49***
Mammary gland	accumulated content	2/50	8/48	13/50**	17/49***
	female aspect	5/50	16/48	31/50***	37/49***
Pancreas	focal hyperplasia	13/49	8/49	10/49	1/49**
	vasculopathy	1/49	10/49*	6/49	1/49
Pituitary gland	diffuse hyperplasia	1/50	12/50**	33/50***	38/49***
	ectasia	7/50	8/50	22/50**	23/49***
	focal hyperplasia	18/50	20/50	31/50*	28/49
Prostate	focal hyperplasia	8/50	3/49	3/50	1/49*
	inspissated material	7/50	1/49	1/50	0/49*
	mineralization	10/50	5/49	3/50	1/49*
	subacute inflammation	16/50	34/49***	38/50***	41/49***
Seminal vesicle	accumulated content	0/48	2/47	1/49	15/48***
	infiltrating granulocytes	0/48	2/47	2/49	6/48*
	inspissated material	0/48	6/47*	5/49	23/48***
Spleen	pigmentation	3/50	15/50**	14/50**	10/49
Testis	accumulated content	13/50	4/50*	8/50	14/49
	degenertion	28/50	32/50	31/50	44/49***
	endocrine hyperplasia	6/50	0/50*	2/50	3/49
	mineralization	14/50	10/50	20/50	32/49***
	vasculopathy	5/50	19/50**	17/50**	12/49

Significance computed by test (two tailed probability): * p < =.05 ** p < =.01 *** p < =.001

NON-TUMUROUS CHANGES: ♀ RAT

Organ/Tissue	Observation	Dosage Group (mg/kg)			
		Control	LD	MD	HD
Adrenal gland	clear cell plaques	9/50	4/50	1/50*	0/50**
Heart	fibrosis	17/44	–	–	6/47**
Kidney	chronic disease mineralization	27/50 19/50	32/50 30/50*	16/50* 34/50**	13/50** 29/50
Liver	proliferation of ducts	31/50	23/50	21/50	16/50**
Lymph node(s), mesenteric	diffuse atrophy	1/50	4/49	10/50*	9/50*
Mammary gland	focal hyperplasia glandular development	7/47 42/49	11/50 50/50*	18/50* 50/50*	9/50 50/50*
Ovary	Sertoli-like cells	28/50	13/50**	8/50***	7/50***
Pancreas	focal hyperplasia	6/50	5/50	0/50*	0/50*
Pituitary gland	diffuse hyperplasia ectasia	13/49 17/49	36/50*** 32/50**	29/50** 30/50*	21/50 18/50
Salivary gland, sublingual gland	chronic inflammation	1/50	0/45	3/44	7/44*
Thymus	cystic	18/37	13/42	9/42*	11/35
Uterus	cyst glandular development pigmentation	6/49 46/49 6/49	1/50 39/50* 0/50*	1/50 41/50 2/50	0/50* 41/50 1/50
Vagina	mucified aspect	18/49	29/49*	25/50	18/50

Significance computed by test (two tailed probability): * $p < =.05$ ** $p < =.01$ *** $p < =.001$

SUMMARY OF NEOPLASMS: 2 YEAR RAT CARCINOGENICITY STUDY

ORGAN/TISSUES	NEOPLASMS	MALES				FEMALES			
		C	LD	MD	HD	C	LD	MD	HD
Mammary gland	adenocarcinoma	0/50	0/48	3/50	13/49***	3/49	14/50**	16/50**	13/50**
	adenoma, adenofibroma, fibroadenoma	0/50	3/48	4/50	3/49	20/49	21/50	27/50	15/50
	carcinoma	0/50	0/48	0/50	2/49	-- No Data--			
	fibroma	0/50	1/48	0/50	1/49	4/49	3/50	0/50	0/50
	TOTAL	0/50	3/48	6/50*	17/49***	25/49	32/50	33/50	23/50
Pancreas endocrine	adenoma Incidental	9/49	9/49	14/49	14/49#	3/50	4/50	4/50	3/50
Soft tissue	fibrosarcoma, fatal	0/50	0/50	2/50	2/50#	0/50	0/50	0/50	1/50
Hematopoietic system	tumor, fatal	2/50	1/50	3/50	0/49	2/50	1/50	1/50	2/50
	tumor, Incidental	2/48	2/49	2/47	1/49	0/48	4/49	3/49	4/48
	TOTAL	4/50	3/50	5/50	1/49	2/48	5/50	4/50	6/50
Cervix	adenocarcinoma					1/50	0/50	0/50	0/50
	sarcoma					2/50	1/50	0/50	1/50
Uterus	adenocarcinoma					2/50	0/50	0/50	0/50
	polyp					4/50	3/50	0/50	0/50
Vagina	sarcoma					2/50	0/50	1/50	0/50
	TOTAL (genital)					11/50	4/50*	1/50**	1/50**

test (one-tailed): * $p<0.05$, ** $p<0.01$, *** $p<0.001$
Peto's trend statistic (no correction for continuity), asymptotic p-value: #$p<0.02$

Table 2 : Cumulative mortality for control animals (50 animals at start of experiment) in cancer studies.

	Experiment no.						FEMALES					
Time (weeks)	1308	1548	1580 a	1580 b	1580 c	1580 d	1594	1649	1694	1987	1881	Comb. %
12	0	0	1	0	0	0	0	1	0	1	0	0.5
16	0	1	1	0	0	0	0	1	0	2	0	0.9
20	0	1	1	0	0	0	0	1	0	3	0	1.1
24	0	1	1	0	0	0	0	1	0	3	0	1.1
28	0	1	1	0	1	0	0	1	0	4	0	1.5
32	0	2	3	0	2	0	0	1	0	5	0	2.4
36	1	2	3	0	2	0	0	1	1	6	0	2.9
40	2	2	3	0	2	0	0	1	1	6	0	3.1
44	2	2	3	0	2	0	0	1	1	7	0	3.3
48	2	2	3	0	2	0	0	2	2	7	0	3.6
52	3	2	5	1	3	1	0	2	2	9	2	5.5
56	3	4	5	1	3	1	1	2	3	9	2	6.2
60	4	5	5	4	4	1	1	4	3	12	7	9.1
64	4	7	6	4	7	3	2	5	5	15	8	12.0
68	6	8	8	6	10	3	4	8	6	17	9	15.5
72	8	8	10	7	12	5	6	10	7	19	10	18.5
76	9	12	11	9	14	11	11	13	11	23	16	25.5
80	12	12	13	15	16	14	18	19	13	25	17	31.6
84	14	14	14	17	17	14	20	21	15	30	20	35.6
88	18	17	17	22	20	18	23	23	18	30	20	41.1
92	20	21	19	25	26	23	30	25	21			46.7
96	22	30	21	28	28	25	30	28	26			52.9
100	27	31	24	32	31	33		30	30			59.5
104	27				35	35		33				65.0
108					37	38		34				72.7
112					38	41						79.0

Table 3 : Incidence of tumor types per tissue in male control mice per experiment and the total procentual occurrence

MALES

Experiment no.	1308	1548	1649	1580c	1580d	1937	1881
Adrenal gland							
Spindle cell tumor, benign	0/48	1/45	0/47	0/47	0/50	0/49	0/50
Bone, Skull (*)							
Osteoma	0/50	0/50	0/50	0/50	1/50	0/50	0/50
Epididymis							
Sarcoma	0/49	0/49	0/47	0/48	0/50	1/50	1/50
Glandular stomach							
Adenocarcinoma			0/49	1/45	0/49	0/49	0/50
Adenoma			0/49	1/45	0/49	0/49	0/50
Harderian gland (*)							
Adenoma	0/50	0/50	1/50	0/50	0/50	0/50	0/50
Hematopoietic system (*)							
Tumor	4/50	4/50	5/50	12/50	2/50	2/50	3/50
- lymphoma	1/50	0/50	0/50	0/50	0/50	0/50	0/50
- lymphosarcoma	0/50	1/50	0/50	6/50	0/50	1/50	0/50
- lymphoid leukemia	3/50	2/50	3/50	5/50	1/50	1/50	3/50
- myeloid leukemia	0/50	0/50	1/50	0/50	0/50	0/50	0/50
- histiocytic tumor	0/50	1/50	1/50	2/50	1/50	0/50	0/50
Lacrimal gland(s) (*)							
Adenoma	0/50	0/50	0/50	0/50	0/50	0/50	1/50
Kidney							
Adenoma	1/50	0/50	0/50	0/50	1/50	0/50	0/50
Adenocarcinoma	0/50	0/50	1/50	0/50	0/50	0/50	0/50
Lip (*)							
Papilloma	0/50	0/50	1/50	0/50	0/50	0/50	0/50
Liver							
Hepatic neoplastic nodule	10/50	9/50	10/50	9/49	14/50	9/49	7/50
Hepatocellular carcinoma	4/50	6/50	6/50	1/49	3/50	3/49	6/50
--- Hepatocellular neoplasia	14/50	12/50	14/50	10/49	15/50	11/49	11/50
Hemangioendothelioma	0/50	1/50	1/50	3/49	4/50	1/49	1/50
Lung							
Primary lung tumor, benign	15/50	11/50	13/50	10/50	13/50	6/50	12/50
Primary lung tumor, malignant	6/50	4/50	9/50	10/50	16/50	6/50	5/50
--- Primary lung tumor	19/50	15/50	21/50	17/50	25/50	9/50	16/50

Table 4 : Incidence of tumor types per tissue in female control mice per experiment and the total procentual occurrence

FEMALES

Experiment no.	1308	1548	1649	1580c	1580d	1987	1881
Adrenal gland							
Adenoma	0/48	0/50	1/50	1/48	0/48	0/49	0/50
Phaechromocytoma	0/48	0/50	0/50	1/48	0/48	0/49	0/50
Spindle cell tumor, benign	1/48	0/50	0/50	0/48	0/48	0/49	0/50
Bone (*)							
Osteoma	0/50	0/50	0/50	1/50	0/50	0/50	0/50
Cardiotal system (*)							
Sarcoma	0/50	0/50	0/50	0/50	1/50	0/50	0/50
Cervix (*)							
Hemangioendothelial sarcoma	0/50	0/50	0/50	1/50	0/50	0/49	0/50
Hemangioendothelioma	0/50	0/50	0/50	0/50	1/50	0/49	0/50
Fibroleiomyosarcoma	0/50	0/50	0/50	1/50	0/50	0/49	0/50
Leiomyosarcoma	0/50	0/50	0/50	0/50	0/50	0/49	1/50
Sarcoma	1/50	0/50	2/50	1/50	0/50	1/49	0/50
Harderian gland (*)							
Adenoma	0/50	0/50	0/50	0/50	1/50	0/50	1/50
Hematopoietic system (*)							
Tumor	5/50	8/50	14/50	12/50	14/50	11/49	11/50
- lymphoma	0/50	0/50	0/50	0/50	0/50	0/49	0/50
- lymphosarcoma	2/50	4/50	3/50	4/50	4/50	6/49	6/50
- lymphoid leukemia	2/50	3/50	6/50	8/50	4/50	3/49	1/50
- myeloid leukemia	1/50	0/50	1/50	0/50	0/50	0/49	0/50
- hystiocytic tumor	0/50	0/50	4/50	0/50	4/50	1/49	3/50
- thymoma	0/50	1/50	0/50	0/50	0/50	1/49	0/50
Liver							
Hepatic neoplastic nodule	2/50	3/50	0/50	0/49	0/50	1/49	1/50
Hepatocellular carcinoma	0/50	0/50	0/50	0/49	0/50	0/49	0/50
--- Hepatocellular neoplasia	2/50	3/50	0/50	0/49	0/50	0/49	1/50
Hemangioendothelial sarcoma	0/50	0/50	0/50	0/49	1/50	0/49	0/50
Hemangioendothelioma	0/50	1/50	1/50	1/49	1/50	1/49	0/50
Hepatocytic carcinoma	0/50	0/50	0/50	0/49	0/50	0/49	0/50
Lung							
Primary lung tumor, benign	7/50	4/50	12/50	9/50	6/50	4/49	8/50
Primary lung tumor, malignant	5/50	3/50	4/50	3/50	7/50	1/49	3/50
--- Primary lung tumor	12/50	6/50	16/50	11/50	11/50	5/49	11/50
Mammary gland							
Adenocarcinoma	3/50	1/47	3/49	1/47	5/48	1/49	2/50
Carcinoma	3/50	0/47	0/49	0/47	0/48	0/49	0/50

Table 4 : Incidence of tumor types per tissue in female control mice per experiment and the total procentual occurrence

FEMALES

Experiment no.	1308	1548	1649	1580c	1580d	1987	1881
Ovary							
Adenoma	0/50	1/50	1/50	1/49	0/49	0/49	0/50
Carcinoma	0/50	1/50	0/50	0/49	0/49	0/49	0/50
Granulosa-theca cell tumor, benign	0/50	0/50	0/50	1/49	0/49	0/49	0/50
Hemangioendothelial sarcoma	0/50	0/50	0/50	1/49	1/49	0/49	0/50
Hemangioendothelioma	0/50	0/50	2/50	0/49	0/49	1/49	0/50
Luteal-cell tumor, benign	1/50	0/50	2/50	1/49	1/49	1/49	0/50
Pancreas							
Endocrine adenoma	0/47	0/49	1/50	0/49	0/47	0/48	0/50
Pituitary gland							
Adenoma	1/45	2/44	1/46	0/40	3/44	2/48	0/49
Carcinoma	0/45	0/44	1/46	0/40	0/44	0/48	0/49
Skin (*)							
Carcinoma, squamous cell	0/50	0/50	0/50	0/50	1/50	0/50	0/50
Soft tissue (*)							
Fibroma	0/50	1/50	0/50	0/50	0/50	0/49	0/50
Fibrosarcoma	0/50	0/50	1/50	0/50	0/50	0/49	0/50
Hemangioendothelial sarcoma	0/50	0/50	0/50	0/50	0/50	1/49	0/50
Hemangioendothelioma	0/50	1/50	0/50	0/50	0/50	0/49	0/50
Sarcoma	1/50	0/50	0/50	0/50	0/50	0/49	1/50
Spleen							
Hemangioendothelial sarcoma	0/50	0/49	0/50	0/49	0/48	1/49	0/50
Hemangioendothelioma	0/50	2/49	1/50	0/49	0/48	1/49	2/50
Thyroid gland							
Adenoma	0/29	0/25	1/33	0/37	1/42	0/49	0/49
Urinary bladder (*)							
Fibroleiomyoma	0/50	1/50	0/50	0/41	0/46	0/40	0/46
Hemangioendothelioma	0/50	1/50	0/50	0/41	0/46	0/40	0/46
Uterus							
Adenocarcinoma	0/50	1/49	2/50	0/50	1/49	0/49	0/50
Adenoma	2/50	2/49	1/50	0/50	1/49	0/49	0/50
Adenoma, polypous	0/50	0/49	0/50	0/50	0/49	2/49	2/50
Carcinoma	0/50	0/49	2/50	0/50	0/49	0/49	0/50
Fibroleiomyoma	0/50	1/49	0/50	0/50	1/49	0/49	0/50
Fibroleiomyosarcoma	0/50	0/49	0/50	2/50	1/49	0/49	0/50
Hemangioendothelioma	0/50	0/49	0/50	2/50	2/49	2/49	0/50
Hemangioma	2/50	0/49	0/50	0/50	0/49	0/49	0/50
Leiomyosarcoma	0/50	0/49	0/50	0/50	0/49	1/49	1/50
Sarcoma	0/50	0/49	2/50	0/50	0/49	1/49	0/50
Vagina							
Carcinoma			1/42				0/43

(*) denominator = number of autopsied animals

000-00164

Table 1: Historical control data of cumulative mortality (50 animals at start of experiment) in carcinogenicity studies in male rats

Time (weeks)	Experiment No.											
	1155	1214	1230	1307	1317	1335	1450	1309	1650	1882	1952	2031
16	0	0	0	0	0	0	0	0	0	0	0	1
20	0	0	0	0	0	0	0	0	0	0	0	1
24	0	0	0	0	0	0	0	0	0	0	0	1
28	0	0	0	0	0	0	0	0	0	0	0	1
32	1	0	0	0	0	0	0	0	0	0	0	1
36	1	0	0	2	0	0	0	0	0	0	0	3
40	1	0	0	2	0	0	0	0	0	0	0	3
44	1	0	0	2	0	0	0	0	0	0	0	4
48	1	0	0	3	0	0	0	0	0	1	0	4
52	1	0	0	4	0	0	0	0	0	1	0	4
56	1	0	0	4	0	0	0	0	0	1	0	5
60	1	0	0	4	0	0	0	1	0	1	0	5
64	1	0	1	5	0	0	0	1	0	2	1	5
68	1	0	1	5	3	1	1	1	0	4	1	5
72	3	1	2	7	4	2	2	2	1	4	2	5
76	5	3	3	8	5	2	2	3	3	5	4	6
80	5	6	4	10	5	4	3	5	4	6	5	6
84	8	6	4	12	5	6	6	8	4	6	5	7
88	10	8	9	15	7	9	12	9	6	6	8	8
92	16	10	13	18	8	9	12	11	7	10	9	8
96	19	10	14	20	14	12	15	12	10	12	13	11
100	20	11	18	14	16	15	19	16	14	16	14	11
104	25	16	21	27	18	16	24	18	18	16	17	15
108	25	16	24	30	18	18	24	18	22	19	19	17
112									30	26		17
116									34	26		
120									36			
124									39			

Table 2: Historical control data of cumulative mortality (50 animals at start of experiment) in carcinogenicity studies in female rats

Time (weeks)	Experiment No.											
	1155	1214	1230	1307	1317	1335	1450	1309	1650	1882	1952	2031
12	0	0	0	0	1	0	0	0	0	0	0	0
16	0	0	0	0	1	0	0	0	0	0	0	0
20	0	0	0	0	1	0	0	0	0	0	0	1
24	0	0	0	0	1	0	0	0	0	0	0	1
28	0	0	0	0	1	0	0	0	0	0	0	1
32	0	0	0	0	1	0	0	0	0	0	0	1
36	0	0	0	0	1	0	0	1	0	0	0	1
40	0	0	0	0	1	0	0	1	0	0	0	1
44	0	0	0	0	1	0	0	2	1	0	0	2
48	0	0	0	0	1	0	0	2	1	0	2	2
52	1	0	0	0	1	0	1	2	1	1	2	2
56	1	0	0	0	1	0	2	4	1	1	3	3
60	2	0	2	0	1	0	3	4	1	1	3	3
64	2	1	2	0	1	1	4	4	1	1	3	3
68	3	2	2	0	1	1	5	6	1	1	3	4
72	3	3	3	2	1	2	6	7	4	1	3	7
76	4	3	6	3	2	3	7	9	5	4	3	7
80	5	5	7	5	4	4	8	9	6	7	6	8
84	6	13	12	5	7	5	8	11	7	7	7	8
88	10	16	13	6	10	7	9	15	8	12	10	9
92	12	17	16	7	15	8	10	15	11	15	10	11
96	17	21	20	7	18	11	12	20	13	17	12	14
100	18	21	22	10	21	16	12	22	18	17	15	16
104	20	24	24	13	23	18	16	23	21	19	23	18
108	20	25	26	16	23	19	16	23	21	22	23	19
112									24	26		19
116									31	26		
120									34			
124									39			

Table 3: Incidence of tumor types per tissue in male control rats per experiment

MALES

Experiment number	1155	1214	1230	1307	1317	1335	1450	1305	1550
Abdominal mesothelia (@)									
Sarcoma	0/50	1/50	0/50	0/50	0/50	0/50	0/50	0/50	0/50
Adrenal gland									
Ganglioneuroma	0/49	0/50	0/50	1/49	2/50	0/50	0/50	0/50	0/50
Phaeochromocytoma	4/49	4/50	13/50	4/49	5/50	6/50	5/50	6/50	8/50
Anus (@)									
Leiomyosarcoma	0/50	0/50	1/50	0/50	0/50	0/50	0/50	0/50	0/50
Auditory subaceous gland (@)									
Carcinoma	1/50	0/50	0/50	0/50	0/50	0/50	0/50	0/50	0/50
Bone									
Osteosarcoma	0/50	1/50	0/50	0/50	0/50	0/50	0/50	0/50	1/47
Brain									
Tumor of glia - glioma	1/48	1/49	0/50	0/50	0/50	0/50	0/50	0/50	0/50
Granular cell tumor	0/48	0/49	0/50	1/50	0/50	0/50	0/50	0/50	1/50
Epididymis									
Mesothelioma	0/50 @	0/50	0/50	0/50	0/50	0/50	0/50	0/50	1/50
Heart									
Sarcoma	1/50	0/50	0/50	0/50	0/50	0/49	0/50	0/50	0/50
Hematopoietic system (@)									
Tumor	0/50	0/50	0/50	1/50	2/50	2/50	4/50	1/50	2/50
Jaw(@)									
Squamous cell carcinoma	3/50	0/50	0/50	1/50	0/50	0/50	2/50	0/50	1/50
Schwannoma, benign	0/50	0/50	0/50	0/50	0/50	0/50	1/50	0/50	0/50
Kidney									
Adenoma	0/50	0/50	0/50	0/50	0/50	1/50	1/50	0/50	0/50
Adenocarcinoma	0/50	1/50	0/50	0/50	0/50	0/50	0/50	0/50	0/50
Carcinoma, transitional cell	0/50	1/50	0/50	0/50	0/50	0/50	0/50	0/50	1/50
Lipoma	0/50	0/50	0/50	0/50	0/50	0/50	0/50	0/50	1/50
Large intestine									
Adenocarcinoma	0/42	0/50	0/50	0/50	0/50	0/50	1/50	0/50	0/50
Liver									
Cholangioma	0/50	0/50	1/50	0/50	0/50	0/50	0/50	0/50	1/50
Hepatic neoplastic nodule	5/50	4/50	2/50	3/50	10/50	5/50	1/50	5/50	2/50
Hepatocellular carcinoma	0/50	0/50	0/50	1/50	0/50	1/50	0/50	1/50	1/50
Hepatocellular neoplasia	5/50	4/50	2/50	4/50	10/50	6/50	1/50	6/50	3/50
Lung									
Carcinoma, squamous cell	0/50	0/50	0/50	0/50	0/50	0/50	0/50	1/50	0/50
Lymph nodes									
Fibrosarcoma	1/36	0/36	0/44	0/35	0/43	0/43	0/42	0/50	0/50
Hemangioendothelial sarcoma	0/36	0/36	0/44	0/35	0/43	0/43	0/42	0/50	4/50
Hemangio(endothelio)ma	1/36	3/36	5/44	1/35	1/43	6/43	0/42	11/50	2/50
Mammary gland									
Adenoma-fibroadenoma	0/49	2/49	1/50	1/50	0/50	0/50	0/50	0/50	0/49
Fibroma	0/49	0/49	0/50	0/50	1/50	0/50	2/50	0/50	0/49

Table 3: Incidence of tumor types per tissue in male control rats per experiment

MALES

Experiment number	1155	1214	1230	1307	1317	1335	1450	1309	1650
Meninges (@)									
Meningioma	0/50	0/50	0/50	0/50	0/50	0/50	0/50	0/50	1/50
Sarcoma	0/50	0/50	0/50	0/50	0/50	1/50	0/50	0/50	0/50
Pancreas									
Adenocarcinoma, endocrine	0/49	0/49	0/50	0/48	0/50	0/50	0/48	1/50	0/49
Adenocarcinoma, exocrine	0/49	0/49	0/50	0/48	0/50	0/50	2/48	2/50	0/49
Adenoma, endocrine	5/49	6/49	9/50	7/48	9/50	9/50	5/48	6/50	7/49
Adenoma, exocrine	6/49	13/49	8/50	11/48	12/50	13/50	15/48	13/50	9/49
Sarcoma	0/49	0/49	0/50	0/48	0/50	0/50	0/48	0/50	1/49
Parathyroid gland									
Adenoma	0/32	0/50	0/50	0/50	1/36	0/50	0/50	0/50	0/50
Pituitary gland									
Adenoma	19/47	15/49	9/48	13/49	11/50	12/50	10/49	4/48	13/50
(adeno)carcinoma	0/47	2/49	0/48	0/49	1/50	1/50	0/49	0/48	3/50
Prostate									
Carcinoma	0/46	0/49	0/50	1/50	0/50	0/49	0/50	0/50	1/49
Sarcoma	0/46	0/49	0/50	0/50	0/50	0/49	0/50	0/50	1/49
Seminal vesicle									
Adenocarcinoma	0/45	0/49	1/50	0/48	0/50	0/49	0/50	0/50	0/49
Carcinoma	0/45	0/49	0/50	0/48	0/50	0/49	0/50	0/50	1/49
Skin (@)									
Adenoma	0/50	0/50	0/50	0/50	0/50	0/50	0/50	0/50	1/50
Carcinoma	1/50	0/50	1/50	0/50	0/50	0/50	0/50	0/50	2/50
Kerato-acanthoma	0/50	1/50	0/50	0/50	0/50	0/50	0/50	0/50	1/50
Papilloma	0/50	1/50	2/50	3/50	1/50	1/50	1/50	5/50	4/50
Small intestine									
Adenocarcinoma	1/46	1/47	0/50	1/47	1/50	1/50	0/50	0/50	0/49
Soft tissue (@)									
(Myxo)fibroma	1/50	3/50	1/50	1/50	3/50	3/50	0/50	1/50	3/50
Fibrosarcoma	1/50	1/50	1/50	0/50	0/50	0/50	0/50	0/50	0/50
Hemangioendothelioma	0/50	0/50	0/50	0/50	0/50	0/50	0/50	0/50	2/50
Hemangioma	0/50	0/50	1/50	0/50	0/50	1/50	0/50	0/50	0/50
Hemangiosarcoma	0/50	0/50	0/50	0/50	0/50	0/50	0/50	1/50	0/50
Histiocytoma	0/50	0/50	0/50	0/50	1/50	0/50	0/50	0/50	0/50
Lipoma	0/50	0/50	0/50	0/50	0/50	0/50	0/50	0/50	1/50
Phaeochromocytoma, malignant	0/50	0/50	0/50	0/50	0/50	0/50	0/50	0/50	1/50
Sarcoma	1/50	0/50	0/50	0/50	0/50	0/50	1/50	1/50	3/50
Spleen									
Fibroma	1/50	0/50	0/50	0/49	0/50	1/49	0/50	0/50	0/50
Glandular stomach (@)									
Adenocarcinoma	0/50	0/50	0/50	1/50	1/50	0/50	0/50	0/50	0/50
Testis									
Leydig cell tumor (benign)	8/50	13/50	15/50	13/50	15/50	17/50	15/50	6/50	5/50
Thyroid gland									
Adenoma (follicular)	4/48	8/49	8/50	10/50	8/50	9/50	8/50	4/50	4/50
(Adeno)carcinoma (follicular)	2/48	5/49	0/50	1/50	0/50	2/50	0/50	1/50	5/50
Adenoma, "light cell" solid	2/48	3/49	4/50	3/50	2/50	2/50	1/50	3/50	3/50

Table 3: Incidence of tumor types per tissue in male control rats per experiment

MALES

Experiment number	1155	1214	1230	1307	1317	1335	1450	1309	1650
Tongue (@)									
Papilloma	0/50	0/50	0/50	1/50	0/50	0/50	0/50	0/50	0/50
Urinary bladder									
Carcinoma	0/48	0/50	1/48	0/47	0/50	0/46	0/50	0/50	0/50
Papilloma, transitional cell	0/48	0/50	0/48	0/47	0/50	0/46	0/50	0/50	0/50

(@) denominator = number of autopsied animals

Table 4. Incidence of tumor types per tissue in female control rats per experiment

FEMALES

Experiment number	1155	1214	1230	1307	1317	1335	1450	1309	1650
Abdominal mesothelia (@)									
Lipoma	0/50	0/50	0/50	0/50	1/50	0/50	0/50	0/50	0/50
Adrenal gland									
Adenoma	0/50	0/50	0/50	0/50	0/50	0/50	0/50	0/50	1/50
Phaeochromocytoma	2/50	1/50	1/50	5/50	2/50	2/50	0/50	2/50	0/50
Auditory sebaceous gland (@)									
Carcinoma	0/50	0/50	0/50	0/50	0/50	0/50	1/50	0/50	0/50
Bone									
Osteosarcoma	0/49	0/50	0/50	0/50	0/50	0/50	0/50	1/50	1/50
Cervix (@)									
Carcinoma, scirrhous	0/50	0/50	0/50	0/50	0/50	0/50	0/50	1/50	0/50
Fibroleiomyosarcoma	0/50	0/50	0/50	0/50	0/50	0/50	0/50	0/50	1/50
Leiomyoma	0/50	0/50	1/50	0/50	0/50	0/50	0/50	0/50	0/50
Sarcoma	0/50	5/50	0/50	3/50	1/50	0/50	2/50	2/50	2/50
Harderian gland (@)									
Adenocarcinoma	0/50	0/50	1/50	0/50	0/50	0/50	0/50	0/50	0/50
Heart									
Hemangioendothelioma	0/50	0/49	0/46	0/50	0/50	1/50	0/50	0/50	0/50
Hematopoietic sytem									
Tumor	1/50	3/50	1/50	0/50	3/50	1/50	0/50	3/50	1/50
Jaw (@)									
Kerato-acanthoma	0/50	0/50	2/50	0/50	0/50	0/50	0/50	0/50	0/50
Carcinoma, squamous cell	0/50	0/50	0/50	0/50	1/50	0/50	1/50	0/50	0/50
Schwannoma, benign	0/50	0/50	0/50	0/50	0/50	0/50	0/50	0/50	0/50
Kidney									
Adenocarcinoma	0/50	0/50	0/50	0/50	1/50	0/50	0/50	0/50	0/50
Adenoma	1/50	0/50	1/50	0/50	0/50	1/50	0/50	0/50	0/50
Lipoma	1/50	0/50	0/50	0/50	0/50	0/50	1/50	0/50	0/50
Liver									
Cholangioma	0/50	0/50	0/50	0/50	0/50	1/50	0/50	0/50	0/50
Hepatic neoplastic nodule	8/50	6/50	1/50	3/50	5/50	8/50	2/50	4/50	8/50
Lung									
Carcinoma	0/50	1/50	0/50	0/50	0/50	0/50	0/50	0/50	0/50
Lymph node									
Hemangio(endothelio)ma	0/40	1/27	1/38	2/39	0/34	0/37	0/43	1/49	0/48
Mammary gland									
Adenoma, fibroadenoma	18/50	22/50	18/50	20/50	16/50	27/50	13/50	19/50	19/50
Carcinoma	0/50	0/50	0/50	0/50	1/50	0/50	0/50	1/50	0/50
Fibroma	1/50	2/50	0/50	0/50	1/50	1/50	2/50	1/50	0/50
Adenocarcinoma	9/50	5/50	5/50	5/50	6/50	3/50	4/50	5/50	7/50
Mouth (@)									
Carcinoma, squamous cell	1/50								

Table 4. Incidence of tumor types per tissue in female control rats per experiment

FEMALES

Experiment number	1155	1214	1230	1307	1317	1335	1309	1450	1650
Ovary									
Sertoli cell tumor, benign	0/49	0/49	0/49	0/50	0/50	0/50	0/49	1/50	0/48
Sertoli cell tumor, malignant	0/49	0/49	0/49	0/50	0/50	0/50	0/49	1/50	0/48
Sertoli cell tumor	0/49	0/49	0/49	0/50	0/50	0/50	0/49	2/50	0/48
Granulosa-theca cell tumor	0/49	1/49	0/49	0/50	0/50	0/50	0/49	2/50	2/48
Carcinoma	0/49	0/49	0/49	1/50	0/50	0/50	0/49	0/50	0/48
Sarcoma	0/49	0/49	0/49	0/50	0/50	1/50	0/49	0/50	0/48
Meninges (@)									
Meningioma	0/50	0/50	0/50	0/50	0/50	0/50	0/50	0/50	1/50
Pancreas									
Adenocarcinoma, exocrine	0/50	0/50	0/50	0/50	1/50	0/50	0/49	0/49	0/49
Adenoma, endocrine	2/50	2/50	3/50	3/50	2/50	1/50	3/49	1/49	5/49
Adenoma, exocrine	0/50	1/50	2/50	2/50	3/50	3/50	1/49	1/49	0/49
Carcinoma, exocrine	0/50	1/50	0/50	0/50	0/50	0/50	0/49	0/49	0/49
Parathyroid gland									
Adenocarcinoma	0/29	0/50	0/50	0/50	0/50	0/50	0/50	0/50	1/34
Pituitary gland									
Adenoma	35/50	29/48	30/48	24/50	27/50	26/49	22/49	25/50	35/50
Adenocarcinoma	0/50	0/48	0/48	1/50	2/50	1/49	0/49	0/50	1/50
Salivary gland(s)									
Adenoma	0/50	1/50	0/50	0/50	0/50	0/50	0/50	0/50	0/50
Skin (@)									
Basal cell carcinoma	0/50	0/50	0/50	0/50	1/50	0/50	0/50	0/50	0/50
Papilloma	0/50	0/50	0/50	0/50	0/50	0/50	1/50	0/50	0/50
Small intestine									
Adenocarcinoma	0/50	0/50	0/47	0/50	1/50	0/50	0/50	0/50	0/48
Fibroleiomyoma	0/50	1/50	0/47	0/50	0/50	0/50	0/50	0/50	0/48
Fibroleiomyosarcoma	0/50	0/50	0/47	0/50	0/50	0/50	0/50	0/50	1/48
Soft tissue (@)									
Lipoma	0/50	0/50	1/50	0/50	0/50	0/50	0/50	0/50	0/50
Hemangioma	1/50	0/50	0/50	0/50	0/50	1/50	0/50	0/50	0/50
Hemangiosarcoma	1/50								
Fibrosarcoma	0/50	0/50	1/50	2/50	0/50	0/50	0/50	0/50	0/50
Sarcoma	0/50	0/50	0/50	0/50	0/50	0/50	0/50	0/50	1/50
Spleen									
Hemangioma	0/50	0/50	0/50	1/50	0/50	0/50	0/50	0/50	0/50
Stomach									
Fibrosarcoma	0/50	0/50	0/50	0/50	0/50	0/50	1/50	0/50	0/50
Thyroid gland									
Adenoma (follicular)	2/49	2/48	4/48	1/49	0/50	1/49	0/50	1/50	2/49
Adenoma, "light cell" solid	4/49	1/48	5/48	0/49	7/50	4/49	1/50	1/50	2/49
Urinary bladder									
Carcinoma	0/48	0/48	0/48	1/49	0/50	0/48	0/50	0/50	0/47
Uterus									
Adenoma, polypous	2/50	4/50	1/50	1/50	6/50	4/50	9/50	4/49	0/50
Adenocarcinoma	4/50	2/50	2/50	4/50	1/50	1/50	0/50	2/49	1/50
Carcinoma	0/50	0/50	0/50	0/50	1/50	0/50	1/50	1/49	1/50
Hemangioendothelioma	0/50	1/50	0/50	0/50	0/50	0/50	0/50	0/49	1/50
Polyp	0/50	0/50	0/50	0/50	0/50	0/50	0/50	0/49	7/50
Sarcoma	1/50	0/50	0/50	0/50	0/50	1/50	1/50	0/49	2/50

Table 4: Incidence of tumor types per tissue in female control rats per experiment

FEMALES

Experiment number	1155	1214	1230	1307	1317	1335	1309	1450	1650
Vagina (@)									
Adenocarcinoma	0/50	0/50	0/50	0/50	0/50	0/50	0/50	0/50	1/48
Leiomyoma	0/50	0/50	1/50	0/50	0/50	0/50	0/50	0/50	0/48
Sarcoma	0/50	0/50	2/50	1/50	1/50	2/50	1/50	0/50	0/48

(@) denominator = number of autopsied animals

Chem

DIVISION OF NEUROPHARMACOLOGICAL DRUG PRODUCTS
Review of Chemistry, Manufacturing, and Controls

NDA #: 20-272 **CHEM.REVIEW # 1** **REVIEW DATE: 31-AUG-92**

SUBMISSIONTYPE	DOCUMENT DATE	CDER DATE	ASSIGNED DATE
ORIGINAL	15-APR-92	17-APR-92	05-MAY-92

NAME & ADDRESS OF APPLICANT: **Janssen** Research Foundation
1125 Trenton-Harbourton Road
Titusville, NJ 08560

DRUG PRODUCT NAME
Proprietary: **RISPERDAL™**
Nonproprietary/USAN: Risperidone
Code Name/#: R 64766
Chem.Type/Ther.Class:

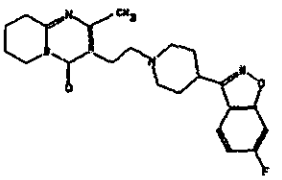
PHARMACOL.CATEGORY/INDICATION: Manifestations of Psychotic Disorders

DOSAGE FORM: Caplets
STRENGTHS: 1, 2, 3, 4, 5 mg
ROUTE OF ADMINISTRATION: Oral
DISPENSED: XXXXX Rx_____OTC

CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

3-[2-[4-(6-Fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]ethyl]-6,7,8,9-tetrahydro-2-methyl-4H-pyrido[1,3-a]pyrimidin-4-one

$C_{23}H_{27}FN_4O_2$ Molecular Weight: 410,49 CAS #: 106266-06-2



SUPPORTING DOCUMENTS: IND
RELATED DOCUMENTS:

CONSULTS: Request the review of environmental impact by Dr. P.G. Vincent. Request consult with the Division of Biometrics (statistical analysis). Request consult with the Division of Biopharmaceutics (dissolution studies).

REMARKS/COMMENTS: See the attached **REVIEW NOTES.**

CONCLUSIONS & RECOMMENDATIONS: Recommend NDA 20-272 **NOT APPROVABLE.** Draft Letter enclosed.

cc:
Orig. NDA 20-272
HFD-120
HFD-120/WJRzeszotarski
HFD-120/KHiggins
HFD-120/SWBlum
HFD-102/CKumkumian[#1 only]
R/D Init by:SWB

W. Janusz Rzeszotarski, Ph.D., Chemist

filename: N020272.000

AMD 12/23/93

REVIEW NOTES - ORIGINAL SUBMISSION

A. DRUG SUBSTANCE

1. DESCRIPTION & CHARACTERIZATION

A. DESCRIPTION

(See front page for names, chemical formula and structure)

Table 1. Description of New Drug Substance (N.D.S.)

Stereochemistry	*Nonchiral*
Appearance	*Slightly beige to almost white powder, free or virtually free from foreign matter.*
Melting Range	*169 - 173°C (polymorphs)*
pKa (by potentiomet.titr.)	*pKa_1 = 8.24; pKa_2 = 3.11*
Solubility (g/mL) amb.temp.	*Water (pH 8.7) 0.0064; 0.1N HCl (pH 5.4) 4.1;*
Solid-State Forms	*Two distinct polymorphic modifications of risperidone (designated as Polymorphs I and II) have been isolated and characterized.* ***Crystallization from ethanol (commercial Synthetic Method III) provides only (within the limits of detection) the thermodynamically stable Polymorph I.*** *Both show similar capillary melting ranges (between 169-173°C) but different (by 8-10°C) endothermic transition peaks.*
Particle Size	*Beerse: ≤ 99 % < 100 µ* *≤ 98 % < 74 µ* *≤ 95 % < 45 µ* *Gurabo: ≤ 99 % < 106 µ* *≤ 98 % < 75 µ* *≤ 95 % < 45 µ*
Partition Coefficient	*Log P = 3.04 measured at pH 9.9*

DEFICIENCIES: 1. We note in your specifications a description of the Drug Substance as being: "free or virtually free from foreign matter." Since the term "virtually free" is not quantitative we beg you to express that term in w/w percentage form.

2. We note a certain discrepancy in your solubility studies (Vol 1.2 p 11), kindly explain the observed differences in solubility of risperidone in 0.01N HCl and citrate-phosphate buffer pH 2.2 (pH of solution 5.8).

B. CHARACTERIZATION/PROOF OF STRUCTURE

The elucidation of structure has been carried out using the Reference Standard (Lot # V 890-273) and the tests applied have been listed at the Ref.Stand. paragraph.

2. MANUFACTURER

Risperidone N.D.S. will be manufactured, processed, tested, packed and labeled by:

Janssen Pharmaceutica
Thurhoutseweg 30
Beerse, Belgium
covered by DMF #

Janssen Pharmaceutica
Janssen Pharmaceutica Laan
Geel, Belgium
covered by DMF #

3. SYNTHESIS/METHOD OF MANUFACTURE:

A. STARTING MATERIALS - SPECS & TESTS (Vol 1.2 pp 93 - 119)

Detailed specifications have been included for the following starting materials:

Starting Materials (Specifications & Suppliers)

STARTING MATERIAL	*CODE #*	*SPECIFICATION*	*SUPPLIER(S)*
2-Acetylbutyrolactone	*000134*	*SPR-RM 89-9 (890407)/RI/Spec.gravity/GC % /water %*	
1,3-Difluorobenzene	*036605*	*SPR-RM 91-30 (910827)/RI/Spec. gravity/IR/ GC : / water % / 1,4- and 1,2-difluorobenzene, fluorobenzene and x-chloro-1,3-difluorobenzene each individual %*	
Hydroxylamine hydrochloride	*004543*	*SPR-RM 90-30 (900412)/Melting Range / Base Titration % min.*	
2-Pyridinamine	*000562*	*SPR-RM 90-29 (900412)/MP/IR/Water-KF :/ Base titration % min/GC % min*	
4-Pyridinecarboxylic acid	*000336*	*SPR-RM 91-1 (910114)/Acid titration % min. /UV/Capillary electrophoretic purity: % Impurities*	

EVALUATION: Acceptable. The 2-acetylbutyrolactone, hydroxylamine hydrochloride and 2-pyridinamine must be re-analyzed after a storage period of one year. 1,3-difluorobenzene and 4-pyridinecarboxylic acid are re-analyzed after two years.

B. SOLVENTS, REAGENTS, ETC. (Vol 1.2 pp 121 - 239)

Specifications and methods for all reagents, solvents and catalysts used in the synthesis have been included. The complete list is as follows:

Activated carbon powder type Norit A supra (Belgium) (Gurabo)
Alcohol anhydrous, denaturated (Belgium) (Gurabo)
Aluminum Chloride
Ammonium hydrochloride
Dichloromethane
N,N-Dimethylacetamide
Glacial Acetic Acid
Hydrochloric acid/2-propanol
Hydrogen
Infusorial earth
Methanol
Methybenzene
4-Methylbenzenesulfonic acid hydrate
N-(1-Methylethyl)-2-propanamine
5 % Palladium on carbon catalyst, 50 % moisture
Phosphonyl chloride
Potassium hydroxide
2-Propanol
2-Propanone
Sodium hydroxide solution 50 %
Thionyl chloride
Thiophene
Water, drinking water (Belgium)
Water for Chemical Process (Gurabo)
Water, purified for chemical synthesis

EVALUATION: Acceptable. The specifications and methods are properly selected. Among the others:

- A specific capillary GC purity method [30 m x 0.32 mm ID column with chemically bonded polydimethylsiloxane phase/He at Pi = 0.5 kg/cm^2]is used for solvents capable to resolve up to over 28 solvents.

- Palladium is measured in the catalyst by AAS using hollow cathode lamp: Palladium Spectr AA/5 mA/position 3.

C. FLOW CHART (Vol 1.2 pp 68 - 69)

The flow chart given below on pages 4 and 5 is for the Synthetic Method were the scale-up methods using the same starting materials and producing the same impurities).

SYNTHETIC SYNTHESIS OF

SYNTHETIC

5 pages purged

EVALUATION: Unacceptable. Vol 1.3 pp 049-59 provides the results of analysis for three Method III batches each produced at Beerse and (six total). Also included are the results of analysis for the additional eighteen (18) batches produced in the past. In the representative six batches the levels of impurities are far lower (%) than the proposed in the specifications limits (% individual, % total). The past 18 batches have the impurity specifications set much higher but do not provide numerical information just the statement "complies."

DEFICIENCIES: 1. Kindly provide us with the justification for the level of impurities set at % total in the N.D.S. specifications. We are unable to find the data justifying a level of that magnitude in the drug substance. We call your attention to the Guideline for Submitting Supporting Documentation in Drug Applications for the Manufacture of Drug Substances, 1987, p 40: "The assay limits established in the NDA for the new drug substance, as well as the limits for impurities, should be based on actual manufacturing results (i.e., from analyses of individual batches)."

2. We note that % of drug substance passes through the μ sieves. Kindly let us know whether μ sieve is the end point of your analysis. If you have additional data on particle size and population below μ, please provide. The issue has been discussed in the 15-JUN-92 meeting and we agreed that the Alpine Air-jet sifter will not do and that the laser scattering analysis is necessary.

Method Evaluation

TEST	*UV Identification of Risperidone/STM-341-01/Vol 1.3 pp 24 - 25*
SAMPLING	
SPECIFICATIONS	*Sample & Standard spectra are identical. Maxima occur at nm*
METHOD	
EVALUATION	*Unacceptable*
DEFICIENCIES	*Sampling plan not provided.*

TEST	*Infrared (IR) Identification of Risperidone/STM-342-01/Vol 1.3 pp 26 - 27*
SAMPLING	
SPECIFICATIONS	*Sample & Standard spectra are identical.*
METHOD	
EVALUATION	*Unacceptable*
DEFICIENCIES	*Sampling plan not provided.*

TEST	*Assay by base titration for Risperidone/STM-345-00/Vol 1.3 p 28*
SAMPLING	
SPECIFICATIONS	*%, calculated on the dried basis*
METHOD	
EVALUATION	*Unacceptable*

DEFICIENCIES	Sampling plan not provided.

TEST	Purity determination of Risperidone by HPLC/STM-343-01/Vol 1.3 pp 29 - 37
SAMPLING	
SPECIFICATIONS	Total Impurities: % / Individual Impurities: %
METHOD	
SYSTEM SUITABILITY	(See method validation Vol 1.3 pp 065-090) The method is specific and stability indicating. Except for two impurities (R76960 and R82354) that coelute all other synthesis impurities and stress-decomposition generated degradants are separated as shown on the model chromatograms of the reference solution (each compound 1%, 15 compounds total) and the system suitability solution (each impurity 1% with regard to R64766).
EVALUATION	Unacceptable
DEFICIENCIES	Sampling plan not provided.

TEST	Polymorphs Determination in Risperidone by Differential Scanning Calorimetry (DSC)/STM-390-01/Vol 1.3 pp 38 - 40
SAMPLING	
SPECIFICATIONS	% Polymorph I
METHOD	
EVALUATION	Unacceptable
DEFICIENCIES	Sampling plan not provided.

TEST	Color, Clarity & Percent Transmittance of Risperidone/STM-344-01/Vol 1.3 pp 42 - 25
SAMPLING	
SPECIFICATIONS	Clear, colorless to slightly yellow, % transmittance
METHOD	
EVALUATION	Unacceptable
DEFICIENCIES	Sampling plan not provided.

TEST	Residual Solvents/STM-398-00/Vol 1.3 pp 43 -47
SAMPLING	

SPECIFICATIONS	*a)methanol ppm; b) ethanol ppm; c) methylbenzene ppm; d) dichloromethane ppm*
METHOD	
EVALUATION	*Unacceptable*
DEFICIENCIES	*Sampling plan not provided.*

TEST	*Particle Size Determination/STM-399-00/Vol 1.3 p 48*
SAMPLING	
SPECIFICATIONS	% μ.
METHOD	
EVALUATION	*Unacceptable*
DEFICIENCIES	*Sampling plan not provided.*

DEFICIENCIES: 1. We were unable to find your sampling plans for testing of the manufactured new drug substance batches. We call you attention to: **21 CFR § 211.110** Sampling and testing of in-process materials and drug products. Kindly clarify.

B. PURITY PROFILE (Vol 1.3 pp 7 - 11)

Two groups of impurities are recognized: these originating from the synthesis and these originating from degradation of the drug substance. The figures below show both groups of compounds. Over twenty five batches (25) of risperidone have been analyzed and the purity profile of twenty three (23) of them presented (Vol 1.3 p 8).

EVALUATION: Unacceptable.
DEFICIENCIES: 1. We are puzzled by your table in Vol 1.3 p 00-00008 listing twenty three (23) batches of risperidone and the impurities encountered. Three (3) methods (of either synthesis or impurities detection, we presume) are mentioned in the table, but unidentified. We are not positive that each method detects (or produces) the same impurities. For example: R72111 seems to be in batches analyzed by method I, R72298 by method II and R82354 by method III. From comments on p 00-00007 we assume that the batches have been presented in chronological order the batch A0101 being the earliest and the batch PUA031 the latest. Kindly explain.

C. MICROBIOLOGY

Not applicable.

7. CONTAINER/CLOSURE SYSTEM FOR DRUG SUBSTANCE STORAGE (Vol 1.2 pp 277-279):

The container-closure system for the drug substance consists of two polyethylene bags, with ties, in a fiberboard container with a metal cap. A certificate of Analysis accompanies each receipt of plastic bags. The polyethylene used to manufacture the bags complies with 21 CFR § 177.1520.

Specifications for the fiber drums and plastic bags are appended.

DEFICIENCIES:

1. We note the absence of DMF references to gal fiber drums (presumed manufacturer and polyethylene bags (presumed suppliers: 7]). Kindly reference the pertinent DMFs, if any.

8. DRUG SUBSTANCE STABILITY (Vol 1.3 pp 00-00156 - 214)

Three batches of the bulk drug substance (PRA 01/01, 02/01, 03/01) were stored at 40°C/80% RH for two months. HPLC purity test indicated that the total of impurities detectable by that method was %.

The long term drug substance stability studies were carried out with batches manufactured in Belgium and . The drug substance manufactured in Belgium was studied more extensively and two of the batches didn't show any impurities appearing at any point. One small batch (PFA181, 0.227kg) appeared to be contaminated with R 82354 that is a manufacturing impurity and also may be stress generated. The studies support the decision to test the drug substance every two years and may support the two years expiry of the drug product.

Stress Stability Studies show that: a) no decomposition occurs in acidic aqueous media (1 N HCl, 5 days, 100°C), b) in basic aqueous media (1 N NaOH, 2 days, 100 °C) two stress products R68833 and R71486 are formed, c) in oxidative medium (hydrogen peroxide, 1 h, 60°C) two N-oxides R71611 and R72064 are formed and d) in neutral media (water, 1 day, 100°C) one stress product R76960 is formed.

Stability studies for drug substance manufactured in Belgium.

Batch #	Manuf. Date	Batch Size (kg)	Storage Conditions	Available Data	Tests	Results/ Comments
PFA151	07/06/89	3.23	a. Room Temperature b. Accelerated Conditions: 1. 40°C/80% RH 2. 50°C 3. Daylight	Room Temp: 24 mo Accelerated: 3 mo Room Temp: 1 mo Accelerated: 1 mo	Appearance Moisture Uptake* Water Assay Purity DSC	Slight discoloration observed in daylight and/or 50°C; no other changes from beginning of study.
PFA161	07/06/89	3.64				
PFA181	08/11/89	0.227				
PUA011	10/11/91	31.7				
PUA021	10/11/91	42.2				
PUA031	10/11/91					

* Test Performed for 40°C/80% RH storage condition only. No impurities were detected at any test point. Similar studies were carried out in

EVALUATION: Acceptable.

B. DRUG PRODUCT

1/2.COMPONENTS/COMPOSITION (Vol 1.4 p 7)

Drug product is to be marketed as film coated tablets: 1 mg (F23), 2 mg (F37), 3 mg (F34), 4 mg (F31) and 5 mg (F38) with **identical core components:**

- Risperidone
- Lactose (Hydrous), NF
- Corn Starch, NF
- Microcrystalline Cellulose, NF
- Hydroxypropyl Methylcellulose
- Magnesium Stearate, NF
- Colloidal Silicon Dioxide, NF
- Sodium Lauryl Sulfate, NF

* removed by in-process drying.

and, the **following film-coating components:**

	X = used; — = not used				
FILM-COATING COMPONENT:	*1 mg (F23)*	*2 mg (F37)*	*3 mg (F34)*	*4 mg (F 31)*	*5 mg (F38)*
Hydroxypropyl Methylcellulose 2910 5 cps, USP	X	X	X	X	X
Propylene Glycol, USP	X	X	X	X	X
Talc, USP	—	X	X	X	X
Titanium Dioxide, USP	—	X	X	X	X
FD&C Yellow #6 Aluminum Lake	—	X	—	—	X
D&C Yellow # 10	—	—	X	X	—
FD&C Blue #2 Aluminum Lake	—	—	—	X	X
	X	X	X	X	X

* *Removed by in-process drying; does not appear in the final product*

Quantitative Composition per Tablet.

	1 mg	*2 mg*	*3 mg*	*4 mg*	*5 mg*
TABLET CORE:	*mg wt %*	*mg wt %*	*mg wt %*	*mg wt %*	*mg wt %*
Risperidone	*1 0.5*	*2 1.0*	*3 1.0*	*4 1.0*	*5 1.0*
Lactose (hydrous), NF					
Corn Starch, NF					
Microcrystalline Cellulose, NF					
HPMC					
Magnesium Stearate, NF					
Colloidal Silicon Dioxide, NF					
Sodium Lauryl Sulfate, NF					

Total:	200 100	200 100	300 100	400 100	500 100
TABLET FILM COATING:					
HPMC					
Propylene Glycol, USP					
Talc, USP	—				
Titanium Dioxide, USP	—				
FD&C Yellow #6 Aluminum Lake # 5287	—		—	—	
FD&C Yellow #6 Aluminum Lake # 5287	—		—	—	—
D&C Yellow # 10	—	—			—
FD&C Blue # 2 Aluminum Lake	—	—	—		
Total:					

Batch Formula for a Full-scale Manufacture

	1 mg	2 mg	3 mg	4 mg	5 mg
TABLET CORE:	kg wt %	kg wt %	kg wt %	kg wt %	kg wt %
Risperidone	0.54 0.5	3 1.0	3 1.0	3 1.0	3 1.0
Lactose (hydrous), NF					
Corn Starch, NF					
Microcrystalline Cellulose, NF					
HPMC					
Magnesium Stearate, NF					
Colloidal Silicon Dioxide, NF					
Sodium Lauryl Sulfate, NF					
I					
Total:					
TABLET FILM COATING:**					
HPMC					
Propylene Glycol, USP					
Talc, USP	—				
Titanium Dioxide, USP	—				
FD&C Yellow #6 Aluminum Lake	—		—	—	
FD&C Yellow #6 Aluminum Lake	—		—	—	—

D&C Yellow # 10	---	—		—
FD&C Blue # 2 Aluminum Lake	---	---	—	
Total:				
Total Number of Tablets:				

Removed by in-process drying; does not appear in the final product.
The individual quantities given for the film-coating components include a 10% overage which may be required due to losses during the film-coating process.

EVALUATION: Unacceptable.
DEFICIENCIES: 1. Our calculations seem to indicate that lactose (hydrous), NF in the batch formulae given (Vol 1.4 p 00-00010) for 2, 3, 4 and 5 mg tablets should be present in wt% and not percent as stated. Kindly explain.
2. The percentage of hydroxypropyl methylcellulose (HPMC) USP is listed as present in the 2 mg tablet film coating either in wt% (Vol 1.4 p 00-00009) or wt% (Vol 1.4 p 00-00010). Kindly clarify which number is the correct one.
3. There are also other more minor discrepancies in the percentage composition given per tablet and per batch (Vol 1.4 pp 00-00009 - 00-00010). May we suggest that you attempt to correct them.

3. SPECIFICATIONS & METHODS FOR INACTIVE COMPONENTS:

A. COMPENDIAL

The compendial (USP/NF) components are tested for conformity to specifications in their current compendial monographs. The inactive components are:

Lactose (Hydrous), NF
Corn Starch, NF
Microcrystalline Cellulose, NF
Hydroxypropyl Methylcellulose

Magnesium Stearate, NF

Colloidal Silicon Dioxide, NF
Sodium Lauryl Sulfate, NF
Propylene Glycol, USP
Talc, USP
Titanium Dioxide

B. NON-COMPENDIAL (Vol 1.4 pp 13 - 30)

The non-compendial dyes will be tested according to specifications set forth in 21 CFR part 74.

DYE	*TEST*	*METHOD*	*METHOD NUMBER*
FD&C Blue # 2 Aluminum Lake	*Identification*	*TLC*	*STM-114*
	Assay	*Visible Spectrophotometry*	*STM-116*
FD&C Yellow # 6 Aluminum Lake	*Identification*	*TLC*	*STM-114*
	Assay	*Visible Spectrophotometry*	*STM-116*
D&C Yellow # 10	*Identification*	*Visible Spectrophotometry*	*STM-348*

	Assay	*Visible Spectrophotometry*	*STM-348*

Samples of Color Additive Certificates included.

4. MANUFACTURER

Drug Product may be: manufactured, tested, packaged, labeled, released and/or controlled by:

(DMF #

or may be also manufactured by:

Janssen Pharmaceutica, n.v.
Turnhoutsweg 30
B-2340
Beerse, Belgium (DMF #

or also packaged and/or labeled by:

(DMF #

5. METHODS OF MANUFACTURING AND PACKAGING:

A. PRODUCTION OPERATIONS (Vol 1.4 pp 48 - 50)

The process is carried in steps:

B. IN-PROCESS CONTROLS & TESTS (Vol 1.4 pp 51- 243, Vol 1.5 pp)

The following in-process tests are carried out for the compression of the core granulations:

1. Weight Variation
2. Thickness
3. Hardness
4. Friability
5. Disintegration Time

Manufacturing directions/in process controls are provided as Master Batch Records for

Master Batch Records for list the equipment needed for manufacture of tablet cores. The Beerse equipment has to be checked from DMF.

The coating operation is carried out in a and conditions are controlled automatically, the resulting final product is tested on site by determination of average weight of coated tablets & yield reconciliation before a sample is send to Quality Assurance.

In-process Specifications for Tablet Cores.

TESTS	*SPECIFICATIONS 1 & 2 mg*	*SPECIFICATIONS 3 mg*	*SPECIFICATIONS 4 mg*	*SPECIFICATIONS 5 mg*	*METHOD*
Weight Variation:					
Average Core Weight	mg *(N=10)*	mg *(N=10)*	mg *(N=10)*	mg *(N=10)*	*Gravi-metric*
Individual Core Weight	mg *(N=10)*	mg *(N=10)*	mg *(N=10)*	mg *(N=10)*	*Gravi-metric*
Thickness	*mm*	*mm*	*mm*	*mm*	*Micromet.*
Hardness	*Kp*	*Kp*	*Kp*	*Kp*	*STM-308*
Friability	*%*	*%*	*%*	*%*	*STM-309*
Disintegration Time	*min*	*min*	*min*	*min*	*USP<701>*

In weight variation and thickness are to be determined every 30 min during the compression process. In Beerse, weight variation and thickness are continuously monitored by computerized compression machines.

Specifications for Film-Coated Bulk Tablets, 1 mg - 5 mg.

Tablet Strength	*Description*	
1 mg	*White, oblong, biconvex, filmcoated tablets with "JANSSEN" inscribed on one side and "R 1" inscribed on the other.*	
2 mg	*Orange, oblong, biconvex, filmcoated tablets with "JANSSEN" inscribed on one side and "R 2" inscribed on the other.*	
3 mg	*Yellow, oblong, biconvex, filmcoated tablets with "JANSSEN" inscribed on one side and "R 3" inscribed on the other.*	
4 mg	*Green, oblong, biconvex, filmcoated tablets with "JANSSEN" inscribed on one side and "R 4" inscribed on the other.*	
5 mg	*Peach, oblong, biconvex, filmcoated tablets with "JANSSEN" inscribed on one side and "R 5" inscribed on the other.*	
TESTS	*SPECIFICATIONS*	*METHOD*
Appearance	*Meets product description*	*Visual*

Identification for Risperidone - HPLC	*RT of the Sample Preparation corresponds to that of the Reference Standard*	*STM-387*
Assay (HPLC)	*90.0 - 110.0 % of Label Claim*	*STM-387*

EVALUATION: Unacceptable.
DEFICIENCIES:
1. As agreed in our meeting of 15-JUN-92, a statement comparing the equipment used in Beerse and has to be issued. Kindly submit such statement.
2. We are troubled by your selection of color codes for the 2 mg and 5 mg tablets. We suspect the two colors: orange and peach are too close and may be mistaken. May we suggest you try to replace the peach color with a color like blue.
3. We recommend that IR (after extraction/isolation of the drug substance from Risperidone Tablets), a specific identity test, be added to identification tests for the drug product. Please refer to: The FDA Guideline for Submitting Supporting Documentation in Drug Applications for Manufacture of Drug Substances, 1987, p 37: "Specific identity test(s) (i.e., infrared (IR), nuclear magnetic resonance (NMR), and mass spectrometry (MS)). The specific identity test(s) should be capable of distinguishing the new drug substance from related compounds. If only one specific identity test is performed, an IR spectrum (KBr pellet) is preferred. Other identity tests (such as UV spectra, or relative mobility [Rf or TR values] by various chromatographic methods) are considered confirmatory rather than specific."

C. REPROCESSING OPERATIONS

None mentioned.

6. REGULATORY SPECIFICATIONS AND METHODS FOR DRUG PRODUCT:

A. SAMPLING PROCEDURES

Not described.

EVALUATION: Unacceptable.
DEFICIENCIES: 1. We note the absence of the sampling plan in your description of the regulatory specifications and methods. We call your attention to: The FDA Guideline for Submitting Documentation for the Manufacture of and controls for Drug Products, 1987, p 7: "Describe the sampling plan that will be used to assure that the sample of the drug product obtained is representative of the batch."

B. REGULATORY SPECIFICATIONS AND METHODS

Finished Product Specifications, 1 to 5 mg Risperidone Tablets.

TESTS	*SPECIFICATION*	*METHOD*
1) Appearance	*Typical*	*Visual*
2) Identification for Risperidone: a) HPLC	*Rt of the sample preparation corresponds to that of the Reference Standard*	*STM-387*
b) IR	*The spectrum of the sample preparation corresponds to that of the Reference Standard*	*STM-393*
3) Content Uniformity (UV)	*Meets requirements of USP <905> for coated tablets*	*STM-392*
4) Assay (HPLC)	*90.0 - 110.0 % of Label Claim*	*STM-387*

5) Degradation Compounds: *Individual (HPLC)* *R76960 (TLC)* *Total A + B*	% % %	*STM-387* *STM-401*
6) Dissolution	*Q = % in min*	*STM-391*

	TESTING INTERVALS (MONTHS)								
TEST NUMBER	*3*	*6*	*9*	*12*	*18*	*24*	*36*	*48*	*60*
1	*X*	*X*	*X*	*X*	*X*	*X*	*X*	*X*	*X*
4	*X*	*X*	*X*	*X*	*X*	*X*	*X*	*X*	*X*
5	*X*	*X*	*X*	*X*	*X*	*X*	*X*	*X*	*X*
6	*X*	*X*	*X*	*X*	*X*	*X*	*X*	*X*	*X*

Stability samples should be stored at 30 ± 2°C.

EVALUATION: Unacceptable.
DEFICIENCIES: 1. We note that your specifications (Vol 1.5 pp 00-00052+) allow for the total of degradation products ("degradants") in the finished drug product %. That limit suggests that you may have a hypothetical situation where the finished drug product carries % of R76960 and four (4) other degradation products in quantities of % each. Kindly identify the other four (4) degradation products and provide justification for their levels in the finished drug product.
2. Kindly identify the batches of the drug product used in toxicological studies and the levels of "degradants" in those batches.

Analytical Methods for the Drug Product.

TEST METHOD	*METHOD #*
Identification: HPLC (Vol 1.5 pp 00-00078+): Column 5µ C18 25 cm x 4.6 mm/3-pump gradient/A=0.02 K2HPO4 pH 7.8 (phosphoric acid), B=acetonitrile, C=methanol/ambient temp/UV 237 nm/Rtime(min): R71486(8.2), R71611(8.8), R68833(9.9), R72064(9.9), Risperidone(13), 4-nitrobenzophenone(15).	*STM-387*
Identification: IR	*STM-393*
Content Uniformity (UV)	*STM-392*
Assay (HPLC)	*STM-387*
Degradants (HPLC)	*STM-387*
R76960 (TLC)	*STM-401*
Dissolution (HPLC)	*STM-391*

EVALUATION: Unacceptable.
DEFICIENCIES: 1. We note that two of risperidone degradation products (R 68833 & R 72064) have identical retention times of 9.9 min when using STM-387-02 method (Vol 1.5 pp 00-0078+). Kindly explain the rationale for using the method.

7. CONTAINER/CLOSURE SYSTEM:

Drug product may be stored:

a. in bulk, in double polyethylene bags, with ties, in a fiberboard container with a metal cap.

b. in HDPE Blake Wide Mouth bottles (60 or 500 tablets) with polypropylene induction closures.

c. in PVC/PE/Aclar blisters with aluminum foil backing.

LoA have been included for the following container related DMFs:
DMF
DMF
DMF
DMF
DMF
DMF
DMF
DMF
DMF
DMF

The specifications are as follow:

COMPONENT	*CODE NO.*	*RESIN/MATERIAL*	*SUPPLIER(S)*
Bulk container	*8000600*	*Fiberboard/paper/metal*	
Polyethylene bag	*8000900*	*Polyethylene*	
40 cc bottle	*1P21X02*	*Gulf 9410, Phillips-Marlex HHM5502, or Marlex HHM 5502 BN white opaque high density polyethylene*	
50 cc -.-	*1P21X03*		
60 cc -.-	*2000400*		
175 cc -.-	*2000500*		
250 cc -.-	*1P21X06*		
325 cc -.-	*2000800*		
375 cc -.-	*2000700*		
28-400 induction closure	*4000600*	*Polypropylene*	
38-400 induction closure	*4000700*	*3M Safeguard 100 or 3M 75M foil liner*	
43-400 induction closure	*4000800*		
Blister foil	*5000100*	*Reynolds #262 aluminum*	

Blister film	*5200100*	*Polyethylene/polyvinyl chloride/Aclar*	

** Alternate suppliers of fiber drums may be used provided the containers meet the cited specifications.*
*** Suppliers of polypropylene caps other than may be used provided the foil liner is identical to that listed in the above table.*

Testing of Packaging Components is addressed in one sentence: "Testing for packaging components which meets the requirements of the current USP is described in the DMF for the respective supplier." (Vol 1.5 p 00-00030) A list and the copies of DMF authorization letters is provided.

EVALUATION: Unacceptable.
DEFICIENCIES: 1. We note your very terse statement: "Testing for packaging components which meets the requirements of the current USP is described in the DMF for the respective supplier." (Vol 1.5 p 00-00030). Regretfully we find it insufficient for our evaluation purposes. Kindly provide us with the description of tests your company will carry out as part of packaging components acceptance process.
2. We agreed in our 15-JUN-92 meeting that a confirmatory identification test will be performed for each packaging component. Kindly include a detailed description of these tests..

8. MICROBIOLOGY: (Vol 1.6 p 00-00012) Performed in the U.S. Study only according to <61> of the current USP.

9. DRUG PRODUCT STABILITY: (Vol 1.6 pp 4+)

A total of 26 stability batches were produced at and Beerse (15). The principal storage conditions are:

U.S. Study:

BULK: 25°C/recorded humidity

Bottles/blisters: 30°C/75 % recorded humidity
40°C/80% R.H.
1000 ft-candles (12K lux) light

Belgium study:

Bottles/blisters: 25°C/recorded humidity
30°C/75 % R.H
40°C/80% R.H.
1000 ft-candles (12K lux) light

Testing intervals:

Bulk 25°C/Recorded Humidity

TEST	*0 months*	*3 months*	*6 months*
Appearance	X	X	X
Assay	X	X	X
Purity	X	X	X

Dissolution	X	X	X
Hardness	X	—	X
Friability	X	—	X
Moisture	X	—	X
Microbial	X	—	X

HDPE BOTTLES & BLISTERS ALL TEMPERATURES ≤ 30°C

TEST	0	3	6	9	12	18	24	36	48mo
Appearance	X	X	X	X	X	X	X	X	X
Assay	X	X	X	X	X	X	X	X	X
Purity	X	X	X	X	X	X	X	X	X
Dissolution	X	X	X	X	X	X	X	X	X
Hardness	X	—	X	—	X	—	X	X	X
Friability	X	—	X	—	X	—	X	X	X
Moisture	X	—	X	—	X	—	X	X	X
Microbial	X	—	—	—	—	—	x	—	X

HDPE BOTTLES & BLISTERS 40°C (Recorded or 80% Relative Humidity)

TEST	0	1	2	3	6 mo
Appearance	X	X	X	X	X
Assay	X	X	X	X	X
Purity	X	X	X	X	X
Dissolution	X	X	X	X	X
Hardness	X	–	–	X	–
Friability	X	–	–	X	–
Moisture	X	–	–	X	–

HDPE BOTTLES & BLISTERS 1000 Ft-candles (12000 lux)

TEST	0	2	7	14 days
Appearance	X	X	X	X
Assay	X	X	X	X
Purity	X	X	X	X
Dissolution	X	—	—	X
Hardness	X	—	—	X
Friability	X	—	—	X

Moisture	X	—	—	X

The stability under high-intensity light appeared to vary from batch to batch but in reality the impurities detected were in the tablets from the beginning. For example: three (3) 3 mg batches (lot # 2691L001, 2691L002 & 2691L003) and one (1) 4 mg batch (lot # 2791I001) SHOW IMPURITIES ON THE DAY ZERO (0). Some color fading could be observed with these studies.

The dissolution tests seem to be different for US and Belgium studies using two different Pharmacopeia (USP 7 Eur), the volumes of dissolution medium vary from 900 mL (4 mg) to 500 mL (1 - 3 mg) and two methods of determination (HPLC & UV) of N.D.S. are used. Request consult with the Division of Biopharmaceutics.

Most of accelerated studies like: high-intensity light or 40°C/80%RH do not show formation of degradants for over 30 days irrespective of packaging. Similarly 30°C/75%RH studies for 6 months report no impurities detected. All formulation/package combinations at 40°C/ambient humidity show no deterioration for 18 months and 36 months at "ambient" (22°C/ambient humidity).

It is claimed that: "Most of the available statistical data suggest that the assay for the drug product will remain within regulatory specifications (i.e.90.0 - 110.0 5 of label claim) for close to 24 months." (Vol 1.6 p 00-00022).

A claim of 24 months stability at 15-30°C when protected from light and moisture is fully supported.

MARKETED STABILITY (Vol 1.6 p 0214)

Sponsor will place the first three batches of marketed drug product on stability. Thereafter, not less than one batch of marketed drug product will be placed on stability. The protocols are as above.

EVALUATION: Request consult with the Division of Biometrics. Request consult with the Division of Biopharmaceutics.

DEFICIENCIES:

1. We agreed during our meeting on 15-JUN-92 that humidity will be reported in all stability studies, including controlled room temperature studies. Kindly expand your stability reports to include humidity.
2. We beg to differ with you on your statement regarding the degradation products in the high-intensity light studies. The statement: "For a few batches in the U.S. study, small amounts (<0.3% total) of degradation products were observed at t_0 but not at the next time point(s)" (Vol 1.6 p 00-00022) disregards the facts that the three (3) 3 mg batches (lot # 2691L001, 2691L002 & 2691L003) and one (1) 4 mg batch (lot # 2791I001) show the same level of impurities throughout the two weeks of high-intensity light experiment. We are not certain whether these impurities were the impurities inherent in manufacturing or indeed the products of degradation. Kindly explain.

C. INVESTIGATIONAL FORMULATIONS

Quantitative and qualitative composition of some of investigational formulations differed from full-scale manufacture in:

a. Amount of drug substance, 6 & 8 mg tablets were manufactured,

b. Total core weight, 2 mg, 3 mg, 4 mg, 5 mg, 6 mg and 8 mg tablets weighing mg total.

c. Use of Polyethylene Glycol NF in tablet film coating.

In addition, a liquid formulation of 2 mg/mL (F21) risperidone was prepared consisting of:

Risperidone	2 mg	mg
		mg
	mg	q.s.
	mg	mL

A table matching the clinical protocol numbers with the formulations used in pivotal clinical/bioequivalence studies is provided (Vol 1.5 p 00-00255.

D. ENVIRONMENTAL ASSESSMENT

Requested the review of environmental impact from Dr. P.G. Vincent.

E. METHODS VALIDATION (Vol 1.5 pp 116 - 249)

Validation data included for each manufacturing site.

1. Content Uniformity by UV. Criteria (Beerse)[1 mg example]:
Specificity [formulation ingredients] **No interference at nm.**
Accuracy [recovery at 100 % label claim] **Recovery: %**
Linearity [% label claim] R^2 =
Range [recovery at % label claim] **% (70%)/ % (130%)**
Precision: **%**
Method transfer
Precision: **% RSD**
Linearity: **Correlation Factor:**
Ruggedness: **The mean values obtained from two analysts at 95 % confidence agree.**

2. Assay/Purity by HPLC. Criteria (Beerse, assay only)[1 mg example]:
Specificity [formulation ingredients, internal standard, stressed placebo, stressed degradation compounds] **No interference at nm**
Linearity % of label claim] R^2 =
Range [recovery at % label claim] **% (20%) / % (120%)**
Accuracy [recovery at 100 % of label claim] **Recovery: %**
Precision: **%**
Stability of analytical solutions: Reference & sample solution over period of 24 hours. Respectively: **Initial 99.5% & 100.3%; 24 hrs 99.1% & 101.2%.**
Method transfer
Precision: **Risperidone/Internal Standard RSD % %**
Linearity [% of label claim]: **R^2 = 0.9999**
Accuracy [recovery at 100 % of label claim]: **%**
Selectivity: **Suitable for identification of stress induced compounds.**
Ruggedness: **RSD variation between analysts acceptable.**

3. Cross validation of Content Uniformity (UV) and Assay (HPLC) Methods.

The composite values (10 tablets ea) for content uniformity test from 16 batches were compared with respective HPLC assay values. The average values (10 tablets ea/16 batches) were identical (98.2 % of label claim).

4. Dissolution. The validation (method transfer) is based on criteria:
Precision: Variation analyst to analyst acceptable.
Linearity: R^2 =
Ruggedness: **RSD variation between analysts acceptable.**

F. LABELLING (Vol 1.9)

Acceptable at this time.

G. ESTABLISHMENT INSPECTION

Inspection Requested.

H. DRAFT DEFICIENCY LETTER

The following chemistry deficiencies need to be corrected to assure that the manufacturing and packaging procedures are appropriate for the drug product and that acceptable limits and analytical methods are used to assure the identity, strength, quality, and purity of the drug product are adequate to assure the product's stability during the planned clinical studies.

1. We note in your specifications a description of the Drug Substance as being: "free or virtually free from foreign matter." Since the term "virtually free" is not quantitative we beg you to express that term in w/w percentage form.

2. We note a certain discrepancy in your solubility studies (Vol 1.2 p 11), kindly explain the observed differences in solubility of risperidone in 0.01N HCl and citrate-phosphate buffer pH 2.2 (pH of solution 5.8). **[An acceptable explanation has been provided in the meeting 15-JUN-92. No need to answer.]**

3. We note that the DMFs
In view of that fact kindly provide a written example of actual practice for each step of new drug substance. We call your attention to: The FDA Guideline for Submitting Supporting Documentation in Drug Applications for Manufacture of Drug Substances, 1987, p 13 : "Besides providing a written description of the synthesis which includes verified ranges for the operating parameters (refer to section II-E [Process Controls] and section IV [CGMP] and for the expected yield, the applicant should provide a written example of actual practice, clearly identified as an example for the reviewer's information."

4. We further ask you to express the quantities and ratios of the reactants employed in manufacturing of the N.D.S. not only in kilograms and liters but also in moles.

5. Kindly provide us with the justification for the level of impurities set at % total in the N.D.S. specifications. We are unable to find the data justifying a level of that magnitude in the drug substance. Au contraire, we note that in stability studies of the batch PFA151 (Vol 1.3 p 00-00161), the one of the batches used to produce the investigational formulations, - "No impurities

Were Detected At Any Test Point." We call your attention to: The FDA Guideline for Submitting Supporting Documentation in Drug Applications for the Manufacture of Drug Substances, 1987, p 40: "The assay limits established in the NDA for the new drug substance, as well as the limits for impurities, should be based on actual manufacturing results (i.e., from analyses of individual batches)."

6. We note tha % of drug substance passes through the μ sieves. Kindly let us know whether μ sieve is the end point of your analysis. If you have additional data on particle size below μ, please provide.

7. We note the absence of the in-process controls assuring that the synthetic and purification procedures are operating properly. Any test that does not belong to the intermediates specifications and tests but is pertinent to determine the reaction's progress should be listed under Reaction Completion/Other Process Tests.

8. We are puzzled by your table in Vol 1.3 p 00-00008 listing twenty three (23) batches of risperidone and the impurities encountered. Three (3) methods (of either synthesis or impurities detection, we presume) are mentioned in the table, but unidentified. We are not positive that each method detects (or produces) the same impurities. For example: R72111 seems to be in batches analyzed by method I, R72298 by method II and R82354 by method III. From comments on p 00-00007 we assume that the batches have been presented in chronological order the batch A0101 being the earliest and the batch PUA031 the latest. Kindly explain. Also, please refer to question # 5 addressing the levels of impurities in N.D.S.

9. We were unable to find your sampling plans for testing of the manufactured new drug substance batches. We call you attention to: **21 CFR § 211.110** Sampling and testing of in-process materials and drug products. Kindly clarify.

10. We note the absence of DMF references to gal fiber drums (presumed manufacturer and polyethylene bags (presumed suppliers: and
Kindly reference the pertinent DMFs, if any.

11. We note the absence of the sampling plan in your description of the regulatory specifications and methods. We call your attention to: The FDA Guideline for Submitting Documentation for the Manufacture of and controls for Drug Products, 1987, p 7: "Describe the sampling plan that will be used to assure that the sample of the drug product obtained is representative of the batch."

12. As agreed in our meeting of 15-JUN-92, a statement comparing the equipment used in Beerse and has to be issued. Kindly submit such statement.

13. We are troubled by your selection of color codes for the 2 mg and 5 mg tablets. (Vol 1.5 p 00-00049) We suspect that the two colors proposed: orange and peach are too close and may be mistaken. May we suggest you try to replace the peach color with a color like blue.

14. We note that the HPLC is to be the only identity test in in-process testing of the Risperidone bulk Film-coated Tablets (Vol 1.5 p 49). We recommend that IR (after extraction/isolation of the drug substance from Risperidone Tablets), a specific identity test, be added to identification tests for the drug product. Please refer to: The FDA Guideline for Submitting Supporting Documentation

in Drug Applications for Manufacture of Drug Substances, 1987, p 37: "Specific identity test(s) (i.e., infrared (IR), nuclear magnetic resonance (NMR), and mass spectrometry (MS)). The specific identity test(s) should be capable of distinguishing the new drug substance from related compounds. If only one specific identity test is performed, an IR spectrum (KBr pellet) is preferred. Other identity tests (such as UV spectra, or relative mobility [Rf or TR values] by various chromatographic methods) are considered confirmatory rather than specific."

15. Our calculations seem to indicate that lactose (hydrous), NF in the batch formulae given (Vol 1.4 p 00-00010) for 2, 3, 4 and 5 mg tablets should be present in wt% and not percent as stated. Kindly explain.

16. The percentage of hydroxypropyl methylcellulose (HPMC) USP is listed as present in the 2 mg tablet film coating either in wt% (Vol 1.4 p 00-00009) or wt% (Vol 1.4 p 00-00010). Kindly clarify which number is the correct one.

17. There are also other more minor discrepancies in the percentage composition given per tablet and per batch (Vol 1.4 pp 00-00009 - 00-00010). May we suggest that you attempt to correct them.

18. We note that two of risperidone degradation products (R 68833 & R 72064) have identical retention times of 9.9 min when using STM-387-02 method (Vol 1.5 pp 00-0078+). Kindly explain the rationale for using the method.

19. We note that your drug product specifications (Vol 1.5 pp 00-00052+) allow for the total of degradation products in the finished drug product % with the R 76960 and other individual "degradants" %. We further note (Vol 1.5 p 00-00221) that the other products of degradation (R 71486, R 71611, R 72064 & R 688330 are: "Not reportable below %." A hypothetical situation comes to mind where the finished drug product carries % of R76960 and % of total impurities, % unidentified. Kindly explain and identify the level of impurities originating from manufacture, and the total and individual level of degradants in the batches of drug product used in clinical and toxicological studies.

20. We note your very terse statement: "Testing for packaging components which meets the requirements of the current USP is described in the DMF for the respective supplier." (Vol 1.5 p 00-00030). Regretfully we find it insufficient for our evaluation purposes. Kindly provide us with the description of tests your company will carry out as part of packaging components acceptance process.

21. We agreed in our 15-JUN-92 meeting that a confirmatory identification test will be performed for each packaging component. Kindly include a detailed description of these tests.

22. We agreed during our meeting on 15-JUN-92 that humidity will be reported in all stability studies, including controlled room temperature studies. Kindly expand your stability reports to include humidity.

23. We beg to differ with you on your statement regarding the degradation products in the high-intensity light studies. The statement: "For a few batches in the U.S. study, small amounts (<0.3% total) of degradation products were observed at t_0 but not at the next time point(s)" (Vol 1.6 p 00-00022) disregards the facts that the three (3) 3 mg batches (lot # 2691L001, 2691L002 & 2691L003) and one (1) 4 mg batch (lot # 2791I001) show the same level of impurities throughout

the two weeks of high-intensity light experiment. We are not certain whether these impurities were the impurities inherent in manufacturing or indeed the products of degradation. Kindly explain.

CHEMIST'S DRAFT LETTER TO APPLICANT

NDA 20-272

Janssen Research Foundation
Attn: Ruth Wasserman
Regulatory Affairs
1125 Trenton-Harbourton Road
Titusville, NJ 08560-0200

Dear Ms Wasserman:

We have the following observations and requests regarding the Chemistry and Manufacturing Controls portions of your Notice:

1. We note in your specifications a description of the Drug Substance as being: "free or virtually free from foreign matter." Since the term "virtually free" is not quantitative we beg you to express that term in w/w percentage form.

2. We note a certain discrepancy in your solubility studies (Vol 1.2 p 11), kindly explain the observed differences in solubility of risperidone in 0.01N HCl and citrate-phosphate buffer pH 2.2 (pH of solution 5.8). **[An acceptable explanation has been provided in the meeting 15-JUN-92. No need to answer.]**

3. We note that the DMFs . In view of that fact kindly provide a written example of actual practice for each step of new drug substance. We call your attention to: The FDA Guideline for Submitting Supporting Documentation in Drug Applications for Manufacture of Drug Substances, 1987, p 13 : "Besides providing a written description of the synthesis which includes verified ranges for the operating parameters (refer to section II-E [Process Controls] and section IV [CGMP] and for the expected yield, the applicant should provide a written example of actual practice, clearly identified as an example for the reviewer's information."

4. We further ask you to express the quantities and ratios of the reactants employed in manufacturing of the N.D.S. not only in kilograms and liters but also in moles.

5. Kindly provide us with the justification for the level of impurities set at % total in the N.D.S. specifications. We are unable to find the data justifying a level of that magnitude in the drug substance. Au contraire, we note that in stability studies of the batch PFA151 (Vol 1.3 p 00-00161), the one of the batches used to produce the investigational formulations, - "No Impurities Were Detected At Any Test Point." We call your attention to: The FDA Guideline for Submitting Supporting Documentation in Drug Applications for the Manufacture of Drug Substances, 1987, p 40: "The assay limits established in the NDA for the new drug substance, as well as the limits for impurities, should be based on actual manufacturing results (i.e., from analyses of individual batches)."

6. We note that % of drug substance passes through the μ sieves. Kindly let us know whether μ sieve is the end point of your analysis. If you have additional data on particle size below μ, please provide.

7. We note the absence of the in-process controls assuring that the synthetic and purification procedures are operating properly. Any test that does not belong to the intermediates specifications and tests but is pertinent to determine the reaction's progress should be listed under Reaction Completion/Other Process Tests.

8. We are puzzled by your table in Vol 1.3 p 00-00008 listing twenty three (23) batches of risperidone and the impurities encountered. Three (3) methods (of either synthesis or impurities detection, we presume) are mentioned in the table, but unidentified. We are not positive that each method detects (or produces) the same impurities. For example: R72111 seems to be in batches analyzed by method I, R72298 by method II and R82354 by method III. From comments on p 00-00007 we assume that the batches have been presented in chronological order the batch A0101 being the earliest and the batch PUA031 the latest. Kindly explain. Also, please refer to question # 5 addressing the levels of impurities in N.D.S.

9. We were unable to find your sampling plans for testing of the manufactured new drug substance batches. We call you attention to: **21 CFR § 211.110** Sampling and testing of in-process materials and drug products. Kindly clarify.

10. We note the absence of DMF references to 10 gal fiber drums (presumed manufacturer

. Kindly reference the pertinent DMFs, if any.

11. We note the absence of the sampling plan in your description of the regulatory specifications and methods. We call your attention to: The FDA Guideline for Submitting Documentation for the Manufacture of and controls for Drug Products, 1987, p 7: "Describe the sampling plan that will be used to assure that the sample of the drug product obtained is representative of the batch."

12. As agreed in our meeting of 15-JUN-92, a statement comparing the equipment used in Beerse and has to be issued. Kindly submit such statement.

13. We are troubled by your selection of color codes for the 2 mg and 5 mg tablets. (Vol 1.5 p 00-00049) We suspect that the two colors proposed: orange and peach are too close and may be mistaken. May we suggest you try to replace the peach color with a color like blue.

14. We note that the HPLC is to be the only identity test in in-process testing of the Risperidone bulk Film-coated Tablets (Vol 1.5 p 49). We recommend that IR (after extraction/isolation of the drug substance from Risperidone Tablets), a specific identity test, be added to identification tests for the drug product. Please refer to: The FDA Guideline for Submitting Supporting Documentation in Drug Applications for Manufacture of Drug Substances, 1987, p 37: "Specific identity test(s) (i.e., infrared (IR), nuclear magnetic resonance (NMR), and mass spectrometry (MS)). The specific identity test(s) should be capable of distinguishing the new drug substance from related compounds. If only one specific identity test is performed, an IR spectrum (KBr pellet) is preferred. Other identity tests (such as UV spectra, or relative mobility [Rf or TR values] by various chromatographic methods) are considered confirmatory rather than specific."

15. Our calculations seem to indicate that lactose (hydrous), NF in the batch formulae given (Vol 1.4 p 00-00010) for 2, 3, 4 and 5 mg tablets should be present in wt% and not percent as stated. Kindly explain.

16. The percentage of hydroxypropyl methylcellulose (HPMC) USP is listed as present in the 2 mg tablet film coating either in wt% (Vol 1.4 p 00-00009) or wt% (Vol 1.4 p 00-00010). Kindly clarify which number is the correct one.

17. There are also other more minor discrepancies in the percentage composition given per tablet and per batch (Vol 1.4 pp 00-00009 - 00-00010). May we suggest that you attempt to correct them.

18. We note that two of risperidone degradation products (R 68833 & R 72064) have identical retention times of 9.9 min when using STM-387-02 method (Vol 1.5 pp 00-0078+). Kindly explain the rationale for using the method.

19. We note that your drug product specifications (Vol 1.5 pp 00-00052+) allow for the total of degradation products in the finished drug product % with the R 76960 and other individual "degradants" %. We further note (Vol 1.5 p 00-00221) that the other products of degradation (R 71486, R 71611, R 72064 & R 688330 are: "Not reportable below %." A hypothetical situation comes to mind where the finished drug product carries % of R76960 and % of total impurities, % unidentified. Kindly explain and identify the level of impurities originating from manufacture, and the total and individual level of degradants in the batches of drug product used in clinical and toxicological studies.

20. We note your very terse statement: "Testing for packaging components which meets the requirements of the current USP is described in the DMF for the respective supplier." (Vol 1.5 p 00-00030). Regretfully we find it insufficient for our evaluation purposes. Kindly provide us with the description of tests your company will carry out as part of packaging components acceptance process.

21. We agreed in our 15-JUN-92 meeting that a confirmatory identification test will be performed for each packaging component. Kindly include a detailed description of these tests.

22. We agreed during our meeting on 15-JUN-92 that humidity will be reported in all stability studies, including controlled room temperature studies. Kindly expand your stability reports to include humidity.

23. We beg to differ with you on your statement regarding the degradation products in the high-intensity light studies. The statement: "For a few batches in the U.S. study, small amounts (% total) of degradation products were observed at t_0 but not at the next time point(s)" (Vol 1.6 p 00-00022) disregards the facts that the three (3) 3 mg batches (lot # 2691L001, 2691L002 & 2691L003) and one (1) 4 mg batch (lot # 2791I001) show the same level of impurities throughout the two weeks of high-intensity light experiment. We are not certain whether these impurities were the impurities inherent in manufacturing or indeed the products of degradation. Kindly explain.

DIVISION OF NEUROPHARMACOLOGICAL DRUG PRODUCTS
Review of Chemistry, Manufacturing, and Controls

NDA #: 20-272 CHEM.REVIEW # 2 REVIEW DATE: 19-AUG-93

SUBMISSIONTYPE	DOCUMENT DATE	CDER DATE	ASSIGNED DATE
ORIG. AMENDMENT	09-JUL-93	10-JUL-93	11-JUL-93

NAME & ADDRESS OF APPLICANT: **Janssen** Research Foundation
1125 Trenton-Harbourton Road
Titusville, NJ 08560

DRUG PRODUCT NAME
Proprietary: **RISPERIDAL**™
Nonproprietary/USAN: Risperidone
Code Name/#: R 64766
Chem.Type/Ther.Class:

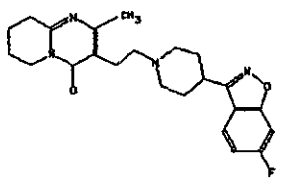
PHARMACOL.CATEGORY/INDICATION: Manifestations of Psychotic Disorders

DOSAGE FORM: Caplets
STRENGTHS: 1, 2, 3, 4, 5 mg
ROUTE OF ADMINISTRATION: Oral
DISPENSED: XXXXX Rx_____OTC

CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

3-[2-[4-(6-Fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]ethyl]-6,7,8,9-tetrahydro-2-methyl-4H-pyrido[1,3-a]pyrimidin-4-one

$C_{23}H_{27}FN_4O_2$ *Molecular Weight: 410,49 CAS #: 106266-06-2*



SUPPORTING DOCUMENTS: IND

RELATED DOCUMENTS:

CONSULTS:

REMARKS/COMMENTS: See the attached REVIEW NOTES.

CONCLUSIONS & RECOMMENDATIONS: Recommend NDA 20-272,as amended, NOT APPROVABLE. Draft Letter enclosed.

cc:
Orig. NDA 20-272
HFD-120
HFD-120/WJRzeszotarski
HFD-120/SHardeman
HFD-120/SWBlum
HFD-102/CKumkumian[#1 only]
R/D Init by:SWB

W. Janusz Rzeszotarski, Ph.D., Chemist

filename: N020272.001

SWB 12/23/93

REVIEW NOTES - ORIGINAL AMENDMENT

THE AMENDMENT PROVIDES FOR:

A. THE RESPONSE TO THE DEFICIENCY LETTER OF 07-MAY-93,

B. A SCORED 1 mg TABLET, and

C. A CHILD RESISTANT CLOSURE AND A SAMPLE BLISTER PACKAGING.

A. THE RESPONSE:

1. We note in your specifications a description of the Drug Substance as being: "free or virtually free from foreign matter." Since the term "virtually free" is not quantitative we ask you to express that term in w/w percentage form.

Sponsor's Response 1. "All batches of risperidone drug substance manufactured to date do not show any visible foreign matter. On this basis, the drug substance description (see specifications in Appendix I) has been revised to state "free from foreign matter" rather than "virtually free from foreign matter."

EVALUATION: Acceptable. (see enclosed Appendix I)

2. We note a certain discrepancy in your solubility studies (Vol 1.2 p 11), kindly explain the observed differences in solubility of risperidone in 0.01N HCl and citrate-phosphate buffer pH 2.2 (pH of solution 5.8). **[An acceptable explanation has been provided in the meeting 15-JUN-92. No need to answer.]**

3. We note that the DMFs . In view of that fact kindly provide a written example of actual practice for each step of new drug substance. We call your attention to: The FDA Guideline for Submitting Supporting Documentation in Drug Applications for Manufacture of Drug Substances, 1987, p 13 : "Besides providing a written description of the synthesis which includes verified ranges for the operating parameters (refer to section II-E [Process Controls] and section IV [CGMP] and for the expected yield, the applicant should provide a written example of actual practice, clearly identified as an example for the reviewer's information."

Sponsor's Response 3. "A representative executed batch record (i.e. the document in which the actual working parameters are noted) for the entire synthesis of risperidone drug substance is provided in Appendix II. As discussed during the FDA/Janssen teleconference of June 22, 1993, this batch record is written in Flemish but can be understood fairly easily since it contains mainly numerical values for the various operating parameters (reaction time, temperature, etc.)."

EVALUATION: Acceptable. (see enclosed Appendix II)

4. We further ask you to express the quantities and ratios of the reactants employed in manufacturing of the N.D.S. not only in kilograms and liters but also in moles.

Sponsor's Response 4. "The manufacturing directions for the drug substance have been revised to include the requested information and are provided in Apendix III."

EVALUATION: Acceptable. (see enclosed Appendix III)

5. Kindly provide us with the justification for the level of impurities set at % total in the N.D.S. specifications. We are unable to find the data justifying a level of that magnitude in the drug substance. Au contraire, we note that in stability studies of the batch PFA151 (Vol 1.3 p 00-00161), the one of the batches used to produce the investigational formulations, - "No Impurities Were Detected At Any Test Point." We call your attention to: The FDA Guideline for Submitting Supporting Documentation in Drug Applications for the Manufacture of Drug Substances, 1987, p 40: "The assay limits established in the NDA for the new drug substance, as well as the limits for impurities, should be based on actual manufacturing results (i.e., from analyses of individual batches)."

Sponsor's Response 5. "...Based on these data (see enclosed), and upon further discussion with FDA during the June 22, 1993 teleconference, the specification for the drug substance purity remains essentially unchanged with the addition of a specification for unknown impurities as follows

Known Impurities: % individual
Unknown Impurities: % individual
Known + Unknown Impurities: % total

EVALUATION: Unacceptable.

DEFICIENCIES:

5D. We can not accept your response # 5 since it is not historically supported by the impurity levels of the drug substance synthesized at Gurabo, Puerto Rico. We suggest you amend your regulatory specifications to read as follows:

Known Impurities: % individual
Unknown Impurities: % individual
Known + Unknown Impurities: % total

6. We note that % of drug substance passes through the μ sieves. Kindly let us know whether μ sieve is the end point of your analysis. If you have additional data on particle size below μ, please provide.

Sponsor's Response 6. (see attached)

EVALUATION: Unacceptable.

DEFICIENCIES:

6D. We note your response # 6 and suggest that you change your particle size regulatory specifications to read as follows:

drug substance particle size: % μ; % μ

7. We note the absence of the in-process controls assuring that the synthetic and purification procedures are operating properly. Any test that does not belong to the intermediates specifications and tests but is pertinent to determine the reaction's progress should be listed under Reaction Completion/Other Process Tests.

Sponsor's Response 7. "The manufacturing directions for the drug substance, provided in Appendix III, have been revised to include the in-process controls summarized in the following table:

Substance Being Synthesized/Purified	*In-Process Control*
T1310	*Determination of unreacted 4-pyridinecarboxylic acid*
T1250	*Determination of unreacted 2-aminopyridine*
T1486	*Determination of unreacted T1250*
T1624	*Determination of unreacted T1486*
Risperidone (R64766)	*Determination of the clarity of the filtrate from crystallization of R64766*

EVALUATION: Acceptable.

8. We are puzzled by your table in Vol 1.3 p 00-00008 listing twenty three (23) batches of risperidone and the impurities encountered. Three (3) methods (of either synthesis or impurities detection, we presume) are mentioned in the table, but unidentified. We are not positive that each method detects (or produces) the same impurities. For example: R72111 seems to be in batches analyzed by method I, R72298 by method II and R82354 by method III. From comments on p 00-00007 we assume that the batches have been presented in chronological order the batch A0101 being the earliest and the batch PUA031 the latest. Kindly explain. Also, please refer to question # 5 addressing the levels of impurities in N.D.S.

Sponsor's Response 8. "The batches in the original NDA (Vol 1.3, p 00-0008) were presented in chronological order of manufacture, with batch A0101 being the earliest and PUA031 the most recent. The manufacturing dates for batches A0101 through PFA271 are given in the original NDA, Vol 1.3 pp 00-00057+; the manufacturing dated for batches PUA011 through PUA031 are given in the original NDA, Vol 1.3 p 00-00175."

EVALUATION: Acceptable. (see enclosed)

9. We were unable to find your sampling plans for testing of the manufactured new drug substance batches. We call you attention to: **21 CFR § 211.110** Sampling and testing of in-process materials and drug products. Kindly clarify.

Sponsor's Response 9. "...every drum is usually sampled."

EVALUATION: Acceptable.

10. We note the absence of DMF references to gal fiber drums (presumed manufacturer nd polyethylene bags (presumed suppliers: and
Kindly reference the pertinent DMFs, if any.

Sponsor's Response 10. "DMFs do not exist for any of the above packaging components."

EVALUATION: Acceptable.

11. We note the absence of the sampling plan in your description of the regulatory specifications and methods. We call your attention to: The FDA Guideline for Submitting Documentation for the Manufacture of and controls for Drug Products, 1987, p 7: "Describe the sampling plan that will be used to assure that the sample of the drug product obtained is representative of the batch."

Sponsor's Response 11. "...sampling plan identical to that described for drug substance in the response to FDA comment #9."

EVALUATION: Acceptable.

12. As agreed in our meeting of 15-JUN-92, a statement comparing the equipment used in Beerse and has to be issued. Kindly submit such statement.

EVALUATION: Acceptable. **NO LONGER GERMANE.**

13. We are troubled by your selection of color codes for the 2 mg and 5 mg tablets. (Vol 1.5 p 00-00049) We suspect that the two colors proposed: orange and peach are too close and may be mistaken. May we suggest you try to replace the peach color with a color like blue.

Sponsor's Response 13. See the attached photographs.

EVALUATION: Acceptable.

14. We note that the HPLC is to be the only identity test in in-process testing of the Risperidone bulk Film-coated Tablets (Vol 1.5 p 49). We recommend that IR (after extraction/isolation of the drug substance from Risperidone Tablets), a specific identity test, be added to identification tests for the drug product. Please refer to: The FDA Guideline for Submitting Supporting Documentation in Drug Applications for Manufacture of Drug Substances, 1987, p 37: "Specific identity test(s) (i.e., infrared (IR), nuclear magnetic resonance (NMR), and mass spectrometry (MS)). The specific identity test(s) should be capable of distinguishing the new drug substance from related compounds. If only one specific identity test is performed, an IR spectrum (KBr pellet) is preferred. Other identity tests (such as UV spectra, or relative mobility [Rf or TR values] by various chromatographic methods) are considered confirmatory rather than specific."

Sponsor's Response 14. "Since Beerse was withdrawn as a drug product manufacturer in the submission of July 1, 1993, the above comment is no longer applicable. Nevertheless, the absence of the IR test from the specifications for bulk material to be shipped from Belgium to is justified as follows: before release, the tablets are fully tested in according to the regulatory finished product specifications (which include both confirmatory (HPLC) and specific (IR) identification tests as cited in the FDA Guidelines) provided in Appendix V of this submission...."

EVALUATION: Acceptable.

15. Our calculations seem to indicate that lactose (hydrous), NF in the batch formulae given (Vol 1.4 p 00-00010) for 2, 3, 4 and 5 mg tablets should be present in wt% and not percent as stated. Kindly explain.

16. The percentage of hydroxypropyl methylcellulose (HPMC) 2910 15 cps, USP is listed as present in the 2 mg tablet film coating either in wt% (Vol 1.4 p 00-00009) or wt% (Vol 1.4 p 00-00010). Kindly clarify which number is the correct one.

17. There are also other more minor discrepancies in the percentage composition given per tablet and per batch (Vol 1.4 pp C0-00009 - 00-00010). May we suggest that you attempt to correct them.

Sponsor's Response 15, 16, 17. ..."The corrected tablet/batch compositions are provided in Tables I-II which follow...."

EVALUATION: Acceptable. (see enclosed)

18. We note that two of risperidone degradation products (R 68833 & R 72064) have identical retention times of 9.9 min when using STM-387-02 method (Vol 1.5 pp 00-0078+). Kindly explain the rationale for using the method.

Sponsor's Response 18."....the retention times of degradants R68833 and R72064 are similar (both typically about 10 min) but are often sufficiently resolved from each other to permit individual quantification."

EVALUATION: Unacceptable.

DEFICIENCIES:

D18. We are rather mystified by your answer to our query # 18. Kindly clarify for us your statement: "....the retention times of degradants R68833 and R72064 are similar (both typically about 10 min) but are often sufficiently resolved from each other to permit individual quantification." We do not agree with your proposal to treat a group of unresolved impurities as a single individual (albeit unknown) impurity but would be grateful if you quote the existing precedent(s).

19. We note that your drug product specifications (Vol 1.5 pp 00-00052+) allow for the total of degradation products in the finished drug product % with the R 76960 and other individual "degradants" %. We further note (Vol 1.5 p 00-00221) that the other products of degradation (R 71486, R 71611, R 72064 & R 688330 are: "Not reportable below %." A hypothetical situation comes to mind where the finished drug product carries ≤ 0.5 % of R76960 and % of total impurities, % unidentified. Kindly explain and identify the level of impurities originating from manufacture, and the total and individual level of degradants in the batches of drug product used in clinical and toxicological studies.

Sponsor's Response 19. See Appendix V & VII.

EVALUATION: Unacceptable.

DEFICIENCIES:

D19. The following is a summary of our understanding of your response to the query # 19.

a) We note that a number of lots of the risperidone tablets, at one time or another but mostly at the third months of the study, failed your proposed specifications. The lots in question are for example: 249L001 (two types of container, same impurity), batch 249L002 (three types of container, two different impurities), etc.

b) We note that the even with the degradants formed, the total of these impurities never rose above the % for the duration of the studies.
c) We also note most of your lots show a dramatic decrease in the assay on the ninth month of the study followed by a steep recovery to or above the release levels. Please explain.
d) We further note the absence of the stability data for all formulations used during the clinical investigations. Please refer to the FDA Guideline for Submitting Documentation for the Stability of Human Drugs and Biologics, 1987, p 41: "*Stability studies conducted for all formulations used during clinical investigations should be summarized as described in the introductory paragraph of Section III, in paragraphs B and C of that section, and in section VII of these guidelines.*"

In view of the above we suggest that you:

A) Amend your stability specifications to read:
Individual degradant content: %
Total degradant content: %

B) Provide the results of stability studies for all formulations used during clinical investigations.

C) Base your expiration date proposal on the actual data as recorded and not as extrapolated.

20. We note your very terse statement: "Testing for packaging components which meets the requirements of the current USP is described in the DMF for the respective supplier." (Vol 1.5 p 00-00030). Regretfully we find it insufficient for our evaluation purposes. Kindly provide us with the description of tests your company will carry out as part of packaging components acceptance process.

21. We agreed in our 15-JUN-92 meeting that a confirmatory identification test will be performed for each packaging component. Kindly include a detailed description of these tests.

Sponsor's Response 20 & 21. ..."Additionally, the following testing is performed by Janssen as part of the acceptance process:
- Visual inspection for adherence to specifications, defects, etc.
- Dimensional verification
- Identification (Confirmatory identification)

EVALUATION: Acceptable.

22. We agreed during our meeting on 15-JUN-92 that humidity will be reported in all stability studies, including controlled room temperature studies. Kindly expand your stability reports to include humidity.

Sponsor's Response 22. "Updated drug substance stability reports are provided in Appendix IV of this submission; the humidities for all stability studies are included in these reports. An updated drug product stability report is provided in Appendix VII of this submission. The humidities for all stability studies are included in the Experimental Section of the report."

EVALUATION: Acceptable.

23. We beg to differ with you on your statement regarding the degradation products in the high-intensity light studies. The statement: "For a few batches in the U.S. study, small amounts (% total) of degradation products were observed at t_0 but not at the next time point(s)" (Vol 1.6 p 00-00022) disregards the facts that the three (3) 3 mg batches (lot # 2691L001, 2691L002 &

2691L003) and one (1) 4 mg batch (lot # 2791I001) show the same level of impurities throughout the two weeks of high-intensity light experiment. We are not certain whether these impurities were the impurities inherent in manufacturing or indeed the products of degradation. Kindly explain.

Sponsor's Response 23. ..."An updated drug product stability report is provided in Appendix VII of this submission."

H. DRAFT DEFICIENCY LETTER

NDA 20-272

Janssen Pharmaceutica
Attn: Maria A. Geigel
1125 Trenton-Harbourton Road
Titusville, NJ 08560-0200

Fax: (609) 730-3091

Dear Ms Geigel:

Please refer to your communication of 09-JUL-93 referring to the above NDA for RISPERDAL (risperidone) Tablets.

We have the following observations and requests regarding the Chemistry and Manufacturing Controls portions of your Notice:

5D. We can not accept your response # 5 since it is not historically supported by the impurity levels of the drug substance synthesized at Gurabo, Puerto Rico. We suggest you amend your regulatory specifications to read as follows:

Known Impurities:	% individual
Unknown Impurities:	% individual
Known + Unknown Impurities:	% total

6D. We note your response # 6 and suggest that you change your particle size regulatory specifications to read as follows:

drug substance particle size: % μ; % μ

D18. We are rather mystified by your answer to our query # 18. Kindly clarify for us your statement: "....the retention times of degradants R68833 and R72064 are similar (both typically about 10 min) but are often sufficiently resolved from each other to permit individual quantification." We do not agree with your proposal to treat a group of unresolved impurities as a single individual (albeit unknown) impurity but would be grateful if you quote the existing precedent(s).

D19. The following is a summary of our understanding of your response to the query # 19.

a) We note that a number of lots of the risperidone tablets, at one time or another but mostly at the third months of the study, failed your proposed specifications. The lots in question are for example: 249L001 (two types of container, same impurity), batch 249L002 (three types of container, two different impurities), etc.

b) We note that the even with the degradants formed, the total of these impurities never rose above the % for the duration of the studies.
c) We also note most of your lots show a dramatic decrease in the assay on the ninth month of the study followed by a steep recovery to or above the release levels. Please explain.
d) We further note the absence of the stability data for all formulations used during the clinical investigations. Please refer to the FDA Guideline for Submitting Documentation for the Stability of Human Drugs and Biologics, 1987, p 41: "*Stability studies conducted for all formulations used during clinical investigations should be summarized as described in the introductory paragraph of Section III, in paragraphs B and C of that section, and in section VII of these guidelines.*"

In view of the above we suggest that you:

A) Amend your stability specifications to read:
Individual degradant content: %
Total degradant content: %

B) Provide the results of stability studies for all formulations used during clinical investigations.

C) Base your expiration date proposal on the actual data as recorded and not as extrapolated.

Please consider the above as an informal communication, the official letter should follow.

Sincerely,

W. Janusz Rzeszotarski, Ph.D.

DIVISION OF NEUROPHARMACOLOGICAL DRUG PRODUCTS
Review of Chemistry, Manufacturing, and Controls

NDA #: 20-272 **CHEM.REVIEW # 3** **REVIEW DATE: 20-SEP-93**

SUBMISSIONTYPE	DOCUMENT DATE	CDER DATE	ASSIGNED DATE
ORIG. AMENDMENT	01-JUL-93	02-JUL-93	16-JUL-93

NAME & ADDRESS OF APPLICANT: **Janssen** Research Foundation
1125 Trenton-Harbourton Road
Titusville, NJ 08560

DRUG PRODUCT NAME
Proprietary: **RISPERIDAL™**
Nonproprietary/USAN: Risperidone
Code Name/#: R 64766
Chem.Type/Ther.Class:

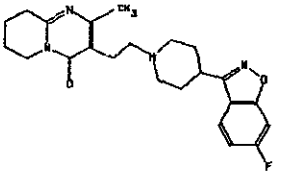
PHARMACOL.CATEGORY/INDICATION: Manifestations of Psychotic Disorders

DOSAGE FORM: Caplets
STRENGTHS: 1, 2, 3, 4, 5 mg
ROUTE OF ADMINISTRATION: Oral
DISPENSED: XXXXX Rx_____OTC

CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

3-[2-[4-(6-Fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]ethyl]-6,7,8,9-tetrahydro-2-methyl-4H-pyrido[1,3-a]pyrimidin-4-one

$C_{23}H_{27}FN_4O_2$ *Molecular Weight: 410,49 CAS #: 106266-06-2*



SUPPORTING DOCUMENTS: IND

RELATED DOCUMENTS:

CONSULTS:

REMARKS/COMMENTS: The amendment provides for withdrawal of Janssen facilities in Belgium as risperidone drug substance and drug product manufacturers.

CONCLUSIONS & RECOMMENDATIONS: Recommend NDA 20-272,as amended, **APPROVABLE.**

cc:
Orig. NDA 20-272
HFD-120
HFD-120/WJRzeszotarski/**20-SEP-93**
HFD-120/SHardeman
HFD-120/SWBium
HFD-102/CKumkumian[#1 only]
R/D Init by:SWB 12/23/93

W. Janusz Rzeszotarski, Ph.D., Chemist

filename: N020272.002

DIVISION OF NEUROPHARMACOLOGICAL DRUG PRODUCTS
Review of Chemistry, Manufacturing, and Controls

NDA #: 20-272

CHEM.REVIEW # 4 **REVIEW DATE: 31-AUG-93**

SUBMISSIONTYPE	DOCUMENT DATE	CDER DATE	ASSIGNED DATE
ORIG. AMENDMENT	10-AUG-93	12-AUG-93	16-AUG-93

NAME & ADDRESS OF APPLICANT:

Janssen Research Foundation
1125 Trenton-Harbourton Road
Titusville, NJ 08560

DRUG PRODUCT NAME
Proprietary: **RISPERIDAL™**
Nonproprietary/USAN: Risperidone
Code Name/#: R 64766
Chem.Type/Ther.Class:

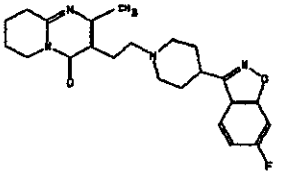
PHARMACOL.CATEGORY/INDICATION: Manifestations of Psychotic Disorders

DOSAGE FORM: Caplets
STRENGTHS: 1, 2, 3, 4, 5 mg
ROUTE OF ADMINISTRATION: Oral
DISPENSED: XXXXX Rx_____OTC

CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

3-[2-[4-(6-Fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]ethyl]-6,7,8,9-tetrahydro-2-methyl-4H-pyrido[1,3-a]pyrimidin-4-one

$C_{23}H_{27}FN_4O_2$ Molecular Weight: 410,49 CAS #: 106266-06-2



SUPPORTING DOCUMENTS: IND

RELATED DOCUMENTS:

CONSULTS: P. VINCENT for EA.

REMARKS/COMMENTS: The amendment provides for a revised ENVIRONMENTAL ASSESSMENT (EA) in response to FDA letter of 04-MAR-93.

CONCLUSIONS & RECOMMENDATIONS: N.A.I. Recommend NDA 20-272, as amended, **APPROVABLE.**

W. Janusz Rzeszotarski, Ph.D., Chemist

cc:
Orig. NDA 20-272
HFD-120
HFD-120/WJRzeszotarski/**31-AUG-93**
HFD-120/SHardeman
HFD-120/SWBlum
HFD-102/CKumkumian[#1 only]
R/D Init by:SWB filename: N020272.003

SWB 12/23/93

DIVISION OF NEUROPHARMACOLOGICAL DRUG PRODUCTS
Review of Chemistry, Manufacturing, and Controls

NDA #: 20-272

CHEM.REVIEW # 5 **REVIEW DATE: 21-OCT-93**

SUBMISSIONTYPE	DOCUMENT DATE	CDER DATE	ASSIGNED DATE
ORIG. AMENDMENT	24-SEP-93	27-SEP-93	01-OCT-93

NAME & ADDRESS OF APPLICANT:

Janssen Research Foundation
1125 Trenton-Harbourton Road
Titusville, NJ 08560

DRUG PRODUCT NAME
Proprietary: **RISPERIDAL™**
Nonproprietary/USAN: Risperidone
Code Name/#: R 64766
Chem.Type/Ther.Class:

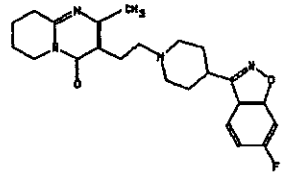
PHARMACOL.CATEGORY/INDICATION: Manifestations of Psychotic Disorders

DOSAGE FORM: Caplets
STRENGTHS: 1, 2, 3, 4, 5 mg
ROUTE OF ADMINISTRATION: Oral
DISPENSED: XXXXX Rx_____OTC

CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

3-[2-[4-(6-Fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]ethyl]-6,7,8,9-tetrahydro-2-methyl-4H-pyrido[1,3-a]pyrimidin-4-one

$C_{23}H_{27}FN_4O_2$ Molecular Weight: 410,49 CAS #: 106266-06-2



SUPPORTING DOCUMENTS: IND
RELATED DOCUMENTS:
CONSULTS: P. VINCENT for EA.

REMARKS/COMMENTS: The amendment provides for an additional/updated chemistry, manufacturing and controls information in response to FDA letter of 19-AUG-93. Also included are minor revisions to the drug product purity and dissolution methods in response to 31-AUG-93 FDA form 483 issued during inspection of the facility.

CONCLUSIONS & RECOMMENDATIONS: The response and the minor revisions are ACCEPTABLE. Recommend NDA 20-272, as amended, **APPROVABLE.**

cc:
Orig. NDA 20-272
HFD-120
HFD-120/WJRzeszotarski/**21-OCT-93**
HFD-120/SHardeman
HFD-120/SWBlum
HFD-102/CKumamian[#1 only]
R/D Init by:SWB 12/23/93

W. Janusz Rzeszotarski, Ph.D., Chemist

filename: N020272.004

REVIEW NOTES. ORIGINAL AMENDMENT

5D. We can not accept your response # 5 since it is not historically supported by the impurity levels of the drug substance synthesized at Gurabo, Puerto Rico. We suggest you amend your regulatory specifications to read as follows:

Known Impurities:	% individual
Unknown Impurities:	% individual
Known + Unknown Impurities:	% total

Sponsor's Response to 5D.

Janssen agrees to amend the drug substance impurity specification as suggested by FDA based on the batch purity overview provided in the July 9, 1993 NDA amendment. The revised specification is provided in Appendix I.

SPECIFICATIONS FOR RISPERIDONE BULK DRUG SUBSTANCE

MATERIAL DESCRIPTION:	*Slightly beige to almost white powder, free from foreign matter.*	
TESTS:		
APPEARANCE:	*Complies with Material Description*	*Visual*
IDENTIFICATION: *UV* *IR*	*Sample and Standard spectra are identical. Maxima occur at nm, nm and nm.* *Sample and Standard spectra are identical.*	*STM-341* *STM-342*
MELTING RANGE:	*169-173°C; ≤ 2°C range between begining and end of melting*	*USP XXII <741> for Class Ia substances*
ASSAY:	*%, calculated onthe dried basis*	*STM-345*
PURITY (HPLC):	*Individual known impurities: %* *Individual unknown impurities: %* *Total impurities: %*	*STM-343*
ASSAY FOR POLYMORPH I:	*%*	*STM-390 (Gurabo)* *STM-400 (Beerse)*
COLOR AND CLARITY:	*Clear, colorless to slightly yellow (10% solution in a mixture of water-acetic acid 18:2, volume)*	*STM-344*
TRANSMITTANCE:	*%*	*STM-344*
LOSS ON DRYING:	*% (using g at 80°C in vacuum for 4 hrs*	*USP XXII <731>*
RESIDUAL SOLVENTS:	*Methanol ppm* *Ethanol ppm* *Methylbenzene ppm* *Dichloromethane ppm*	*STM-398*
RESIDUE ON IGNITION:	*% (using g of substance)*	*USP XXII <281>*
HEAVY METALS:	*ppm*	*USP XXII <231> Meth II*

PARTICLE SIZE ANALYSIS: BEERSE (Sieve):	μ μ μ μ μ μ μ μ	*STM-399* *STM-399*
MISCELLANEOUS:	*NONE*	*NONE*

EVALUATION: Acceptable.

6D. We note your response # 6 and suggest that you change your particle size regulatory specifications to read as follows:

Drug Substance Particle Size: % μ; % μ

Sponsor's Response to 6D.

See the above list of specifications.

EVALUATION: Acceptable.

D18. We are rather mystified by your answer to our query # 18. Kindly clarify for us your statement: "....the retention times of degradants R68833 and R72064 are similar (both typically about 10 min) but are often sufficiently resolved from each other to permit individual quantification." We do not agree with your proposal to treat a group of unresolved impurities as a single individual (albeit unknown) impurity but would be grateful if you quote the existing precedent(s).

Sponsor's Response to D18.

As agreed in the August 20, 1993 FDA/Janssen teleconference, Janssen commits to evaluate modification of the degradant method on a post-approval basis. The goal will be to achieve routine separation of R68833 and R72064.

EVALUATION: Acceptable.

D19. The following is a summary of our understanding of your response to the query # 19.

a) We note that a number of lots of the risperidone tablets, at one time or another but mostly at the third months of the study, failed your proposed specifications. The lots in question are for example: 249L001 (two types of container, same impurity), batch 249L002 (three types of container, two different impurities), etc. Please explain.
b) We note that the even with the degradants formed, the total of these impurities never rose above the % for the duration of the studies.
c) We also note most of your lots show a dramatic decrease in the assay on the ninth month of the study followed by a steep recovery to or above the release levels. Please explain.

d) We further note the absence of the stability data for all formulations used during the clinical investigations. Please refer to the FDA Guideline for Submitting Documentation for the Stability of Human Drugs and Biologics, 1987, p 41: ***"Stability studies conducted for all formulations used during clinical investigations should be summarized as described in the introductory paragraph of Section III, in paragraphs B and C of that section, and in section VII of these guidelines."***

In view of the above we suggest that you:

A) Amend your stability specifications to read:
Individual Degradant Content: %
Total Degradant Content: %

B) Provide the results of stability studies for all formulations used during clinical investigations.

C) Base your expiration date proposal on the actual data as recorded and not as extrapolated.

Sponsor's Response to D19.

(Also see the attached and the Appendices II and III.)

Re: a) "Some of the high degradant values .....were erronously assigned. A revised stability report.....in preparation."

Re: b) "Jansen acknowledges that,.....the total degradant levels do not exceed % during the stability studies, accoprdingly, Janssen has revised the drug product specification to NMT % total degradants."

Re: c) "Janssen acknowledges that many assay results obtained at the nine month stability .....were considerably lower..." "...this was noted and investigated,...."

Re: d) "A complete summary ...are provided in Appendix III of this submission."

EVALUATION: a) Disscussed during the inspection in Puerto Rico. Acceptable.
b) This is the level observed in clinical trial samples on stability studies. Acceptable.
c) During the inspection there was no evidence of extensive investigation. Compliance call.
d) Acceptable.

MEMORANDUM OF MEETING///TELEPHONE CONVERSATION

NDA 20-272

DATE: 15-JUN-92

PRODUCT NAME: Risperidal (Risperidone)
COMPANY: Janssen Research Foundation

Conversation with: Maria A. Geigel, Steven Pikulin, Ph.D.

Telephone #: **Telecon:** **Meeting:XXXX**

(BACKGROUND) Risperidone NDA has been filed on 15-APR-92 for 1, 2, 3, 4, 5 mg caplets for Manifestations of Psychotic Disorders.

The meeting was requested by Maria Geigel (Director, Technical Regulatory Affairs) to discuss the progress of the review process and to prepare ground for the receipt of Draft Deficiency Letter and preparation of NDA Amendment in response to it.

Ms Geigel thanked Dr. Blum for agreeing to meet and in the introduction to Janssen Pharmaceutica described the deployment of various Janssen facilities in Belgium and their relationship to each other (at most 45 km apart). The drug substance may actually be manufactured at two different sites: Beerse & Geel, depending on the availability of desired equipment.

Dr. Blum initiated the discussion by asking about the end size of the NDS particles (% of them pass through μ sieve) as the result of milling at both sites, at Beerse and Dr. Pikulin promised to look into it and respond in a greater detail than the data presented in the application. It was agreed that both; upper and lower limits should be set for the particle size specifications.

Dr. Rzeszotarski inquired about the absence of separate specifications for the Reference Standard and Janssen position on that issue. Dr. Blum explained that although the specifications itself aren't required it should be stated very explicitly how the Reference Standard would be prepared and analyzed. Ms Geigel and Dr. Pikulin promised to add that statement to the report listing the results of the Reference Standard extensive analysis.

Dr. Rzeszotarski mentioned the absence of in-process controls and lack of written examples of actual practice for each step of new drug substance. Dr. Blum reemphasized the necessity of having these two items in the application and Dr. Rzeszotarski followed with actual reading of the application's examples he found particularly vague and giving parameters too broad to be acceptable. Ms Geigel presented that it is the Janssen's policy to be as broad as possible in the practical ranges of manufacturing parameters in order to avoid the tedious route of supplements in the future should the changes be introduced.

Dr. Pikulin presented literature examples as a follow up of the telephone conversation with Dr. Rzeszotarski on the difference in the solubility of different salts of the same base depending on the degree of hydration of the counterion.

The issue of the drug substance stability was discussed and it was agreed that at the present the duration of the stability studies at makes them unacceptable and that the information will be amended once the additional information becomes available.

Dr. Blum asked how the inks and containers will pass through the acceptance tests and what will be their identity tests. Dr. Pikulin responded that all the inks are of CRF material and the identity tests will be run according to the USP. Dr. Blum reemphasized the need to carry out one's own identity tests and to avoid the over-reliance on the supplier's Certificate of Analysis.

Dr. Blum raised the question of equipment compatibility at the sites in Belgium and and inquired about the size of the fluid bed granulators and their maximal throughput. Dr. Pikulin agreed that there are the differences in size of given pieces of machinery and promised to pay particular attention to the changes in the drug product friability and dissolution as a function of the batch and granulator size. It was agreed that the inspectors reviewing the facilities in both countries should confer and compare notes on the performance of the granulators.

On Dr. Blum's insistence and in view of the stability studies in progress (especially in Ms. Geigel promised to rework the Stability Commitment to embrace the agreement to conduct and complete the studies, report their results and take action by withdrawing from the market any lots found to be outside of the approved specifications.

It was further agreed that the company will await Agency's Deficiency Letter to be posted within a month from the meeting and respond to that letter in form of an amendment.

In closing Ms. Geigel and Dr. Pikulin thanked Dr. Blum for the meeting and clarification of the discussed issues that should positively impact the fate of the application.

W. Janusz Rzeszotarski, Ph.D., Chemist

INIT: SWB
cc: KHiggins

Filename: TCMM92.006

Date: 12-21-93 6:04pm
From: Stanley W. Blum:HFN120:CDB
To: JRZESZOTARSKI, SHARDEMAN, PDAVID
cc: SBLUM, TLAUGHREN
Subj: RISPERDAL COMPLIANCE SCENE

I talked with Mark Lynch [Branch Chief, DMPQ, HFD-324] about his memo dated 02-DEC-93 which recommended WITHHOLDING approval for NDA 20-272, Risperdal.

He will ponder whether Compliance now has enough info to change their opinion and recommend APPROVABLE/APPROVAL. I indicated that this was our [HFD-120] desire, that Compliance find things O.K. so as to avoid having to over-rule them. Compliance should have received the firm's responses to the 483 on the three particular points of concern:

1 -- they did not investigate a couple of cases where the drug substance or drug product was outside of the limits during stability studies [WJR says that this was like being above limit at 3 months or at 9 months depending on n.d.s. or product, but within at all other times].
This has been a common occurrence [the occasional aberrant datum during stability] in virtually every NDA I have ever seen. Until the Barr Decision, failure to investigate such an event was not regarded as a capital crime -- ML says Compliance now take this very seriously.
[NB: this may be a sticking point]

2 -- they did not investigate 'uncontrolled background adjustments which affected the integration area of peaks'. The explanation is simple: the software was flawed; the firm has replaced it with software [per 24-SEP-93 AM], and the problem no longer exists. This was discussed by WJR and the firm; the SJN-DO inspector presumably knows also.
I do not know if the firm explained this in their response to the 483 to SJN-DO and thence CDER Compliance, but it has been corrected.

3 -- they did not investigate to explain foreign peaks in HPLC chromatograms of dissolution samples. WJR and the SJN-DO inspector discussed this situation: the dissolution samples are in 0.1N HCl and on introduction to the HPLC mobile phase there is considerable interaction and pH change, which shows up as 'foreign peaks'.
Again, I do not know if the firm explained this to SJN-DO and thence to CDER Compliance.

I will continue pursuit of Mark Lynch, who sounded willing to reverse the Compliance evaluation if they had the information. He is well aware of the need for rapid decision. In the event that they are unable to do so, I will prepare a memo over-ruling them, as is meet and right so to do.

STAN

MAY - 3 1993

DIVISION OF NEUROPHARMACOLOGICAL DRUG PRODUCTS
Review of Chemistry, Manufacturing, and Controls

NDA #: 20-272

CHEM.REVIEW # 1 **REVIEW DATE: 31-AUG-92**

SUBMISSIONTYPE	DOCUMENT DATE	CDER DATE	ASSIGNED DATE
N CORRESPONDENCE	09-JUL-92	13-JUL-92	14-JUL-92

NAME & ADDRESS OF APPLICANT:

Janssen Research Foundation
1125 Trenton-Harbourton Road
Titusville, NJ 08560

DRUG PRODUCT NAME
Proprietary: **RISPERIDAL™**
Nonproprietary/USAN: Risperidone
Code Name/#: R 64766
Chem.Type/Ther.Class:

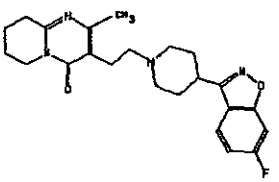
PHARMACOL.CATEGORY/INDICATION: Manifestations of Psychotic Disorders

DOSAGE FORM: Caplets
STRENGTHS: 1, 2, 3, 4, 5 mg
ROUTE OF ADMINISTRATION: Oral
DISPENSED: XXXXX Rx_____OTC

CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

3-[2-[4-(6-Fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]ethyl]-6,7,8,9-tetrahydro-2-methyl-4H-pyrido[1,3-a]pyrimidin-4-one

$C_{23}H_{27}FN_4O_2$ Molecular Weight: 410,49 CAS #: 106266-06-2



SUPPORTING DOCUMENTS: IND

RELATED DOCUMENTS:

REMARKS/COMMENTS: The correspondence provides applicant's summary of discussion held at the Agency on 15-JUN-92. In the summary the applicant lists and agrees to provide the additional information requested by the Agency at that meeting.

CONCLUSIONS & RECOMMENDATIONS: N.A.I.

cc:
Orig. NDA 20-272
HFD-120
HFD-120/WJRzeszotarski
HFD-120/KHiggins
HFD-120/SWBlum
HFD-102/CKumkumian[#1 only]
R/D Init by:SWB 5/2/93

W. Janusz Rzeszotarski, Ph.D., Chemist

filename: N020272.C01

Stat

Statistical Review and Evaluation

NDA #: 20-272 Date: MAR 10 1993

Applicant: Janssen Pharmaceutica

Name of Drug: Risperidal (Risperidone) Caplets

Documents Reviewed:

1. NDA submission volume 1.30-1.31, "Oral Carcinogenicity Study in Swiss Mice", Experiment No. 1927, Nov. 1991.

2. NDA submission volume 1.32-1.34, "Oral Carcinogenicity Study in Wistar Rats", Experiment No. 1928, Nov. 1991.

3. NDA special submission, Data Diskettes and Three Sets of Hardcopy of the Animal Data, Date of Document, May 1, 1992.

I. Background

Two animal carcinogenicity studies (one in rats and one in mice) were included in this NDA submission. The purpose of this study was to determine and assess the carcinogenic potential of Risperidone (R 64766) when administered orally by admixture with the diet to rats and mice for 25 and 18 months, respectively. Dr. Lois Freed, HFD-120, who is the reviewing pharmacologist of this NDA has requested the Division of Biometrics to perform the statistical review and evaluation of these two studies. The data submitted on computer floppy diskettes were used in the reviewer's independent analyses.

II. The Rat Study

II. a. Design

In this study, 200 male and 200 female Charles River SPF Wistar rats were randomly and equally distributed to three treatment groups and one control group. Risperidone was administered orally by admixture with the diet to the rats at doses equivalent to 0.63, 2.5, or 10 mg/kg/day for 25 months. Control animals received normal, non-medicated diet. The animals were observed at least once a day for clinical signs during the treatment. Body weight was measured every week for the first 24 weeks and monthly thereafter. Food consumption was recorded weekly for the first 24 weeks and monthly thereafter. Dosing period is from February 12, 1988 to March 29, 1990. Any animals died or found to be in a moribund condition during the course of the study and all surviving rats at the end of treatment were sacrificed and examined microscopically.

II. b. Sponsor's Analyses

The methods described in the paper of Peto et al. ("Guidelines for Simple, Sensitive Significance Tests for Carcinogenic Effects in Long-Term Animal Experiments", In Long-Term and Short-Term Screening Assays for Carcinogens: A Critical Appraisal, International Agency for Research on Cancer Monographs, Annex to Supplement 2, World Health Organization, 311-426, 1980) were used to test the trend in mortality data. The Chi-square test on two-by-two contingency tables was used to compare the mortality rates of each dose group with the control group.

The above analyses revealed that there was a statistically significant ($P < 0.0001$) dose related trend for mortality in males and slightly positive trend ($p = 0.056$) in females. Results of the test show a significantly ($p < 0.05$) higher mortality during the last 3 to 4 months of the study in medium and high male groups. Mortality rate at low dose male group was not affected. In female rats, mortality rates at low and medium dose groups were not affected, while a somewhat increased mortality for the high dose group was observed.

The sponsor indicated that after 24 calendar months (26 lunar months), mortality in the control groups was 28% in males and females. Therefore it was decided to extend the study to 25 calendar months (or 111 weeks, or 28 lunar months) when mortality was about 50% in the control group and the low dose group of both males and females. At the end of the study, the mortality rates were 48%, 58%, 78%, and 74% for male control, low, medium, and high dose groups; and 50%, 42%, 54%, and 60% for female control, low, medium, and high dose groups.

The methods described in the paper of Peto et al. (1980) were used to test the linear trend in the tumor data. The analysis was designed to deal with possible differences of intercurrent mortality among treatment groups. Equidistant dose levels 0, 1, 2, and 3 were used for the control, low, medium, and high dose groups. When the asymptotic p-value was at least marginally statistically significant ($p < 0.10$) and when the total number of tumor bearing animals in all treatment groups was 8 or less, the exact age-adjusted test was used.

First, an age-adjusted analysis was carried out for both male and female rats to test a possible positive trend for animals bearing fatal, and/or incidental tumors. In male rats, the age adjusted analysis for fatal tumor bearing males showed a positive trend in proportion of fatal tumor bearing males ($p = 0.009$), and not in proportion of incidental tumor bearing animals. In female rats, the age adjusted analysis did not reveal any positive trend in proportions of fatal and/or incidental tumor bearing animals. Tables 1 and 2 listed the results.

Tables 3 and 4 listed the tumor incidence rates and p-values of

various tumor types for male and female rats. Regarding the incidences of the various tumor types, a positive dose related trend was found for mammary adenocarcinoma ($p < 0.00001$; see Table 5) and pancreatic endocrine adenoma ($p = 0.0182$; see Table 6) in males and mammary gland adenocarcinoma ($p = 0.019$; see Table 7) in females.

Based on the above results, the sponsor concluded that "a dose related increase in mammary gland neoplasms (mainly adenocarcinoma) in males and females, and an increase in pancreatic endocrine adenoma in males were observed, whereas a dose related decrease was seen in the neoplasms of the female genital tract (vagina, cervix and uterus). These changes are typically prolactin-mediated and expected to occur for any drug with potent dopamine D_2-antagonism. With regard to prolactin-independent neoplasia, tumor incidences did not show any drug related, statistically significant increase, indicating that risperidone is not a primary carcinogen."

II.c. Reviewer's Analyses and Comments

The Cox test and the generalized Wilcoxon test described in the paper of Thomas, Breslow, and Gart ("Trend and Homogeneity Analyses of Proportions and Life Table Data", Computers and Biomedical Research, 10, 373-381, 1977) were used to test for heterogeneity in survival distribution. The p-values of the Cox test were 0.0002 and 0.3216 for males and females, respectively. Hence, there was a statistically significant difference (at 0.05 level) in the survival distribution in male rats. No significant difference in the survival distribution was detected in female rats. A similar conclusion was obtained in the generalized Wilcoxon test. The p-values of the test were 0.0001 and 0.3238 for males and females, respectively.

The intercurrent mortality rates for both male and female rats (see Table 8) were tested for linear trend according to the death rate method described in the paper of Peto et al. (1980) using the time intervals 0-50, 51-80, and 81-110 weeks. The actual dose levels 0, 0.63, 2.5, and 10 mg/kg/day were the scores assigned to the control, low, medium, and high dose groups, respectively. The results of the analyses showed that there was a significant (at 0.05 level) linear trend in the intercurrent mortality rate in male rats ($p = 0.012$). No significant (at 0.05 level) linear trend in the intercurrent mortality rate in female rats ($p = 0.0782$) was detected.

The methods described in Peto et al. (1980) and the methods of age-adjusted exact permutation trend test were used to test the linear trend in the tumor data. The results of the above analyses showed that there was a significant (at 0.05 level) positive linear trend in mammary gland adenocarcinoma ($p < 0.00001$) in male rats. There was a marginally statistically significant linear trend in pancreas endocrine adenoma in male rats ($p = 0.0626$). Although there was no statistically significant (at 0.05 level) linear trend in mammary

gland adenocarcinoma (p = 0.0885) in female rats, mammary gland adenoma (p = 0.3365), and mammary gland carcinoma (p = 0.0797) in male rats, the incidence rates of these tumors in treated groups are higher than those of control groups. The incidence rates of mammary gland adenocarcinoma in female rats are 3/50, 14/50, 16/50, and 13/50 in control, low, medium, and high dose groups, respectively. The incidence rates of mammary gland adenoma and carcinoma in male rats are 0/50, 3/50, 4/50, 3/50 and 0/50, 0/50, 0/50, 2/50 in control, low, medium, and high dose groups, respectively. The incidence rates of mammary gland adenocarcinoma and pancreas endocrine adenoma in male rats are given in Tables 9 and 10.

III. The Mouse Study

III. a. Design

In this study, 200 male and 200 female Charles River SPF Albino Swiss mice were randomly and equally distributed to three treatment groups and one control group. Risperidone was administered orally by admixture with the diet to the mice at doses equivalent to 0.63, 2.5, or 10 mg/kg/day for 18 months. Control animals received normal, non-medicated diet. These doses were chosen based upon a 3-month dose range finding study. The animals were observed at least once a day for clinical signs during the treatment. Body weight was measured initially, at weekly intervals during the first 12 months of the study and monthly thereafter. Food consumption was recorded weekly for the first 52 weeks and monthly thereafter. Dosing period is from August 28, 1988 to March 2, 1990. Any animals died or found to be in a moribund condition during the course of the study and all surviving mice at the end of treatment were sacrificed and examined microscopically.

III. b. Sponsor's Analyses

The methods described in the paper of Peto et al. (1980) were used to test the trend in mortality data. The test on two-by-two contingency tables was used to compare the mortality rates of each dose group with the control group.

Trend analyses using peto test revealed that there was no significant linear trend for mortality in male mice (p = 0.22). However, a positive linear trend for mortality (p = 0.016) was detected in female mice. Table 11 listed the mortality rates for male and female mice. Intergroup comparison using the test showed that the mortality rate in the various dosage groups was comparable to that of the control group in male mice. In female mice, mortality rate in low dose group was comparable to that of the control group while in medium and high dose groups, the mortality was slightly, but not statistically significantly, increased. At the end of the study, the overall mortality rates were 46%, 32%, 48%, and 50% for male control, low, medium, and high dose groups, and 52%, 50%, 64%, and 66% for female control, low, medium, and high dose groups.

Similar to the rat study, the methods described in Peto et al. (1980) and the exact age-adjusted trend test were used to test the tumor data for each organ. Equidistant dose levels 0, 1, 2, and 3 were used for the control, low, medium, and high dose groups.

First, using peto's methodology, an age-adjusted analysis was carried out for both male and female mice to test a possible positive trend in proportion of animals bearing fatal, and/or incidental tumors. In male mice, the age adjusted analysis did not reveal any positive linear trend in proportion of animals bearing fatal or incidental tumors. In female mice, a positive linear trend was observed in the incidence of fatal tumor bearing animals ($p = 0.004$) and in the incidence of animals bearing incidental tumors ($p < 0.0001$). Tables 12 and 13 listed the above results.

Regarding the incidence of the various tumor types (see Tables 14 and 15), age-adjusted analysis did not reveal any positive linear trend for any tumor type in male mice. The incidence of benign primary lung tumors showed a negative linear trend. In female mice, a positive dose related linear trend was found in primary lung tumor ($p = 0.0445$; see Table 16), mammary gland adenocarcinoma ($p < 0.00001$; see Table 17) and pituitary gland adenoma ($p < 0.00001$; see Table 18).

The sponsor indicated that a positive linear trend in primary lung tumors is considered coincidental and is related to the rather low control incidence (3/50) when compared to the historical control values. Table 19 listed the historical control data for primary lung tumor, mammary gland adenocarcinoma and pituitary gland adenoma. Noted that the sponsor did not specify the sources and dates of the historical control data.

Based on the above results, the sponsor concluded that "risperidone did not increase the incidence of any tumor type in male mice when dosed at 0.63, 2.5, and 10 mg/kg/day. In female mice, a positive trend was observed for the incidence of animals bearing fatal or incidental neoplasms. The incidence of mammary gland neoplasms, especially adenocarcinomas, and pituitary gland adenomas showed a dose related increase. These prolactin-dependent effects are typical for rodents and can be expected for any drug with dopamine D_2-receptor blocking activity. With regard to prolactin-independent neoplasms, tumor incidences were comparable between groups."

III.c. Reviewer's analyses and Comments

The Cox test and the generalized Wilcoxon test described in the paper of Thomas et al. (1977) were used to test for heterogeneity in survival distribution. The p-values of the Cox test were 0.3183 and 0.1193 for males and females, respectively. Hence, there was no statistically significant difference (at 0.05 level) in the survival distribution in either male or female mice. A similar conclusion was

obtained in the generalized Wilcoxon test. The p-values were 0.3265 and 0.1016 for males and females, respectively.

The intercurrent mortality rates for both male and female mice (see Table 20) were tested for linear trend according to the death rate method described in the paper of Peto et al. (1980) using the time intervals 0-50, 51-70, and 71-77 (female)/ 71-78 (male) weeks. The actual dose levels 0, 0.63, 2.5, or 10 were the scores assigned to the control, low, medium, and high dose groups, respectively. The results of the analyses showed that there was no significant (at 0.05 level) linear trend in the intercurrent mortality rate in male mice ($p = 0.1403$). However, there was a significant linear trend in the intercurrent mortality rate in female mice ($p = 0.0278$).

The methods described in Peto et al. (1980) and the methods of age-adjusted exact permutation trend test were used to test the linear trend in the tumor data. The results of the above analyses showed that there were statistically significant (at 0.05 level) positive linear trends in mammary gland adenocarcinoma ($p = 0.0001$) and pituitary gland adenoma ($p < 0.00001$) in female mice. There was a marginally statistically significant positive linear trend in benign primary lung tumor in female mice ($p = 0.0839$; incidence rates: 2/50, 5/50, 4/50, and 6/50 for control, low, medium, and high dose groups). There was a marginally significant positive linear trend in malignant primary lung tumor in male mice ($p = 0.0537$; incidence rates: 1/50, 4/50, 2/50, and 6/50 for control, low, medium, and high dose groups). The incidence rates of mammary gland adenocarcinoma and pituitary gland adenoma in female mice are given in Tables 21-22.

IV. Summary

IV. a. The Rat Study

The oncogenic potential of risperidal was evaluated in this rat study when administered orally by admixture with the diet to the rats at doses equivalent to 0, 0.63, 2.5 or 10 mg/kg/day for 25 months.

The Cox and the generalized Wilcoxon methods were used to test the heterogeneity in survival distribution. The test results revealed that there was no statistically significant difference (at 0.05 level) in the survival distribution in female rats in both tests. However, there was a statistically significant difference in the survival distribution in male rats (Cox: $p = 0.0002$; Wilcoxon: $p = 0.0001$). Note that the generalized Wilcoxon test places greater weights on early deaths in a study. The Cox test places equal weights on all deaths.

The statistical methods given in the paper of Peto et al. (1980) and an exact permutation trend test were used to test the positive linear trend in intercurrent mortality and incidental tumor rates. Applying the above methods to the data on sponsor's computer diskettes, the results of the analyses showed that there was a significant (at 0.05

level) positive linear trend in the intercurrent mortality rate in male rats ($p = 0.012$). No significant (at 0.05 level) linear trend in the intercurrent mortality rate in female rats ($p = 0.0782$) was detected.

Results of tumor data analyses showed that there was a significant (at 0.05 level) positive linear trend in mammary gland adenocarcinoma ($p < 0.00001$) in male rats. There was a marginally statistically significant positive linear trend in pancreas endocrine adenoma in male rats ($p = 0.0626$). Although there was no statistically significant (at 0.05 level) positive linear trend in mammary gland adenocarcinoma ($p = 0.0885$) in female rats, mammary gland adenoma ($p = 0.3365$), and mammary gland carcinoma ($p = 0.0797$) in male rats, the incidence rates of these tumors in treated groups are higher than those of control groups. The incidence rates of mammary gland adenocarcinoma in female rats are 3/50, 14/50, 16/50, and 13/50 for control, low, medium, and high dose groups, respectively. The incidence rates of mammary gland adenoma and carcinoma in male rats are 0/50, 3/50, 4/50, 3/50 and 0/50, 0/50, 0/50, 2/50 for control, low, medium, and high dose groups, respectively.

IV. b. The Mouse study

The oncogenic potential of risperidal was evaluated in this mouse study when administered orally by admixture with the diet to the mice at doses equivalent to 0, 0.63, 2.5, or 10 mg/kg/day for 18 months.

The Cox and the generalized Wilcoxon methods were used to test the heterogeneity in survival distribution. The test results revealed that there was no statistically significant difference (at 0.05 level) in the survival distribution in either male or female mice.

The statistical methods given in the paper of Peto et al. (1980) and an exact permutation trend test were used to test the positive linear trend in intercurrent mortality and incidental tumor rates. Applying the above methods to the data on sponsor's computer diskettes, the results of the analyses showed that there was no significant (at 0.05 level) linear trend in the intercurrent mortality rate in male mice ($p = 0.1403$). However, there was a significant linear trend in the intercurrent mortality rate in female mice ($p = 0.0278$).

Results of tumor data analyses showed that there were statistically significant (at 0.05 level) positive linear trends in mammary gland adenocarcinoma ($p = 0.0001$) and pituitary gland adenoma ($p < 0.00001$) in female mice. There was a marginally statistically significant positive linear trend in benign primary lung tumor in female mice ($p = 0.0839$; incidence rates: 2/50, 5/50, 4/50, and 6/50 for control, low, medium, and high dose groups). There was also a marginally significant positive linear trend in malignant primary lung tumor in male mice ($p = 0.0537$; incidence rates: 1/50, 4/50, 2/50, and 6/50 for control, low, medium, and high dose groups).

Daphne Lin

Daphne Lin, Ph.D.
Mathematical Statistician

Concur: Karl K. Lin 3/8/93
Karl K. Lin, Ph.D., Group Leader, SARB

cc: Original NDA 20-272
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HFD-715/Dr. Daphne Lin
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HFD-715/DRU 2.1.1, Risperidal, Janssen Pharmaceutica

Table 1

JANSSEN PHARMACEUTICA NV
Department of Toxicology

EXPERIMENT : 1928
Carcinogenicity study
R 64766 - FOOD - RAT - 24 MONTH

TUMOR BEARING MALES

Age adjusted test for positive dose-related trend (a)

Lunar month	Control (b)	Low (b)	Medium (b)	High (b)	Trend	Variance	z-value	p-value (1-tailed)	
Animals bearing FATAL tumor(s)									
5	0 / 50	0 / 50	1 / 50	0 / 50	0.500	1.250	0.447		
8	0 / 50	1 / 50	0 / 49	0 / 50	-0.497	1.255	-0.444		
11	0 / 49	0 / 49	1 / 49	0 / 49	0.500	1.250	0.447		
13	0 / 49	0 / 49	0 / 48	1 / 49	1.503	1.255	1.341		
16	1 / 49	0 / 47	0 / 48	0 / 48	-1.495	1.260	-1.331		
18	0 / 48	0 / 47	1 / 47	0 / 48	0.500	1.261	0.445		
19	0 / 48	0 / 47	1 / 45	0 / 47	0.513	1.266	0.456		
20	0 / 47	1 / 47	1 / 43	1 / 45	1.582	3.739	0.818		
21	1 / 47	1 / 45	1 / 41	0 / 43	-1.364	3.768	-0.702		
22	1 / 46	0 / 44	2 / 38	0 / 43	-0.368	3.822	-0.188		
23	1 / 45	0 / 44	0 / 35	1 / 43	0.090	2.588	0.056		
24	1 / 43	0 / 43	0 / 32	8 / 41	10.981	11.140	3.290		
25	2 / 41	0 / 41	1 / 29	3 / 32	2.818	7.250	1.047		
26	1 / 38	1 / 39	4 / 25	1 / 26	2.867	8.082	1.009		
27	2 / 36	1 / 34	1 / 13	1 / 17	0.450	5.556	0.191		
28	0 / 31	3 / 26	0 / 11	0 / 16	-0.429	3.635	-0.225		
All					18.152	58.376	2.376	0.009	**
(c)	10 / 50	8 / 50	14 / 50	16 / 50					
Animals bearing only INCIDENTAL tumor(s)									
1 - 18	0 / 1	0 / 2	0 / 2	0 / 2	0.000	0.000	0.000		
19 - 21	1 / 1	0 / 1	0 / 4	1 / 3	-1.000	1.556	-0.802		
22 - 23	1 / 1	0 / 1	3 / 4	0 / 1	-0.857	1.551	-0.688		
24	0 / 1	2 / 2	2 / 3	1 / 1	1.143	1.361	0.980		
25	1 / 1	2 / 2	2 / 3	2 / 3	-1.222	1.728	-0.930		
26	1 / 1	3 / 4	6 / 8	7 / 8	0.381	2.560	0.238		
27	3 / 3	5 / 7	1 / 1	0 / 0	-0.364	0.595	-0.471		
28	5 / 5	1 / 2	0 / 0	3 / 3	0.100	1.690	0.077		
Terminal	22 / 26	17 / 21	10 / 11	8 / 13	-4.831	14.017	-1.290		
All					-6.650	25.057	-1.329	0.908	
(c)	34 / 40	30 / 42	24 / 36	22 / 34					
Animals bearing FATAL and / or INCIDENTAL tumor(s)									
Total					11.502	83.432	1.259	0.104	
(c)	44 / 50	38 / 50	38 / 50	38 / 50					

(a) Peto monograph, WHO, IARC, Lyon, 1980, pp. 386 - 387, p. 371 , dose levels 0, 1, 2, 3.
(b) Number observed / number at risk
(c) Number of tumor bearing animals / total number of animals

Table 2

JANSSEN PHARMACEUTICA NV
Department of Toxicology

EXPERIMENT : 1928
Carcinogenicity study
R 64766 - FOOD - RAT - 24 MONTH

TUMOR BEARING FEMALES

Lunar month	Control (b)	Low (b)	Medium (b)	High (b)	Trend	Variance	z-value	p-value (1-tailed)
	Age adjusted test for positive dose-related trend (a)							
	Animals bearing FATAL tumor(s)							
11	0 / 50	0 / 50	0 / 49	1 / 50	1.503	1.255	1.341	
13	1 / 50	0 / 50	0 / 49	0 / 49	-1.490	1.250	-1.333	
14	1 / 49	0 / 50	0 / 49	1 / 49	0.005	2.477	0.003	
16	1 / 47	0 / 50	0 / 49	0 / 48	-1.505	1.229	-1.358	
17	0 / 46	1 / 50	0 / 49	0 / 47	-0.505	1.219	-0.458	
19	0 / 46	0 / 49	0 / 49	1 / 47	1.492	1.224	1.349	
20	1 / 46	1 / 48	2 / 49	0 / 46	-1.011	4.816	-0.460	
21	1 / 45	1 / 47	1 / 47	1 / 46	-0.032	4.854	-0.015	
22	2 / 44	4 / 46	2 / 46	4 / 45	1.901	13.896	0.510	
23	0 / 42	1 / 41	1 / 43	1 / 40	1.536	3.668	0.802	
24	0 / 42	2 / 40	4 / 42	5 / 39	8.736	12.833	2.439	
25	2 / 42	2 / 38	4 / 38	3 / 33	3.483	12.683	0.978	
26	4 / 40	3 / 36	2 / 34	4 / 29	1.137	14.563	0.298	
27	5 / 36	2 / 32	5 / 31	0 / 23	-4.033	12.986	-1.119	
28	3 / 28	1 / 30	3 / 26	3 / 23	1.888	10.939	0.571	
All					13.105	99.893	1.311	0.095
(c)	21 / 50	18 / 50	24 / 50	24 / 50				
	Animals bearing only INCIDENTAL tumor(s)							
1 - 18	0 / 1	0 / 0	0 / 1	0 / 1	0.000	0.000	0.000	
19 - 23	0 / 0	2 / 2	0 / 1	1 / 1	-0.250	0.688	-0.302	
24 - 28	2 / 3	1 / 1	1 / 1	4 / 4	1.667	1.778	1.250	
Terminal	23 / 25	24 / 29	21 / 23	15 / 20	-4.515	14.115	-1.202	
All					-3.099	16.580	-0.761	0.777
(c)	25 / 29	27 / 32	22 / 26	20 / 26				
	Animals bearing FATAL and / or INCIDENTAL tumor(s)							
Total					10.006	116.473	0.927	0.177
(c)	46 / 50	45 / 50	46 / 50	44 / 50				

(a) Peto monograph, WHO, IARC, Lyon, 1980, pp. 386 - 387, p. 371 , dose levels 0, 1, 2, 3.
(b) Number observed / number at risk
(c) Number of tumor bearing anim

JANSSEN PHARMACEUTICA NV
Department of toxicology

EXPERIMENT: 1928
Carcinogenicity study
R 64766 - FOOD - RAT - 24 MONTH

Table 3

HISTOPATHOLOGY : TUMORS
Incidence per dosage group

Organ or tissue : tumor	Males: Dosage group (mg / kg) 0	0.63	2.5	10	(a) P (1-sided) for trend
Abdominal mesothelia : Mesothelial sarcoma	0 / 50	1 / 50	0 / 50	0 / 49	(b) 0.5510
Adrenal gland : Adenoma	0 / 50	0 / 50	1 / 50	0 / 49	(b) 0.2230
Adrenal gland : Phaeochromocytoma, benign	3 / 50	7 / 50	6 / 50	6 / 49	(b) 0.0687
Bone : Osteosarcoma	1 / 50	0 / 50	0 / 50	0 / 49	(b) 0.9085
Ear : Carcinoma, squamous cell	0 / 50	0 / 50	0 / 50	1 / 49	(c) 0.2513
Ear : Papilloma	0 / 50	1 / 50	0 / 50	0 / 49	(b) 0.5556
Epididymis : Mesothelioma	1 / 50	0 / 50	0 / 50	0 / 49	(b) 0.8512
Heart : Mesothelioma	1 / 50	0 / 50	0 / 50	0 / 49	(b) 0.9413
Hematopoietic system : tumor	4 / 50	3 / 50	5 / 50	1 / 49	(b) 0.6543
Jaw : Carcinoma, squamous cell	1 / 50	0 / 50	0 / 50	0 / 49	(b) 0.8885
Kidney : Adenoma	0 / 50	1 / 50	0 / 50	0 / 49	(b) 0.5269
Kidney, pelvis : Carcinoma	0 / 50	0 / 50	1 / 50	0 / 49	(b) 0.2848
Kidney : Liposarcoma	0 / 50	1 / 50	0 / 50	0 / 49	(b) 0.5000
Liver : Hepatic neoplastic nodule	6 / 50	4 / 50	6 / 50	4 / 49	(b) 0.4101
Liver : Hepatocytic carcinoma	1 / 50	0 / 50	0 / 50	0 / 49	(b) 0.9199
Liver : Hepatocytic neoplasia	7 / 50	4 / 50	6 / 50	4 / 49	(b) 0.5381
Lymph node(s), mesenteric : Hemangioendothelial sarcoma	0 / 49	0 / 49	0 / 50	1 / 47	(c) 0.1831
Lymph node(s), maxillary : Hemangioendothelioma	1 / 50	0 / 50	0 / 50	0 / 49	(b) 0.8274
Lymph node(s), mesenteric : Hemangioendothelioma	6 / 49	3 / 49	2 / 50	1 / 47	(b) 0.9286
Mammary gland : Adenocarcinoma	0 / 50	0 / 48	3 / 50	13 / 49	(b) 0.0000 ***
Mammary gland : Adenoma, Adenofibroma, Fibroadenoma	0 / 50	3 / 48	4 / 50	3 / 49	(b) 0.0826
Mammary gland : Carcinoma	0 / 50	0 / 48	0 / 50	2 / 49	(c) 0.0653
Mammary gland : Fibroma	0 / 50	1 / 48	0 / 50	1 / 49	(b) 0.1415
Nervous system : Meningioma	2 / 50	0 / 50	0 / 50	0 / 49	(b) 0.9287
Pancreas : Adenoma, endocrine	9 / 49	9 / 49	14 / 49	14 / 49	(b) 0.0182 *
Pancreas : Adenoma, exocrine	10 / 49	6 / 49	3 / 49	1 / 49	(b) 0.9982
Pituitary gland : Adenoma	14 / 50	19 / 50	13 / 50	14 / 49	(b) 0.3238
Rectum : Adenocarcinoma	1 / 50	0 / 50	1 / 50	0 / 49	(b) 0.6545
Seminal vesicle : Fibrosarcoma	0 / 48	0 / 47	1 / 49	0 / 48	(b) 0.3160
Skin : Carcinoma, squamous cell	0 / 50	1 / 50	0 / 50	0 / 49	(b) 0.6992
Skin : Papilloma	3 / 50	5 / 50	2 / 50	2 / 49	(b) 0.8263
Small intestine : Adenocarcinoma	0 / 50	0 / 50	0 / 50	1 / 49	(b) 0.1182
Soft tissue : Fibroma	0 / 50	3 / 50	1 / 50	0 / 49	(b) 0.4581
Soft tissue : Fibrosarcoma	1 / 50	0 / 50	2 / 50	2 / 49	(b) 0.1114
Soft tissue : Hemangiopericytoma, malignant	0 / 50	0 / 50	1 / 50	0 / 49	(b) 0.2638
Soft tissue : Lipoma	1 / 50	1 / 50	1 / 50	0 / 49	(b) 0.8412
Soft tissue : Sarcoma	1 / 50	1 / 50	1 / 50	0 / 49	(b) 0.7345
Stomach : Papilloma, squamous cell	0 / 50	0 / 50	0 / 50	1 / 49	(c) 0.2639
Testis : Leydig cell tumor, benign	4 / 50	0 / 50	2 / 50	2 / 49	(b) 0.6607
Thyroid gland : Adenoma	3 / 50	4 / 50	2 / 49	3 / 47	(b) 0.1725
Thyroid gland : Adenoma, "light cell" solid	4 / 50	3 / 50	2 / 49	1 / 47	(b) 0.8126

(a) Age-adjusted analysis, taking into account the cohort of observation (Peto monograph, WHO, IARC, Lyon, 1980, pp. 311-426); dose levels 0, 1, 2, 3. P-values are either asymptotic (b) or "exact" (c).
(b) Asymptotic p-value of Peto's trend statistic (no correction for continuity).
(c) "Exact" p-value of the age-adjusted test

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EXPERIMENT: 1928
Carcinogenicity study
R 64766 - FOOD - RAT - 24 MONTH

Table 4

HISTOPATHOLOGY : TUMORS
Incidence per dosage group

Females					
Organ or tissue : tumor	Dosage group (mg / kg)				(a)
	0	0.63	2.5	10	P (1-sided) for trend
Adrenal gland : Adenoma	0 / 50	1 / 50	0 / 50	0 / 50	(b) 0.6123
Adrenal gland : Ganglioneuroma	0 / 50	0 / 50	0 / 50	1 / 50	(c) 0.2062
Adrenal gland : Phaeochromocytoma, benign	1 / 50	3 / 50	1 / 50	3 / 50	(b) 0.2445
Adrenal gland : Phaeochromocytoma, malignant	0 / 50	1 / 50	0 / 50	0 / 50	(b) 0.6416
Adrenal gland : Phaeochromocytoma, benign a/o malignant	1 / 50	4 / 50	1 / 50	3 / 50	(b) 0.2966
Cervix : Adenocarcinoma	1 / 50	0 / 50	0 / 50	0 / 50	(b) 0.9013
Cervix : Sarcoma	2 / 50	1 / 50	0 / 50	1 / 50	(b) 0.8075
Ear : Carcinoma	0 / 50	1 / 50	0 / 50	0 / 50	(b) 0.6764
Ear : Papilloma	0 / 50	1 / 50	0 / 50	0 / 50	(b) 0.7097
Heart : Sarcoma	1 / 50	0 / 50	0 / 50	0 / 50	(b) 0.9013
Hematopoietic system : tumor	2 / 50	5 / 50	4 / 50	6 / 50	(b) 0.1067
Jaw : Carcinoma, squamous cell	0 / 50	0 / 50	1 / 50	0 / 50	(b) 0.2714
Kidney : Adenocarcinoma	1 / 50	0 / 50	0 / 50	0 / 50	(b) 0.8442
Kidney : Adenoma	0 / 50	0 / 50	0 / 50	1 / 50	(b) 0.1111
Kidney, pelvis : Polyp	1 / 50	0 / 50	0 / 50	1 / 50	(b) 0.3761
Kidney : Sarcoma	1 / 50	0 / 50	0 / 50	0 / 50	(b) 0.9129
Liver : Hepatic neoplastic nodule	7 / 50	7 / 50	6 / 50	6 / 50	(b) 0.5126
Liver : Hepatocytic carcinoma	1 / 50	0 / 50	0 / 50	0 / 50	(b) 0.9013
Liver : Hepatocytic neoplasia	8 / 50	7 / 50	6 / 50	6 / 50	(b) 0.6168
Lymph node(s) : Hemangioendothelioma	2 / 50	2 / 49	1 / 50	0 / 50	(b) 0.9053
Mammary gland : Adenocarcinoma	3 / 49	14 / 50	16 / 50	13 / 50	(b) 0.0019 **
Mammary gland : Adenoma, Fibroadenoma, Adenofibroma	20 / 49	21 / 50	27 / 50	15 / 50	(b) 0.3987
Mammary gland : Fibroma	4 / 49	3 / 50	0 / 50	0 / 50	(b) 0.9962
Nose : Basal cell carcinoma	1 / 50	0 / 50	0 / 50	0 / 50	(b) 0.8896
Ovary : Granulosa-theca cell tumor, benign	0 / 50	1 / 50	0 / 50	0 / 50	(b) 0.6416
Ovary : Sertoli cell tumor, benign	1 / 50	0 / 50	0 / 50	1 / 50	(b) 0.4980
Pancreas : Adenocarcinoma, exocrine	0 / 50	1 / 50	0 / 50	0 / 50	(b) 0.5432
Pancreas : Adenoma, endocrine	3 / 50	4 / 50	4 / 50	3 / 50	(b) 0.4978
Pancreas : Adenoma, exocrine	3 / 50	4 / 50	0 / 50	0 / 50	(b) 0.9832
Parathyroid gland : Adenoma	0 / 34	0 / 28	1 / 38	0 / 34	(b) 0 2999
Pituitary gland : Adenoma	28 / 49	20 / 50	30 / 50	29 / 50	(b) 0.1022
Salivary gland(s) : Carcinosarcoma	0 / 50	0 / 50	1 / 50	0 / 50	(b) 0.2714
Skin : Papilloma	0 / 50	0 / 50	1 / 50	1 / 50	(b) 0.1035
Soft tissue : Fibroma	0 / 50	1 / 50	0 / 50	0 / 50	(b) 0.6764
Soft tissue : Fibrosarcoma	0 / 50	0 / 50	0 / 50	1 / 50	(c) 0.2393
Soft tissue : Hemangioendothelioma	0 / 50	1 / 50	0 / 50	0 / 50	(b) 0 6416
Soft tissue : Lipoma	2 / 50	0 / 50	1 / 50	0 / 50	(b) 0.8703
Thyroid gland : Adenocarcinoma	2 / 50	0 / 50	0 / 50	1 / 50	(b) 0.7200
Thyroid gland : Adenoma	1 / 50	1 / 50	0 / 50	1 / 50	(b) 0.5891
Thyroid gland : Adenoma, "light cell" solid	2 / 50	3 / 50	0 / 50	1 / 50	(b) 0.7871
Thyroid gland : Carcinoma, "light cell" solid	0 / 50	0 / 50	1 / 50	0 / 50	(b) 0.2841
Urinary bladder : Papilloma, transitional cell	0 / 50	0 / 50	1 / 50	0 / 50	(b) 0.2866
Uterus : Adenocarcinoma	2 / 49	0 / 50	0 / 50	0 / 50	(b) 0.9631
Uterus : Polyp	4 / 49	3 / 50	0 / 50	0 / 50	(b) 0.9932
Vagina : Sarcoma	2 / 49	0 / 49	1 / 50	0 / 50	(b) 0.8632

(a) Age-adjusted analysis, taking into account the context of observation (Peto monograph, WHO, IARC, Lyon, 1980, pp. 311-426); dose levels 0, 1, 2, 3. P-values are either asymptotic (b) or "exact" (c).
(b) Asymptotic p-value of Peto's trend statistic (no correction for continuity).
(c) "Exact" p-value of the age-adjusted test

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Table 5

EXPERIMENT : 1928
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Mammary gland : Adenocarcinoma in males

Lunar month	Control (d)	Low (d)	Medium (d)	High (d)	Trend	Variance	z-value	p-value (1-sided) (b)	(c)
	Age adjusted test for positive dose-related trend (a)								
	Animals bearing FATAL tumor of interest								
20	0 / 47	0 / 47	0 / 43	1 / 45	1.527	1.260	1.361		
24	0 / 43	0 / 43	0 / 32	4 / 41	5.214	5.116	2.747		
27	0 / 36	0 / 34	0 / 13	1 / 17	1.890	1.158	1.756		
All					9.631	7.534	3.509	0.0002 ***	
(e)	0 / 50	0 / 48	0 / 50	6 / 49					
	Animals bearing INCIDENTAL tumor of interest								
1 - 24	0 / 9	0 / 9	0 / 21	0 / 12	0.000	0.000	0.000		
25	0 / 3	0 / 2	0 / 4	1 / 6	1.133	1.316	0.988		
26 - 27	0 / 7	0 / 13	1 / 14	2 / 9	3.256	2.822	1.938		
28	0 / 5	0 / 4	0 / 0	1 / 3	1.917	1.410	1.614		
Terminal	0 / 26	0 / 20	2 / 11	3 / 13	7.214	5.872	2.977		
All					13.520	11.419	4.001	0.0000 ***	
(e)	0 / 50	0 / 48	3 / 50	7 / 43					
	Animals bearing FATAL or INCIDENTAL tumor of interest								
Total					23.151	18.953	5.318	0.0000 ***	
(e)	0 / 50	0 / 48	3 / 50	13 / 49					

(a) Peto monograph, WHO, IARC, Lyon, 1980, pp. 311-426; dose levels 0, 1, 2, 3.
(b) Asymptotic p-value of Peto's trend statistic (no correction for continuity).
(c) "Exact" p-value of the age-adjusted test

(d) Number observed / number at risk
(e) Number of animals with tumor of interest / number of animals examined histologically for this organ

Positive animals sorted chronologically
Control
No positive animals
0.63 mg / kg
No positive animals
2.5 mg / kg
A: M141 M105 M116 S: s26 t28 t28
10 mg / kg
A: M189 M180 M188 M168 M191 M167 M184 M174 M152 M155 M161 M178 M183 S: S20 S24 S24 s24 S24 s25 s26 s26 S27 d28 t28 t28 t28

A: Animal number
S: Status at necropsy (d=dead,s=sacrificed,t=sacrificed terminally with INCIDENTAL tumor) + month
(D=dead,S=sacrificed with FATAL tumor) + month

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Table 6

EXPERIMENT : 1928
Carcinogenicity study
R 64766 - FOOD - RAT - 24 MONTH

Pancreas : Adenoma, endocrine in males

Lunar month	Control (d)	Low (d)	Medium (d)	High (d)	Trend	Variance	z-value	p-value (1-sided) (b)	(c)
			Animals bearing INCIDENTAL tumor of interest						
1 - 19	0 / 2	0 / 3	0 / 7	0 / 4	0.000	0.000	0.000		
20 - 23	0 / 4	0 / 4	1 / 10	1 / 4	1.727	1.826	1.278		
24	0 / 2	0 / 2	2 / 3	1 / 9	0.438	2.996	0.253		
25 - 28	3 / 15	3 / 19	7 / 18	7 / 19	6.451	17.511	1.542		
Terminal	6 / 26	6 / 21	4 / 11	5 / 13	4.746	16.443	1.105		
All					13.362	40.776	2.093	0.0182	*
(e)	9 / 49	9 / 49	14 / 49	14 / 49					
			Animals bearing FATAL or INCIDENTAL tumor of interest						
Total					13.362	40.776	2.093	0.0182	*
(e)	9 / 49	9 / 49	14 / 49	14 / 49					

(a) Peto monograph, WHO, IARC, Lyon, 1980, pp. 311-426; dose levels 0, 1, 2, 3.
(b) Asymptotic p-value of Peto's trend statistic (no correction for continuity).
(c) "Exact" p-value of the age-adjusted test

(d) Number observed / number at risk
(e) Number of animals with tumor of interest / number of animals examined histologically for this organ

Positive animals sorted chronologically

Control

A: C40 C26 C6 C5 C10 C13 C14 C18 C27
S: d25 s27 s28 t28 t28 t28 t28 t28 t28

0.63 mg / kg

A: L88 L67 L91 L51 L52 L60 L64 L75 L86
S: s26 s27 s27 t28 t28 t28 t28 t28 t28

2.5 mg / kg

A: M120 M138 M147 M117 M121 M137 M129 M145 M133 M104 M105 M116 M127 M136
S. s20 s24 s24 s25 s25 d26 s26 s26 s26 d27 t28 t28 t28 t28

10 mg / kg

A: H176 H168 H175 H167 H193 H194 H182 H157 H153 H151 H161 H164 H177 H183
S: s20 s24 d25 s25 d25 d25 s26 s28 s28 t28 t28 t28 t28 t28

A: Animal number
S. Status at necropsy (d=dead,s=sacrificed,t=sacrificed terminally with INCIDENTAL tumor) + month
(D=dead,S=sacrificed with FATAL tumor) + month

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Table 7

EXPERIMENT : 1928
Carcinogenicity study
R 64766 - FOOD - RAT -- 24 MONTH

Mammary gland : Adenocarcinoma in females

Lunar month	Control (d)	Low (d)	Medium (d)	High (d)	Trend	Variance	z-value	p-value (1-sided) (b)	(c)
Age adjusted test for positive dose-related trend (a)									
Animals bearing FATAL tumor of interest									
19	0 / 46	0 / 49	0 / 49	1 / 47	1.492	1.224	1.349		
22	0 / 44	1 / 46	0 / 46	1 / 45	0.983	2.453	0.628		
23	0 / 42	0 / 41	0 / 43	1 / 40	1.512	1.238	1.3		
25	0 / 42	0 / 38	1 / 38	1 / 33	2.179	2.454	1.38		
26	1 / 40	1 / 36	1 / 34	1 / 29	0.504	4.801	0.230		
27	0 / 36	1 / 32	0 / 31	0 / 23	-0.336	1.190	-0.308		
28	0 / 28	1 / 30	1 / 26	1 / 23	1.766	3.519	0.942		
All					8.100	16.879	1.972		*
(e)	1 / 49	4 / 50	3 / 50	6 / 50					
Animals bearing INCIDENTAL tumor of interest									
1 - 21	0 / 5	0 / 4	0 / 4	0 / 4	0.000	0.000	0.000		
22 - 27	0 / 15	0 / 13	2 / 18	2 / 18	3.563	4.635	1.620		
28	0 / 3	0 / 0	1 / 2	0 / 2	0.571	1.673	0.442		
Terminal	2 / 25	10 / 29	10 / 23	5 / 20	7.423	22.958	1.549		
All					11.557	29.467	2.129	0.0166	*
(e)	2 / 48	10 / 46	13 / 47	7 / 44					
Animals bearing FATAL or INCIDENTAL tumor of interest									
Total					19.657	46.346	2.887	0.0019	**
(e)	3 / 49	14 / 50	16 / 50	13 / 50					

(a) Peto monograph, WHO, IARC, Lyon, 1980, pp. 311-426; dose levels 0, 1, 2, 3.
(b) Asymptotic p-value of Peto's trend statistic (no correction for continuity).
(c) "Exact" p-value of the age-adjusted test

(d) Number observed / number at risk
(e) Number of animals with tumor of interest / number of animals examined histologically for this organ

Positive animals sorted chronologically

Control

A: C239 C224 C231
S: S26 t28 t28

0.63 mg / kg

A: L259 L285 L261 L269 L255 L264 L271 L272 L277 L280 L288 L290 L291 L300
S: S22 S26 S27 S28 t28 t28 t28 t28 t28 t28 t28 t28 t28 t28

2.5 mg / kg

A: M346 M305 M319 M349 M315 M312 M303 M307 M313 M324 M325 M329 M331 M337 M343 M344
S: s22 s24 S25 S26 S28 s28 t28 t28 t28 t28 t28 t28 t28 t28 t28 t28

10 mg / kg

A: H375 H382 H351 H378 H306 H355 H361 H394 H359 H367 H372 H392 H397
S: S10 S22 S23 s24 s24 S25 S26 S28 t28 t28 t28 t28 t28

A: Animal number
S: Status at necropsy (d=dead,s=sacrificed,t=sacrificed terminally with INCIDENTAL tumor) + month
(D=dead,S=sacrificed with FATAL tumor) + month

Table 8
Intercurrent Mortality Rates
Male Rats

Weeks	Control			Low			Medium			High		
	S	D	%	S	D	%	S	D	%	S	D	%
0-50	50	1	2	50	1	2	50	2	4	50	1	2
51-80	49	2	4.1	49	4	8.1	48	7	14.6	49	6	12.
81-110	47	21	44.7	45	24	53.3	41	30	73.2	43	30	70.
Term.	26			21			11			13		

Female Rats

Weeks	Control			Low			Medium			High		
	S	D	%	S	D	%	S	D	%	S	D	%
0-50	50	0	0	50	0	0	50	1	2	50	1	2
51-80	50	5	10	50	3	6	49	2	4.1	49	3	6.1
81-110	45	20	44.4	47	18	38.3	47	24	51.1	46	26	56.5
Term.	25			29			23			20		

Notes: S: Number of animals starting during the period
D: Deaths
%: Percent of death during the period

Table 9
Tumor Incidence Rates
Male Rats, Mammary Gland Adenocarcinoma

Weeks	Control		Low		Medium		High	
	T	N	T	N	T	N	T	N
0-50	0	1	0	1	0	2	0	1
51-80	0	2	0	4	0	7	1	6
81-110	0	21	0	24	1	30	9	30
Terminal	0	26	0	21	2	11	3	13
Total	0	50	0	50	3	50	13	50

Table 10
Tumor Incidence Rates
Male Rats, Pancreas Endocrine Adenoma

Weeks	Control		Low		Medium		High	
	T	N	T	N	T	N	T	N
0-50	0	1	0	1	0	2	0	1
51-80	0	2	0	4	1	7	1	6
81-110	3	21	3	24	9	30	8	30
Terminal	6	26	6	21	4	11	5	13
Total	9	50	9	50	14	50	14	50

Notes: T: Number of necropsies with the above tumor.
N: Number of necropsies.

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Table 11

EXPERIMENT : 1927
Carcinogenicity study
R 64766 - FOOD - MICE - 18 MONTH

OVERALL MORTALITY

Luner month	Control (b)	Low (b)	Medium (b)	High (b)	Trend	Variance	z-value	p-value (1-tailed)	
			Test for positive dose-related trend (a)						
			MALES						
2	0 / 50	0 / 50	1 / 50	0 / 50	0.500	1.250	0.447		
5	1 / 50	1 / 50	0 / 49	0 / 50	-1.995	2.497	-1.262		
6	0 / 49	0 / 49	2 / 49	0 / 50	0.985	2.497	0.623		
9	1 / 49	0 / 49	0 / 47	1 / 50	-0.005	2.518	-0.003		
10	0 / 48	0 / 49	0 / 47	1 / 49	1.497	1.255	1.337		
11	0 / 48	0 / 49	0 / 47	1 / 48	1.505	1.250	1.346		
12	1 / 48	0 / 49	1 / 47	1 / 47	0.539	3.694	0.281		
13	1 / 47	1 / 49	0 / 46	0 / 46	-1.968	2.465	-1.254		
14	2 / 46	0 / 48	1 / 46	1 / 46	-0.978	4.876	-0.443		
15	4 / 44	3 / 48	4 / 45	4 / 45	0.500	16.996	0.121		
16	4 / 40	2 / 45	3 / 41	3 / 41	-0.964	13.670	-0.261		
17	2 / 36	3 / 43	3 / 38	2 / 38	-0.032	11.344	-0.010		
18	1 / 34	3 / 40	3 / 35	4 / 36	4.462	12.442	1.265		
19	4 / 33	3 / 37	4 / 32	4 / 32	0.948	16.364	0.234		
20	2 / 29	0 / 34	2 / 28	3 / 28	2.765	8.016	0.976		
All					7.758	101.136	0.771	0.220	
(c)	23 / 50	16 / 50	24 / 50	25 / 50					
			FEMALES						
2	0 / 50	0 / 50	0 / 50	1 / 50	1.500	1.250	1.342		
3	0 / 50	0 / 50	1 / 50	0 / 49	0.508	1.245	0.455		
4	0 / 50	0 / 50	0 / 49	1 / 49	1.510	1.250	1.351		
6	1 / 50	0 / 50	0 / 49	0 / 48	-1.482	1.245	-1.329		
7	0 / 49	0 / 50	0 / 49	1 / 48	1.510	1.240	1.356		
8	0 / 49	0 / 50	1 / 49	1 / 47	2.036	2.456	1.299		
9	0 / 49	1 / 50	1 / 48	2 / 46	3.114	4.857	1.413		
10	0 / 49	3 / 49	2 / 47	0 / 44	-0.275	6.029	-0.112		
11	1 / 49	1 / 46	0 / 45	2 / 44	1.174	4.953	0.527		
12	0 / 48	0 / 45	2 / 45	0 / 42	1.100	2.481	0.698		
13	2 / 48	0 / 45	1 / 43	2 / 42	0.781	6.148	0.315		
14	2 / 46	3 / 45	3 / 42	4 / 40	3.728	13.934	0.999		
15	5 / 44	7 / 42	4 / 39	6 / 36	1.845	23.638	0.379		
16	2 / 39	2 / 35	1 / 35	2 / 30	0.180	8.258	0.063		
17	2 / 37	4 / 33	9 / 34	3 / 28	5.773	19.191	1.318		
18	5 / 35	3 / 29	2 / 25	4 / 25	0.088	15.863	0.022		
19	3 / 30	1 / 26	2 / 23	3 / 21	1.850	10.320	0.576		
20	3 / 27	0 / 25	3 / 21	1 / 18	-0.308	7.905	-0.109		
All					24.631	132.264	2.142	0.016	*
(c)	26 / 50	25 / 50	32 / 50	33 / 50					

(a) Peto monograph, WHO, IARC, Lyon, 1980, pp. 386 - 387, dose levels 0, 1, 2, 3.
(b) Number observed / number at risk
(c) Number of animals (dead or preterminally sacrificed) / total number of animals

Table 12

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EXPERIMENT : 1927
Carcinogenicity study
R 64766 - FOOD - MICE - 18 MONTH

TUMOR BEARING MALES

Tumor month	Control (b)	Low (b)	Medium (b)	High (b)	Trend	Variance	z-value	p-value (1-tailed)
			Age adjusted test for positive dose-related trend (a)					
			Animals bearing FATAL tumor(s)					
5	1 / 50	0 / 50	0 / 49	0 / 50	-1.497	1.255	-1.337	
6	0 / 49	0 / 49	1 / 49	0 / 50	0.492	1.255	0.440	
17	0 / 36	1 / 43	0 / 38	0 / 38	-0.503	1.205	-0.458	
18	0 / 34	0 / 40	0 / 35	1 / 36	1.497	1.216	1.357	
19	1 / 33	0 / 37	0 / 32	0 / 32	-1.470	1.219	-1.331	
20	0 / 29	0 / 34	0 / 28	1 / 28	1.538	1.207	1.400	
All					0.056	7.356	0.021	0.492
(c)	2 / 50	1 / 50	1 / 50	2 / 50				
			Animals bearing only INCIDENTAL tumor(s)					
1 - 14	0 / 5	0 / 2	0 / 4	0 / 5	0.000	0.000	0.000	
15 - 18	2 / 11	2 / 10	1 / 13	5 / 12	3.348	9.966	1.060	
19 - 20	2 / 5	2 / 3	1 / 6	1 / 6	-2.900	5.869	-1.197	
Terminal	10 / 27	18 / 34	10 / 26	12 / 25	2.125	32.806	0.371	
All					2.573	48.641	0.369	0.356
(c)	14 / 48	22 / 49	12 / 49	18 / 48				
			Animals bearing FATAL and / or INCIDENTAL tumor(s)					
Total					2.629	55.997	0.351	0.363
(c)	16 / 50	23 / 50	13 / 50	20 / 50				

(a) Peto monograph, WHO, IARC, Lyon, 1980, pp. 386 - 387, p. 371 , dose levels 0, 1, 2, 3.
(b) Number observed / number at risk
(c) Number of tumor bearing animals / total number of animals

Table 13

JANSSEN PHARMACEUTICA NV
Department of Toxicology

EXPERIMENT : 1927
Carcinogenicity study
R 64766 - FOOD - MICE - 18 MONTH

TUMOR BEARING FEMALES

Lunar month	Control (b)	Low (b)	Medium (b)	High (b)	Trend	Variance	z-value	p-value (1-tailed)
			Age adjusted test for positive dose-related trend (a)					
			Animals bearing FATAL tumor(s)					
9	0 / 49	0 / 50	1 / 48	0 / 46	0.528	1.234	0.476	
10	0 / 49	2 / 49	0 / 47	0 / 44	-0.910	2.451	-0.581	
11	0 / 49	0 / 46	0 / 45	1 / 44	1.543	1.259	1.376	
13	0 / 48	0 / 45	0 / 43	1 / 42	1.556	1.258	1.387	
15	1 / 44	0 / 42	1 / 39	0 / 36	-0.832	2.458	-0.531	
16	1 / 39	1 / 35	0 / 35	2 / 30	1.388	4.826	0.632	
17	0 / 37	0 / 33	7 / 34	2 / 28	7.386	10.353	2.296	
18	0 / 35	1 / 29	2 / 25	1 / 25	2.596	4.986	1.163	
19	0 / 30	0 / 26	1 / 23	0 / 21	0.650	1.248	0.582	
20	1 / 27	0 / 25	2 / 21	1 / 18	1.681	4.679	0.777	
All					15.589	34.751	2.644	0.004 **
(c)	3 / 50	4 / 50	14 / 50	8 / 50				
			Animals bearing only INCIDENTAL tumor(s)					
1 - 9	0 / 1	0 / 1	0 / 2	0 / 6	0.000	0.000	0.000	
10 - 17	0 / 12	2 / 17	4 / 14	8 / 13	13.000	12.218	3.719	
18 - 19	3 , 8	2 / 3	0 / 1	3 / 6	0.778	8.264	0.271	
20	1 / 2	0 / 0	1 / 1	0 / 0	0.667	0.889	0.707	
Terminal	6 / 24	16 / 25	13 / 18	16 / 17	22.000	24.300	4.463	
All					36.444	45.672	5.393	0.000 ***
(c)	10 / 47	20 / 46	18 / 36	27 / 42				
			Animals bearing FATAL and / or INCIDENTAL tumor(s)					
Total					52.033	80.423	5.802	0.000 ***
(c)	13 / 50	26 / 50	32 / 50	35 / 50				

(a) Peto monograph, WHO, IARC, Lyon, 1980, pp. 386 - 387, p. 371 , dose levels 0, 1, 2, 3.
(b) Number observed / number at risk .
(c) Number of tumor bearing animals / total number of animals

000-00114

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Department of toxicology

Table 14

EXPERIMENT: 1927
Carcinogenicity study
R 64766 - FOOD - MICE - 18 MONTH

HISTOPATHOLOGY : TUMORS
Incidence per dosage group

Organ or tissue : tumor	Males				
	Dosage group (mg / kg)				(a)
	0	0.63	2.5	10	P (1-sided) for trend
Bone : Sarcoma	1 / 50	0 / 50	0 / 50	0 / 50	(b) 0.9085
Hematopoietic system : tumor	1 / 50	1 / 50	1 / 50	0 / 50	(b) 0.7831
Kidney : Adenocarcinoma	0 / 50	0 / 50	0 / 49	1 / 50	(c) 0.2232
Lacrimal gland(s) : Adenoma	0 / 50	0 / 50	0 / 50	1 / 50	(c) 0.2232
Liver : Hemangioendothelioma	0 / 50	0 / 50	1 / 49	1 / 50	(c) 0.1597
Liver : Hepatic neoplastic nodule	3 / 50	7 / 50	6 / 49	5 / 50	(b) 0.2629
Liver : Hepatocytic carcinoma	0 / 50	3 / 50	3 / 49	2 / 50	(b) 0.1786
Liver : Hepatocytic neoplasia	3 / 50	9 / 50	8 / 49	6 / 50	(b) 0.2059
Lung : Primary lung tumor, benign	14 / 50	12 / 50	3 / 50	5 / 50	(b) 0.9985
Lung : Primary lung tumor, malignant	1 / 50	4 / 50	2 / 50	6 / 50	(b) 0.0001
Lung : Primary lung tumor	14 / 50	16 / 50	5 / 50	10 / 50	(b) 0.9515
Pituitary gland : Adenoma	0 / 45	0 / 40	0 / 45	1 / 47	(b) 0.1926
Seminal vesicle : Carcinosarcoma	0 / 50	0 / 50	0 / 50	1 / 50	(c) 0.2232
Small intestine : Adenocarcinoma	0 / 50	0 / 50	0 / 50	1 / 50	(c) 0.2483
Testis : Leydig cell tumor, benign	0 / 50	1 / 50	0 / 48	0 / 50	(b) 0.6568

(a) Age-adjusted analysis, taking into account the context of observation (Peto monograph, WHO, IARC, Lyon, 1980, pp. 311-426); dose levels 0, 1, 2, 3. P-values are either asymptotic (b) or "exact" (c).
(b) Asymptotic p-value of Peto's trend statistic (no correction for continuity).
(c) "Exact" p-value of the age-adjusted test

000-0011b

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Table 15

EXPERIMENT: 1927
Carcinogenicity study
R 84766 - FOOD - MICE - 18 MONTH

HISTOPATHOLOGY : TUMORS
Incidence per dosage group

Organ or tissue : tumor	Dosage group (mg / kg) 0	0.63	2.5	10	(a) P (1-sided) for trend	
					Females	
Adrenal gland : Phaeochromocytoma, benign	0 / 49	0 / 49	1 / 45	0 / 49	(b) 0.2763	
Hematopoietic system : tumor	7 / 50	8 / 50	5 / 50	4 / 50	(b) 0.7085	
Lacrimal gland(s) : Adenocarcinoma	0 / 50	0 / 50	0 / 50	1 / 50	(c) 0.2024	
Lacrimal gland(s) : Adenoma	0 / 50	0 / 50	1 / 50	0 / 50	(b) 0.2713	
Liver : Hemangioendothelioma	0 / 50	1 / 50	0 / 50	1 / 50	(b) 0.2270	
Liver : Hepatic neoplastic nodule	0 / 50	1 / 50	2 / 50	0 / 50	(b) 0.3346	
Liver : Hepatocytic carcinoma	1 / 50	0 / 50	0 / 50	0 / 50	(b) 0.8884	
Liver : Hepatocytic neoplasia	1 / 50	1 / 50	2 / 50	0 / 50	(b) 0.5944	
Lung : Primary lung tumor, benign	2 / 50	5 / 50	4 / 50	6 / 50	(b) 0.0557	
Lung : Primary lung tumor, malignant	1 / 50	1 / 50	3 / 50	1 / 50	(b) 0.2462	
Lung : Primary lung tumor	3 / 50	6 / 50	6 / 50	7 / 50	(b) 0.0445	*
Mammary gland : Adenocarcinoma	0 / 50	7 / 50	18 / 47	17 / 48	(b) 0.0000	***
Mammary gland : Carcinosarcoma	0 / 50	0 / 50	1 / 47	0 / 48	(b) 0.2679	
Mammary gland : Fibroadenoma	0 / 50	0 / 50	1 / 47	0 / 48	(b) 0.3321	
Mammary gland : Sarcoma	0 / 50	0 / 50	1 / 47	0 / 48	(b) 0.2831	
Ovary : Granulosa-theca cell tumor, benign	0 / 49	1 / 50	0 / 46	0 / 49	(b) 0.6191	
Ovary : Hemangioendothelial sarcoma	1 / 49	0 / 50	0 / 46	0 / 49	(b) 0.8866	
Ovary : Hemangioendothelioma	0 / 49	0 / 50	1 / 46	0 / 49	(b) 0.2691	
Pituitary gland : Adenoma	1 / 48	2 / 46	13 / 45	21 / 48	(b) 0.0000	***
Skin : Carcinoma	0 / 50	0 / 50	1 / 50	0 / 50	(b) 0.2944	
Soft tissue : Fibrosarcoma	0 / 50	1 / 50	0 / 50	1 / 50	(b) 0.1931	
Uterus : Fibroleiomyosarcoma	0 / 50	0 / 50	1 / 50	0 / 50	(b) 0.3171	
Uterus : Hemangioendothelial sarcoma	0 / 50	0 / 50	1 / 50	0 / 50	(b) 0.2713	
Uterus : Hemangioendothelioma	0 / 50	1 / 50	0 / 50	1 / 50	(b) 0.1931	
Uterus : Polyp	2 / 50	0 / 50	2 / 50	1 / 50	(b) 0.5169	

(a) Age-adjusted analysis, taking into account the context of observation (Peto monograph, WHO, IARC, Lyon, 1980, pp. 311-426); dose levels 0, 1, 2, 3. P-values are either asymptotic (b) or "exact" (c).
(b) Asymptotic p-value of Peto's trend statistic (no correction for continuity).
(c) "Exact" p-value of the age-adjusted test

000-00117

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Department of Toxicology

Table 16

EXPERIMENT : 1627
Carcinogenicity study
R 64766 - FOOD - MICE - 18 MONTH

Lung : Primary lung tumor in females

Lunar month	Control (d)	Low (d)	Medium (d)	High (d)	Trend	Variance	z-value	p-value (1-sided) (b)	(c)
	Age adjusted test for positive dose-related trend (a)								
	Animals bearing FATAL tumor of interest								
11	0 / 49	0 / 46	0 / 45	1 / 44	1.543	1.259	1.376		
All					1.543	1.259	1.376	0.0845	
(e)	0 / 50	0 / 50	0 / 50	1 / 50					
	Animals bearing INCIDENTAL tumor of interest								
1 - 9	0 / 1	0 / 1	0 / 3	0 / 6	0.000	0.000	0.000		
10 - 17	0 / 14	1 / 20	1 / 22	2 / 18	2.622	4.242	1.273		
18 - 19	1 / 8	1 / 4	0 / 4	1 / 7	-0.304	4.228	-0.148		
20	1 / 3	0 / 0	2 / 3	0 / 1	0.143	2.694	0.087		
Terminal	1 / 24	4 / 25	3 / 18	3 / 17	4.333	11.594	1.273		
All					6.793	22.758	1.424	0.0772	
(e)	3 / 50	6 / 50	6 / 50	6 / 49					
	Animals bearing FATAL or INCIDENTAL tumor of interest								
Total					8.337	24.017	1.701	0.0445	*
(e)	3 / 50	6 / 50	6 / 50	7 / 50					

(a) Peto monograph, WHO, IARC, Lyon, 1980, pp. 311-426; dose levels 0, 1, 2, 3.
(b) Asymptotic p-value of Peto's trend statistic (no correction for continuity).
(c) "Exact" p-value of the age-adjusted test

(d) Number observed / number at risk
(e) Number of animals with tumor of interest / number of animals examined histologically for this organ

Positive animals sorted chronologically
Control
A: C228 C213 C244 S: s18 d20 t20
0.63 mg / kg
A: L257 L277 L261 L272 L287 L289 S: d16 s18 t20 t20 t20 t20
2.5 mg / kg
A: M328 M324 M337 M305 M323 M332 S: s10 d20 d20 t20 t20 t20
10 mg / kg
A: M386 M392 M363 M371 M376 M377 M400 S: S11 s11 s15 s19 t20 t20 t20

A: Animal number
S: Status at necropsy (d=dead,s=sacrificed,t=sacrificed terminally with INCIDENTAL tumor) + month
(D=dead,S=sacrificed with FATAL tumor) + month

000-00143

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Table 17

EXPERIMENT : 1927
Carcinogenicity study
R 64768 - FOOD - MICE - 18 MONTH

Mammary gland : Adenocarcinoma in females

Lunar month	Control (d)	Low (d)	Medium (d)	High (d)	Trend	Variance	z-value	p-value (1-sided) (b)	(c)
Age adjusted test for positive dose-related trend (a)									
Animals bearing FATAL tumor of interest									
10	0 / 49	1 / 49	0 / 47	0 / 44	-0.455	1.232	-0.410		
13	0 / 48	0 / 45	0 / 43	1 / 42	1.556	1.258	1.387		
15	0 / 44	0 / 42	1 / 39	0 / 35	0.594	1.229	0.536		
16	0 / 39	0 / 35	0 / 35	2 / 30	3.194	2.449	2.041		
17	0 / 37	0 / 33	5 / 34	1 / 28	4.591	7.070	1.727		
20	0 / 27	0 / 25	1 / 21	0 / 18	0.670	1.210	0.609		
All					10.150	14.448	2.670	0.0038	**
(e)	0 / 50	1 / 50	7 / 47	4 / 48					
Animals bearing INCIDENTAL tumor of interest									
1 - 9	0 / 1	0 / 1	0 / 3	0 / 6	0.000	0.000	0.000		
10 - 16	0 / 12	2 / 15	0 / 12	0 / 11	-0.880	2.285	-0.582		
17 - 19	0 / 10	0 / 8	2 / 7	3 / 9	5.794	5.994	2.367		
20	0 / 3	0 / 0	1 / 2	0 / 1	0.833	1.472	0.687		
Terminal	0 / 24	4 / 25	8 / 16	10 / 17	21.024	19.625	4.722		
All					26.772	29.577	4.923	0.0000	***
(e)	0 / 50	6 / 49	11 / 40	13 / 44					
Animals bearing FATAL or INCIDENTAL tumor of interest									
Total					36.922	44.025	5.565	0.0000	***
(e)	0 / 50	7 / 50	18 / 47	17 / 48					

(a) Peto monograph, WHO, IARC, Lyon, 1980, pp. 311-426; dose levels 0, 1, 2, 3.
(b) Asymptotic p-value of Peto's trend statistic (no correction for continuity).
(c) "Exact" p-value of the age-adjusted test

(d) Number observed / number at risk
(e) Number of animals with tumor of interest / number of animals examined histologically for this organ

Positive animals sorted chronologically

Control

No positive animals

0.63 mg / kg

A:	L275	L283	L290	L261	L286	L289	L295
S:	s10	S10	s14	t20	t20	t20	t20

2.5 mg / kg

A:	M314	M325	M335	M342	M348	M349	M338	M334	M308	M337	M305	M309	M310	M319	M323	M327	M330	M345
S:	S15	S17	S17	S17	S17	S17	s18	d19	s20	D20	t20	t20	t20	t20	t20	t20	t20	t20

10 mg / kg

A:	H375	H361	H383	H355	H367	H372	H395	H356	H357	H362	H374	H376	H377	H378	H391	H399	H400
S:	S13	S16	S16	s17	S17	s17	s18	t20	t20	t20	t20	t20	t20	t20	t20	t20	t20

A: Animal number
S: Status at necropsy (d=dead,s=sacrificed,t=sacrificed terminally with INCIDENTAL tumor) + month
(D=dead,S=sacrificed with FATAL tumor) + month

000-00144

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Table 18

EXPERIMENT : 1927
Carcinogenicity study
R 64766 - FOOD - MICE - 18 MONTH

Pituitary gland : Adenoma in females

Lunar month	Control (d)	Low (d)	Medium (d)	High (d)	Trend	Variance	z-value	p-value (1-sided) (b)	(c)
	Age adjusted test for positive dose-related trend (a)								
	Animals bearing FATAL tumor of interest								
17	0 / 37	0 / 33	1 / 33	1 / 28	2.206	2.445	1.411		
18	0 / 35	0 / 28	0 / 25	1 / 25	1.646	1.291	1.449		
19	0 / 30	0 / 26	1 / 22	0 / 21	0.857	1.256	0.586		
20	0 / 27	0 / 25	0 / 21	1 / 18	1.670	1.210	1.518		
All					6.179	6.201	2.481	0.0066	**
(e)	0 / 48	0 / 46	2 / 45	3 / 48					
	Animals bearing INCIDENTAL tumor of interest								
1 - 12	0 / 2	0 / 5	0 / 6	0 / 8	0.000	0.000	0.000		
13 - 14	0 / 4	0 / 3	0 / 4	2 / 5	2.750	2.538	1.726		
15 - 19	0 / 17	0 / 16	2 / 14	6 / 15	10.516	9.051	3.495		
20	0 / 3	0 / 0	1 / 3	0 / 0	1.000	1.000	1.000		
Terminal	1 / 22	2 / 22	8 / 16	10 / 17	19.364	19.255	4.413		
All					33.630	31.844	5.959	0.0000	***
(e)	1 / 48	2 / 46	11 / 43	18 / 45					
	Animals bearing FATAL or INCIDENTAL tumor of interest								
Total					39.809	38.045	6.454	0.0000	***
(e)	1 / 48	2 / 46	13 / 45	21 / 48					

(a) Peto monograph, WHO, IARC, Lyon, 1980, pp. 311-426; dose levels 0, 1, 2, 3.
(b) Asymptotic p-value of Peto's trend statistic (no correction for continuity).
(c) "Exact" p-value of the age-adjusted test

(d) Number observed / number at risk
(e) Number of animals with tumor of interest / number of animals examined histologically for this organ

Positive animals sorted chronologically

Control

A: C249
S: t20

0.63 mg / kg

A: L256 L293
S: t20 t20

2.5 mg / kg

A: M313 M331 M336 M334 M324 M305 M310 M319 M330 M332 M336 M344 M345
S: S17 s17 s18 D19 d20 t20 t20 t20 t20 t20 t20 t20 t20

10 mg / kg

A: H387 H354 H369 H373 H366 H393 H372 H367 H361 H359 H385 H356 H357 H360 H362 H374 H377 H388 H391 H396 H398
S: s13 d14 s15 s15 s15 s16 S17 s17 S18 s18 D20 t20 t20 t20 t20 t20 t20 t20 t20 t20 t20

A: Animal number
S: Status at necropsy (d=dead,s=sacrificed,t=sacrificed terminally with INCIDENTAL tumor) + month
(D=dead,S=sacrificed with FATAL tumor) + month

000-00151

Table 19

Table 4 : Incidence of tumor types per tissue in female control mice per experiment and the total procentual occurrence

FEMALES

Experiment no.	1306	1548	1649	1580c	1580d	1987	1881
Adrenal gland							
Adenoma	0/48	0/50	1/50	1/48	0/48	0/49	0/50
Phaechromocytoma	0/48	0/50	0/50	1/48	0/48	0/49	0/50
Spindle cell tumor, benign	1/48	0/50	0/50	0/48	0/48	0/49	0/50
Bone (*)							
Osteoma	0/50	0/50	0/50	1/50	0/50	0/50	0/50
Cardial system (*)							
Sarcoma	0/50	0/50	0/50	0/50	1/50	0/50	0/50
Cervix (*)							
Hemangioendothelial sarcoma	0/50	0/50	0/50	1/50	0/50	0/49	0/50
Hemangioendothelioma	0/50	0/50	0/50	0/50	1/50	0/49	0/50
Fibroleiomyosarcoma	0/50	0/50	0/50	1/50	0/50	0/49	0/50
Leiomyosarcoma	0/50	0/50	0/50	0/50	0/50	0/49	1/50
Sarcoma	1/50	0/50	2/50	1/50	0/50	1/49	0/50
Harderian gland (*)							
Adenoma	0/50	0/50	0/50	0/50	1/50	0/50	1/50
Hematopoietic system (*)							
Tumor	5/50	8/50	14/50	12/50	14/50	11/49	11/50
- lymphoma	0/50	0/50	0/50	0/50	0/50	0/49	0/50
- lymphosarcoma	2/50	4/50	3/50	4/50	4/50	6/49	6/50
- lymphoid leukemia	2/50	3/50	6/50	8/50	4/50	3/49	1/50
- myeloid leukemia	1/50	0/50	1/50	0/50	0/50	0/49	0/50
- hystiocytic tumor	0/50	0/50	4/50	0/50	4/50	1/49	3/50
- thymoma	0/50	1/50	0/50	0/50	0/50	1/49	0/50
Liver							
Hepatic neoplastic nodule	2/50	3/50	0/50	0/49	0/50	1/49	1/50
Hepatocellular carcinoma	0/50	0/50	0/50	0/49	0/50	0/49	0/50
-- Hepatocellular neoplasia	2/50	3/50	0/50	0/49	0/50	0/49	1/50
Hemangioendothelial sarcoma	0/50	0/50	0/50	0/49	1/50	0/49	0/50
Hemangioendothelioma	0/50	1/50	1/50	1/49	1/50	1/49	0/50
Hepatocytic carcinoma	0/50	0/.50	0/50	0/49	0/50	0/49	0/50
Lung							
Primary lung tumor, benign	7/50	4/50	12/50	9/50	6/50	4/49	8/50
Primary lung tumor, malignant	5/50	3/50	4/50	3/50	7/50	1/49	3/50
--- Primary lung tumor	12/50	6/50	16/50	11/50	11/50	5/49	11/50
Mammary gland							
Adenocarcinoma	3/50	1/47	3/49	1/47	5/48	1/49	2/50
Carcinoma	3/50	0/47	0/49	0/47	0/48	0/49	0/50

Table 19 (continued)

Table 4 : Incidence of tumor types per tissue in female control mice per experiment and the total procentual occurrence

FEMALES

Experiment no.	1308	1548	1649	1580c	1580d	1987	1881
Ovary							
Adenoma	0/50	1/50	1/50	1/49	0/49	0/49	0/50
Carcinoma	0/50	1/50	0/50	0/49	0/49	0/49	0/50
Granulosa-theca cell tumor, benign	0/50	0/50	0/50	1/49	0/49	0/49	0/50
Hemangioendothelial sarcoma	0/50	0/50	0/50	1/49	1/49	0/49	0/50
Hemangioendothelioma	0/50	0/50	2/50	0/49	0/49	1/49	0/50
Luteal-cell tumor, benign	1/50	0/50	2/50	1/49	1/49	1/49	0/50
Pancreas							
Endocrine adenoma	0/47	0/49	1/50	0/49	0/47	0/48	0/50
Pituitary gland							
Adenoma	1/45	2/44	1/46	0/40	3/44	2/48	0/49
Carcinoma	0/45	0/44	1/46	0/40	0/44	0/48	0/49
Skin (*)							
Carcinoma, squamous cell	0/50	0/50	0/50	0/50	1/50	0/50	0/50
Soft tissue (*)							
Fibroma	0/50	1/50	0/50	0/50	0/50	0/49	0/50
Fibrosarcoma	0/50	0/50	1/50	0/50	0/50	0/49	0/50
Hemangioendothelial sarcoma	0/50	0/50	0/50	0/50	0/50	1/49	0/50
Hemangioendothelioma	0/50	1/50	0/50	0/50	0/50	0/49	0/50
Sarcoma	1/50	0/50	0/50	0/50	0/50	0/49	1/50
Spleen							
Hemangioendothelial sarcoma	0/50	0/49	0/50	0/49	0/48	1/49	0/50
Hemangioendothelioma	0/50	2/49	1/50	0/49	0/48	1/49	2/50
Thyroid gland							
Adenoma	0/29	0/25	1/33	0/37	1/42	0/49	0/49
Urinary bladder (*)							
Fibroleiomyoma	0/50	1/50	0/50	0/41	0/46	0/40	0/46
Hemangioendothelioma	0/50	1/50	0/50	0/41	0/46	0/40	0/46
Uterus							
Adenocarcinoma	0/50	1/49	2/50	0/50	1/49	0/49	0/50
Adenoma	2/50	2/49	1/50	0/50	1/49	0/49	0/50
Adenoma, polypous	0/50	0/49	0/50	0/50	0/49	2/49	2/50
Carcinoma	0/50	0/49	2/50	0/50	0/49	0/49	0/50
Fibroleiomyoma	0/50	1/49	0/50	0/50	1/49	0/49	0/50
Fibroleiomyosarcoma	0/50	0/49	0/50	2/50	1/49	0/49	0/50
Hemangioendothelioma	0/50	0/49	0/50	2/50	2/49	2/49	0/50
Hemangioma	2/50	0/49	0/50	0/50	0/49	0/49	0/50
Leiomyosarcoma	0/50	0/49	0/50	0/50	0/49	1/49	1/50
Sarcoma	0/50	0/49	2/50	0/50	0/49	1/49	0/50
Vagina							
Carcinoma			1/42				0/43

(*) denominator = number of autopsied animals

000-00164

Table 20
Intercurrent Mortality Rates
Male Mice

Weeks	Control			Low			Medium			High		
	S	D	%	S	D	%	S	D	%	S	D	%
0-50	50	3	6	50	2	4	50	4	8	50	4	8
51-70	47	13	27.6	48	9	18.7	46	13	28.3	46	12	26.0
71-78	34	7	20.6	39	5	12.8	33	7	21.2	34	9	26.5
Term.	27			34			26			25		

Female Mice

Weeks	Control			Low			Medium			High		
	S	D	%	S	D	%	S	D	%	S	D	%
0-50	50	3	6	50	5	10	50	7	14	50	8	16
51-70	47	14	29.8	45	18	40	43	18	41.8	42	21	50
71-77	33	9	27.3	27	2	7.4	25	7	28	21	4	19
Term.	24			25			18			17		

Notes: S: Number of animals starting during the period
D: Deaths
%: Percent of death during the period

Table 21
Tumor Incidence Rates
Female Mice, Mammary Gland Adenocarcinoma

Weeks	Control		Low		Medium		High	
	T	N	T	N	T	N	T	N
0-50	0	3	2	5	0	7	0	8
51-70	0	14	1	18	6	18	7	21
71-77	0	9	0	2	4	7	0	4
Terminal	0	24	4	25	8	18	10	17
Total	0	50	7	50	18	50	17	50

Table 22
Tumor Incidence Rates
Female Mice, Pituitary Gland Adenoma

Weeks	Control		Low		Medium		High	
	T	N	T	N	T	N	T	N
0-50	0	3	0	5	0	7	0	8
51-70	0	14	0	18	2	18	10	21
71-77	0	9	0	2	3	7	1	4
Terminal	1	24	2	25	8	18	10	17
Total	1	50	2	50	13	50	21	50

Notes: T: Number of necropsies with the above tumor.
N: Number of necropsies.

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Chronological listing — MALES

Dosage group : Control

f (fatal)
c (could be fatal)
i (incidental)
p (probably incidental)

Week	Animal number	Death status	Organ	Tumor type	B (Benign) M (Malignant)	
18	27	S	Hematopoietic system	tumor, malignant	M	f
57	40	S	Lung	Primary lung tumor, benign	B	i
66	49	S	Lung	Primary lung tumor, benign	B	i
73	33	S	Liver	Hepatic neoplastic nodule	B	i
74	10	D	Lung	Primary lung tumor, malignant	M	p
			Lung	Primary lung tumor, benign	B	i
			Bone	Sarcoma	M	c
75	48	D	Lung	Primary lung tumor, benign	B	i
79	4	T	Lung	Primary lung tumor, benign	B	
79	12	T	Lung	Primary lung tumor, benign	B	
79	14	T	Lung	Primary lung tumor, benign	B	
			Liver	Hepatic neoplastic nodule	B	
79	25	T	Lung	Primary lung tumor, benign	B	
79	30	T	Lung	Primary lung tumor, benign	B	
79	34	T	Lung	Primary lung tumor, benign	B	
79	36	T	Lung	Primary lung tumor, benign	B	
79	43	T	Lung	Primary lung tumor, benign	B	
79	46	T	Lung	Primary lung tumor, benign	B	
79	50	T	Lung	Primary lung tumor, benign	B	
			Liver	Hepatic neoplastic nodule	B	

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Chronological listing — MALES

Dosage group : R 64766 0.63 mg / kg

Week	Animal number	Death status	Organ	Tumor type	B (Benign) M (Malignant)	f (fatal) c (could be fatal) i (incidental) p (probably incidental)
60	73	D	Lung	Primary lung tumor, benign	B	i
60	78	S	Liver	Hepatic neoplastic nodule	B	i
			Lung	Primary lung tumor, malignant	M	i
65	84	S	Hematopoietic system	tumor, malignant	M	f
73	63	S	Liver	Hepatocytic carcinoma	M	i
76	57	D	Liver	Hepatocytic carcinoma	M	p
			Lung	Primary lung tumor, malignant	M	i
79	53	T	Testis	Leydig cell tumor, benign	B	
79	56	T	Liver	Hepatic neoplastic nodule	B	
79	59	T	Lung	Primary lung tumor, benign	B	
79	65	T	Lung	Primary lung tumor, benign	B	
79	71	T	Lung	Primary lung tumor, benign	B	
79	74	T	Liver	Hepatic neoplastic nodule	B	
79	79	T	Liver	Hepatic neoplastic nodule	B	
79	80	T	Lung	Primary lung tumor, benign	B	
79	82	T	Lung	Primary lung tumor, malignant	M	
79	83	T	Lung	Primary lung tumor, benign	B	
79	87	T	Lung	Primary lung tumor, benign	B	
			Liver	Hepatic neoplastic nodule	B	
79	88	T	Liver	Hepatic neoplastic nodule	B	
79	90	T	Lung	Primary lung tumor, benign	B	
			Liver	Hepatocytic carcinoma	M	
			Liver	Hepatic neoplastic nodule	B	
79	91	T	Lung	Primary lung tumor, benign	B	
79	94	T	Lung	Primary lung tumor, benign	B	
79	96	T	Lung	Primary lung tumor, malignant	M	
79	98	T	Lung	Primary lung tumor, benign	B	
79	100	T	Lung	Primary lung tumor, benign	B	

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Chronological listing — MALES

Dosage group : R 64766 2.5 mg / kg

Week	Animal number	Death status	Organ	Tumor type	B (Benign) M (Malignant)	f (fatal) c (could be fatal) i (incidental) p (probably incidental)
23	141	D	Hematopoietic system	tumor, malignant	M	f
63	101	S	Liver	Hepatic neoplastic nodule	B	i
76	131	S	Lung	Primary lung tumor, malignant	M	i
79	103	T	Lung	Primary lung tumor, benign	B	
79	107	T	Lung	Primary lung tumor, malignant	M	
79	118	T	Liver	Hepatic neoplastic nodule	B	
79	119	T	Liver	Hepatocytic carcinoma	M	
			Liver	Hepatic neoplastic nodule	B	
79	122	T	Liver	Hepatic neoplastic nodule	B	
79	126	T	Liver	Hepatic neoplastic nodule	B	
79	127	T	Lung	Primary lung tumor, benign	B	
79	137	T	Lung	Primary lung tumor, benign	B	
			Liver	Hemangioendothelioma	B	
			Liver	Hepatocytic carcinoma	M	
79	138	T	Liver	Hepatocytic carcinoma	M	
79	144	T	Liver	Hepatic neoplastic nodule	B	

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Chronological listing — MALES

Dosage group : R 64766 10 mg / kg

Week	Animal number	Death status	Organ	Tumor type	B (Benign) M (Malignant)	f (fatal) c (could be fatal) i (incidental) p (probably incidental)
59	190	S	Liver	Hepatic neoplastic nodule	B	i
62	186	D	Lung	Primary lung tumor, benign	B	i
67	193	S	Liver	Hepatic neoplastic nodule	B	i
68	188	S	Liver	Hepatocytic carcinoma	M	i
69	167	S	Small intestine	Adenocarcinoma	M	c
72	171	S	Lung	Primary lung tumor, malignant	M	i
76	174	S	Lung	Primary lung tumor, malignant	M	i
78	173	D	Pituitary gland	Adenoma	B	i
			Liver	Hemangioendothelioma	B	f
79	155	T	Lung	Primary lung tumor, benign	B	
79	156	T	Lung	Primary lung tumor, benign	B	
79	161	T	Kidney	Adenocarcinoma	M	
79	163	T	Liver	Hepatocytic carcinoma	M	
			Liver	Hepatic neoplastic nodule	B	
79	168	T	Lung	Primary lung tumor, malignant	M	
			Lung	Primary lung tumor, benign	B	
79	169	T	Lung	Primary lung tumor, malignant	M	
79	172	T	Seminal vesicle	Carcinosarcoma	M	
79	185	T	Liver	Hepatic neoplastic nodule	B	
79	192	T	Lung	Primary lung tumor, malignant	M	
			Liver	Hepatic neoplastic nodule	B	
79	194	T	Lung	Primary lung tumor, malignant	M	
79	197	T	Lung	Primary lung tumor, benign	B	
79	198	T	Lacrimal gland(s)	Adenoma	B	

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Chronological listing — FEMALES

Dosage group : Control

Week	Animal number	Death status	Organ	Tumor type	B (Benign) M (Malignant)	f (fatal) c (could be fatal) i (incidental) p (probably incidental)
59	235	D	Hematopoietic system	tumor, malignant	M	f
64	242	D	Hematopoietic system	tumor, malignant	M	f
69	208	S	Hematopoietic system	tumor, malignant	M	p
69	221	S	Hematopoietic system	tumor, benign	B	p
71	228	S	Lung	Primary lung tumor, benign	B	i
77	227	S	Ovary	Hemangioendothelial sarcoma	M	f
78	213	D	Lung	Primary lung tumor, malignant	M	i
78	214	T	Hematopoietic system	tumor, malignant	M	
78	215	T	Hematopoietic system	tumor, malignant	M	
			Liver	Hepatocytic carcinoma	M	
78	223	T	Uterus	Polyp	B	
79	243	T	Hematopoietic system	tumor, malignant	M	
79	244	T	Lung	Primary lung tumor, benign	B	
			Uterus	Polyp	B	
79	249	T	Pituitary gland	Adenoma	B	

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Chronological listing — FEMALES

Dosage group : R 64766 0.63 mg / kg

f (fatal)
c (could be fatal)
i (incidental)
p (probably incidental)

Week	Animal number	Death status	Organ	Tumor type	B (Benign) M (Malignant)	
38	275	S	Mammary gland	Adenocarcinoma	M	p
39	258	S	Hematopoietic system	tumor, malignant	M	f
40	283	S	Mammary gland	Adenocarcinoma	M	f
53	290	S	Mammary gland	Adenocarcinoma	M	i
61	257	D	Lung	Primary lung tumor, benign	B	i
			Hematopoietic system	tumor, malignant	M	f
69	277	S	Lung	Primary lung tumor, malignant	M	i
71	274	S	Hematopoietic system	tumor, malignant	M	f
76	270	S	Liver	Hemangioendothelioma	B	i
78	251	T	Hematopoietic system	tumor, malignant	M	
78	256	T	Pituitary gland	Adenoma	B	
78	261	T	Mammary gland	Adenocarcinoma	M	
			Lung	Primary lung tumor, benign	B	
78	272	T	Liver	Hepatic neoplastic nodule	B	
			Lung	Primary lung tumor, benign	B	
78	273	T	Uterus	Hemangioendothelioma	B	
79	284	T	Hematopoietic system	tumor, benign	B	
79	285	T	Hematopoietic system	tumor, malignant	M	
79	286	T	Mammary gland	Adenocarcinoma	M	
79	287	T	Lung	Primary lung tumor, benign	B	
79	288	T	Ovary	Granulosa-theca cell tumor, benign	B	
79	289	T	Mammary gland	Adenocarcinoma	M	
			Lung	Primary lung tumor, benign	B	
79	293	T	Pituitary gland	Adenoma	B	
79	295	T	Mammary gland	Adenocarcinoma	M	
79	296	T	Hematopoietic system	tumor, malignant	M	
79	299	T	Soft tissue	Fibrosarcoma	M	
79	300	T	Hematopoietic system	tumor, malignant	M	

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Chronological listing — FEMALES

Dosage group : R 64766 2.5 mg / kg

f (fatal)
c (could be fatal)
i (incidental)
p (probably incidental)

Animal number	Death status	Organ	Tumor type	B (Benign) M (Malignant)	
Week					
36 312	S	Uterus	Fibroleiomyosarcoma	M	f
37 328	S	Lung	Primary lung tumor, benign	B	i
47 329	D	Uterus	Polyp	B	i
59 314	S	Mammary gland	Adenocarcinoma	M	f
62 317	S	Uterus	Polyp	B	i
65 313	S	Pituitary gland	Adenoma	B	f
65 331	S	Pituitary gland	Adenoma	B	i
65 343	S	Skin	Carcinoma	M	c
67 349	S	Mammary gland	Adenocarcinoma	M	f
		Liver	Hepatic neoplastic nodule	B	i
67 325	S	Mammary gland	Adenocarcinoma	M	c
		Mammary gland	Fibroadenoma	B	i
		Hematopoietic system	tumor, malignant	M	i
68 342	S	Mammary gland	Adenocarcinoma	M	f
68 348	S	Mammary gland	Adenocarcinoma	M	c
68 335	S	Mammary gland	Adenocarcinoma	M	f
71 338	S	Pituitary gland	Adenoma	B	i
		Mammary gland	Adenocarcinoma	M	p
		Mammary gland	Sarcoma	M	f
71 304	S	Hematopoietic system	tumor, malignant	M	f
74 334	D	Pituitary gland	Adenoma	B	f
		Mammary gland	Adenocarcinoma	M	i
77 324	D	Pituitary gland	Adenoma	B	p
		Hematopoietic system	tumor, malignant	M	f
		Lung	Primary lung tumor, benign	B	i
78 308	S	Mammary gland	Adenocarcinoma	M	i
		Ovary	Hemangioendothelioma	B	i
78 337	D	Mammary gland	Adenocarcinoma	M	f
		Lung	Primary lung tumor, malignant	M	i
78 305	T	Mammary gland	Carcinosarcoma	M	
		Mammary gland	Adenocarcinoma	M	
		Pituitary gland	Adenoma	B	
		Lung	Primary lung tumor, malignant	M	
		Lung	Primary lung tumor, benign	B	
		Hematopoietic system	tumor, benign	B	
		Liver	Hepatic neoplastic nodule	B	
78 307	T	Hematopoietic system	tumor, malignant	M	
78 309	T	Mammary gland	Adenocarcinoma	M	
78 310	T	Mammary gland	Adenocarcinoma	M	
		Pituitary gland	Adenoma	B	
78 319	T	Mammary gland	Adenocarcinoma	M	
		Pituitary gland	Adenoma	B	

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Chronological listing — FEMALES

Dosage group : R 64766 2.5 mg / kg

f (fatal)
c (could be fatal)
i (incidental)
p (probably incidental)

Week	Animal number	Death status	Organ	Tumor type	B (Benign) M (Malignant)
78	321	T	Adrenal gland	Phaeochromocytoma, benign	B
78	323	T	Mammary gland	Adenocarcinoma	M
			Lung	Primary lung tumor, benign	B
			Lacrimal gland(s)	Adenoma	B
78	327	T	Mammary gland	Adenocarcinoma	M
79	330	T	Mammary gland	Adenocarcinoma	M
			Pituitary gland	Adenoma	B
79	332	T	Pituitary gland	Adenoma	B
			Lung	Primary lung tumor, malignant	M
			Uterus	Hemangioendothelial sarcoma	M
79	336	T	Pituitary gland	Adenoma	B
79	344	T	Pituitary gland	Adenoma	B
79	345	T	Pituitary gland	Adenoma	B
			Mammary gland	Adenocarcinoma	M

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Chronological listing — FEMALES

Dosage group : R 64766 10 mg / kg

f (fatal)
c (could be fatal)
i (incidental)
p (probably incidental)

Week	Animal number	Death status	Organ	Tumor type	B (Benign) M (Malignant)	
42	392	S	Lung	Primary lung tumor, benign	B	i
43	386	S	Lung	Primary lung tumor, malignant	M	f
51	387	S	Pituitary gland	Adenoma	B	i
51	375	S	Mammary gland	Adenocarcinoma	M	f
53	354	D	Pituitary gland	Adenoma	B	i
58	366	S	Pituitary gland	Adenoma	B	p
59	363	S	Lung	Primary lung tumor, benign	B	i
60	369	S	Pituitary gland	Adenoma	B	i
60	373	S	Pituitary gland	Adenoma	B	i
64	381	S	Mammary gland	Adenocarcinoma	M	f
64	393	S	Pituitary gland	Adenoma	B	p
			Mammary gland	Adenocarcinoma	M	f
65	372	S	Mammary gland	Adenocarcinoma	M	i
			Pituitary gland	Adenoma	B	c
65	367	S	Mammary gland	Adenocarcinoma	M	f
			Pituitary gland	Adenoma	B	i
68	355	S	Mammary gland	Adenocarcinoma	M	i
69	395	S	Mammary gland	Adenocarcinoma	M	i
69	359	S	Pituitary gland	Adenoma	B	p
70	361	S	Pituitary gland	Adenoma	B	f
73	371	S	Lung	Primary lung tumor, benign	B	i
78	365	D	Pituitary gland	Adenoma	B	c
78	356	T	Pituitary gland	Adenoma	B	
			Mammary gland	Adenocarcinoma	M	
78	357	T	Mammary gland	Adenocarcinoma	M	
			Pituitary gland	Adenoma	B	
78	360	T	Pituitary gland	Adenoma	B	
			Liver	Hemangioendothelioma	B	
78	362	T	Mammary gland	Adenocarcinoma	M	
			Pituitary gland	Adenoma	B	
			Soft tissue	Fibrosarcoma	M	
			Uterus	Hemangioendothelioma	B	
78	370	T	Hematopoietic system	tumor, malignant	M	
78	374	T	Mammary gland	Adenocarcinoma	M	
			Pituitary gland	Adenoma	B	
78	376	T	Mammary gland	Adenocarcinoma	M	
			Lung	Primary lung tumor, benign	B	
78	377	T	Mammary gland	Adenocarcinoma	M	
			Lung	Primary lung tumor, benign	B	
			Pituitary gland	Adenoma	B	

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Chronological listing — FEMALES

Dosage group : R 64766 10 mg / kg

f (fatal)
c (could be fatal)
i (incidental)
p (probably incidental)

Week	Animal number	Death status	Organ	Tumor type	B (Benign) M (Malignant)
78	378	T	Mammary gland	Adenocarcinoma	M
			Hematopoietic system	tumor, benign	B
78	388	T	Pituitary gland	Adenoma	B
			Hematopoietic system	tumor, malignant	M
78	390	T	Hematopoietic system	tumor, benign	B
79	391	T	Mammary gland	Adenocarcinoma	M
			Pituitary gland	Adenoma	B
79	396	T	Lacrimal gland(s)	Adenocarcinoma	M
			Pituitary gland	Adenoma	B
79	398	T	Pituitary gland	Adenoma	B
			Uterus	Polyp	B
79	399	T	Mammary gland	Adenocarcinoma	M
79	400	T	Mammary gland	Adenocarcinoma	M
			Lung	Primary lung tumor, benign	B

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Summary of animal deaths and sacrifices — MALES

	Control							0.63 mg							2.5 mg							10 mg						
Week	E	D	S	T	N	NP	W	E	D	S	T	N	NP	W	E	D	S	T	N	NP	W	E	D	S	T	N	NP	W
5	50	0	0	0	0	0	0	50	0	0	0	0	0	0	50	1	0	0	1	0	0	50	0	0	0	0	0	0
18	50	0	1	0	1	0	0	50	0	0	0	0	0	0	49	0	0	0	0	0	0	50	0	0	0	0	0	0
19	49	0	0	0	0	0	0	50	0	1	0	1	0	0	49	0	0	0	0	0	0	50	0	0	0	0	0	0
23	49	0	0	0	0	0	0	49	0	0	0	0	0	0	49	1	1	0	1	1	0	50	0	0	0	0	0	0
33	49	0	1	0	1	0	0	49	0	0	0	0	0	0	47	0	0	0	0	0	0	50	0	0	0	0	0	0
34	48	0	0	0	0	0	0	49	0	0	0	0	0	0	47	0	0	0	0	0	0	50	1	0	0	1	0	0
37	48	0	0	0	0	0	0	49	0	0	0	0	0	0	47	0	0	0	0	0	0	49	0	1	0	1	0	0
42	48	0	0	0	0	0	0	49	0	0	0	0	0	0	47	0	0	0	0	0	0	48	1	0	0	1	0	0
47	48	0	1	0	1	0	0	49	0	0	0	0	0	0	47	0	1	0	1	0	0	47	0	0	0	0	0	0
48	47	0	0	0	0	0	0	49	0	0	0	0	0	0	46	0	0	0	0	0	0	47	0	1	0	1	0	0
49	47	0	0	0	0	0	0	49	0	1	0	1	0	0	46	0	0	0	0	0	0	46	0	0	0	0	0	0
51	47	0	1	0	1	0	0	48	0	0	0	0	0	0	46	0	0	0	0	0	0	46	0	0	0	0	0	0
55	46	0	1	0	1	0	0	48	0	0	0	0	0	0	46	0	1	0	1	0	0	46	1	0	0	1	0	0
56	45	0	1	0	1	0	0	48	0	0	0	0	0	0	45	0	0	0	0	0	0	45	0	0	0	0	0	0
57	44	0	1	0	1	0	0	48	0	0	0	0	0	0	45	0	1	0	1	0	0	45	0	0	0	0	0	0
58	43	0	0	0	0	0	0	48	0	0	0	0	0	0	44	0	1	0	1	0	0	45	0	1	0	1	0	0
59	43	1	1	0	2	0	0	48	1	0	0	1	0	0	43	1	1	0	2	0	0	44	0	3	0	3	0	0
60	41	1	0	0	1	0	0	47	1	1	0	2	0	0	41	0	0	0	0	0	0	41	0	0	0	0	0	0
62	40	0	1	0	1	0	0	45	0	0	0	0	0	0	41	0	1	0	1	0	0	41	1	0	0	1	0	0
63	39	1	2	0	3	0	0	45	0	1	0	1	0	0	40	0	1	0	1	0	0	40	1	1	0	2	0	0
64	36	0	0	0	0	0	0	44	1	0	0	1	0	0	39	0	1	0	1	0	0	38	0	0	0	0	0	0
65	36	0	0	0	0	0	0	43	1	2	0	3	0	0	38	0	0	0	0	0	0	38	0	0	0	0	0	0
66	36	0	1	0	[illegible]	0	0	40	0	0	0	0	0	0	38	1	0	0	1	0	0	38	0	0	0	0	0	0
67	35	0	1	0	[illegible]	0	0	40	0	0	0	0	0	0	37	0	1	0	1	0	0	38	0	1	0	1	0	0
68	34	0	0	0	0	0	0	40	0	0	0	0	0	0	36	0	1	0	1	0	0	37	0	1	0	1	0	0
69	34	0	0	0	0	0	0	40	0	0	0	0	0	0	35	1	1	0	2	0	0	36	1	1	0	2	0	0
70	34	0	0	0	0	0	0	40	1	0	0	1	0	0	33	0	0	0	0	0	0	34	0	0	0	0	0	0
71	34	0	1	0	1	0	0	39	0	2	0	2	0	0	33	0	1	0	1	0	0	34	0	1	0	1	0	0
72	33	0	0	0	0	0	0	37	0	0	0	0	0	0	32	0	0	0	0	0	0	33	0	1	0	1	0	0
73	33	0	2	0	2	0	0	37	0	2	0	2	0	0	32	1	1	0	2	0	0	32	0	1	0	1	0	0
74	31	1	0	0	1	0	0	35	0	0	0	0	0	0	30	0	0	0	0	0	0	31	1	0	0	1	0	0
75	30	1	0	0	1	0	0	35	0	0	0	0	0	0	30	0	0	0	0	0	0	30	0	1	0	1	0	0
76	29	0	0	0	0	0	0	35	1	0	0	1	0	0	30	1	1	0	2	0	0	29	0	1	0	1	0	0
77	29	2	0	0	2	0	0	34	0	0	0	0	0	0	28	1	0	0	1	0	0	28	0	1	0	1	0	0
78	27	0	0	0	0	0	0	34	0	0	0	0	0	0	27	0	0	0	0	0	0	27	2	0	0	2	0	0
79	27	0	0	27	27	0	0	34	0	0	34	34	0	0	27	1	0	26	27	0	0	25	0	0	25	25	0	0

E= number entering period D= deaths S= sacrificed T= terminal
N= necropsied completely NP= necropsied to some extent W= total autolysis

JANSSEN PHARMACEUTICA NV
Department of toxicology
EXPERIMENT: 1927
Carcinogenicity study
R 64766 - FOOD - MICE - 18 MONTH

Summary of animal deaths and sacrifices — FEMALES

	Control							0.63 mg							2.5 mg							10 mg						
Week	E	D	S	T	N	NP	W	E	D	S	T	N	NP	W	E	D	S	T	N	NP	W	E	D	S	T	N	NP	W
5	50	0	0	0	0	0	0	50	0	0	0	0	0	0	50	0	0	0	0	0	0	50	0	1	0	1	0	0
10	50	0	0	0	0	0	0	50	0	0	0	0	0	0	50	0	1	0	1	0	0	49	0	0	0	0	0	0
15	50	0	0	0	0	0	0	50	0	0	0	0	0	0	49	0	0	0	0	0	0	49	0	1	0	1	0	0
22	50	0	1	0	1	0	0	50	0	0	0	0	0	0	49	0	0	0	0	0	0	48	0	0	0	0	0	0
27	49	0	0	0	0	0	0	50	0	0	0	0	0	0	49	0	0	0	0	0	0	48	1	0	0	1	0	0
30	49	0	0	0	0	0	0	50	0	0	0	0	0	0	49	0	1	0	1	0	0	47	0	0	0	0	0	0
32	49	0	0	0	0	0	0	50	0	0	0	0	0	0	48	0	0	0	0	0	0	47	0	1	0	1	0	0
33	49	0	0	0	0	0	0	50	0	0	0	0	0	0	48	0	0	0	0	0	0	46	0	2	0	2	0	0
35	49	0	0	0	0	0	0	50	1	0	0	1	0	0	48	0	0	0	0	0	0	44	0	0	0	0	0	0
36	49	0	0	0	0	0	0	49	0	0	0	0	0	0	48	0	1	0	1	0	0	44	0	0	0	0	0	0
37	49	0	0	0	0	0	0	49	0	0	0	0	0	0	47	0	2	0	2	0	0	44	0	0	0	0	0	0
38	49	0	0	0	0	0	0	49	0	1	0	1	0	0	45	0	0	0	0	0	0	44	0	0	0	0	0	0
39	49	0	0	0	0	0	0	48	0	1	0	1	0	0	45	0	0	0	0	0	0	44	0	0	0	0	0	0
40	49	0	0	0	0	0	0	47	0	1	0	1	0	0	45	0	0	0	0	0	0	44	0	0	0	0	0	0
41	49	0	0	0	0	0	0	46	0	1	0	1	0	0	45	0	0	0	0	0	0	44	0	0	0	0	0	0
42	49	0	0	0	0	0	0	45	0	0	0	0	0	0	45	0	0	0	0	0	0	44	0	1	0	1	0	0
43	49	0	0	0	0	0	0	45	0	0	0	0	0	0	45	0	0	0	0	0	0	43	0	1	0	1	0	0
44	49	0	1	0	1	0	0	45	0	0	0	0	0	0	45	0	0	0	0	0	0	42	0	0	0	0	0	0
47	48	0	0	0	0	0	0	45	0	0	0	0	0	0	45	1	0	0	1	0	0	42	0	0	0	0	0	0
48	48	0	0	0	0	0	0	45	0	0	0	0	0	0	44	1	0	0	1	0	0	42	0	0	0	0	0	0
49	48	1	0	0	1	0	0	45	0	0	0	0	0	0	43	0	0	0	0	0	0	42	0	0	0	0	0	0
51	47	0	1	0	1	0	0	45	0	0	0	0	0	0	43	1	0	0	1	0	0	42	0	2	0	2	0	0
53	46	0	0	0	0	0	0	45	0	3	0	3	0	0	42	0	2	0	2	0	0	40	1	1	0	2	0	0
54	46	0	1	0	1	0	0	42	0	0	0	0	0	0	40	1	0	0	1	0	0	38	0	0	0	0	0	0
55	45	0	0	0	0	0	0	42	0	0	0	0	0	0	39	0	0	0	0	0	0	38	1	0	0	1	0	0
56	45	0	1	0	1	0	0	42	0	0	0	0	0	0	39	0	0	0	0	0	0	37	1	0	0	1	0	0
57	44	0	1	0	1	0	0	42	0	1	0	1	0	0	39	0	0	0	0	0	0	36	0	0	0	0	0	0
58	43	0	1	0	1	0	0	41	0	1	0	1	0	0	39	0	2	0	2	0	0	36	0	1	0	1	0	0
59	42	1	0	0	1	0	0	40	0	1	0	1	0	0	37	0	1	0	1	0	0	35	0	2	0	2	0	0
60	41	0	2	0	2	0	0	39	1	3	0	4	0	0	36	0	1	0	1	0	0	33	0	3	0	3	0	0
61	39	0	0	0	0	0	0	35	1	0	0	1	0	0	35	0	0	0	0	0	0	30	0	0	0	0	0	0
62	39	0	0	0	0	0	0	34	0	0	0	0	0	0	35	0	1	0	1	0	0	30	0	0	0	0	0	0
63	39	0	0	0	0	0	0	34	0	1	0	1	0	0	34	0	0	0	0	0	0	30	0	0	0	0	0	0
64	39	1	1	0	2	0	0	33	0	0	0	0	0	0	34	0	0	0	0	0	0	30	0	2	0	2	0	0
65	37	0	1	0	1	0	0	33	0	1	0	1	0	0	34	0	3	0	3	0	0	28	0	2	0	2	0	0
66	36	0	0	0	0	0	0	32	0	1	0	1	0	0	31	0	0	0	0	0	0	26	0	0	0	0	0	0
67	36	0	1	0	1	0	0	31	0	1	0	1	0	0	31	0	2	0	2	0	0	26	0	0	0	0	0	0
68	35	0	0	0	0	0	0	30	0	1	0	1	0	0	29	0	4	0	4	0	0	26	0	1	0	1	0	0
69	35	0	2	0	2	0	0	29	0	2	0	2	0	0	25	0	0	0	0	0	0	25	0	3	0	3	0	0
70	33	0	0	0	0	0	0	27	0	0	0	0	0	0	25	0	0	0	0	0	0	22	0	1	0	1	0	0
71	33	0	2	0	2	0	0	27	0	1	0	1	0	0	25	0	2	0	2	0	0	21	0	0	0	0	0	0
72	31	0	1	0	1	0	0	26	0	0	0	0	0	0	23	0	0	0	0	0	0	21	0	0	0	0	0	0
73	30	0	1	0	1	0	0	26	0	0	0	0	0	0	23	0	0	0	0	0	0	21	0	1	0	1	0	0
74	29	0	1	0	1	0	0	26	0	0	0	0	0	0	23	1	1	0	2	0	0	20	0	1	0	1	0	0
75	28	0	0	0	0	0	0	26	0	0	0	0	0	0	21	0	0	0	0	0	0	19	1	0	0	1	0	0
76	28	1	0	0	1	0	0	26	0	1	0	1	0	0	21	0	0	0	0	0	0	18	0	0	0	0	0	0
77	27	0	1	0	1	0	0	25	0	0	0	0	0	0	21	1	0	0	1	0	0	18	0	0	0	0	0	0
78	26	2	0	12	14	0	0	25	0	0	12	12	0	0	20	1	1	12	14	0	0	18	1	0	12	13	0	0
79	12	0	0	12	12	0	0	13	0	0	13	13	0	0	6	0	0	6	6	0	0	5	0	0	5	5	0	0

E= number entering period D= deaths S= sacrificed T= terminal
N= necropsied completely NP= necropsied to some extent W= total autolysis

---------- SEX=F ----------

		DOSE GROUP			
		C	L	M	H
		N	N	N	N
ORGAN	TUMOR				
		37	26	18	15
Adrenal	Phaeochr	.	.	1	.
Hematopo	Hematopo	7	8	5	4
Lacrimal	Adenocar	.	.	.	1
	Adenoma	.	.	1	.
Liver	Hemangio	.	1	.	1
	Hepatic	.	1	2	.
	Hepatocy	1	.	.	.
Lung	Primary	3	6	6	7
Mammary	Adenocar	.	7	18	17
	Carcinos	.	.	1	.
	Fibroade	.	.	1	.
	Sarcoma	.	.	1	.
Ovary	Granulos	.	1	.	.
	Hemangio	1	.	1	.
Pituitar	Adenoma	1	2	13	21
Skin	Carcinom	.	.	1	.
Soft	Fibrosar	.	1	.	1
Uterus	Fibrolei	.	.	1	.
	Hemangio	.	1	1	1

(CONTINUED)

SEX=F

		DOSE GROUP			
		C	L	M	H
		N	N	N	N
ORGAN	TUMOR				
Uterus	Polyp	2	.	2	1

(CONTINUED)

SEX=F

		TOTAL
		N
ORGAN	TUMOR	
		96
Adrenal	Phaeochr	1
Hematopo	Hematopo	24
Lacrimal	Adenocar	1
	Adenoma	1
Liver	Hemangio	2
	Hepatic	3
	Hepatocy	1
Lung	Primary	22
Mammary	Adenocar	42
	Carcinos	1
	Fibroade	1
	Sarcoma	1
Ovary	Granulos	1
	Hemangio	2
Pituitar	Adenoma	37
Skin	Carcinom	1
Soft	Fibrosar	2
Uterus	Fibrolei	1
	Hemangio	3
	Polyp	5

SEX=M

		DOSE GROUP			
		C	L	M	H
		N	N	N	N
ORGAN	TUMOR				
		34	27	37	30
Bone	Sarcoma	1	.	.	.
Hematopo	Hematopo	1	1	1	.
Kidney	Adenocar	.	.	.	1
Lacrimal	Adenoma	.	.	.	1
Liver	Hemangio	.	.	1	1
	Hepatic	3	7	6	5
	Hepatocy	.	3	3	2
Lung	Primary	14	16	5	10
Pituitar	Adenoma	.	.	.	1
Seminal	Carcinos	.	.	.	1
Small	Adenocar	.	.	.	1
Testis	Leydig	.	1	.	.

(CONTINUED)

SEX=M

		TOTAL
		N
ORGAN	TUMOR	
		128
Bone	Sarcoma	1
Hematopo	Hematopo	3
Kidney	Adenocar	1
Lacrimal	Adenoma	1
Liver	Hemangio	2
	Hepatic	21
	Hepatocy	8
Lung	Primary	45
Pituitar	Adenoma	1
Seminal	Carcinos	1
Small	Adenocar	1
Testis	Leydig	1

JANSSEN PHARMACEUTICA NV
Department of toxicology
EXPERIMENT: 1928
Carcinogenicity study
R 64766 - FOOD - RAT - 24 MONTH

NDA 20-272

Chronological listing — MALES

Dosage group : Control

f (fatal)
c (could be fatal)
i (incidental)
p (probably incidental)

Week	Animal number	Death status	Organ	Tumor type	B (Benign) M (Malignant)	
64	24	D	Bone	Osteosarcoma	M	f
			Heart	Mesothelioma	B	i
76	37	S	Adrenal gland	Phaeochromocytoma, benign	B	i
82	16	S	Hematopoietic system	tumor, malignant	M	f
85	9	S	Soft tissue	Sarcoma	M	f
90	2	S	Pituitary gland	Adenoma	B	i
91	20	S	Pituitary gland	Adenoma	B	f
			Soft tissue	Fibrosarcoma	M	i
93	28	S	Soft tissue	Lipoma	B	f
97	40	D	Pancreas	Adenoma, endocrine	B	i
98	35	S	Hematopoietic system	tumor, malignant	M	f
98	36	S	Jaw	Carcinoma, squamous cell	M	f
			Pituitary gland	Adenoma	B	i
			Thyroid gland	Adenoma, "light cell" solid	B	i
101	22	S	Skin	Papilloma	B	i
			Testis	Leydig cell tumor, benign	B	i
102	48	S	Pituitary gland	Adenoma	B	c
			Liver	Hepatocytic carcinoma	M	p
105	50	D	Pancreas	Adenoma, exocrine	B	i
106	39	S	Testis	Leydig cell tumor, benign	B	i
			Pancreas	Adenoma, exocrine	B	i
			Nervous system	Meningioma	B	f
106	26	S	Pancreas	Adenoma, exocrine	B	i
			Pancreas	Adenoma, endocrine	B	i
107	49	S	Pituitary gland	Adenoma	B	c
			Adrenal gland	Phaeochromocytoma, benign	B	i
			Liver	Hepatic neoplastic nodule	B	i
108	4	S	Hematopoietic system	tumor, malignant	M	i
			Lymph node(s), mesenteric	Hemangioendothelioma	B	i
109	29	D	Pituitary gland	Adenoma	B	i
109	31	S	Thyroid gland	Adenoma, "light cell" solid	B	i
110	12	D	Lymph node(s), maxillary	Hemangioendothelioma	B	i
			Lymph node(s), mesenteric	Hemangioendothelioma	B	i
110	21	D	Testis	Leydig cell tumor, benign	B	i
110	6	S	Liver	Hepatic neoplastic nodule	B	i
			Pancreas	Adenoma, endocrine	B	i
111	3	T	Nervous system	Meningioma	B	
111	5	T	Pancreas	Adenoma, endocrine	B	
111	8	T	Thyroid gland	Adenoma	B	
111	10	T	Rectum	Adenocarcinoma	M	
			Pancreas	Adenoma, endocrine	B	
			Pancreas	Adenoma, exocrine	B	
			Pituitary gland	Adenoma	B	
			Thyroid gland	Adenoma	B	

JANSSEN PHARMACEUTICA NV
Department of toxicology
EXPERIMENT: 1928
Carcinogenicity study
R 64766 - FOOD - RAT - 24 MONTH

Chronological listing — MALES

Dosage group : Control

f (fatal)
c (could be fatal)
i (incidental)
p (probably incidental)

Week	Animal number	Death status	Organ	Tumor type	B (Benign) M (Malignant)
111	11	T	Thyroid gland	Adenoma	B
			Pancreas	Adenoma, exocrine	B
111	13	T	Pancreas	Adenoma, endocrine	B
			Pancreas	Adenoma, exocrine	B
111	14	T	Adrenal gland	Phaeochromocytoma, benign	B
			Pituitary gland	Adenoma	B
			Pancreas	Adenoma, endocrine	B
111	15	T	Pituitary gland	Adenoma	B
111	17	T	Testis	Leydig cell tumor, benign	B
			Liver	Hepatic neoplastic nodule	B
			Pituitary gland	Adenoma	B
111	18	T	Pancreas	Adenoma, exocrine	B
			Pancreas	Adenoma, endocrine	B
			Pituitary gland	Adenoma	B
111	19	T	Thyroid gland	Adenoma, "light cell" solid	B
			Epididymis	Mesothelioma	B
111	27	T	Pancreas	Adenoma, endocrine	B
111	30	T	Lymph node(s), mesenteric	Hemangioendothelioma	B
111	32	T	Pancreas	Adenoma, exocrine	B
			Skin	Papilloma	B
			Pituitary gland	Adenoma	B
111	33	T	Hematopoietic system	tumor, malignant	M
111	34	T	Liver	Hepatic neoplastic nodule	B
111	41	T	Lymph node(s), mesenteric	Hemangioendothelioma	B
111	42	T	Thyroid gland	Adenoma, "light cell" solid	B
			Skin	Papilloma	B
111	43	T	Lymph node(s), mesenteric	Hemangioendothelioma	B
111	44	T	Liver	Hepatic neoplastic nodule	B
			Lymph node(s), mesenteric	Hemangioendothelioma	B
			Pituitary gland	Adenoma	B
111	46	T	Pituitary gland	Adenoma	B
			Liver	Hepatic neoplastic nodule	B
			Pancreas	Adenoma, exocrine	B
111	47	T	Pancreas	Adenoma, exocrine	B

JANSSEN PHARMACEUTICA NV
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EXPERIMENT: 1928
Carcinogenicity study
R 64766 - FOOD - RAT - 24 MONTH

Chronological listing — MALES

Dosage group : R 64766 0.63 mg / kg

f (fatal)
c (could be fatal)
i (incidental)
p (probably incidental)

Week	Animal number	Death status	Organ	Tumor type	B (Benign) M (Malignant)	
31	96	S	Hematopoietic system	tumor, malignant	M	f
80	67	S	Pituitary gland	Adenoma	B	f
			Thyroid gland	Adenoma, "light cell" solid	B	i
81	100	S	Pituitary gland	Adenoma	B	f
95	98	S	Skin	Papilloma	B	i
95	85	S	Pancreas	Adenoma, exocrine	B	i
			Skin	Papilloma	B	i
97	58	D	Skin	Carcinoma, squamous cell	M	i
			Pituitary gland	Adenoma	B	p
97	54	D	Pancreas	Adenoma, exocrine	B	i
101	78	S	Pituitary gland	Adenoma	B	i
			Pancreas	Adenoma, exocrine	B	i
			Soft tissue	Sarcoma	M	f
			Adrenal gland	Phaeochromocytoma, benign	B	i
102	88	S	Soft tissue	Lipoma	B	i
			Pituitary gland	Adenoma	B	i
			Pancreas	Adenoma, endocrine	B	i
102	61	D	Mammary gland	Adenoma, Adenofibroma, Fibroadenoma	B	i
			Pituitary gland	Adenoma	B	i
			Pancreas	Adenoma, exocrine	B	i
104	66	S	Pituitary gland	Adenoma	B	i
			Adrenal gland	Phaeochromocytoma, benign	B	i
106	87	S	Skin	Papilloma	B	i
			Pituitary gland	Adenoma	B	f
			Pancreas	Adenoma, endocrine	B	i
106	91	S	Pituitary gland	Adenoma	B	p
			Liver	Hepatic neoplastic nodule	B	i
			Pancreas	Adenoma, endocrine	B	i
107	94	D	Skin	Papilloma	B	i
108	53	S	Adrenal gland	Phaeochromocytoma, benign	B	i
108	84	D	Pituitary gland	Adenoma	B	i
			Pancreas	Adenoma, exocrine	B	i
108	77	D	Kidney	Liposarcoma	M	p
109	65	D	Abdominal mesothelia	Mesothelial sarcoma	M	f
			Pancreas	Adenoma, exocrine	B	i
			Pituitary gland	Adenoma	B	i
			Adrenal gland	Phaeochromocytoma, benign	B	i
109	71	S	Mammary gland	Adenoma, Adenofibroma, Fibroadenoma	B	p
			Mammary gland	Fibroma	B	c
109	79	S	Mammary gland	Adenoma, Adenofibroma, Fibroadenoma	B	i
			Pituitary gland	Adenoma	B	f
109	55	S	Thyroid gland	Adenoma	B	i
			Kidney	Adenoma	B	i
111	51	T	Lymph node(s), mesenteric	Hemangioendothelioma	B	
			Thyroid gland	Adenoma, "light cell" solid	B	
			Pancreas	Adenoma, endocrine	B	

JANSSEN PHARMACEUTICA NV
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EXPERIMENT: 1928
Carcinogenicity study
R 64766 - FOOD - RAT - 24 MONTH

Chronological listing — MALES

Dosage group : R 64766 0.63 mg / kg

Week	Animal number	Death status	Organ	Tumor type	B (Benign) M (Malignant)
111	52	T	Liver	Hepatic neoplastic nodule	B
			Pancreas	Adenoma, endocrine	B
111	60	T	Pancreas	Adenoma, endocrine	B
			Pituitary gland	Adenoma	B
111	62	T	Soft tissue	Fibroma	B
			Adrenal gland	Phaeochromocytoma, benign	B
111	64	T	Pancreas	Adenoma, endocrine	B
111	68	T	Skin	Papilloma	B
			Pituitary gland	Adenoma	B
			Thyroid gland	Adenoma	B
111	70	T	Soft tissue	Fibroma	B
111	73	T	Ear	Papilloma	B
111	75	T	Thyroid gland	Adenoma	B
			Pancreas	Adenoma, endocrine	B
111	80	T	Lymph node(s), mesenteric	Hemangioendothelioma	B
			Liver	Hepatic neoplastic nodule	B
			Thyroid gland	Adenoma, "light cell" solid	B
111	81	T	Pituitary gland	Adenoma	B
111	86	T	Pituitary gland	Adenoma	B
			Pancreas	Adenoma, endocrine	B
			Adrenal gland	Phaeochromocytoma, benign	B
111	90	T	Thyroid gland	Adenoma	B
111	93	T	Pituitary gland	Adenoma	B
			Lymph node(s), mesenteric	Hemangioendothelioma	B
			Hematopoietic system	tumor, malignant	M
111	95	T	Pituitary gland	Adenoma	B
			Liver	Hepatic neoplastic nodule	B
111	97	T	Hematopoietic system	tumor, malignant	M
111	99	T	Soft tissue	Fibroma	B
			Pituitary gland	Adenoma	B
			Adrenal gland	Phaeochromocytoma, benign	B

f (fatal)
c (could be fatal)
i (incidental)
p (probably incidental)

JANSSEN PHARMACEUTICA NV
Department of toxicology
EXPERIMENT: 1928
Carcinogenicity study
R 64766 - FOOD - RAT - 24 MONTH

Chronological listing — MALES

Dosage group : R 64766 2.5 mg / kg

f (fatal)
c (could be fatal)
i (incidental)
p (probably incidental)

Week	Animal number	Death status	Organ	Tumor type	B (Benign) M (Malignant)	
18	135	S	Hematopoietic system	tumor, malignant	M	f
41	107	S	Hematopoietic system	tumor, malignant	M	f
71	148	D	Soft tissue	Lipoma	B	i
			Hematopoietic system	tumor, malignant	M	f
75	132	S	Pituitary gland	Adenoma	B	f
79	120	S	Rectum	Adenocarcinoma	M	f
			Pancreas	Adenoma, endocrine	B	i
81	119	D	Pituitary gland	Adenoma	B	c
86	101	D	Mammary gland	Adenoma, Adenofibroma, Fibroadenoma	B	i
87	106	D	Seminal vesicle	Fibrosarcoma	M	f
88	142	S	Soft tissue	Sarcoma	M	f
			Liver	Hepatic neoplastic nodule	B	i
			Adrenal gland	Phaeochromocytoma, benign	B	i
89	130	D	Pituitary gland	Adenoma	B	i
			Skin	Papilloma	B	i
90	111	S	Thyroid gland	Adenoma, "light cell" solid	B	i
95	138	S	Pancreas	Adenoma, endocrine	B	i
			Skin	Papilloma	B	i
95	147	S	Pancreas	Adenoma, endocrine	B	i
98	115	S	Kidney, pelvis	Carcinoma	M	f
			Pituitary gland	Adenoma	B	i
99	121	S	Pancreas	Adenoma, endocrine	B	i
99	117	S	Pancreas	Adenoma, endocrine	B	i
101	113	S	Liver	Hepatic neoplastic nodule	B	i
101	139	S	Soft tissue	Fibrosarcoma	M	f
			Pancreas	Adenoma, exocrine	B	i
101	129	S	Mammary gland	Adenoma, Adenofibroma, Fibroadenoma	B	i
			Pancreas	Adenoma, endocrine	B	i
101	133	S	Pituitary gland	Adenoma	B	i
			Pancreas	Adenoma, endocrine	B	i
			Adrenal gland	Phaeochromocytoma, benign	B	i
101	124	S	Pituitary gland	Adenoma	B	i
101	112	S	Liver	Hepatic neoplastic nodule	B	i
102	145	S	Mammary gland	Adenoma, Adenofibroma, Fibroadenoma	B	c
			Pancreas	Adenoma, endocrine	B	i
			Pancreas	Adenoma, exocrine	B	i
			Testis	Leydig cell tumor, benign	B	i
103	137	D	Pancreas	Adenoma, endocrine	B	i
104	141	S	Mammary gland	Adenoma, Adenofibroma, Fibroadenoma	B	p
			Mammary gland	Adenocarcinoma	M	p
			Soft tissue	Hemangiopericytoma, malignant	M	c
			Lymph node(s), mesenteric	Hemangioendothelioma	B	p
			Liver	Hepatic neoplastic nodule	B	i

JANSSEN PHARMACEUTICA NV
Department of toxicology
EXPERIMENT: 1926
Carcinogenicity study
R 64766 - FOOD - RAT - 24 MONTH

Chronological listing — MALES

Dosage group : R 64766 2.5 mg / kg

f (fatal)
c (could be fatal)
i (incidental)
p (probably incidental)

Week	Animal number	Death status	Organ	Tumor type	B (Benign) M (Malignant)	
104	150	S	Soft tissue	Fibroma	B	f
			Hematopoietic system	tumor, malignant	M	i
105	125	S	Soft tissue	Fibrosarcoma	M	f
			Pituitary gland	Adenoma	B	i
			Adrenal gland	Phaeochromocytoma, benign	B	i
108	104	D	Pancreas	Adenoma, endocrine	B	i
			Thyroid gland	Adenoma	B	i
111	103	T	Adrenal gland	Adenoma	B	
			Pituitary gland	Adenoma	B	
111	105	T	Mammary gland	Adenocarcinoma	M	
			Pituitary gland	Adenoma	B	
			Pancreas	Adenoma, endocrine	B	
111	108	T	Lymph node(s), mesenteric	Hemangioendothelioma	B	
111	114	T	Thyroid gland	Adenoma	B	
			Pancreas	Adenoma, exocrine	B	
			Testis	Leydig cell tumor, benign	B	
111	116	T	Mammary gland	Adenocarcinoma	M	
			Thyroid gland	Adenoma, "light cell" solid	B	
			Liver	Hepatic neoplastic nodule	B	
			Pancreas	Adenoma, endocrine	B	
			Pituitary gland	Adenoma	B	
111	127	T	Hematopoietic system	tumor, benign	B	
			Pancreas	Adenoma, endocrine	B	
111	131	T	Pituitary gland	Adenoma	B	
			Adrenal gland	Phaeochromocytoma, benign	B	
111	136	T	Liver	Hepatic neoplastic nodule	B	
			Pancreas	Adenoma, endocrine	B	
			Adrenal gland	Phaeochromocytoma, benign	B	
111	143	T	Pituitary gland	Adenoma	B	
111	144	T	Pituitary gland	Adenoma	B	
			Adrenal gland	Phaeochromocytoma, benign	B	

JANSSEN PHARMACEUTICA NV
Department of toxicology
EXPERIMENT: 1928
Carcinogenicity study
R 64766 - FOOD - RAT - 24 MONTH

Chronological listing — MALES

Dosage group : R 64766 10 mg / kg

f (fatal)
c (could be fatal)
i (incidental)
p (probably incidental)

Animal number	Death Week	status	Organ	Tumor type	B (Benign) M (Malignant)	
51	186	S	Ear	Carcinoma, squamous cell	M	f
79	176	S	Pancreas	Adenoma, endocrine	B	i
79	189	S	Mammary gland	Adenocarcinoma	M	f
92	156	S	Pituitary gland	Adenoma	B	i
			Soft tissue	Fibrosarcoma	M	f
			Liver	Hepatic neoplastic nodule	B	i
93	169	S	Mammary gland	Adenoma, Adenofibroma, Fibroadenoma	B	i
			Pituitary gland	Adenoma	B	i
			Mammary gland	Carcinoma	M	f
93	195	S	Soft tissue	Fibrosarcoma	M	f
94	192	D	Pituitary gland	Adenoma	B	c
94	190	S	Mammary gland	Carcinoma	M	f
95	168	S	Mammary gland	Adenocarcinoma	M	f
			Mammary gland	Adenoma, Adenofibroma, Fibroadenoma	B	i
			Pancreas	Adenoma, endocrine	B	i
95	191	S	Mammary gland	Adenocarcinoma	M	c
			Small intestine	Adenocarcinoma	M	p
95	188	S	Mammary gland	Adenocarcinoma	M	f
95	180	S	Mammary gland	Adenocarcinoma	M	f
96	160	D	Adrenal gland	Phaeochromocytoma, benign	B	i
97	193	D	Pituitary gland	Adenoma	B	i
			Mammary gland	Adenoma, Adenofibroma, Fibroadenoma	B	f
			Pancreas	Adenoma, endocrine	B	i
98	175	D	Pancreas	Adenoma, endocrine	B	i
			Pituitary gland	Adenoma	B	c
			Stomach	Papilloma, squamous cell	B	i
100	194	D	Pituitary gland	Adenoma	B	f
			Pancreas	Adenoma, endocrine	B	i
100	167	S	Pituitary gland	Adenoma	B	i
			Mammary gland	Adenocarcinoma	M	i
			Pancreas	Adenoma, endocrine	B	i
100	198	S	Testis	Leydig cell tumor, benign	B	i
101	182	S	Skin	Papilloma	B	i
			Pituitary gland	Adenoma	B	i
			Pancreas	Adenoma, endocrine	B	i
			Thyroid gland	Adenoma	B	i
101	184	S	Mammary gland	Adenocarcinoma	M	p
			Lymph node(s), mesenteric	Hemangioendothelioma	B	p
			Adrenal gland	Phaeochromocytoma, benign	B	i
101	163	S	Pancreas	Adenoma, exocrine	B	i
101	199	S	Pituitary gland	Adenoma	B	c
102	174	S	Mammary gland	Adenocarcinoma	M	i
			Liver	Hepatic neoplastic nodule	B	i

JANSSEN PHARMACEUTICA NV
Department of toxicology
EXPERIMENT: 1928
Carcinogenicity study
R 64766 - FOOD - RAT - 24 MONTH

Chronological listing — MALES

Dosage group : R 64766 10 mg / kg

Week	Animal number	Death status	Organ	Tumor type	B (Benign) M (Malignant)	f (fatal) c (could be fatal) i (incidental) p (probably incidental)
102	200	D	Pituitary gland	Adenoma	B	i
103	181	S	Pituitary gland	Adenoma	B	i
103	187	S	Pituitary gland	Adenoma	B	i
107	152	S	Mammary gland	Adenocarcinoma	M	f
			Adrenal gland	Phaeochromocytoma, benign	B	i
109	153	S	Pancreas	Adenoma, endocrine	B	i
110	155	D	Mammary gland	Adenocarcinoma	M	i
			Skin	Papilloma	B	i
			Thyroid gland	Adenoma	B	i
110	157	S	Pancreas	Adenoma, endocrine	B	i
111	151	T	Pancreas	Adenoma, endocrine	B	
			Adrenal gland	Phaeochromocytoma, benign	B	
111	161	T	Mammary gland	Adenocarcinoma	M	
			Pituitary gland	Adenoma	B	
			Thyroid gland	Adenoma	B	
			Adrenal gland	Phaeochromocytoma, benign	B	
			Pancreas	Adenoma, endocrine	B	
			Liver	Hepatic neoplastic nodule	B	
111	162	T	Lymph node(s), mesenteric	Hemangioendothelial sarcoma	M	
			Adrenal gland	Phaeochromocytoma, benign	B	
111	164	T	Pancreas	Adenoma, endocrine	B	
111	173	T	Pituitary gland	Adenoma	B	
			Thyroid gland	Adenoma, "light cell" solid	B	
111	177	T	Mammary gland	Fibroma	B	
			Pancreas	Adenoma, endocrine	B	
			Liver	Hepatic neoplastic nodule	B	
111	178	T	Mammary gland	Adenocarcinoma	M	
111	183	T	Mammary gland	Adenocarcinoma	M	
			Testis	Leydig cell tumor, benign	B	
			Pancreas	Adenoma, endocrine	B	
			Hematopoietic system	tumor, benign	B	

JANSSEN PHARMACEUTICA NV
Department of toxicology
EXPERIMENT: 1928
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R 64766 - FOOD - RAT - 24 MONTH

Chronological listing — FEMALES

Dosage group : Control

Week	Animal number	Death status	Organ	Tumor type	B (Benign) M (Malignant)	f (fatal) c (could be fatal) i (incidental) p (probably incidental)
52	222	S	Cervix	Sarcoma	M	f
53	243	S	Pituitary gland	Adenoma	B	f
			Uterus	Polyp	B	i
64	201	S	Pituitary gland	Adenoma	B	f
78	208	S	Kidney	Sarcoma	M	f
84	250	S	Hematopoietic system	tumor, malignant	M	f
85	236	S	Pituitary gland	Adenoma	B	f
85	238	S	Soft tissue	Lipoma	B	i
			Mammary gland	Adenoma, Fibroadenoma, Adenofibroma	B	f
			Pituitary gland	Adenoma	B	c
100	210	S	Mammary gland	Adenoma, Fibroadenoma, Adenofibroma	B	p
			Pituitary gland	Adenoma	B	f
100	226	S	Mammary gland	Fibroma	B	p
			Pituitary gland	Adenoma	B	c
			Vagina	Sarcoma	M	f
101	219	S	Thyroid gland	Adenocarcinoma	M	p
			Mammary gland	Adenoma, Fibroadenoma, Adenofibroma	B	i
			Hematopoietic system	tumor, malignant	M	f
101	239	S	Mammary gland	Adenocarcinoma	M	f
			Vagina	Sarcoma	M	i
			Pituitary gland	Adenoma	B	i
104	221	S	Mammary gland	Fibroma	B	p
			Uterus	Adenocarcinoma	M	f
104	217	S	Pituitary gland	Adenoma	B	f
105	235	S	Nose	Basal cell carcinoma	M	f
106	246	S	Pituitary gland	Adenoma	B	c
106	212	S	Pituitary gland	Adenoma	B	f
			Kidney	Adenocarcinoma	M	p
			Kidney	Adenoma	B	p
107	237	S	Pituitary gland	Adenoma	B	c
			Liver	Hepatic neoplastic nodule	B	i
107	202	S	Mammary gland	Adenoma, Fibroadenoma, Adenofibroma	B	p
			Pituitary gland	Adenoma	B	f
108	245	S	Mammary gland	Adenoma, Fibroadenoma, Adenofibroma	B	p
			Soft tissue	Lipoma	B	i
108	242	D	Liver	Hepatic neoplastic nodule	B	i
109	220	S	Pituitary gland	Adenoma	B	c
			Pancreas	Adenoma, endocrine	B	i
109	211	S	Mammary gland	Adenoma, Fibroadenoma, Adenofibroma	B	f
			Liver	Hepatic neoplastic nodule	B	i
110	215	S	Pituitary gland	Adenoma	B	f
			Mammary gland	Adenoma, Fibroadenoma, Adenofibroma	B	i
111	203	T	Pituitary gland	Adenoma	B	
			Uterus	Polyp	B	
			Pancreas	Adenoma, endocrine	B	

JANSSEN PHARMACEUTICA NV
Department of toxicology
EXPERIMENT: 1928
Carcinogenicity study
R 64766 - FOOD - RAT - 24 MONTH

Chronological listing — FEMALES

Dosage group : Control

f (fatal)
c (could be fatal)
i (incidental)
p (probably incidental)

Week	Animal number	Death status	Organ	Tumor type	B (Benign) M (Malignant)	
111	204	T	Pituitary gland	Adenoma	B	
111	205	T	Mammary gland	Adenoma, Fibroadenoma, Adenofibroma	B	
			Heart	Sarcoma	M	
111	207	T	Mammary gland	Adenoma, Fibroadenoma, Adenofibroma	B	
111	213	T	Pituitary gland	Adenoma	B	
			Mammary gland	Adenoma, Fibroadenoma, Adenofibroma	B	
			Liver	Hepatic neoplastic nodule	B	
			Pancreas	Adenoma, exocrine	B	
111	216	T	Pituitary gland	Adenoma	B	
			Uterus	Adenocarcinoma	M	
			Cervix	Adenocarcinoma	M	
111	218	T	Mammary gland	Adenoma, Fibroadenoma, Adenofibroma	B	
			Pituitary gland	Adenoma	B	
111	223	T	Pituitary gland	Adenoma	B	
			Mammary gland	Adenoma, Fibroadenoma, Adenofibroma	B	
			Lymph node(s)	Hemangioendothelioma	B	
			Liver	Hepatic neoplastic nodule	B	
111	224	T	Mammary gland	Fibroma	B	
			Mammary gland	Adenoma, Fibroadenoma, Adenofibroma	B	
			Mammary gland	Adenocarcinoma	M	
			Pituitary gland	Adenoma	B	
111	225	T	Pituitary gland	Adenoma	B	
			Cervix	Sarcoma	M	
			Thyroid gland	Adenoma, "light cell" solid	B	
111	227	T	Mammary gland	Adenoma, Fibroadenoma, Adenofibroma	B	
			Thyroid gland	Adenocarcinoma	M	
			Lymph node(s)	Hemangioendothelioma	B	
			Pancreas	Adenoma, endocrine	B	
			Ovary	Sertoli cell tumor, benign	B	
111	229	T	Mammary gland	Adenoma, Fibroadenoma, Adenofibroma	B	
111	230	T	Mammary gland	Adenoma, Fibroadenoma, Adenofibroma	B	
			Pancreas	Adenoma, exocrine	B	
			Liver	Hepatic neoplastic nodule	B	
			Pituitary gland	Adenoma	B	
			Thyroid gland	Adenoma, "light cell" solid	B	
111	231	T	Pituitary gland	Adenoma	B	
			Mammary gland	Adenocarcinoma	M	
111	232	T	Mammary gland	Fibroma	B	
			Adrenal gland	Phaeochromocytoma, benign	B	
111	233	T	Liver	Hepatic neoplastic nodule	B	
			Uterus	Polyp	B	
			Pituitary gland	Adenoma	B	
111	234	T	Mammary gland	Adenoma, Fibroadenoma, Adenofibroma	B	
			Pituitary gland	Adenoma	B	
111	240	T	Mammary gland	Adenoma, Fibroadenoma, Adenofibroma	B	
			Thyroid gland	Adenoma	B	
111	241	T	Uterus	Polyp	B	
111	244	T	Pituitary gland	Adenoma	B	

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EXPERIMENT: 1928
Carcinogenicity study
R 04766 - FOOD - RAT - 24 MONTH

Chronological listing — FEMALES

Dosage group : Control

f (fatal)
c (could be fatal)
i (incidental)
p (probably incidental)

Week	Animal number	Death status	Organ	Tumor type	B (Benign) M (Malignant)
111	247	T	Liver	Hepatocytic carcinoma	M
			Pituitary gland	Adenoma	B
111	248	T	Mammary gland	Adenoma, Fibroadenoma, Adenofibroma	B
111	249	T	Mammary gland	Adenoma, Fibroadenoma, Adenofibroma	B
			Pancreas	Adenoma, exocrine	B

JANSSEN PHARMACEUTICA NV
Department of toxicology
EXPERIMENT: 1928
Carcinogenicity study
R 64766 - FOOD - RAT - 24 MONTH

Chronological listing — FEMALES

Dosage group : R 64766 0.63 mg / kg

f (fatal)
c (could be fatal)
i (incidental)
p (probably incidental)

Week	Animal number	Death status	Organ	Tumor type	B (Benign) M (Malignant)	
65	266	S	Mammary gland	Fibroma	B	i
			Soft tissue	Fibroma	B	c
76	254	S	Mammary gland	Adenoma, Fibroadenoma, Adenofibroma	B	i
79	267	S	Ear	Papilloma	B	i
			Mammary gland	Adenoma, Fibroadenoma, Adenofibroma	B	f
			Mammary gland	Fibroma	B	i
83	289	S	Pituitary gland	Adenoma	B	c
			Mammary gland	Adenoma, Fibroadenoma, Adenofibroma	B	i
85	259	S	Mammary gland	Adenocarcinoma	M	f
			Pituitary gland	Adenoma	B	p
85	251	S	Pituitary gland	Adenoma	B	f
87	273	S	Ear	Carcinoma	M	f
87	258	S	Mammary gland	Adenoma, Fibroadenoma, Adenofibroma	B	f
			Pituitary gland	Adenoma	B	p
88	284	S	Thyroid gland	Adenoma	B	i
92	256	S	Mammary gland	Adenoma, Fibroadenoma, Adenofibroma	B	f
			Hematopoietic system	tumor, benign	B	p
			Adrenal gland	Phaeochromocytoma, benign	B	i
			Pancreas	Adenoma, exocrine	B	i
95	268	S	Mammary gland	Adenoma, Fibroadenoma, Adenofibroma	B	f
			Pancreas	Adenoma, endocrine	B	i
95	295	D	Pituitary gland	Adenoma	B	f
			Pancreas	Adenoma, endocrine	B	i
			Lymph node(s)	Hemangioendothelioma	B	i
99	276	S	Pituitary gland	Adenoma	B	f
100	286	S	Hematopoietic system	tumor, malignant	M	f
			Liver	Hepatic neoplastic nodule	B	i
			Pituitary gland	Adenoma	B	p
102	281	S	Pituitary gland	Adenoma	B	f
			Mammary gland	Adenoma, Fibroadenoma, Adenofibroma	B	i
			Liver	Hepatic neoplastic nodule	B	i
			Adrenal gland	Phaeochromocytoma, benign	B	i
			Adrenal gland	Adenoma	B	i
102	296	D	Pituitary gland	Adenoma	B	p
102	297	S	Mammary gland	Adenoma, Fibroadenoma, Adenofibroma	B	f
			Hematopoietic system	tumor, benign	B	i
			Hematopoietic system	tumor, malignant	M	p
103	285	S	Mammary gland	Adenocarcinoma	M	f
			Mammary gland	Adenoma, Fibroadenoma, Adenofibroma	B	p
105	261	S	Mammary gland	Adenocarcinoma	M	f
			Pituitary gland	Adenoma	B	p
			Pancreas	Adenocarcinoma, exocrine	M	i
			Thyroid gland	Adenoma, "light cell" solid	B	i
105	253	S	Mammary gland	Adenoma, Fibroadenoma, Adenofibroma	B	i
			Pituitary gland	Adenoma	B	f
			Pancreas	Adenoma, exocrine	B	i

JANSSEN PHARMACEUTICA NV
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EXPERIMENT: 1928
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R 64766 - FOOD - RAT - 24 MONTH

Chronological listing

FEMALES

Dosage group : R 64766 0.63 mg / kg

f (fatal)
c (could be fatal)
i (incidental)
p (probably incidental)

Week	Animal number	Death status	Organ	Tumor type	B (Benign) M (Malignant)	
109	269	S	Mammary gland	Adenocarcinoma	M	f
111	252	T	Mammary gland	Adenoma, Fibroadenoma, Adenofibroma	B	
			Pituitary gland	Adenoma	B	
			Hematopoietic system	tumor, benign	B	
111	255	T	Mammary gland	Adenoma, Fibroadenoma, Adenofibroma	B	
			Mammary gland	Adenocarcinoma	M	
			Adrenal gland	Phaeochromocytoma, malignant	M	
111	260	T	Ovary	Granulosa-theca cell tumor, benign	B	
111	262	T	Mammary gland	Adenoma, Fibroadenoma, Adenofibroma	B	
111	263	T	Mammary gland	Adenoma, Fibroadenoma, Adenofibroma	B	
			Liver	Hepatic neoplastic nodule	B	
			Pituitary gland	Adenoma	B	
111	264	T	Mammary gland	Adenocarcinoma	M	
			Pituitary gland	Adenoma	B	
111	265	T	Liver	Hepatic neoplastic nodule	B	
111	270	T	Pituitary gland	Adenoma	B	
111	271	T	Mammary gland	Adenocarcinoma	M	
			Adrenal gland	Phaeochromocytoma, benign	B	
			Cervix	Sarcoma	M	
			Pituitary gland	Adenoma	B	
111	272	T	Pituitary gland	Adenoma	B	
			Uterus	Polyp	B	
			Mammary gland	Adenocarcinoma	M	
			Pancreas	Adenoma, exocrine	B	
111	274	T	Pituitary gland	Adenoma	B	
			Mammary gland	Adenoma, Fibroadenoma, Adenofibroma	B	
111	277	T	Mammary gland	Adenoma, Fibroadenoma, Adenofibroma	B	
			Mammary gland	Adenocarcinoma	M	
			Lymph node(s)	Hemangioendothelioma	B	
111	278	T	Uterus	Polyp	B	
111	280	T	Mammary gland	Adenocarcinoma	M	
			Pituitary gland	Adenoma	B	
			Liver	Hepatic neoplastic nodule	B	
			Pancreas	Adenoma, exocrine	B	
			Pancreas	Adenoma, endocrine	B	
111	282	T	Hematopoietic system	tumor, malignant	M	
			Liver	Hepatic neoplastic nodule	B	
111	283	T	Mammary gland	Adenoma, Fibroadenoma, Adenofibroma	B	
			Thyroid gland	Adenoma, "light cell" solid	B	
111	288	T	Mammary gland	Adenocarcinoma	M	
			Liver	Hepatic neoplastic nodule	B	
111	290	T	Thyroid gland	Adenoma, "light cell" solid	B	
			Mammary gland	Adenoma, Fibroadenoma, Adenofibroma	B	
			Mammary gland	Adenocarcinoma	M	
			Mammary gland	Fibroma	B	
111	291	T	Mammary gland	Adenocarcinoma	M	

JANSSEN PHARMACEUTICA NV
Department of toxicology
EXPERIMENT: 1928
Carcinogenicity study
R 64766 - FOOD - RAT - 24 MONTH

Chronological listing — FEMALES

Dosage group : R 64766 0.63 mg / kg

f (fatal)
c (could be fatal)
i (incidental)
p (probably incidental)

Week	Animal number	Death status	Organ	Tumor type	B (Benign) M (Malignant)	
111	292	T	Mammary gland	Adenoma, Fibroadenoma, Adenofibroma	B	
			Uterus	Polyp	B	
111	293	T	Soft tissue	Hemangioendothelioma	B	
111	294	T	Pancreas	Adenoma, endocrine	B	
			Mammary gland	Adenoma, Fibroadenoma, Adenofibroma	B	
111	299	T	Mammary gland	Adenoma, Fibroadenoma, Adenofibroma	B	
111	300	T	Mammary gland	Adenocarcinoma	M	
			Pituitary gland	Adenoma	B	

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EXPERIMENT: 1928
Carcinogenicity study
R 64766 - FOOD - RAT - 24 MONTH

Chronological listing — FEMALES

Dosage group : R 64766 2.5 mg / kg

f (fatal)
c (could be fatal)
i (incidental)
p (probably incidental)

Week	Animal number	Death status	Organ	Tumor type	B (Benign) M (Malignant)	
78	309	S	Mammary gland	Adenoma, Fibroadenoma, Adenofibroma	B	f
			Pituitary gland	Adenoma	B	i
79	342	S	Pituitary gland	Adenoma	B	f
83	306	S	Pituitary gland	Adenoma	B	f
			Skin	Papilloma	B	i
86	346	S	Pituitary gland	Adenoma	B	f
			Mammary gland	Adenoma, Fibroadenoma, Adenofibroma	B	i
			Mammary gland	Adenocarcinoma	M	i
87	340	S	Mammary gland	Adenoma, Fibroadenoma, Adenofibroma	B	f
90	348	S	Pituitary gland	Adenoma	B	c
			Hematopoietic system	tumor, malignant	M	i
94	333	S	Pituitary gland	Adenoma	B	c
			Pancreas	Adenoma, endocrine	B	i
95	332	S	Mammary gland	Adenoma, Fibroadenoma, Adenofibroma	B	f
95	326	S	Mammary gland	Adenoma, Fibroadenoma, Adenofibroma	B	f
			Pituitary gland	Adenoma	B	i
96	305	S	Mammary gland	Adenocarcinoma	M	p
			Pituitary gland	Adenoma	B	f
			Hematopoietic system	tumor, malignant	M	i
98	339	S	Pituitary gland	Adenoma	B	f
			Mammary gland	Adenoma, Fibroadenoma, Adenofibroma	B	i
100	308	S	Pituitary gland	Adenoma	B	f
			Mammary gland	Adenoma, Fibroadenoma, Adenofibroma	B	c
100	347	S	Pituitary gland	Adenoma	B	f
100	319	S	Mammary gland	Adenocarcinoma	M	f
			Mammary gland	Adenoma, Fibroadenoma, Adenofibroma	B	i
			Pancreas	Adenoma, endocrine	B	i
102	345	S	Pituitary gland	Adenoma	B	p
			Mammary gland	Adenoma, Fibroadenoma, Adenofibroma	B	i
			Liver	Hepatic neoplastic nodule	B	i
			Hematopoietic system	tumor, malignant	M	f
104	334	S	Thyroid gland	Carcinoma, "light cell" solid	M	p
104	349	S	Mammary gland	Adenoma, Fibroadenoma, Adenofibroma	B	f
			Mammary gland	Adenocarcinoma	M	c
105	310	S	Pituitary gland	Adenoma	B	f
105	350	S	Pituitary gland	Adenoma	B	f
			Mammary gland	Adenoma, Fibroadenoma, Adenofibroma	B	i
106	302	S	Mammary gland	Adenoma, Fibroadenoma, Adenofibroma	B	f
			Pituitary gland	Adenoma	B	i
108	335	S	Pituitary gland	Adenoma	B	c
108	316	S	Salivary gland(s)	Carcinosarcoma	M	f
			Jaw	Carcinoma, squamous cell	M	c
			Pituitary gland	Adenoma	B	i
			Soft tissue	Lipoma	B	i

JANSSEN PHARMACEUTICA NV
Department of toxicology
EXPERIMENT: 1928
Carcinogenicity study
R 64766 - FOOD - RAT - 24 MONTH

Chronological listing — FEMALES

Dosage group : R 64766 2.5 mg / kg

f (fatal)
c (could be fatal)
i (incidental)
p (probably incidental)

Week	Animal number	Death status	Organ	Tumor type	B (Benign) M (Malignant)	
109	311	S	Pituitary gland	Adenoma	B	c
			Mammary gland	Adenoma, Fibroadenoma, Adenofibroma	B	i
109	315	S	Pituitary gland	Adenoma	B	i
			Mammary gland	Adenocarcinoma	M	f
			Vagina	Sarcoma	M	f
111	312	S	Mammary gland	Adenocarcinoma	M	p
			Mammary gland	Adenoma, Fibroadenoma, Adenofibroma	B	f
			Pituitary gland	Adenoma	B	i
			Pancreas	Adenoma, endocrine	B	i
111	301	T	Mammary gland	Adenoma, Fibroadenoma, Adenofibroma	B	
111	303	T	Mammary gland	Adenocarcinoma	M	
			Pituitary gland	Adenoma	B	
			Pancreas	Adenoma, endocrine	B	
111	304	T	Liver	Hepatic neoplastic nodule	B	
			Pituitary gland	Adenoma	B	
111	307	T	Mammary gland	Adenocarcinoma	M	
			Mammary gland	Adenoma, Fibroadenoma, Adenofibroma	B	
			Pituitary gland	Adenoma	B	
111	313	T	Mammary gland	Adenocarcinoma	M	
			Pituitary gland	Adenoma	B	
111	314	T	Pituitary gland	Adenoma	B	
			Urinary bladder	Papilloma, transitional cell	B	
111	317	T	Mammary gland	Adenoma, Fibroadenoma, Adenofibroma	B	
			Hematopoietic system	tumor, malignant	M	
			Liver	Hepatic neoplastic nodule	B	
111	318	T	Mammary gland	Adenoma, Fibroadenoma, Adenofibroma	B	
111	320	T	Mammary gland	Adenoma, Fibroadenoma, Adenofibroma	B	
111	321	T	Liver	Hepatic neoplastic nodule	B	
			Pituitary gland	Adenoma	B	
111	322	T	Mammary gland	Adenoma, Fibroadenoma, Adenofibroma	B	
			Pituitary gland	Adenoma	B	
111	323	T	Mammary gland	Adenoma, Fibroadenoma, Adenofibroma	B	
111	324	T	Mammary gland	Adenoma, Fibroadenoma, Adenofibroma	B	
			Mammary gland	Adenocarcinoma	M	
			Liver	Hepatic neoplastic nodule	B	
111	325	T	Mammary gland	Adenocarcinoma	M	
111	329	T	Mammary gland	Adenocarcinoma	M	
			Mammary gland	Adenoma, Fibroadenoma, Adenofibroma	B	
			Parathyroid gland	Adenoma	B	
111	330	T	Pituitary gland	Adenoma	B	
111	331	T	Mammary gland	Adenocarcinoma	M	
111	336	T	Mammary gland	Adenoma, Fibroadenoma, Adenofibroma	B	
			Pituitary gland	Adenoma	B	
111	337	T	Mammary gland	Adenoma, Fibroadenoma, Adenofibroma	B	
			Mammary gland	Adenocarcinoma	M	
			Pituitary gland	Adenoma	B	

JANSSEN PHARMACEUTICA NV
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R 64766 - FOOD - RAT - 24 MONTH

Chronological listing FEMALES

Dosage group : R 64766 2.5 mg / kg

f (fatal)
c (could be fatal)
i (incidental)
p (probably incidental)

Week	Animal number	Death status	Organ	Tumor type	B (Benign) M (Malignant)
111	343	T	Mammary gland	Adenocarcinoma	M
			Mammary gland	Adenoma, Fibroadenoma, Adenofibroma	B
			Liver	Hepatic neoplastic nodule	B
			Adrenal gland	Phaeochromocytoma, benign	B
			Lymph node(s)	Hemangioendothelioma	B
111	344	T	Mammary gland	Adenoma, Fibroadenoma, Adenofibroma	B
			Mammary gland	Adenocarcinoma	M

JANSSEN PHARMACEUTICA NV
Department of toxicology
EXPERIMENT: 1928
Carcinogenicity study
R 64766 - FOOD - RAT - 24 MONTH

Chronological listing — FEMALES

Dosage group : R 64766 10 mg / kg

f (fatal)
c (could be fatal)
i (incidental)
p (probably incidental)

Week	Animal number	Death status	Organ	Tumor type	B (Benign) M (Malignant)	
43	362	S	Pituitary gland	Adenoma	B	f
			Kidney	Adenoma	B	i
56	384	S	Hematopoietic system	tumor, malignant	M	f
73	375	S	Mammary gland	Adenocarcinoma	M	f
84	385	D	Pituitary gland	Adenoma	B	f
			Mammary gland	Adenoma, Fibroadenoma, Adenofibroma	B	i
			Cervix	Sarcoma	M	i
86	368	S	Pituitary gland	Adenoma	B	c
86	357	S	Pituitary gland	Adenoma	B	f
86	382	S	Mammary gland	Adenocarcinoma	M	f
			Pituitary gland	Adenoma	B	c
86	399	D	Pituitary gland	Adenoma	B	i
			Liver	Hepatic neoplastic nodule	B	i
			Adrenal gland	Phaeochromocytoma, benign	B	i
88	376	D	Pituitary gland	Adenoma	B	f
91	351	S	Pituitary gland	Adenoma	B	c
			Mammary gland	Adenocarcinoma	M	f
93	379	D	Pancreas	Adenoma, endocrine	B	i
93	369	D	Hematopoietic system	tumor, malignant	M	f
94	398	S	Mammary gland	Adenoma, Fibroadenoma, Adenofibroma	B	c
			Mammary gland	Adenocarcinoma	M	i
			Pituitary gland	Adenoma	B	i
94	383	S	Pituitary gland	Adenoma	B	c
95	352	S	Pituitary gland	Adenoma	B	f
95	378	S	Pituitary gland	Adenoma	B	c
			Mammary gland	Adenoma, Fibroadenoma, Adenofibroma	B	p
			Mammary gland	Adenocarcinoma	M	i
			Soft tissue	Fibrosarcoma	M	c
			Hematopoietic system	tumor, benign	B	p
98	353	S	Pituitary gland	Adenoma	B	f
99	363	S	Pituitary gland	Adenoma	B	i
100	355	S	Mammary gland	Adenocarcinoma	M	f
100	388	S	Mammary gland	Adenoma, Fibroadenoma, Adenofibroma	B	f
			Liver	Hepatic neoplastic nodule	B	i
103	361	S	Mammary gland	Adenoma, Fibroadenoma, Adenofibroma	B	f
			Mammary gland	Adenocarcinoma	M	c
103	391	S	Mammary gland	Adenoma, Fibroadenoma, Adenofibroma	B	f
104	377	S	Mammary gland	Adenoma, Fibroadenoma, Adenofibroma	B	i
104	371	S	Mammary gland	Adenoma, Fibroadenoma, Adenofibroma	B	c
			Pituitary gland	Adenoma	B	c
104	364	S	Pituitary gland	Adenoma	B	i

JANSSEN PHARMACEUTICA NV
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Carcinogenicity study
R 64766 - FOOD - RAT - 24 MONTH

Chronological listing — FEMALES

Dosage group : R 64766 10 mg / kg

f (fatal)
c (could be fatal)
i (incidental)
p (probably incidental)

Week	Animal number	Death status	Organ	Tumor type	B (Benign) M (Malignant)	
104	366	S	Pituitary gland	Adenoma	B	f
			Mammary gland	Adenoma, Fibroadenoma, Adenofibroma	B	i
109	373	S	Pituitary gland	Adenoma	B	c
110	380	S	Pituitary gland	Adenoma	B	c
110	394	S	Pituitary gland	Adenoma	B	i
			Mammary gland	Adenocarcinoma	M	f
			Hematopoietic system	tumor, malignant	M	i
			Ovary	Sertoli cell tumor, benign	B	i
111	354	T	Pituitary gland	Adenoma	B	
111	358	T	Mammary gland	Adenoma, Fibroadenoma, Adenofibroma	B	
			Thyroid gland	Adenocarcinoma	M	
			Pituitary gland	Adenoma	B	
111	359	T	Mammary gland	Adenoma, Fibroadenoma, Adenofibroma	B	
			Mammary gland	Adenocarcinoma	M	
111	360	T	Pituitary gland	Adenoma	B	
			Liver	Hepatic neoplastic nodule	B	
111	367	T	Mammary gland	Adenocarcinoma	M	
			Skin	Papilloma	B	
111	370	T	Pituitary gland	Adenoma	B	
			Adrenal gland	Phaeochromocytoma, benign	B	
111	372	T	Mammary gland	Adenocarcinoma	M	
111	389	T	Mammary gland	Adenoma, Fibroadenoma, Adenofibroma	B	
			Liver	Hepatic neoplastic nodule	B	
			Kidney	Adenoma	B	
111	390	T	Hematopoietic system	tumor, benign	B	
			Pituitary gland	Adenoma	B	
			Thyroid gland	Adenoma, "light cell" solid	B	
111	392	T	Mammary gland	Adenocarcinoma	M	
			Liver	Hepatic neoplastic nodule	B	
111	393	T	Adrenal gland	Phaeochromocytoma, benign	B	
			Adrenal gland	Ganglioneuroma	B	
111	395	T	Pituitary gland	Adenoma	B	
			Mammary gland	Adenoma, Fibroadenoma, Adenofibroma	B	
			Pancreas	Adenoma, endocrine	B	
111	396	T	Pituitary gland	Adenoma	B	
			Mammary gland	Adenoma, Fibroadenoma, Adenofibroma	B	
			Pancreas	Adenoma, endocrine	B	
111	397	T	Mammary gland	Adenocarcinoma	M	
			Mammary gland	Adenoma, Fibroadenoma, Adenofibroma	B	
			Pituitary gland	Adenoma	B	
			Thyroid gland	Adenoma	B	
			Hematopoietic system	tumor, malignant	M	
111	400	T	Pituitary gland	Adenoma	B	
			Liver	Hepatic neoplastic nodule	B	

JANSSEN PHARMACEUTICA NV
Department of toxicology
EXPERIMENT: 1928
Carcinogenicity study
R 64766 - FOOD - RAT - 24 MONTH

Summary of animal deaths and sacrifices — MALES

	Control							0.63 mg							2.5 mg							10 mg						
Week	E	D	S	T	N	MP	M	E	D	S	T	N	MP	M	E	D	S	T	N	MP	M	E	D	S	T	N	MP	M
18	50	0	0	0	0	0	0	50	0	0	0	0	0	0	50	0	1	0	1	0	0	50	0	0	0	0	0	0
31	50	0	0	0	0	0	0	50	0	1	0	1	0	0	49	0	0	0	0	0	0	50	0	0	0	0	0	0
32	50	0	0	0	0	0	0	49	0	0	0	0	0	0	49	0	0	0	0	0	0	50	1	0	0	0	0	1
39	50	1	0	0	1	0	0	49	0	0	0	0	0	0	49	0	0	0	0	0	0	49	0	0	0	0	0	0
41	49	0	0	0	0	0	0	49	0	0	0	0	0	0	49	0	1	0	1	0	0	49	0	0	0	0	0	0
51	49	0	0	0	0	0	0	49	0	0	0	0	0	0	48	0	0	0	0	0	0	49	0	1	0	1	0	0
58	49	0	0	0	0	0	0	49	0	1	0	1	0	0	48	0	0	0	0	0	0	48	0	0	0	0	0	0
60	49	0	0	0	0	0	0	48	0	1	0	1	0	0	48	0	0	0	0	0	0	48	0	0	0	0	0	0
64	49	1	0	0	1	0	0	47	0	0	0	0	0	0	48	1	0	0	1	0	0	48	0	0	0	0	0	0
70	48	0	0	0	0	0	0	47	0	0	0	0	0	0	47	0	0	0	0	0	0	48	1	0	0	1	0	0
71	48	0	0	0	0	0	0	47	0	0	0	0	0	0	47	1	0	0	1	0	0	47	0	0	0	0	0	0
72	48	0	0	0	0	0	0	47	0	0	0	0	0	0	46	0	1	0	1	0	0	47	0	0	0	0	0	0
73	48	0	0	0	0	0	0	47	0	0	0	0	0	0	45	1	0	0	1	0	0	47	0	0	0	0	0	0
75	48	0	0	0	0	0	0	47	0	0	0	0	0	0	44	0	1	0	1	0	0	47	1	0	0	1	0	0
76	48	0	1	0	1	0	0	47	0	0	0	0	0	0	43	0	0	0	0	0	0	46	0	1	0	1	0	0
77	47	0	0	0	0	0	0	47	1	0	0	1	0	0	43	0	0	0	0	0	0	45	0	0	0	0	0	0
79	47	0	0	0	0	0	0	46	0	0	0	0	0	0	43	0	2	0	2	0	0	45	0	2	0	2	0	0
80	47	0	0	0	0	0	0	46	0	1	0	1	0	0	41	0	0	0	0	0	0	43	0	0	0	0	0	0
81	47	0	0	0	0	0	0	45	0	1	0	1	0	0	41	1	0	0	1	0	0	43	0	0	0	0	0	0
82	47	0	1	0	1	0	0	44	0	0	0	0	0	0	40	0	0	0	0	0	0	43	0	0	0	0	0	0
83	46	0	0	0	0	0	0	44	0	0	0	0	0	0	40	0	1	0	1	0	0	43	0	0	0	0	0	0
84	46	0	0	0	0	0	0	44	0	0	0	0	0	0	39	1	0	0	1	0	0	43	0	0	0	0	0	0
85	46	0	1	0	1	0	0	44	0	0	0	0	0	0	38	0	0	0	0	0	0	43	0	0	0	0	0	0
86	45	0	0	0	0	0	0	44	0	0	0	0	0	0	38	1	0	0	1	0	0	43	0	0	0	0	0	0
87	45	0	0	0	0	0	0	44	0	0	0	0	0	0	37	1	0	0	1	0	0	43	0	0	0	0	0	0
88	45	0	0	0	0	0	0	44	0	0	0	0	0	0	36	0	1	0	1	0	0	43	0	0	0	0	0	0
89	45	0	0	0	0	0	0	44	0	0	0	0	0	0	35	1	0	0	1	0	0	43	0	0	0	0	0	0
90	45	0	1	0	1	0	0	44	0	0	0	0	0	0	34	0	1	0	1	0	0	43	0	0	0	0	0	0
91	44	0	1	0	1	0	0	44	0	0	0	0	0	0	33	0	0	0	0	0	0	43	0	0	0	0	0	0
92	43	0	0	0	0	0	0	44	0	1	0	1	0	0	33	1	0	0	1	0	0	43	1	1	0	2	0	0
93	43	0	1	0	1	0	0	43	0	0	0	0	0	0	32	0	0	0	0	0	0	41	0	2	0	2	0	0
94	42	0	1	0	1	0	0	43	0	0	0	0	0	0	32	0	1	0	1	0	0	39	1	1	0	2	0	0
95	41	0	0	0	0	0	0	43	0	2	0	2	0	0	31	0	2	0	2	0	0	37	0	4	0	4	0	0
96	41	0	0	0	0	0	0	41	0	0	0	0	0	0	29	0	0	0	0	0	0	33	1	0	0	1	0	0
97	41	1	0	0	1	0	0	41	2	0	0	2	0	0	29	0	0	0	0	0	0	32	1	0	0	1	0	0
98	40	0	2	0	2	0	0	39	0	0	0	0	0	0	29	0	1	0	1	0	0	31	1	0	0	1	0	0
99	38	0	0	0	0	0	0	39	0	0	0	0	0	0	28	1	2	0	3	0	0	30	1	0	0	1	0	0
100	38	0	0	0	0	0	0	39	0	0	0	0	0	0	25	0	0	0	0	0	0	29	1	2	0	3	0	0
101	38	0	1	0	1	0	0	39	0	2	0	2	0	0	25	0	8	0	8	0	0	26	0	5	0	5	0	0
102	37	0	1	0	1	0	0	37	1	1	0	2	0	0	17	0	1	0	1	0	0	21	1	1	0	2	0	0
103	36	0	0	0	0	0	0	35	0	0	0	0	0	0	16	1	0	0	1	0	0	19	0	2	0	2	0	0
104	36	0	0	0	0	0	0	35	0	1	0	1	0	0	15	0	2	0	2	0	0	17	0	0	0	0	0	0
105	36	1	0	0	1	0	0	34	0	1	0	1	0	0	13	0	1	0	1	0	0	17	0	0	0	0	0	0
106	35	0	2	0	2	0	0	33	0	3	0	3	0	0	12	0	0	0	0	0	0	17	0	0	0	0	0	0
107	33	0	1	0	1	0	0	30	1	0	0	1	0	0	12	0	0	0	0	0	0	17	0	1	0	1	0	0
108	32	0	1	0	1	0	0	29	2	1	0	3	0	0	12	1	0	0	1	0	0	16	0	0	0	0	0	0
109	31	1	1	0	2	0	0	26	1	3	0	4	0	0	11	0	0	0	0	0	0	16	0	1	0	1	0	0
110	29	2	1	0	3	0	0	22	1	0	0	1	0	0	11	0	0	0	0	0	0	15	1	1	0	2	0	0
111	26	0	0	26	26	0	0	21	0	0	21	21	0	0	11	0	0	11	11	0	0	13	0	0	13	13	0	0

E= number entering period D= deaths S= sacrificed T= terminal
N= necropsied completely MP= necropsied to some extent M= total autolysis

JANSSEN PHARMACEUTICA NV
Department of toxicology
EXPERIMENT: 1928
Carcinogenicity study
R 64766 - FOOD - RAT - 24 MONTH

Summary of animal deaths and sacrifices — FEMALES

	Control							0.63 mg							2.5 mg							10 mg						
Week	E	D	S	T	N	NP	W	E	D	S	T	N	NP	W	E	D	S	T	N	NP	W	E	D	S	T	N	NP	W
13	50	0	0	0	0	0	0	50	0	0	0	0	0	0	50	1	0	0	1	0	0	50	0	0	0	0	0	0
43	50	0	0	0	0	0	0	50	0	0	0	0	0	0	49	0	0	0	0	0	0	50	0	1	0	1	0	0
52	50	0	1	0	1	0	0	50	0	0	0	0	0	0	49	0	0	0	0	0	0	49	0	0	0	0	0	0
53	49	1	1	0	1	1	0	50	0	0	0	0	0	0	49	0	0	0	0	0	0	49	0	0	0	0	0	0
56	47	0	0	0	0	0	0	50	0	0	0	0	0	0	49	0	0	0	0	0	0	49	0	1	0	1	0	0
62	47	0	0	0	0	0	0	50	0	0	0	0	0	0	49	0	0	0	0	0	0	48	1	0	0	1	0	0
64	47	0	1	0	1	0	0	50	0	0	0	0	0	0	49	0	0	0	0	0	0	47	0	0	0	0	0	0
65	46	0	0	0	0	0	0	50	0	1	0	1	0	0	49	0	0	0	0	0	0	47	0	0	0	0	0	0
73	46	0	0	0	0	0	0	49	0	0	0	0	0	0	49	0	0	0	0	0	0	47	0	1	0	1	0	0
76	46	0	0	0	0	0	0	49	0	1	0	1	0	0	49	0	0	0	0	0	0	46	0	0	0	0	0	0
78	46	0	1	0	1	0	0	48	0	0	0	0	0	0	49	0	1	0	1	0	0	46	0	0	0	0	0	0
79	45	0	0	0	0	0	0	48	0	1	0	1	0	0	48	0	1	0	1	0	0	46	0	0	0	0	0	0
83	45	0	0	0	0	0	0	47	0	1	0	1	0	0	47	0	1	0	1	0	0	46	0	0	0	0	0	0
84	45	0	1	0	1	0	0	46	0	0	0	0	0	0	46	0	0	0	0	0	0	46	1	0	0	1	0	0
85	44	0	2	0	2	0	0	46	0	2	0	2	0	0	46	0	0	0	0	0	0	45	0	0	0	0	0	0
86	42	0	0	0	0	0	0	44	0	0	0	0	0	0	46	0	1	0	1	0	0	45	1	3	0	4	0	0
87	42	0	0	0	0	0	0	44	0	2	0	2	0	0	45	0	1	0	1	0	0	41	0	0	0	0	0	0
88	42	0	0	0	0	0	0	42	0	1	0	1	0	0	44	1	0	0	1	0	0	41	1	0	0	1	0	0
90	42	0	0	0	0	0	0	41	0	0	0	0	0	0	43	0	1	0	1	0	0	40	0	0	0	0	0	0
91	42	0	0	0	0	0	0	41	0	0	0	0	0	0	42	0	0	0	0	0	0	40	0	1	0	1	0	0
92	42	0	0	0	0	0	0	41	0	1	0	1	0	0	42	0	0	0	0	0	0	39	0	0	0	0	0	0
93	42	0	0	0	0	0	0	40	0	0	0	0	0	0	42	0	0	0	0	0	0	39	2	0	0	2	0	0
94	42	0	0	0	0	0	0	40	0	0	0	0	0	0	42	0	1	0	1	0	0	37	0	2	0	2	0	0
95	42	0	0	0	0	0	0	40	1	1	0	2	0	0	41	0	2	0	2	0	0	35	0	2	0	2	0	0
96	42	0	0	0	0	0	0	38	0	0	0	0	0	0	39	0	1	0	1	0	0	33	0	0	0	0	0	0
98	42	0	0	0	0	0	0	38	0	0	0	0	0	0	38	0	1	0	1	0	0	33	0	1	0	1	0	0
99	42	0	0	0	0	0	0	38	0	1	0	1	0	0	37	0	0	0	0	0	0	32	0	1	0	1	0	0
100	42	0	2	0	2	0	0	37	0	1	0	1	0	0	37	0	3	0	3	0	0	31	0	2	0	2	0	0
101	40	0	2	0	2	0	0	36	0	0	0	0	0	0	34	0	0	0	0	0	0	29	0	0	0	0	0	0
102	38	0	0	0	0	0	0	36	1	2	0	3	0	0	34	0	1	0	1	0	0	29	0	0	0	0	[illegible]	0
103	38	0	0	0	0	0	0	33	0	1	0	1	0	0	33	0	0	0	0	0	0	29	0	2	0	2		0
104	38	0	2	0	2	0	0	32	0	0	0	0	0	0	33	0	2	0	2	0	0	27	0	4	0	4	0	0
105	36	0	1	0	1	0	0	32	0	2	0	2	0	0	31	0	2	0	2	0	0	23	0	0	0	0	0	0
106	35	0	2	0	2	0	0	30	0	0	0	0	0	0	29	0	1	0	1	0	0	23	0	0	0	0	0	0
107	33	0	2	0	2	0	0	30	0	0	0	0	0	0	28	0	0	0	0	0	0	23	0	0	0	0	0	0
108	31	1	2	0	3	0	0	30	0	0	0	0	0	0	28	0	2	0	2	0	0	23	0	0	0	0	0	0
109	28	0	2	0	2	0	0	30	0	1	0	1	0	0	26	0	2	0	2	0	0	23	0	1	0	1	0	0
110	26	0	1	0	1	0	0	29	0	0	0	0	0	0	24	0	0	0	0	0	0	22	0	2	0	2	0	0
111	25	0	0	25	25	0	0	29	0	0	29	29	0	0	24	0	1	23	24	0	0	20	0	0	20	20	0	0

E= number entering period D= deaths S= sacrificed T= terminal
N= necropsied completely NP= necropsied to some extent W= total autolysis

SEX=F

		DOSE GROUP			
		C	L	M	H
		N	N	N	N
ORGAN	TUMOR				
		4	5	4	6
Adrenal	Adenoma	.	1	.	.
	Ganglion	.	.	.	1
	Phaeochr	1	4	1	3
Cervix	Adenocar	1	.	.	.
	Sarcoma	2	1	.	1
Ear	Carcinom	.	1	.	.
	Papillom	.	1	.	.
Heart	Sarcoma	1	.	.	.
Hematopo	Hematopo	2	5	4	6
Jaw	Carcinom	.	.	1	.
Kidney	Adenocar	1	.	.	.
	Adenoma	.	.	.	1
	Polyp	1	.	.	1
	Sarcoma	1	.	.	.
Liver	Hepatic	7	7	6	6
	Hepatocy	1	.	.	.
Lymph	Hemangio	2	2	1	.
Mammary	Adenocar	3	14	16	13
	Adenoma	20	21	27	15

(CONTINUED)

SEX=F

		DOSE GROUP			
		C	L	M	H
		N	N	N	N
ORGAN	TUMOR				
Mammary	Fibroma	4	3	.	.
Nose	Basal	1	.	.	.
Ovary	Granulos	.	1	.	.
	Sertoli	1	.	.	1
Pancreas	Adenocar	.	1	.	.
	Adenoma,	6	7	4	3
Parathyr	Adenoma	.	.	1	.
Pituitar	Adenoma	28	20	30	29
Salivary	Carcinos	.	.	1	.
Skin	Papillom	.	.	1	1
Soft	Fibroma	.	1	.	.
	Fibrosar	.	.	.	1
	Hemangio	.	1	.	.
	Lipoma	2	.	1	.
Thyroid	Adenocar	2	.	.	1
	Adenoma	1	1	.	1
	Adenoma,	2	3	.	1
	Carcinom	.	.	1	.
Urinary	Papillom	.	.	1	.
Uterus	Adenocar	2	.	.	.

(CONTINUED)

SEX=F

		DOSE GROUP			
		C	L	M	H
		N	N	N	N
ORGAN	TUMOR				
Uterus	Polyp	4	3	.	.
Vagina	Sarcoma	2	.	1	.

(CONTINUED)

SEX=F

		TOTAL
		N
ORGAN	TUMOR	
		19
Adrenal	Adenoma	1
	Ganglion	1
	Phaeochr	9
Cervix	Adenocar	1
	Sarcoma	4
Ear	Carcinom	1
	Papillom	1
Heart	Sarcoma	1
Hematopo	Hematopo	17
Jaw	Carcinom	1
Kidney	Adenocar	1
	Adenoma	1
	Polyp	2
	Sarcoma	1
Liver	Hepatic	26
	Hepatocy	1
Lymph	Hemangio	5
Mammary	Adenocar	46
	Adenoma	83
	Fibroma	7

(CONTINUED)

SEX=F

		TOTAL
		N
ORGAN	TUMOR	
Nose	Basal	1
Ovary	Granulos	1
	Sertoli	2
Pancreas	Adenocar	1
	Adenoma,	20
Parathyr	Adenoma	1
Pituitar	Adenoma	107
Salivary	Carcinos	1
Skin	Papillom	2
Soft	Fibroma	1
	Fibrosar	1
	Hemangio	1
	Lipoma	3
Thyroid	Adenocar	3
	Adenoma	3
	Adenoma,	6
	Carcinom	1
Urinary	Papillom	1
Uterus	Adenocar	2
	Polyp	7
Vagina	Sarcoma	3

SEX=M

		DOSE GROUP			
		C	L	M	H
		N	N	N	N
ORGAN	TUMOR				
		6	12	12	12
Abdomina	Mesothel	.	1	.	.
Adrenal	Adenoma	.	.	1	.
	Phaeochr	3	7	6	6
Bone	Osteosar	1	.	.	.
Ear	Carcinom	.	.	.	1
	Papillom	.	1	.	.
Epididym	Mesothel	1	.	.	.
Heart	Mesothel	1	.	.	.
Hematopo	Hematopo	4	3	5	1
Jaw	Carcinom	1	.	.	.
Kidney	Adenoma	.	1	.	.
	Carcinom	.	.	1	.
	Liposarc	.	1	.	.
Liver	Hepatic	6	4	6	4
	Hepatocy	1	.	.	.
Lymph	Hemangio	6	3	2	2
Mammary	Adenocar	.	.	3	13
	Adenoma	.	3	4	3
	Carcinom	.	.	.	2

(CONTINUED)

SEX=M

		DOSE GROUP			
		C	L	M	H
		N	N	N	N
ORGAN	TUMOR				
Mammary	Fibroma	.	1	.	1
Nervous	Meningio	2	.	.	.
Pancreas	Adenoma,	15	15	16	15
Pituitar	Adenoma	14	19	13	14
Rectum	Adenocar	1	.	1	.
Seminal	Fibrosar	.	.	1	.
Skin	Carcinom	.	1	.	.
	Papillom	3	5	2	2
Small	Adenocar	.	.	.	1
Soft	Fibroma	.	3	1	.
	Fibrosar	1	.	2	2
	Hemangio	.	.	1	.
	Lipoma	1	1	1	.
	Sarcoma	1	1	1	.
Stomach	Papillom	.	.	.	1
Testis	Leydig	4	.	2	2
Thyroid	Adenoma	3	4	2	3
	Adenoma,	4	3	2	1

(CONTINUED)

SEX=M

		TOTAL
		N
ORGAN	TUMOR	
		42
Abdomina	Mesothel	1
Adrenal	Adenoma	1
	Phaeochr	22
Bone	Osteosar	1
Ear	Carcinom	1
	Papillom	1
Epididym	Mesothel	1
Heart	Mesothel	1
Hematopo	Hematopo	13
Jaw	Carcinom	1
Kidney	Adenoma	1
	Carcinom	1
	Liposarc	1
Liver	Hepatic	20
	Hepatocy	1
Lymph	Hemangio	13
Mammary	Adenocar	16
	Adenoma	10
	Carcinom	2
	Fibroma	2

(CONTINUED)

SEX=M

		TOTAL
		N
ORGAN	TUMOR	
Nervous	Meningio	2
Pancreas	Adenoma,	61
Pituitar	Adenoma	60
Rectum	Adenocar	2
Seminal	Fibrosar	1
Skin	Carcinom	1
	Papillom	12
Small	Adenocar	1
Soft	Fibroma	4
	Fibrosar	5
	Hemangio	1
	Lipoma	3
	Sarcoma	3
Stomach	Papillom	1
Testis	Leydig	8
Thyroid	Adenoma	12
	Adenoma,	10

Statistical Review and Evaluation

NDA#: 20-272/Class 1-P

Applicant: Janssen Research Foundation

Name of Drug: Risperidal (risperidone) tablets

Documents Reviewed: Vols 1.110, 1.117, 1.134, received 4/15/1992

Medical Officer: Andrew Mosholder, M.D., HFD-120

Background

The sponsor has submitted 3 randomized, controlled, double-blind, multicenter trials (201: 6 weeks, 204: 8 weeks, 024: 8 weeks) in support of risperidone as a safe and effective treatment for schizophrenia. Trials 201 and 204 are placebo controlled, while 024 is a foreign dose-ranging study with 1 mg risperidone as the lowest dose.

This review summarizes the results of these trials with respect to four clinical endpoints which measured change from baseline: 1) Total BPRS (Brief Psychiatric Rating Scale), 2) the following 'Key' subset of the BPRS scales: hallucinatory behavior, conceptual disorganization, suspiciousness and unusual thought content, 3) negative symptoms (Total SANS in 201 and Total negative PANSS in 204, 024), and 4) clinical global impression of severity (CGI).

In addition, the results for BPRS and its Key subset are illustrated using time-to-event techniques. These estimate the duration of 'response', defined in terms of risperidone patients' performance relative to the natural course of the illness (estimated by the experience of placebo patients) over the length of the studies. 'Non-responders' are also examined.

Summary of Studies

Patient Numbers and Drop outs

Table 1 displays the number of patients randomized to each treatment for each study, together with the number of observed patients at each time point. In study 201, patients could be titrated up to 10 mg risperidone and 20 mg haloperidol during the first two weeks. In studies 204 and 024, patients were titrated up to their assigned dose group during the first week.

Table 2 and Figures 1 to 3 illustrate the probability of remaining

in each trial over time. The p-values less than .05 in the last column of table 2 indicate that in studies 201 and 204, placebo patients dropped out at rates statistically significantly greater than those who were taking risperidone. Approximately 50% of the risperidone patients completed studies 201 and 204.

Tables 2A,B, and C display the reasons and distributions of drop outs for each study. Insufficient response and adverse events account for the majority of drop outs.

Summary Analyses- Completer, Last Observation Carried Forward (LOCF) and the Role of Drop Outs

Table 3 summarizes the completers' mean changes from baseline and p-values (in parentheses) associated with comparisons to placebo in studies 201 and 204 and risperidone 1 mg in study 024. Note that in studies 204 and 024, increasing the dose does not lead to increasing effect.

In the LOCF analyses, all p-values were statistically significant for risperidone groups with respect to Total BPRS, Key BPRS and CGI. See medical officer's review.

Table 4 displays mean changes from baseline for Total Negative Symptoms.

Figures 4-9 display the sometimes dramatic effect of drop outs on the conversion of marginal or non-statistically significant completer group comparisons to highly statistically significant LOCF comparisons. Note that the first four groups of bars indicate the change from baseline among **drop outs,** whereas the last two groups of bars refer to the last week **completer** and **LOCF** comparisons, respectively. In studies 201 and 204, placebo drop outs fared worse than active drug drop outs nearly uniformly over time for all four clinical endpoints. There is a mixed response in study 024.

Exploratory Analyses of 'Responders'

Patient's Baseline as Response Criterion

The preceding results indicate that, on the whole, patients who took risperidone experienced greater remission of symptoms than those on placebo. However, due to the substantial number of patients who left the study prematurely, it is difficult to assign a 'treatment effect'. One alternative is simply to compute the number of patients who were at least 'minimally improved' on the CGI scale at the end of the study and divide that number by the number of patients in the intent-to-treat cohort (either identical to or close to the number of randomized patients). The difference between the percentages (drug-placebo) estimates **the fraction of patients who receive a benefit attributable to the drug, given all**

the patients to whom it had been administered. This assumes, of course, that patients in the trial are reasonably representative of the patients who will receive the drug and that the reasons and rates for discontinuing use of the drug in the trial represent what will happen in regular clinical practice. For instance, in study 201, the percentages are 49% and 26% for risperidone and placebo, respectively. In study 204, they are 53%, 47%, 48%, and 21% for RISP 6, 10, 16, and placebo, respectively. Pooling results from these trials provides an estimate of 27% with a 95% confidence interval of 18%-36% for the 'attributable fraction'.

Alternatively, we can ask the question:'Given the patients who remain in the study until the end, what is the fraction of patients whose improvement is attributable to risperidone (conditional probability)'? In this case, the denominators are the numbers of patients who completed the study. Pooling patients from the two trials produces 65% for placebo and 81% for risperidone, resulting in an attributable fraction of 16%. Since the number of patients is substantially reduced by the end of the trials, the 95% confidence interval is wide: 1%-31%.

The profiles of improvement categories ('minimally improved', 'much improved', and 'very much improved') are also instructive. For placebo patients, the ratios are 2:5:4, whereas those for risperidone are 2:8:5. Thus, risperidone patients have a greater overall response which is differentially weighted toward 'much improved'.

Natural Course of Illness as Response Criterion

Another approach considers three features not included in the foregoing analysis: 1) it allows statements about the probability of benefiting **over the time course of the trials** in the presence of drop outs, 2) it defines the treatment group comparison by comparing the experience of those on drug **directly to the distribution of placebo patients' experience over time**, thus comparing experience of being on drug to the natural course of the illness, and 3) it offers an approach to describing 'clinical effect' when the outcome is essentially continuous in nature.

Rather than defining a 'responder' as one who achieves an arbitrarily determined change from his/her own baseline, we define a 'responder' as a patient whose, for instance, Total BPRS change from baseline is greater than the placebo group's median at week 1 of the trial. We then ask the question: "What is the probability that a typical patient will remain 'in response' for lengths of time defined by the visit schedule?" Such a 'life table' approach is the preferred method in mortality studies. However, in the present case, we measure the time to the first failure to be in response.

The Effect of Non-random Drop Outs

If drop outs in these trials had been random, then such an approach would yield relatively unbiased estimates of the probabilities we seek. However, the substantial loss of patients (censoring) is largely due to lack of effectiveness of the treatment (drug or placebo). Thus, as the trial progresses, the patients who 'survive' are not necessarily representative of the entire original cohort. Since patients on **all** treatments are dropping out, the bias washes out somewhat; however, the substantially greater drop out rates among placebo patients contributes to the conservativeness of the procedure. Two other features which make the procedure conservative are the following:

1) By far the more important is the likelihood that placebo patients who drop out are in worse condition than placebo patients who remain in the trial. This means that the placebo median change from baseline is overestimated (in terms of benefit) at each time point. Thus the standard for the drug patient is likely more difficult to meet than if the placebo patients had dropped out randomly.

2) The patient can 'respond' subsequent to 'failing'.

Consequently, the resulting probabilities of being in better condition than at least half the placebo patients (natural course) are lower bounds on the true probabilities.

Results

Table 5 displays the placebo groups' median changes from baseline for Total BPRS and Key BPRS.

Table 6 displays the percentage of responders in each risperidone group.

Table 7 displays (lower bound) probabilities for being in response for Total BPRS and Key BPRS. Only the 3 highest dose groups in study 204 are included. In an attempt to use all relevant information in the two studies, data have been pooled in the following way: 1) in Study 204, life table estimates have been pooled over the 3 risperidone groups and 2) that estimate and those from study 201 have been pooled. The fact that the trials' durations were slightly different is unlikely to affect the general conclusion. For Total BPRS, a 95% confidence interval for the probability of maintaining a condition better than the half of those not taking the drug throughout the entire study is centered at 54% with a range of %, while that for Key BPRS is centered at 66% with a range of %.

As stated earlier, these estimates suffer from the fact that we are

asking a question about the likely fate of a 'typical' patient on medication who started the trial (i.e., about an unconditional event) when likelihood of terminating prematurely is not random. An alternative quantity is the conditional probability of falling out of response given that a patient has 'survived' to a particular point in the trial. This perspective controls for risperidone patients dropping out, but is still subject to the underestimate of response due to the worse condition of placebo drop outs relative to continuing placebo patients.

Using information necessary for the calculation of the unconditional probabilities, we can estimate the conditional probabilities of falling out of response. They are relatively constant over time in the range of %. Thus, given that a patient is still in the trial at any particular visit, the probability of he/she remaining in response at least until the next visit is between %.

Responders Who Failed and Non-Responders Who Responded

It is of interest to note that over the 4 risperidone groups used in the pooled analysis, only % of the **original responders** 'responded' subsequent to failing.

In addition, 45% of those who **did not respond at week 1** never responded in the trial. Equal numbers of 'never-responders' left the trial at weeks 1, 2 and at the last visit. Very few patients left the trial between these times.

Finally, of those who **did not respond at week 1 who eventually responded**, very few attained a **sustained** response.

Conclusions

The results of these trials indicate that risperidone produces statistically significantly greater amelioration of selected symptoms of schizophrenia. Due to substantial non-random censoring, it is difficult to assign a particular 'treatment effect'. However, two approaches to estimating clinical prognosis suggest that:

1) On the basis of CGI severity, approximately % of patients started on risperidone will experience at least minimal improvement attributable to the drug within 8 weeks. This estimate assumes that clinical practice approximately reflects the treatment regimens in the trials.

2) On the basis of the natural course of the illness, as measured by Total and Key BPRS items over a period of 8 weeks in the placebo group, 60% is a conservative estimate of the fraction of patients who do better than half of those who do not take risperidone (beating the placebo median).

David Hoberman, Ph.D.
Mathematical Statistician

Concur: Dr. Nevius SEN 4-20-93

Dr. Dubey 4-20-93

This review consists of 5 pages of text, 11 tables and 9 figures

cc: NDA# 20-272
Orig. HFD-120
HFD-120/Dr. Laughren
HFD-120/Dr. Mosholder
HFD-120/Dr. Leber
HFD-120/Mr. Hardeman
HFD-344/Dr. Lisook
HFD-713/Dr. Hoberman
HFD-713/Dr. Nevius
HFD-713/Dr. Dubey [DRU 1.3.2 NDA]
chron.

Table 1

Study 201

	Rand	Base	Wk 1	Wk 2	Wk 3	Wk 4	Wk 6
RISP	53	50	49	36	40	33	28
HAL	53	52	52	40	35	26	23
PBO	54	51	51	40	26	21	16

Study 204

	Rand	Base	Wk 1	Wk 2	Wk 4	Wk 6	Wk 8
RISP 2mg	87	87	87	75	55	42	35
RISP 6mg	86	84	84	79	67	55	54
RISP 10mg	87	82	80	72	59	53	47
RISP 16mg	88	84	83	74	68	56	55
HAL 20mg	87	85	85	72	52	41	37
PBO	88	83	82	67	48	34	26

Study 024

	Rand	Base	Wk 1	Wk 2	Wk 4	Wk 6	Wk 8
RISP 1mg	229	224	219	204	186	167	167
RISP 4mg	227	225	219	212	188	179	178
RISP 8mg	230	227	222	207	187	171	171
RISP 12mg	226	224	222	210	183	160	160
RISP 16mg	224	219	216	201	173	158	155
HAL 10mg	226	223	217	200	179	165	162

TABLE 2

Survival Analysis

Time in Days From Entry to Drop-out for All Reasons

Estimates

Risperidone Study 201

Treatment Group	Intent-to-Treat Sample	Number Completed	Estimate**	P-value*
Placebo	54	17	31.0	--
Risperidone	53	27	52.8	0.0358
Haloperidol	53	22	43.4	0.1896

*Pairwise comparisons to placebo using the logrank test
**At 42 days

Risperidone Study 204

Treatment Group	Intent-to-Treat Sample	Number Completed	Estimate**	P-value*
Placebo	88	27	30.7	--
Ris. 2mg	87	36	41.2	0.0729
Ris. 6mg	86	53	60.9	<0.0001
Ris. 10mg	87	48	55.2	0.0020
Ris. 16mg	88	54	61.4	<0.0001
Hal. 20mg	87	36	41.1	0.1050

*Pairwise comparisons to placebo using the logrank test
**At 56 days

Risperidone Study 024

Treatment Group	Intent-to-Treat Sample	Number Completed	Estimate**	P-value*
Ris. 1mg	229	171	76.3	--
Ris. 4mg	227	182	80.5	0.1504
Ris. 8mg	230	174	76.0	0.8622
Ris. 12mg	226	164	73.3	0.6614
Ris. 16mg	224	165	74.0	0.7495
Hal. 10mg	226	163	72.5	0.4949

*Pairwise comparisons to placebo using the logrank test
**At 56 days

00-00008

TABLE 2A

Number (%) of Patients Prematurely Discontinued From Study 201

Reason	Placebo	Risperidone	Haloperdol
Adverse Event	7 (13%)	6 (11.3%)	7 (13.2%)
Lack of Response	20 (37%)	8 (15.1%)	6 (11.3%)
Withdrew Consent	2 (3.7%)	2 (3.8%)	5 (9.4%)
Uncooperative	4 (7.4%)	9 (17%)	11 (20.8%)
Lost to Followup	2 (3.7%)	0	2 (3.8%)
Ineligible	1 (1.9%)	0	0
Other	1 (1.9%)	1 (1.9%)	0
Total	37 (68.5%)	26 (49.1%)	31 (58.5%)

TABLE 2B

PATIENTS PREMATURELY DISCONTINUED FROM STUDY 204

Reason	Placebo n=88	Ris 2 mg n=87	Ris 6 mg n=86	Ris 10 mg n=87	Ris 16 mg n=88	Hal 20 mg n=87
Adverse event	3 (3.4%)	2 (2.3%)	9 (10.5%)	4 (4.6%)	9 (10.2%)	6 (6.9%)
Insufficient Response	51 (58.0%)	41 (47.1%)	12 (14.0%)	25 (28.7%)	18 (20.5%)	36 (41.4%)
Withdrew Consent	3 (3.4%)	5 (5.7%)	4 (4.7%)	3 (3.4%)	2 (2.3%)	2 (2.3%)
Uncooperative	4 (4.5%)	3 (3.4%)	6 (7.0%)	4 (4.6%)	2 (2.3%)	6 (6.9%)
Lost to follow up	0	0	1 (1.2%)	0	1 (1.1%)	1 (1.1%)
Other	0	0	2 (2.3%)	3 (3.4%)	2 (2.3%)	0

TABLE 2C

Number of dropouts by treatment group in Study 024

Reason	Ris 1 mg n=229	Ris 4 mg n=227	Ris 8 mg n=230	Ris 12 mg n=226	Ris 16 mg n=224	Hal 10 mg n=226	Total
Adverse experience	18	15	17	22	31	23	126
Death	0	0	0	0	1	0	1
Suicidal	2	1	1	3	0	2	9
Insufficient response	40	16	24	32	20	22	154
Intercurrent disease	2	0	0	1	1	0	4
Intercurrent event	2	0	2	2	2	0	2
Intercurrent treatment	0	0	0	0	1	2	3
Lost to follow up	3	4	4	6	4	5	26
Selection criteria not met	1	0	1	0	0	0	2
Sufficient response	0	1	0	1	0	1	3
Patient's decision	3	7	9	6	7	15	47
Lack of motivation	3	5	5	5	5	5	28
Uncooperative	0	5	4	7	8	5	29
Other	1	2	1	1	3	3	11
Unspecified	0	0	0	0	0	0	1
Total (%)	58 (25%)	45 (20%)	56 (24%)	62 (27%)	59 (26%)	63 (28%)	343 (25%)

Table 3
Completers

Change From Baseline

Study 201

	Total BPRS	Key BPRS	Tot Neg Symp	CGI Sev
RISP	-15.2 (.273)	-6.1 (.104)	-9.8 (.481)	-1.1 (.373)
HAL	-14.0 (.949)	-5.9 (.627)	-11.0 (.896)	-0.9 (.895)
PBO	-12.9	-4.9	-13.9	-0.9

Study 204

	Total BPRS	Key BPRS	Tot Neg Symp	CGI Sev
RISP 2mg	-10.7 (.220)	-2.9 (.235)	-4.7 (.925)	-0.6 (.513)
RISP 6mg	-14.9 (.009)	-4.8 (.001)	-5.2 (.726)	-1.2 (.004)
RISP 10mg	-11.9 (.164)	-3.8 (.041)	-3.1 (.326)	-1.1 (.042)
RISP 16mg	-11.4 (.255)	-3.9 (.030)	-4.4 (.686)	-0.8 (.253)
HAL 20mg	-8.9 (.509)	-3.6 (.078)	-3.7 (.613)	-0.8 (.193)
PBO	-6.9	-1.7	-4.4	-0.5

Study 024

	Total BPRS	Key BPRS	Tot Neg Symp	CGI Sev
RISP 4mg	-12.4 (.018)	-3.1 (.200)	-6.2 (.518)	-0.9 (.001)
RISP 8mg	-13.6 (.001)	-4.0 (.002)	-7.0 (.098)	-1.0 (.005)
RISP 12mg	-11.6 (.206)	-3.4 (.138)	-5.9 (.881)	-0.9 (.074)
RISP 16mg	-12.3 (.050)	-3.8 (.014)	-6.0 (.795)	-1.0 (.005)
HAL 10mg	-10.8 (.430)	-3.5 (.046)	-6.1 (.779)	-0.8 (.156)
RISP 1mg	-9.9	-2.7	-5.9	-0.6

Table 4

LOCF Negative Symptoms

Change From Baseline (P-Value)

Study 201

RISP	-9.8	(.056)
HALO	-8.5	(.150)
PLACEBO	-2.8	

Study 204

RISP 2mg	-1.3	(.145)
RISP 6mg	-3.9	(.091)
RISP 10mg	-1.9	(.048)
RISP 16mg	-3.1	(.002)
HALO 20mg	-0.7	(.301)
PLACEBO	+0.2	

Study 024

RISP 4mg	-5.5	(.124)
RISP 8mg	-5.2	(.256)
RISP 12mg	-5.0	(.472)
RISP 16mg	-5.2	(.369)
HALO 10mg	-4.8	(.706)
RISP 1mg	-4.5	

Table 5

Placebo Medians

Change From Baseline

Study 201

Week	N	BPRSD	N	Key BPRSD
1	51	-1.0	51	-1.0
2	40	-5.0	40	-1.0
3	26	-7.0	26	-2.5
4	21	-6.0	21	-2.0
6	16	-10.0	16	-3.5

Study 204

Week	N	BPRSD	N	Key BPRSD
1	82	-1.5	82	0.0
2	67	-4.0	67	-1.0
4	48	-6.0	48	-1.0
6	34	-3.5	34	-1.5
8	26	-10.5	26	-2.0

Table 6

Percent Responders

Study	Total BPRSD	Key BPRSD
201 RISP	38/50 (76%)	30/50 (60%)
204 RISP 6	61/84 (73%)	51/84 (61%)
RISP 10	47/82 (57%)	49/82 (60%)
RISP 16	55/84 (65%)	50/84 (60%)

Table 7 (Cont.)

Study 204

Response Probability Estimates

Total BPRSD

Week	Risp 6mg	Risp 10mg	Risp 16mg
2	.83	.73	.90
4	.69	.53	.77
6	.67	.53	.75
8	.58	.50	.59

Key BPRSD

Week	Risp 6mg	Risp 10mg	Risp 16mg
2	.92	.81	.76
4	.86	.71	.68
6	.81	.71	.61
8	.74	.64	.55

Table 7

Study 201

Response Probability Estimates

Risperidone

Week	Total BPRSD	Key BPRSD
2	.83	.96
3	.66	.82
4	.60	.77
6	.48	.72

Pooled Data

Week	Total BPRSD	Key BPRSD
2	.83	.85
4	.67	.76
6	.64	.72
8	.54	.66

RISPER[illegible]IE 201 STUDY
PATIENTS PREMATURELY DISCONTINUED FOR ALL REASONS

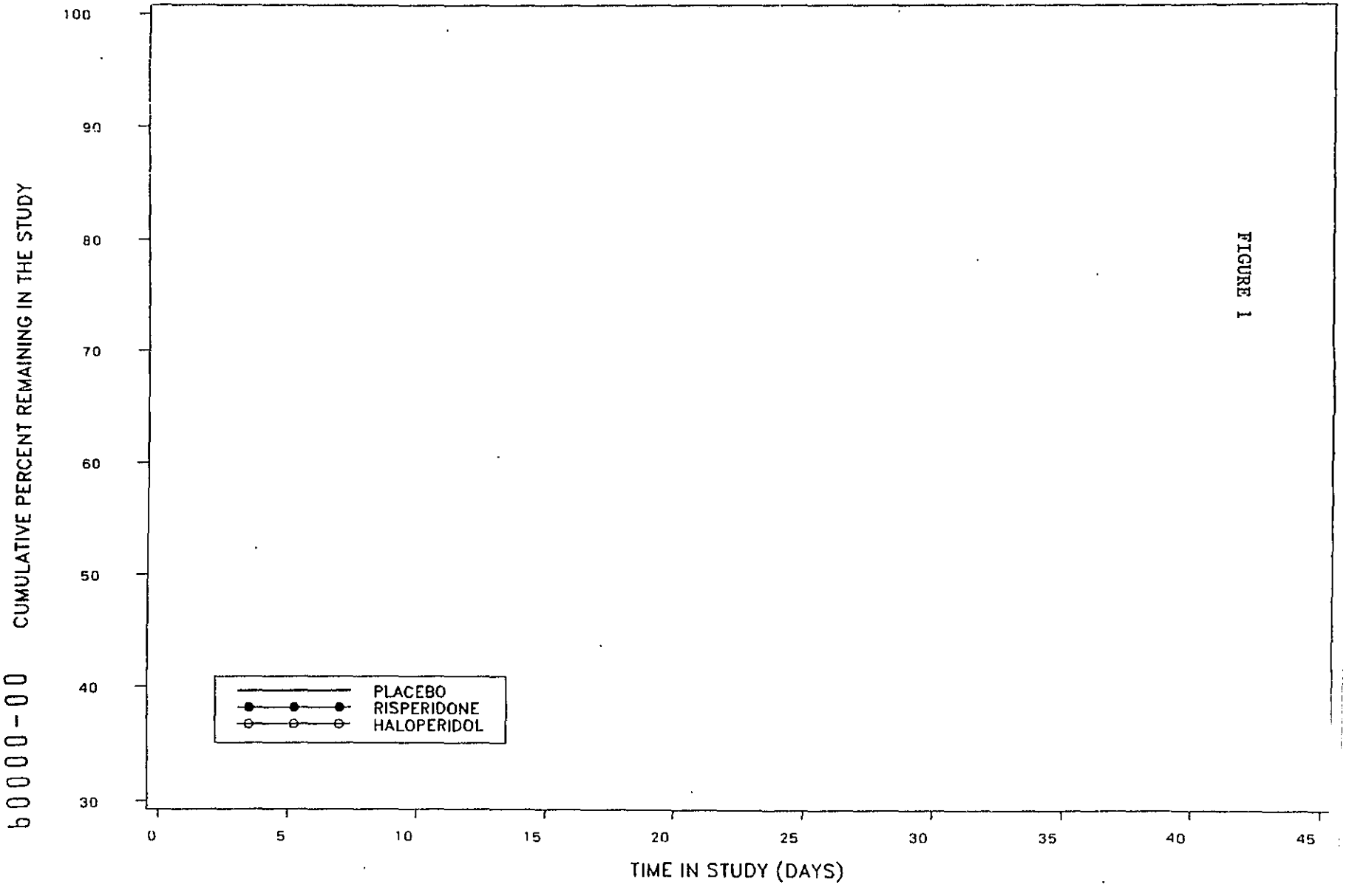

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FIGURE 1

RISPERIDO 204 STUDY
PATIENTS PREMATURELY DI ONTINUED FOR ALL REASONS

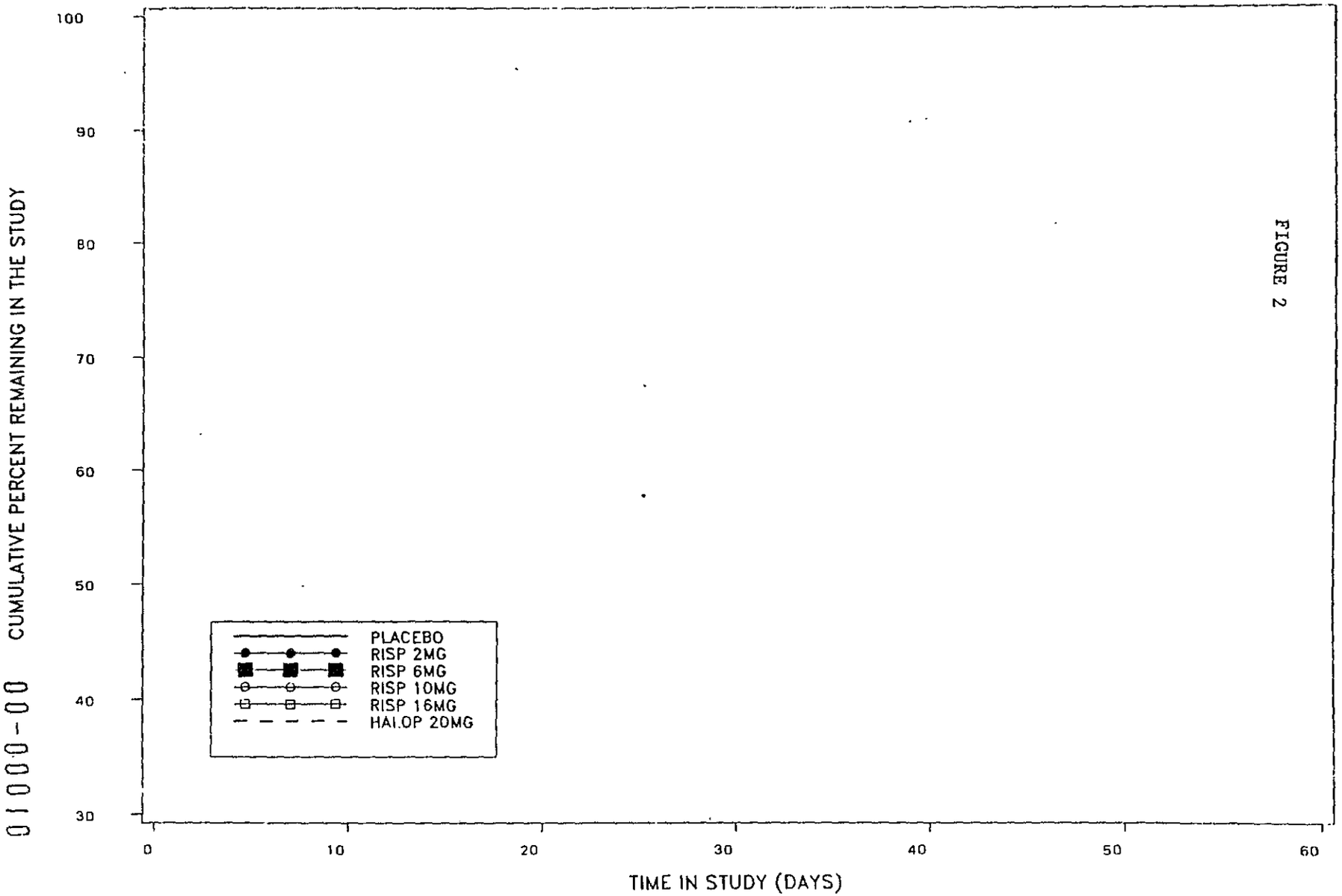

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FIGURE 2

RISPERI. E 024 STUDY
PATIENTS PREMATURELY DISCONTINUED FOR ALL REASONS

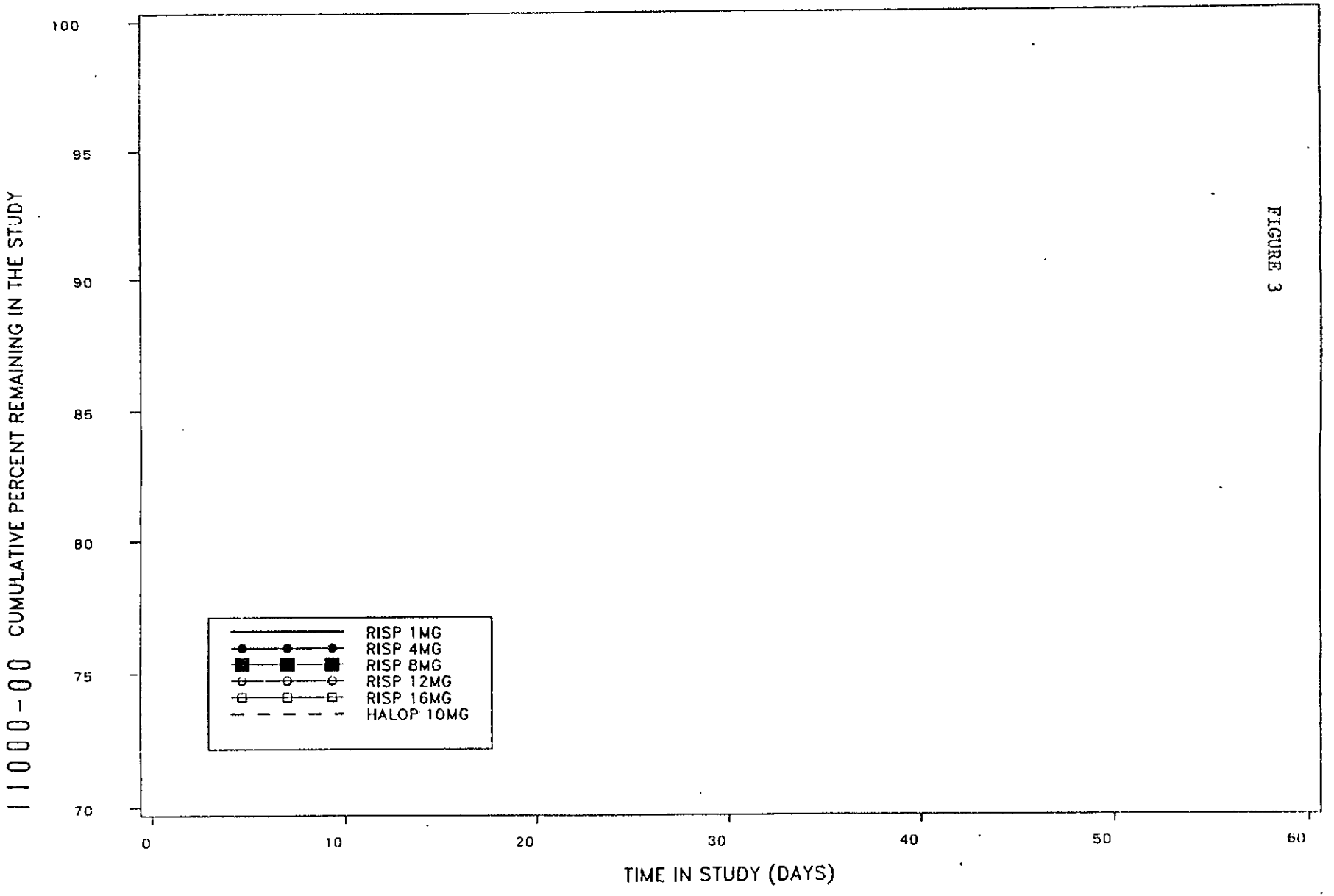
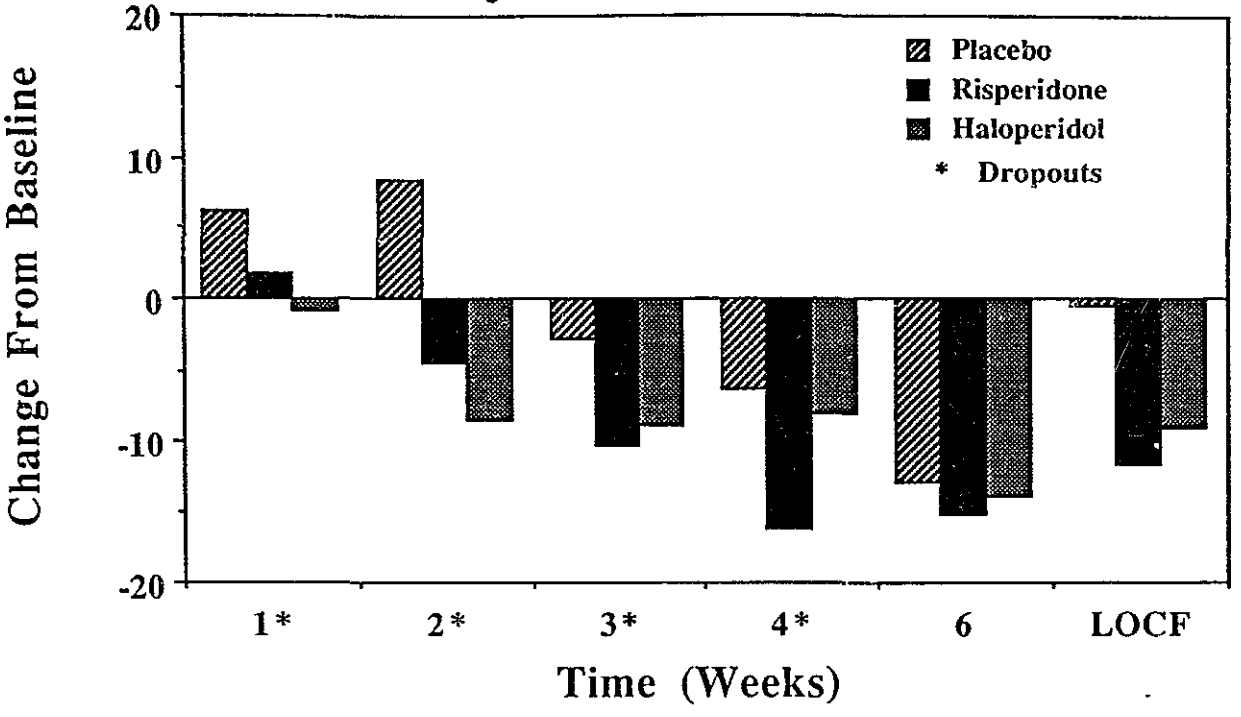


FIGURE 3

FIGURE 4
Study 201: Total BPRS



Study 201: Total Key BPRS

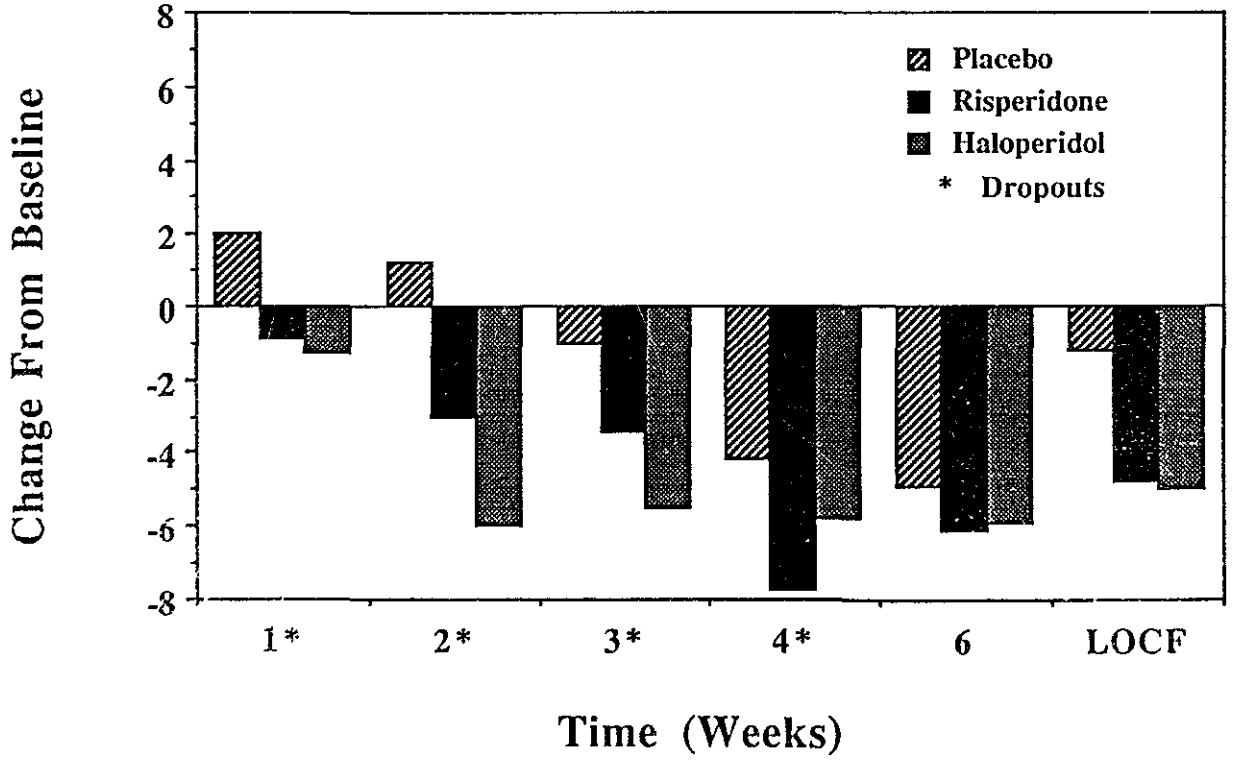
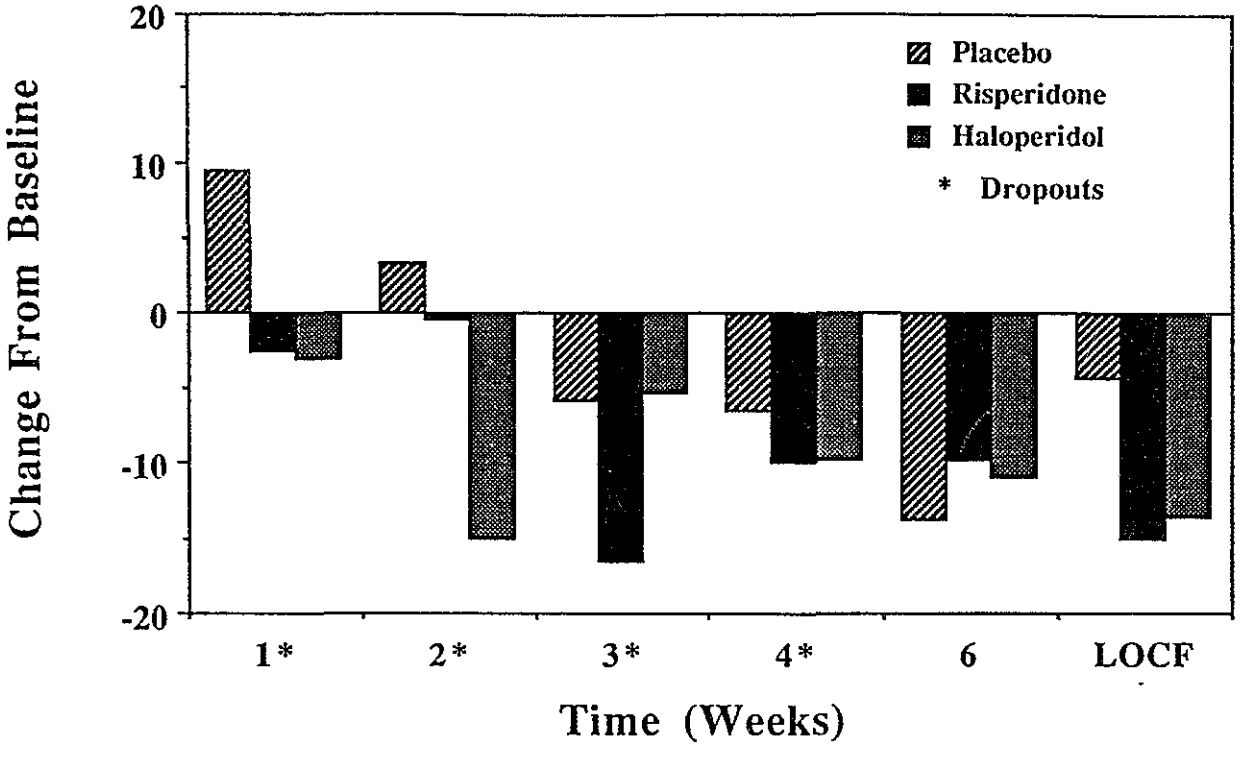


FIGURE 5
Study 201: Total Sans Score



Study 201: CGI - Severity

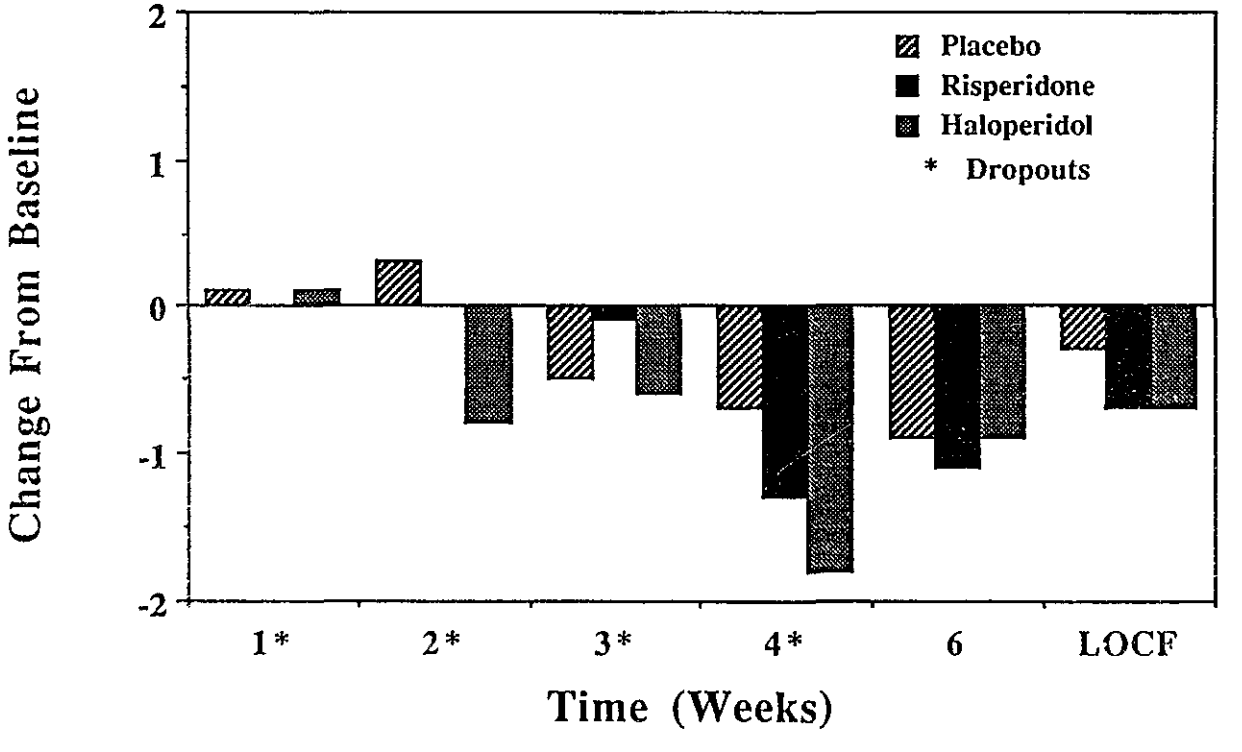
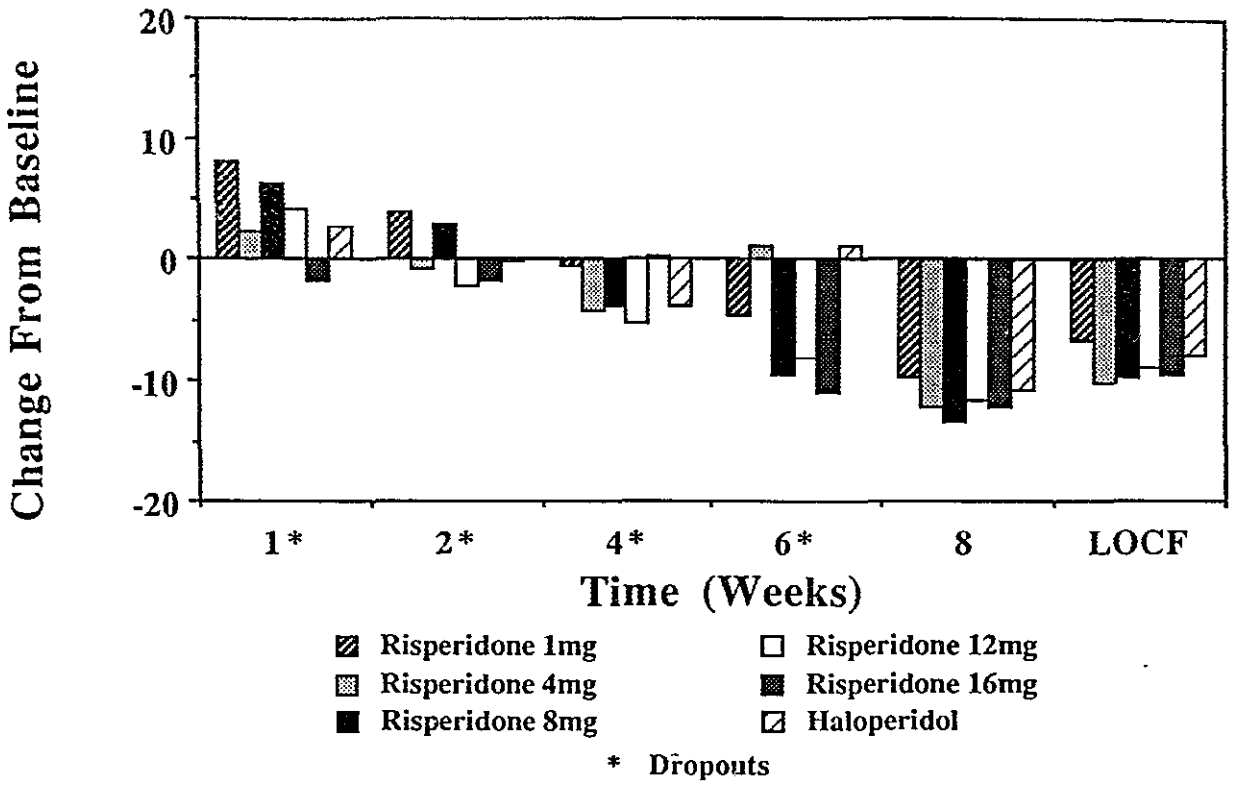


FIGURE 6
Study 024: Total Derived BPRS



Study 024: Total Key BPRS

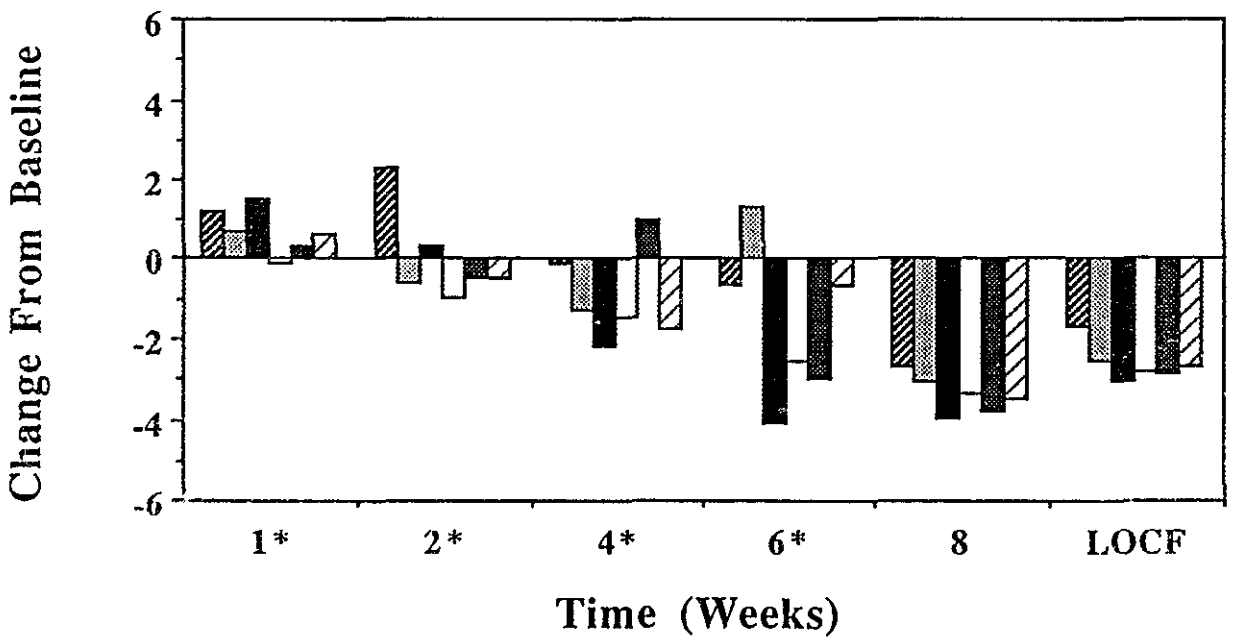
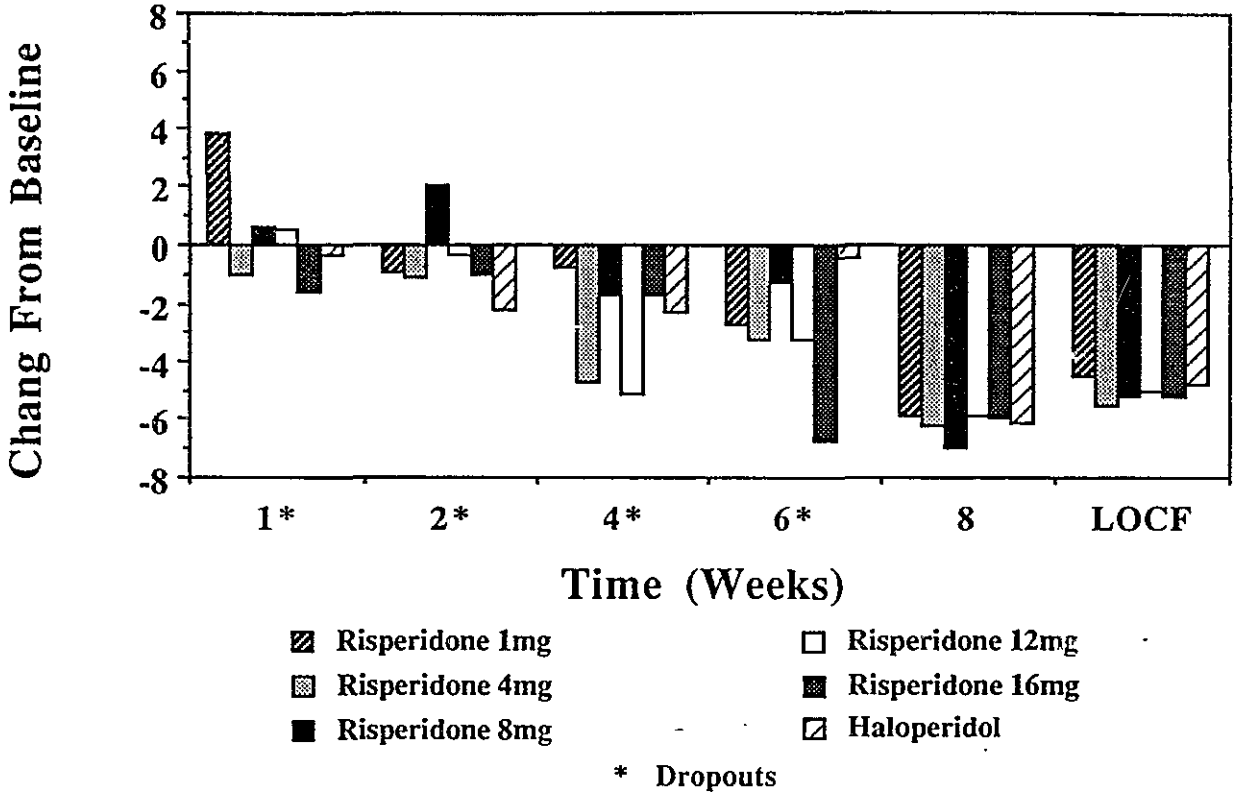


FIGURE 7
Study 024: Total Negative PANSS



Study 024: CGI - Severity

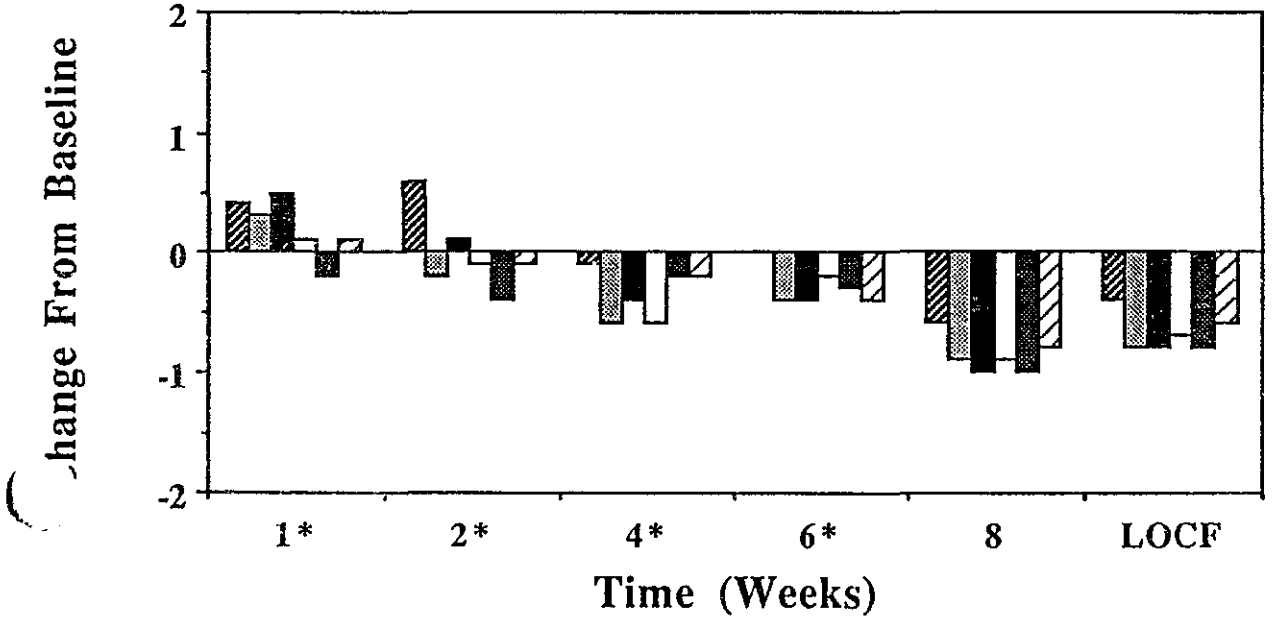
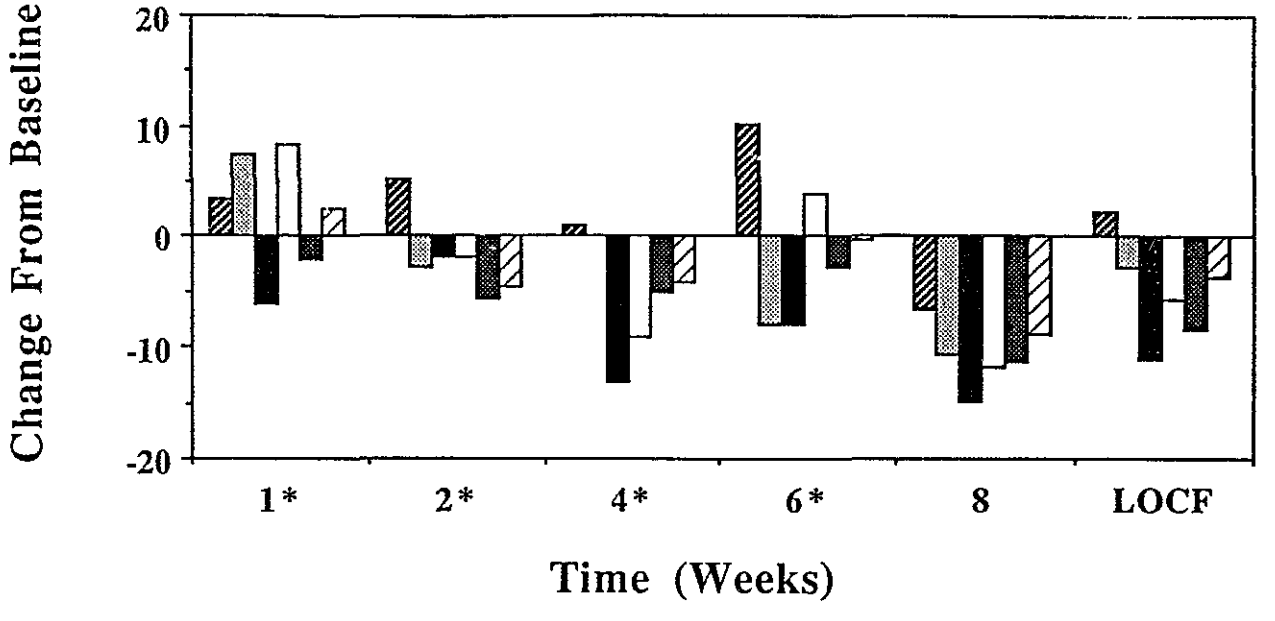


FIGURE 8
Study 204: Total Derived BPRS



Placebo
Risperidone 2mg
Risperidone 6mg
Risperidone 10mg
Risperidone 16mg
Haloperidol

* Dropouts

Study 204: Total Key BPRS

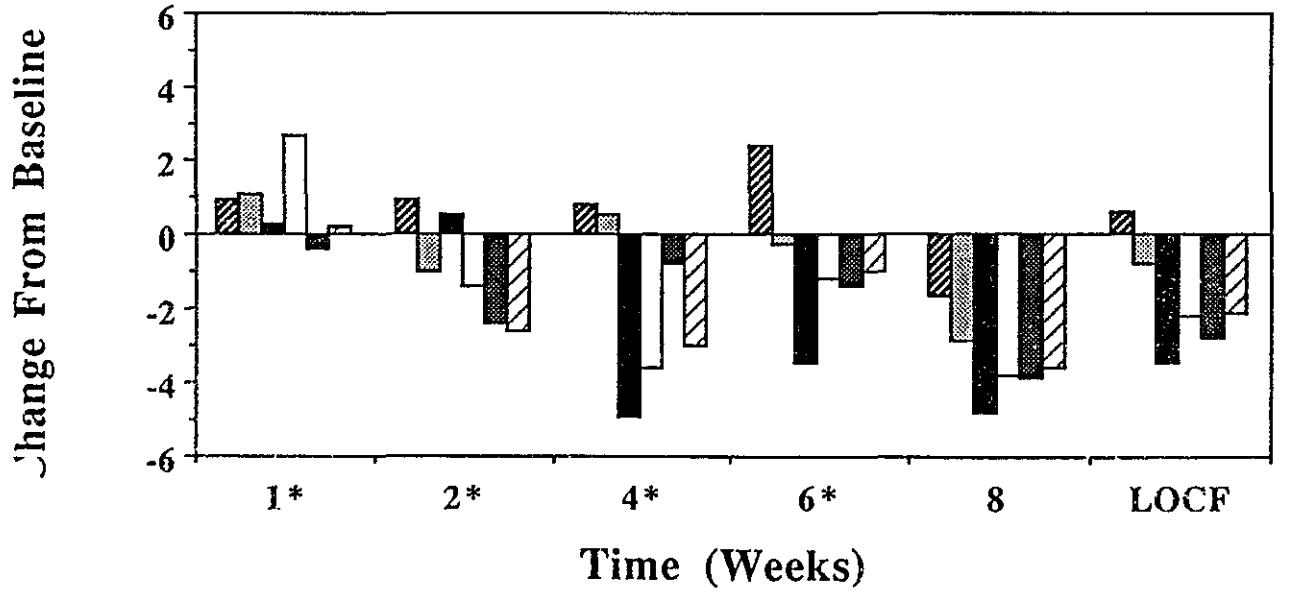
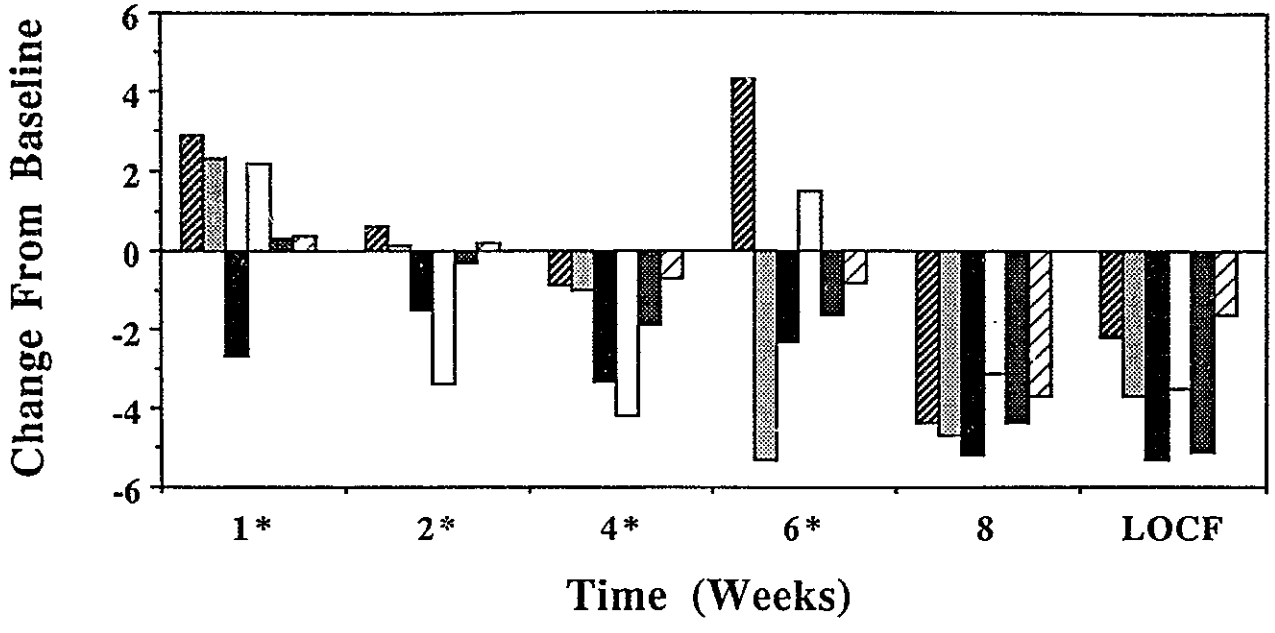


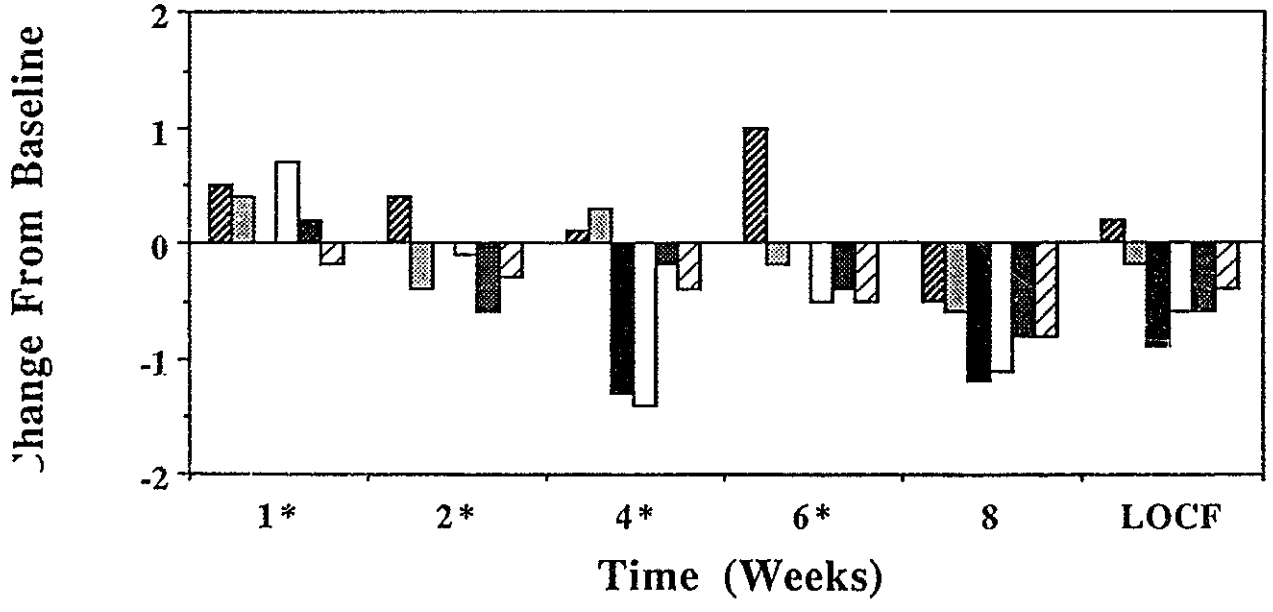
FIGURE 9
Study 204: Total Negative PANSS



Placebo
Risperidone 10mg
Risperidone 2mg
Risperidone 16mg
Risperidone 6mg
Haloperidol

* Dropouts

Study 204: CGI - Severity



[redacted] Dr. Fitzgerald

M E M O R A N D U M

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: July 1, 1993

FROM: Joseph DeGeorge, Ph.D. 7/1/93
(Acting) Assistant Director for Pharmacology
Office of Drug Evaluation I and II

SUBJECT: CAC Committee Review of Risperidone

TO: Paul Leber, M.D.
Director
Division of Neuropharmacology Drug Products

The CDER Carcinogenicity Assessment Committee met on June 21, 1993 to discuss the findings from rodent carcinogenicity studies on Risperidone as requested by Dr. Fitzgerald of the Division of Neuropharmacological Drug Products (HFD 120). Present for the discussion were Dr. Fitzgerald, Dr. Freed, Dr. Osterberg, Dr. DeFelice, Dr. DeWitt. Dr. Dou Jean, Dr. Choudary, Dr. Jordan, Dr. DeGeorge, Dr. Contrera, Dr. Whitehurst (for Dr. Taylor), Dr. Jacobs (for Dr. Farrelly), Dr. Fairweather, Dr. Butler, Dr. Lin, Dr. Laughren, Dr. Goldman, and Dr. Greenman (by telecon). The CAC members were asked to address three specific questions:

1. Is the male segment of the mouse carcinogenicity study adequate? Was an MTD reached?

2. What is the relevance of the increased incidence of mammary gland adenocarcinoma in male and female rats and female mice to potential human risk for mammary cancer?

3. Are the positive trends in the incidence of primary lung tumors (female mice) and soft tissue fibrosarcomas (fatal, male rats) of concern? Are there implications for human risk?

Documents presented to the Committee for consideration included Dr. Freed's review of the dose ranging and carcinogenicity studies for mice and rats (June 2, 1993; includes tabulated Sponsor's findings), a comparison of tumor findings for FDA approved and non-approved antipsychotics (prepared by Dr. Freed), the Statistical Review and Evaluation (March 10, 1993, prepared by Dr. Lin), the FDA Toxicology Advisory Committee Report on Antipsychotic Drugs (August 12, 1977), expert reviews of the data (prepared independently by: Dr. S. Eustis of NIEHS, June 16,

1993; Dr. D. Sheehan of NCTR, June 21, 1993; Dr. D. Greenman of NCTR, June 21, 1993). Dr. Freed also provided an oral overview of the findings. The following points were considered particularly important in the committee's deliberations:

1. The high dose in male mice, while not eliciting toxicity sufficient to be a MTD when considered alone, exhibited toxicity that was similar (but less severe) to that of female mice at identical doses and which reduced survival of females.

2. Systemic exposure to drug was not assessed sufficiently to allow conclusions to be drawn for adequacy of dosing in mouse.

3. The profile of tumor findings in female rat and mouse overlapped with the profiles observed for other antipsychotics, but was not identical with any one particular antipsychotic. The tumors identified have been associated with hormonally responsive sites in rodents.

4. The findings of increased mammary gland adenocarcinoma in male rat were unique among investigated antipsychotics, and were associated with prolactin elevation in male rat and accompanying feminization of male mammary tissue in the study.

5. The findings of increased trends for primary lung tumors in mice were only marginally significant in females, within the range of historical controls, and were associated in both males and females with reduced incidence of focal hyperplasia.

6. The finding of increased soft tissue fibrosarcomas (fatal, male rats) was dependent upon attribution as to cause of death. Inclusion of one non-fatal fibrosarcomas identified in the control group resulted in no significant finding for this tumor type.

7. There is presently no epidemiologic data indicating increased risk for breast cancer for humans using antipsychotics. Prolactin levels are elevated in humans, as in rodents, following treatment with antipsychotic agents.

In consideration of the above information it was the committee's judgement that:

1. The carcinogenicity studies as conducted were acceptable tests of the potential for risperidone to produce tumors in rodents. Additional carcinogenicity

studies need not be performed by the Sponsor (12 supporting, 1 opposed).

2. There was additional concern for the findings of mammary adenocarcinomas in male rats (8 supporting, 5 opposed), but that this additional concern could be adequately addressed through product labeling (if approved) by stating the tumor findings for rodents and indicating the unknown relevancy of these findings for human risk (unanimous support).

3. There was no concern for the positive trends in mouse primary lung tumors or fibrosarcomas (unanimous consent).

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Fonsi

CC: Original NDA 20-272 HFD-120
FONSI File 20272
Docket File
P. Vincent HFD-102

ENVIRONMENTAL ASSESSMENT

AND

FINDING OF NO SIGNIFICANT IMPACT

FOR

Risperdal
(risperidone)

Tablets 1,2,3,4,5 mg

NDA 20-272

FOOD AND DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH

FINDING OF NO SIGNIFICANT IMPACT

NDA 20-272

Risperdal
(risperidone)
Tablets 1,2,3,4,5 mg

The Food and Drug Administration (FDA) recognizes the National Environmental Policy Act of 1969 (NEPA) as the national charter for protection, restoration, and enhancement of the environment. NEPA establishes policy, sets goals (section 101), and provides procedures (section 102) for carrying out the policy.

Environmental information is to be available to the public and the decisionmaker before decisions are made about actions that may significantly affect the quality of the human environment; FDA actions are to be supported by accurate scientific analyses; and environmental documents are to concentrate on timely and significant issues, not to amass needless detail.

The Food and Drug Administration Center for Drug Evaluation and Research has carefully considered the potential environmental impact of this action and has concluded that this action will not have a significant effect on the quality of the human environment and that an environmental impact statement therefore will not be prepared.

In support of their new drug application for risperidone , Janssen Research Foundation has conducted a number of environmental studies and prepared an environmental assessment (21 CFR 25.31a(a) (attached) which evaluates the potential environmental impacts of the manufacture, use and disposal of the product.

The Center for Drug Evaluation and Research has concluded that the product can be manufactured and used without any expected adverse environmental effects. Precautions taken at the sites of manufacture of the bulk product and its final formulation are

expected to minimize occupational exposures and environmental release. Any residues of risperidone or its major metabolites entering the environment as a result of administering the drug to humans are expected to rapidly degrade.

12/28/93
DATE

Phillip G. Vincent, Ph. D.
Environmental Assessment Officer
Center for Drug Evaluation and Research

12/28/93
DATE

Charles S. Kumkumian, Ph. D.
Assistant Director (Chemistry)
Office of Drug Evaluation I
Center for Drug Evaluation and Research

Attachment: environmental assessment

STATEMENT OF CONFIDENTIALITY

This copy of the Environmental Assessment contains, in Confidential Appendices A through J, confidential trade secrets or information from which these trade secrets can be derived. This material could be beneficial to competitors and, therefore, the Confidential Appendices should not be duplicated for distribution. A nonconfidential Environmental Assessment, suitable for public disclosure, may be obtained by duplication of all sections of this Environmental Assessment except for Confidential Appendices A through J.

ENVIRONMENTAL ASSESSMENT.

1. DATE.

July, 1993

2. NAME OF APPLICANT.

Janssen Pharmaceutica N.V. on behalf of Janssen Research Foundation, Titusville, New Jersey.

3. ADDRESS.

Janssen Pharmaceutica N.V.
Turnhoutseweg 30
2340 Beerse
Belgium

4. DESCRIPTION OF THE PROPOSED ACTION.

a. Brief description of requested approval.

The purpose of this NDA application is to request approval from FDA to market RISPERDAL® (Risperidone) 1, 2, 3, 4 and 5 mg caplets, a new drug for use in the treatment of the symptoms of psychotic diseases.

b. Need for the action.

Psychotic disorders affect a growing number of people in the US each year. As a result of the often profound psychological and social effects of these afflictions, the need for more effective therapies becomes apparent.

Risperidone is a safe and efficacious antipsychotic agent which exhibits both serotonin S2 and dopamine D2 receptor blocking activity. [1,2] It appears to have a favorable effect on both positive (hallucinations, delusions and thought disorders) and negative (emotional withdrawl, blunted effect, poverty of speech and avolition) symptoms usually associated with psychotic diseases. This combination is not shared by the so-called "classic" neuroleptics, which generally have greater effect on the positive symptoms and less, if any, effect on the negative symptoms of psychotic diseases.

The drug substance is formulated into a caplet dosage form for oral administration.

c. Location where product is produced.

Risperidone *drug substance* (starting from the final synthetic intermediate T16? 'l be produced by:

Additionally, the *intermediates* used in the synthesis of risperidone drug substance produced by:

Janssen Pharmaceutica
Turnhoutseweg 30
2340 Beerse, Belgium

Janssen Pharmaceutica
Janssen Pharmaceuticalaan 3
2240 Geel, Belgium

The *drug product* (RISPERDAL® caplets) will be manufactured, processed, packaged, labeled and tested by:

d. Locations where product will be used and disposed of.

Use of drug product

The use of the drug product, RISPERDAL® caplets, is limited to patients being treated for the symptoms of psychotic disorders. Treatment will occur in patients located throughout the USA. The drug product will be available for use only by prescription. A draft of the labeling is in Appendix 1.

Disposal of Drug Substance and Drug Product

Waste resulting from manufacture, testing and packaging in Beerse and Geel of drug substance, or from rejected or outdated drug substance, will be transported from Beerse and Geel to the following licensed waste processor:

Waste resulting from manufacture, testing and packaging in of drug substance and drug product, or from rejected or outdated drug substance, will be transported from to the following licensed waste processors:

Waste resulting from rejected, returned or outdated drug product will be transported to the following licensed waste processor:

e. Types of environments present at and adjacent to those in (d).

Manufacturing Sites

Janssen Pharmaceutica Beerse is located on a parcel of 148 acres. The site is surrounded with residential type housing and has its primary access from state road No. N 14 connecting Antwerp to Turnhout. The terrain is flat and the climate is temperate.

Janssen Pharmaceutica Geel is located on a parcel of 99 acres in the Geel industrial area. The industrial area is bounded to the north by the channel "Albertkanaal" and to the south by highway E313 connecting Antwerp to Achen. The terrain is flat and the climate is temperate.

Location maps can be found in Appendix 2.

Waste Processing Sites

5. IDENTIFICATION OF CHEMICAL SUBSTANCES THAT ARE THE SUBJECT OF THE PROPOSED ACTION.

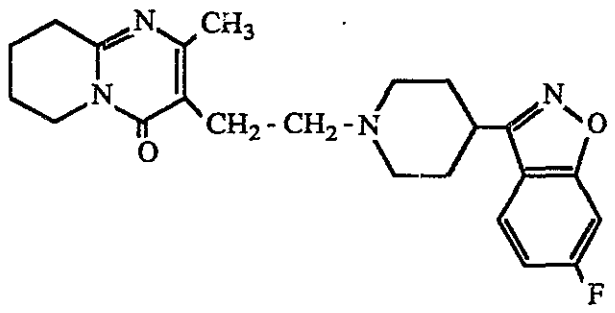
5.1 Drug Substance: R 64766: Risperidone

Complete nomenclature: 3-[2-4-(6-fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]ethyl]-6,7,8,9-tetrahydro-2-methyl-4H-pyrido[1,2-a]pyrimidin-4-one

CAS Registration number: 106266-06-2

Molecular weight: 410.49

Structural formula:



Physical description: Risperidone is a slightly beige to almost white powder, free from visible foreign matter

Water solubility (25 °C):

in water	7.19×10^{-2}	g/l (pH=8.4)
in buffer pH5	2.67×10^{1}	g/l (pH=6.0)
in buffer pH7	1.03×10^{0}	g/l (pH=7.1)
in buffer pH 9	7.03×10^{-2}	g/l (pH=9.0)

Octanol/Water Partition coefficient (log P):

in 1-octanol/buffer pH 5	log P = 0.22 (pH=5.0)
in 1-octanol/buffer pH 7	log P = 1.67 (pH=7.0)
in 1-octanol/buffer pH 9	log P = 2.91 (pH=9.0)

Vapor pressure: 3.17×10^{-4} Pa

Dissociation constants:

pKa1 = 8.28 (piperidine moiety)
pKa2 = 3.12 (pyrimidine moiety)

Melting point: 171.0 °C

Density / relative density: 1.018×10^{3} kg/m^3

Impurities and Additives: Information is available in Confidential Appendix A.

More information on the drug substance is available in Confidential Appendix A and in Item 7.

00-00019

5. IDENTIFICATION OF CHEMICAL SUBSTANCES THAT ARE THE SUBJECT OF THE PROPOSED ACTION. (CONT'D.)

Information about the synthesis of risperidone is available in Confidential Appendix A. The synthesis of risperidone consists of a number of chemical reactions. A flow chart describing the synthetic processes is given in Figure 5.1. In this flow chart the releases into the environment are also given, which relates to Item 6 of this EA.

5.2 Synthesis starting materials and intermediates of the synthesis

Detailed information on the synthesis starting materials and the intermediates, as well as Material Safety Data Sheets for these substances, are provided in Confidential Appendix A.

FIGURE 5.1. FLOWCHART OF SYNTHETIC PROCESSES

5. IDENTIFICATION OF CHEMICAL SUBSTANCES THAT ARE THE SUBJECT OF THE PROPOSED ACTION.(CONT'D.)

5.3 Drug Product.

The drug product will be manufactured at the facility in

Risperidone 1 mg oral f.c. caplet, Formula Number F23
Risperidone 2 mg oral f.c. caplet, Formula Number F24
Risperidone 3 mg oral f.c. caplet, Formula Number F34
Risperidone 4 mg oral f.c. caplet, Formula Number F31
Risperidone 5 mg oral f.c. caplet, Formula Number F38

Composition of RISPERDAL® oral tablets:

Formula Number	F 23	F 24	F 34	F 31	F 38
Tablet core (*)	mg	mg	mg	mg	mg
Risperidone	1	2	3	4	5
Lactose (hydrous), NF					
Corn starch, NF					
Microcrystalline Cellulose, NF					
HPMC ,USP					
Magnesium Stearate, NF					
Colloidal Silicon Dioxide, NF					
Sodium Lauryl Sulfate, NF					
Film-coating (*)	mg	mg	mg	mg	mg
HPMC USP					
Propylene Glycol, USP					
Titanium Dioxide, USP					
Talc, USP					
FD&C Yellow#6 Aluminum lake					
D&C Yellow #10					
FD&C Blue #2 Aluminum lake		-	-		

* With the exception of risperidone (which is assayed in the tablets), these represent theoretical amounts based upon the manufacturing formula.
* * Removed by in-process drying; does not appear in final product.

6. INTRODUCTION OF SUBSTANCES INTO THE ENVIRONMENT.

Items 6a-6d are presented below for each site which produces drug substance and/or drug product.

As mentioned in Item 4c, risperidone drug substance (starting from final intermediate T1624) and drug product will be produced in only the drug substance *intermediates* will be produced in Beerse and Geel. For the purposes of this assessment, the Beerse and Geel sites are treated as if they perform the total synthesis of risperidone drug substance. In this manner, we take into account the worst-case scenario (i.e. total synthesis of risperidone at both Belgian sites).

The concentrations of substances expected to enter the environment as a result of use and/or disposal is discussed in item 6e, which follows 6a-6d.

6.1. JANSSEN PHARMACEUTICA - BEERSE - BELGIUM.

This production site will produce the drug substance at the chemical production unit. This synthesis consists of a number of chemical reactions including crystallization and centrifugation using various raw materials.

6.1.1. Waste water.

A. List of substances to be emitted:

Drug substance

All reactions are carried out in closed glass-lined or stainless steel jacketed vessels within a controlled temperature and pressure range.

The water layer originated from the synthesis process is lead to the central waste water treatment plant, where all waste waters from the site are assembled.
The aqueous layers with high B.O.D./ C.O.D. content from "*drug substance*" production have a B.O.D.(Biological Oxygen Demand) range of mg/l and a C.O.D. (Chemical Oxygen Demand) range of mg/l.

Detailed information on the introduction of substances into the environment is available in the Confidential Appendix C.

B. The controls exercised

All waste water is chanelled through a system of sewers to a central two stages biological waste water treatment plant. No water is pumped into the environment untreated, whether it is industrial waste water or sewage from the normal sanitary facilities.

Description of the Waste Water Treatment Plant

The waste water treatment plant (WWTP) at Beerse has a population equivalent of this means that it has sufficient capacity (2340 kg. B.O.D./day) to process the waste water of inhabitants.

00-00023

Certain types of waste water, which would otherwise disturb the normal biological process, are pre-treated (oxidation, sedimentation, adsorption on activated charcoal, ion exchange) before entering the main treatment plant, or are transported to another company for special treatment (solidification, incineration).

The waste water (after pre-treatment, if necessary) first undergoes physicochemical treatment, which makes subsequent biological processing possible. This consists of breaking down the organic substances in two steps by aerobic degradation. In the tertiary treatment stage, the last remaining impurities are filtered out.

The solid residue is transported to specialized waste disposal companies. Here, too, a preventive approach is adopted. The cooling water which is needed for the production of chemicals is not discharged into the sewers but is recycled in cooling towers. Inside the towers the water is cooled to ambient air temperature so that it can be re-used in the production process.

A more detailed description of the WWTP is available in Appendix 3.

C. Citation of, and statement of compliance with, applicable emission requirements at Federal, State and local levels.

The effluent from the WWTP is discharged in compliance with the requirements set forth in the Janssen Pharmaceutica-Beerse "Waste water discharge permit," Ref to Appendix 4. The permit is obtained from the Flemish regional authorities "Vlaamse Maatschappij voor Waterzuivering." dated December 14, 1984.

Major requirements :

- Flow rate	7000 m^3/day
- pH	6.5 - 9.0
- B.O.D.	15 mg/l
- C.O.D.	150 mg/l
- Suspended solids	60 mg/l

D. The effect of approval upon compliance with current emission requirements at the production site

Based upon the waste water treatment controls described above, along with the relatively minor projected amounts of raw materials to be emitted into the waste water (see Confidential Appendix C), the proposed action is not expected to adversely affect the waste water treatment plant efficiency and is not expected to have impact on compliance with current waste legislation or to violate the current permit.

6.1.2 Air Emissions.

A. List of substances to be emitted:

The list of substances expected to be emitted into the environment is available in the Confidential Appendix C.

B. The controls exercised

Drug substance

Emissions from drug substance production containing organic - Volatile Organic Compound (VOC) - and inorganic emissions, are discharged to the atmosphere through a scrubber system. In addition all reactors are equiped with their own cooler condensing system.

Description of the scrubber

The chemical production units are provided with a two stage scrubber system. The first step consists of continuous addition of water to absorb the HCl. During the second step SO_2 is absorbed with NaOH.

Description of the VOC Abatement Emission Control system.

In the near future the VOC from the drug substance production will be controlled with a two stage activated carbon adsorption system (similar to the system which is planned at Geel; see Item 6.2.2.). The basic engineering is completed and the installation of the system is planned for 1993.

C. Citation of, and statement of compliance with, applicable emission requirements at Federal, State and local levels.

Air emissions are in compliance with the requirements set forth in the Janssen Pharmaceutica-Beerse " Permit to operate," Ref to appendix 4.
The permit is obtained from the Flemish regional authorities "Administratie voor Ruimtelijke Ordening en Leefmilieu." and is dated April 23, 1987.
Major requirements : Ref to appendix 4.

D. The effect of approval upon compliance with current emission requirements at the production site

Based upon the air emission controls described above, along with the relatively minor amounts of substances expected to be released to the atmosphere (see Confidential Appendix C), the proposed action is not expected to have impact on compliance with the current waste legislation or to violate the current permit.

6.1.3. Solid Waste

A. List of substances to be emitted:

The sludge obtained by the waste water treatment and the filter cake generated after filtration (drug substance) account for the majority of the solid waste that will be incinerated.

Packaging materials and process solvents will either be recuperated or incinerated depending on their composition.

The list of substances expected to be emitted into the environment is available in the Confidential Appendix C.

B. The controls exercised

No waste treatment is done at the site. Waste is temporarily stored in appropriate containers and at regular times hauled by a licensed transporter to a licensed high temperature waste incinerator. A manifest system is used.

Recuperation takes place at third-party facilities; however, some solvent recuperation will be done at the distillation unit at Janssen, Beerse.

C. Citation of, and statement of compliance with, applicable emission requirements at Federal, State and local levels.

Waste treatment is done in compliance with the Flemish regional waste legislation. Since no treatment takes place at the site, no special permit for treatment is required. However, monthly and yearly reports to the authorities are required.
Monthly report in appendix 4.

D. The effect of approval upon compliance with current emission requirements at the production site

Based upon the small expected amounts of solid waste (see Confidential Appendix C), along with the fact that no waste treatment is done at the production site, the proposed action is not expected to have impact on compliance with the current waste legislation.

6.2. JANSSEN PHARMACEUTICA - GEEL - BELGIUM.

This production site will produce the drug substance risperidone at the chemical production unit. This synthesis consists of a number of chemical reactions including crystallization and centrifugation, using various raw materials or intermediates.

6.2.1. Waste water.

A. List of substances to be emitted:

All reactions are carried out in closed glass-lined or stainless steel jacketed vessels within a controlled temperature and pressure range.

The water layer originated from the synthesis process is lead to the central waste water treatment plant, where all waste waters from the site are assembled.
The aqueous layers with high B.O.D./ C.O.D. content from "drug substance" production have a B.O.D.(Biological Oxygen Demand) ange of mg/l and a C.O.D. (Chemical Oxygen Demand) range of mg/l.

Detailed information on the introduction of substances into the environment is available in the Confidential Appendix C.

B. The controls exercised

All waste water is chanelled through a system of sewers to a central two stages biological waste water treatment plant. No water is pumped into the environment untreated, whether it is industrial waste water or sewage from the normal sanitary facilities.

Description of the Waste Water Treatment Plant

The waste water treatment plant (WWTP) has a population equivalent of this means that it has sufficient capacity (2840 kg. B.O.D./day) to process the waste water of inhabitants.

Certain types of waste water, which would otherwise disturb the normal biological process, are pre-treated (oxidation, sedimentation, adsorption on activated charcoal, ion exchange) before entering the main treatment plant, or are transported to another company for special treatment (solidification, incineration).

The waste water (after pre-treatment, if necessary) first undergoes physicochemical treatment, which makes subsequent biological processing possible. This consists of breaking down the organic substances in two steps by aerobic degradation. In the tertiary treatment stage the last remaining impurities are filtered out.

The solid residue is transported to specialized waste disposal companies. Here, too, a preventive approach is adopted. The cooling water which is needed for the production of chemicals is not discharged into the sewers but is recycled in cooling towers.
Inside the towers the water is cooled to ambient air temperature so that it can be re-used in the production process.

A more detailed description of the WWTP is available in Appendix 3.

The WWTP has been extended and has now a capacity of kg B.O.D./day (population equivalent of). The extension consisted of an extra equalisation unit, an activated sludge unit, a trickling filter, a final settling unit, a sludgehandling unit, thickners and a compressor building.

In order to minimize offensive emissions for the local residents the thrickling filter, the equalisation unit, the neutralisation unit and the sludgehandling unit were covered over. The installation has been in use since September 1992.

C. Citation of, and statement of compliance with, applicable emission requirements at Federal, State and local levels.

The effluent from the WWTP is discharged in compliance with the requirements set forth in the Janssen Pharmaceutica-Geel "Environmental permit," Ref to Appendix 5.
The permit is obtained from the Flemish regional authorities "Provinciebestuur Antwerpen." dated October 1, 1992.

Major requirements :

- Flow rate	3000 m^3/day
- pH	6.0 - 9.5
- B.O.D.	950 mg/l
- C.O.D.	1950 mg/l
- Suspended solids	1000 mg/l

D. The effect of approval upon compliance with current emission requirements at the production site

Based upon the waste water treatment controls described above, along with the relatively minor projected amounts of raw materials to be emitted into the waste water (see Confidential Appendix C), the proposed action is not expected to adversely affect the waste water treatment plant efficiency and is not expected to have impact on compliance with current waste legislation or to violate the current permit.

6.2.2 Air Emissions.

A. List of substances to be emitted:

The list of substances expected to be emitted into the environment is available in the Confidential Appendix C.

B. The controls exercised

Emissions from drug substance production containing organic - Volatile Organic Compound (VOC) - and inorganic emissions, are discharged to the atmosphere through a scrubber system. In addition all reactors are equiped with their own cooler condensing system.

Description of the scrubber

The chemical production units are provided with a two stage scrubber system. The first step consists of continuous addition of water to absorb the HCl. During the second step SO_2 is absorbed with NaOH.

Description of the VOC Abatement Emission Control system.

VOC from the drug substance production will be controlled with a two stage activated carbon adsorption system. The basic engineering is completed and the installation of the system is planned for 1993.

The **VOC Abatement Emission Control system** consists of the following major components:

* The *preconditioning unit* with three Solvent Loaden Air (SLA) blower assemblies, steam reheat coils and relative humidity controls.

* The activated carbon *Adsorption Unit* with adsorbers, related equipment, initial charge of activated carbon, fully-automatic controls and inlet and exhaust analyzers.

* The *Steam Regeneration Unit:* The Carbon Adsorption System will include a Steam Regeneration Unit with heat exchanger, pump, tanks, steam regenerator, automatic controls and related components for revaporization and closed loop recycling of the water layer to produce low pressure steam for regeneration of the carbon beds.

* A *common Distillation Unit* to process the combined decanter water phases from the carbon adsorption systems. The Distillation System includes heat exchangers, tanks, pumps, column, automatic controls and related equipment for the removal and concentration of the solvents contained in the water layer.

The solvents contained in the water layer will either be recuperated by third parties, either be incinerated by a licensed high temperature waste incinerator.

C. Citation of, and statement of compliance with, applicable emission requirements at Federal, State and local levels.

Air emissions are in compliance with the requirements set forth in the Janssen Pharmaceutica-Geel " Permit to operate," Ref to Appendix 5.
The permit is obtained from the Flemish regional authorities "Administratie voor Ruimtelijke Ordening en Leefmilieu." and is dated November 26, 1987.
Major requirements : Ref to Appendix 5.

D. The effect of approval upon compliance with current emission requirements at the production site

Based upon the air emission controls described above, along with the relatively minor amounts of substances expected to be released to the atmosphere (see Confidential Appendix C), the proposed action is not expected to have impact on compliance with the current waste legislation or to violate the current permit.

6.2.3. Solid Waste

A. List of substances to be emitted:

The sludge obtained by the waste water treatment and the filter cake generated after filtration , account for the majority of the solid waste that will be incinerated.
Process solvents will either be recuperated or incinerated depending on their composition.

B. The controls exercised

No waste treatment is done at the site. Waste is temporarilly stored in appropriate containers and at regular times hauled by a licensed transporter to a licensed high temperature waste incinerator. A manifest system is used.

Recuperation takes place at third-party facilities; however, some solvent recuperation will be done at the distillation unit at Janssen, Beerse.

C. Citation of, and statement of compliance with, applicable emission requirements at Federal, State and local levels.

Waste treatment is done in compliance with the Flemish regional waste legislation. Since no treatment takes place at the site no special permit for treatment is required. However monthly and yearly reports to the authorities are required.
Monthly report in Appendix 5.

D. The effect of approval upon compliance with current emission requirements at the production site

Based upon the small expected amounts of solid waste (see Confidential Appendix C), along with the fact that no waste treatment is done at the production site, the proposed action is not expected to have impact on compliance with the current waste legislation.

6. INTRODUCTION OF SUBSTANCES INTO THE ENVIRONMENT.

The site at Gurabo, Puerto Rico has facilities both for chemical and pharmaceutical production. Only a part of the synthesis of risperidone is conducted at this site, starting from Janssen intermediates. Also manufacturing of the drug product (caplets) will take place at the Gurabo site.

6.3.1. Waste water.

A. List of substances to be emitted:

Drug substance

All reactions are carried out in closed glass-lined or stainless steel jacketed vessels within a controlled temperature and pressure range.

The water layer originated from the synthesis process is lead to the waste water treatment plant.The aqueous layers with high B.O.D./ C.O.D. content from "drug substance" production have a B.O.D.(Biological Oxygen Demand) range of mg/l and a C.O.D. (Chemical Oxygen Demand) range of mg/l.

Drug product

The manufacturing of the risperidone tablets occurs in stainless steel containers. It consists of sieving and mixing the ingredients, spraying a solution in a fluidized-bed granulator, drying and sieving the granules. The pressing to tablets occurs in a rotary tablet press. Following product removal, the process containers are cleaned and rinsed with water. Aqueous layers from "drug product" production have a low B.O.D./ C.O.D. content. The B.O.D. range lies between mg/l and the C.O.D. range between mg/l.

Detailed information on the introduction of substances into the environment is available in Confidential Appendix C.

B. The controls exercised

Description of the Waste Water Treatment System

The combined process waste waters from come into two aerated tanks with a capacity of gallons each. Effluent from the equalization tanks is pumped to the pH adjustment tanks. After the pH adjustment tanks, the separation of solids (already flocculated and coagulated by the addition of polymers) takes place. The underflow from such clarifier is pumped to the sludge digestor. The effluent from the primary clarifier is transfered to an equalisation tank with a gallons capacity and than to the bioreactor for the secondary biological treatment.

Powdered activated carbon is added at the entrance of the bioreactor to improve the B.O.D. and C.O.D. removal efficiency. After biological treatment, the water flows to the secondary clarifiers to separate the sludge from the water effluent. The water effluent is pumped to a holding tank. The aerobic digestor tank is designed to further stabilize the biological solids prior to dewatering and disposal.

The two stages biological waste water treatment system has a capacity from 900 kg B.O.D./day.

00-00032

C. Citation of, and statement of compliance with, applicable emission requirements at Federal, State and local levels.

The effluent from the WWTP is discharged in compliance with the requirements set forth in the "Industrial Bulk waste water discharge permit.", issued by "The Puerto Rico Aqueduct and Sewer Authority" dated April 20, 1992
The permit is available in Appendix 6.

Major requirements :

* *Bulk discharge into the Puerto Nuevo Treatment Plant.*

- Flow rate 7000 m^3/day
- pH 6.5 - 9.0
- B.O.D. 175 mg/l
- C.O.D. 300 mg/l.

The permittee shall not discharge to Puerto Nuevo PWWTP more than tank-trucks per day. gallons per day.)

D. The effect of approval upon compliance with current emission requirements at the production site

Based upon the waste water treatment controls described above, along with the relatively minor projected amounts of raw materials to be emitted into the waste water (see Confidential Appendix C), the proposed action is not expected to adversely affect the waste water treatment plant efficiency and is not expected to have impact on compliance with current waste legislation or to violate the current permit.

6.3.2 Air Emissions.

A. List of substances to be emitted:

The list of substances expected to be emitted into the environment is available in Confidential Appendix C.

B. The controls exercised

Drug substance

Emissions from drug substance production are discharged to the atmosphere through a two stage scrubber system.
In addition all reactors are equiped with their own cooler condensing system.
The emissions contain organic - Volatile Organic Compound (VOC) - and inorganic emissions.

Description of the scrubber

The chemical production units are provided with a two stage scrubber system. The first step consists of continuous addition of water to absorb the HCl. During the second step SO_2 is absorbed with NaOH.

Description of the VOC Abatement Emission Control system.

In the near future the VOC from the drug substance production will be controlled with a two stage activated carbon adsorption system (similar to the system which is planned at Geel; see Item 6.2.2.). The basic engineering is completed and the installation of the system is planned for 1993.

Drug product

The manufacturing process for the finished product operation consists of weighing, processing by automatic sieving and mixing and formulating in the tablet form.
Dust emissions from the drug product production are controlled with a high efficiency, dust filtration system. Emissions are negligible.

C. Citation of, and statement of compliance with, applicable emission requirements at Federal, State and local levels.

Air emissions are in compliance with the requirements set forth in the Janssen Inc. " Air emission permit.", dated March, 1992.
The permit is obtained from the Puerto Rico Environmental Quality Board.

The permit and the major requirements are available in Appendix 6.

D. The effect of approval upon compliance with current emission requirements at the production site

Based upon the air emission controls described above, along with the relatively minor amounts of substances expected to be released to the atmosphere (see Confidential Appendix C), the proposed action is not expected to have impact on compliance with the current waste legislation or to violate the current permit.

6.3.3. Solid Waste

A. List of substances to be emitted:

The sludge obtained by the waste water treatment will be disposed of by landfilling.
The filter cake generated after filtration (drug substance), the off spec formulations, the dust filters and some packaging materials (drug product) account for the majority of the solid waste that will be incinerated.
Packaging materials and process solvents will either be recuperated or incinerated depending on their composition.

B. The controls exercised

No hazardous waste treatment is done at the site. Waste is temporarilly stored in appropriate containers and at regular times hauled by a licensed transporter to a licensed high temperature waste incinerator.

A RCRA part B permit was obtained on August 11, 1986.

C. Citation of, and statement of compliance with, applicable emission requirements at Federal, State and local levels.

Hazardous and solid waste treatment, storage and disposal is done in compliance with the requirements set forth in the RCRA permit #PRD-980536049, available in Appendix 6.

D. The effect of approval upon compliance with current emission requirements at the production site

Based upon the small expected amounts of solid waste (see Confidential Appendix C), along with the fact that no waste treatment is done at the production site, the proposed action is not expected to have impact on compliance with the current waste legislation.

6. INTRODUCTION OF SUBSTANCES INTO THE ENVIRONMENT.

E. Estimate of the Concentrations of Substances Expected to Enter the Environment as a Result of Use and/or Disposal of Products Affected by the Action.

1. Maximum Expected Emitted Concentration (MEEC) of risperidone in Wastewater from Use of Drug Product

The maximum expected emitted concentration (MEEC) of risperidone in wastewater from use of the drug product has been estimated based upon the mathematical formula provided in the PMA interim guidance document. [3] The corresponding calculation is provided in Appendix F.

The MEEC is based on certain assumptions, including dosing an estimate of the number of patients that would be prescribed the drug during the fifth year of marketing at the maximum therapeutic dose. In addition, although risperidone is the administered drug, a portion of the dose is excreted as metabolites, the predominant one of which arises from oxidative hydroxylation (see Appendix H). This is not taken into account in the calculation in Appendix F. However, this has no significant bearing on the MEEC calculation since the primary metabolite is of approximately the same molecular weight as risperidone.

2. Expected Environmental Concentration (EEC) of risperidone in the Aquatic Environment from Use of Drug Product

The expected environmental concentration (EEC) of risperidone in the aquatic environment from use of the drug product has been estimated by correcting the MEEC by appropriate factors based upon processes that would be expected to remove and/or dilute risperidone present in wastewater. The corresponding calculation is provided in Appendix F. Based upon information provided in Item 7, sorption of the drug onto sludge/sediment at the wastewater treatment facility and dilution of the effluent wastewater by the receiving surface waters are the anticipated primary removal/dilution processes. Taken together, these factors would be expected to reduce the MEEC of risperidone by at least several orders of magnitude.

3. Expected Emissions from Disposal

No substances are expected to enter the environment from disposal because solid waste from manufacturing, packaging, labeling, quality control testing, and distribution (i.e. waste resulting from rejected, returned or outdated substance/product) is disposed of by incineration or landfilling.

7. FATE OF EMITTED SUBSTANCES IN THE ENVIRONMENT

The purpose of this section is to present information relevant to the fate and transport of risperidone. Assessment of the fate/transport scenario of risperidone requires an evaluation of processes affecting its structural transformations and its partitioning between the environmental media air, soil and water. These processes include hydrolysis, photolysis, oxidation, volatilization, sorption, bioaccumulation and biodegradation.

For the purposes of the fate studies, risperidone has been chosen as the study molecule. A rationale for this choice is provided in Confidential Appendix G.

A summary of the environmental fate and transport of risperidone is provided in Table 7A. A concluding statement regarding the probable fate of risperidone in the environment is provided in section 7.4 .

7 1. AIR

Atmospheric processes are not relevant to the environmental fate of risperidone, because it is released only to sewage treatment facilities where volatilization of drug substance to the atmosphere could not be an operative process. Moreover, risperidone is not a volatile substance, as indicated by its low vapor pressure, which was calculated to be 3.17×10^{-4} Pa (= 3.13×10^{-9} atm) according to the method developed by Mackay et al.[4, 5, 6]

7.2. SOIL

7.2.1. Soil Sorption/Desorption

In the soil sorption/desorption studies, three different soils were used, all of which showed that risperidone is adsorped strongly to soil with minor degrees of desorption. The octanol-water partition coefficient (log P of about 1.4 at pH 5.0 to log P of about 4 at pH 9.1 in aqueous media) corroborates the results of sorption to lipophilic material.

Since sewage sludge /sediment is ordinarily disposed of by incineration or landfilling (which constitute final disposal), other soil environmental processes which may deplete risperidone need not be considered.

7.3. WATER

Aquatic processes are not considered to be very significant to the environmental fate of risperidone in the water of the sewage treatment facility or the surface water that potentially receives the effluent, since the risperidone present in waste water will be strongly sorbed to the waste sludge/sediment. Thus, there will be little or no tendency for risperidone to be released to the effluent water. Nevertheless, to the small extent that risperidone may be released to the aquatic environment, the possible fate of risperidone due to various aquatic environmental processes is considered in this section.

7.3.1 Hydrolysis

The hydrolysis of risperidone was examined following the FDA handbook PB 87-175345, test 3.09. The preliminary test was conducted at 50°C in buffer solutions at pHs 5-9. At each pH, <10% decomposition was observed after 5 days. Thus, risperidone is considered hydrolytically stable.

7.3.2 Photolysis

Risperidone exhibits a moderately intense absorption maximum at about 275 nm (log emax of about 4) which extends to about 300 nm. The sum of wavelength distributions of atmospheric sunlight less than 300 nm accounts for <1% of total atmospheric sunlight. [7] Furthermore, since only negligible amounts of risperidone would be expected to become desorbed from the sediment and transported upward to the shallow depths of the surface water (where exposure to sunlight would be maximized), photochemical processes are not considered to be environmentally significant.

7.3.3 Oxidation

Hydroxyl (and alkylperoxy) radicals, generated in surface water from the photolysis of naturally occurring substances that absorb terrestrial sunlight [8], have been observed to oxidize many organic chemicals [9]. However, as a model, thermally induced oxidative decomposition of risperidone using hydrogen peroxide (a potential source of hydroxyl and peroxy radicals) results in the formation of only a small amount of oxidation products (see Confidential Appendix E). Nevertheless, since other oxidative pathways may be available from photochemically generated radicals, it is conceivable that photochemical processes could contribute to the degradation of small amounts of risperidone that may be released to the effluent water.

7.3.4. Sorption

As discussed in section 7.2.1., the sorption/desorption study and the octanol-water partition coefficient indicates that risperidone will mainly become sorbed to lipophilic material in sewage sludge or sediment.

7.3.5. Volatilization

The octanol-water partition coefficient indicates that risperidone will be strongly sorbed to sludge/sediment and so will only be available in very low concentrations at the water surface. This factor, taken together with its low vapor pressure, ensures that volatilization will not be a significant process in the aquatic media.

7.3.6. Biodegradation

The biodegradability of risperidone was investigated according to the FDA Handbook: PB 87-175345, test 3.11. A composite inoculum, consisting of secundary effluent from a domestic waste water treatment plant and soil extract, was used. The inoculum was specifically adapted to the test and reference substance before the start of the biodegradation test. Risperidone cannot be regarded as biodegradable under the used test conditions. However, the CO2 evolution test is a simple screening test for ready biodegradability. This negative result does not necessarily mean that the chemical will not be biodegraded under relevant environmental conditions.

7.3.7 Bioconcentration

The bioconcentration factor (BCF) has been defined as the concentration of a chemical in an organism divided by the concentration of the chemical in water. The bioconcentration factor for fish can be calculated from the following equation: [10]

$\log BCF = 0.79 \log K_{ow} - 0.40 \qquad (r^2 = 0.926; n = 122)$

where: K_{ow} = octanol-water partition coefficient

r^2 = the coefficient of determination (proportionate reduction in error)

n = the number of chemicals from which the regression was developed

Using the octanol-water partition coefficient ($\log K_{ow} = 1.67$) determined for risperidone in water, the log BCF calculated by this method is 0.92. This value indicates that the tendency for bioconcentration of risperidone in aquatic life is negligible. [11]

7.4 Probable Fate of Risperidone in Environmental Systems

Based upon the fate studies provided in Confidential Appendix E, waste risperidone will partition predominanly to the sludge in the waste water treatment facilities. The predominant pathway for its destruction is by sorption onto waste sludge/sediment, which is then disposed of by incineration or landfill. Other processes, such as biodegradation, may also contribute to depletion of risperidone. The processes that may affect the environmental fate of risperidone are summarized in Table 7A.

The maximum expected emitted concentration (MEEC) of risperidone in the waste water from the use of drug product has been estimated (see Confidential Appendix D). As discussed in Item 6.e, this calculation does not take into account other factors such as the favorable partitioning of risperidone to the waste sludge (which might be expected to reduce the MEEC by two to four orders of magnitude) and dilution of the effluent from the waste water to the receiving body of surface water (which may vary by a factor of about 10^{-7} for fast-flowing rivers to essentially no dilution for settling ponds or intermittently dry drainage channels [12,13]). Taking these factors into consideration, it can be concluded that the actual concentration of risperidone which is emitted to the aquatic environment will be at least several orders of magnitude less than the MEEC.

TABLE 7A. SUMMARY OF ENVIRONMENTAL FATE AND TRANSPORT OF RISPERIDONE

ENVIRONMENTAL PROCESS	SUMMARY STATEMENT
Hydrolysis	Risperidone can be considered hydrolytically stable based upon direct measurements between pH 5-9
Photolysis	Photolysis is not considered significant since only negligible amounts of risperidone will become exposed to low-wavelength sunlight
Oxidation	Oxidation of risperidone by hydroxyl radicals may occur slowly in aqueous media as modeled using hydrogen peroxide (a potential source of hydroxyl radicals)
Sorption	Risperidone will be strongly sorbed to sewage sludge and sediment based upon octanol-water partition data and soil sorption/desorption studies
Volatilization	Volatilization is an unlikely transport process for risperidone because of its extremely low estimated vapor pressure and its propensity to be sorbed to sludge/sediment
Biodegradation	Biodegradation of risperidone can not be excluded under actual environmental conditions (although it does not occur with a simple CO_2 evolution test)
Bioconcentration	Risperidone is not considered to have a tendency for bioconcentration

8. EFFECT OF EMITTED SUBSTANCES IN THE ENVIRONMENT

The purpose of this section is to predict the effect of risperidone at the ecosystem level in each of the environmental media (air, soil and water) based upon (to the extent applicable) quantitative comparison between the introduction/fate scenario of risperidone (Items 6-7) and toxicity data for relevant organsims/species in each environmental compartment.

Toxicity data are summarized in 8.1-8.5 below and are further described in Confidential Appendix F. The environmental effects are summarized in 8.6 and Table 8A.

8.1. Algal Assay

The effect of risperidone on the growth of two species, being the unicellular green alga *Selenastrum capricornutum* and the unicellular blue green alga *Microcystis aeruginosa* was investigated following the FDA Handbook test 4.01: Algal Assay.

The effect on the growth of *Selenastrum capricornutum:*
The exposure period was 10 days because the plateau-phase was reached. Test concentrations were mg/L. Risperidone exerts a slight effect on growth at 10 mg/L; at the higher concentrations, algal growth is more significantly inhibited. However, as discussed in Item 8.6, the test levels at which inhibition is observed are much greater than the effective environmental concentration of risperidone.

The effect on the growth of *Microcystis aeruginosa :*
The exposure period was 10 days because the plateau-phase was reached. Test concentrations were mg/L. At first, risperidone exerts a delay in the growth of the alga Microcystis aeruginosa at the 100 mg/L level. Later on, the growth is stimulated at this concentration, so eventually the maximum standing crop of the alga is not affected.

8.2. Toxicity Towards Microbial Organisms

To determine if risperidone would affect the development of environmentally important bacteria, fungi or blue-green alga, the Microbial Growth Inhibition test was performed according to the FDA Handbook: PB 87-175345, test 4.02: Microbial Growth Inhibition. Representative species of 5 different groups, being free-living nitrogen fixing bacteria, blue-green alga, soil bacteria, ascomycetes and moulds, were tested for their sensitivity to risperidone. The growth of the 2 bacteria, the blue-green alga and Penicillium were not affected by concentrations of risperidone up to 100 ppm. Although the compound caused a slight retardation of the growth of Tricoderma at first, the MIC-values (minimum inhibitory concentration) of all organisms are situated above ppm. Thus, the actual concentrations of risperidone in the sewage system or surface water will not affect the development of these environmentally important micro-organisms.

8.3. Daphnia Acute Toxicity

The acute toxicity of risperidone in the water-flea *Daphnia magna* was investigated following the FDA Handbook: PB 87-175345, test 4.08: Daphnia Acute Toxicity. Nominal test substance concentrations were mg risperidone per liter. The exposure period was 48 hours and the number of immobile daphnids was recorded daily. Based on the nominal concentrations of risperidone in the test vessels the EC_{50} - 48 h value in the water-flea *Daphnia magna* was mg/l .

8.4. Freshwater Fish Acute Toxicity

The acute toxicity of risperidone in the Bluegill sunfish *Lepomis macrochirus* was investigated in a static fish test as described in the FDA Handbook: PB 87-175345, test 4.11: Freshwater Fish Acute Toxicity. Nominal test concentrations were and mg risperidone per liter. The exposure period was 96 hours. The behaviour and the mortality of the Bluegill sunfish were recorded daily. The LC_{50} - 96 h value of risperidone in the Bluegill sunfish was 5.8 mg risperidone per liter.

8.5 Toxicity in Mammalian Species

The toxicological effects of risperidone on several mammals (mouse, rat, dog) have been determined and are discussed further in Appendix F. The worst case of acute oral toxicity occured in male and female mongrel dogs, where the LD_{50} was 18.3 mg/kg . (The percentage mortality after 14 days was used to calculate the LD_{50} values by probit analysis.)

8.6 Conclusions

In accordance with 21 CFR 25.15 (b)(6), the criterion concentration of risperidone (for risperidone to be defined as toxic in the environment) would be % of the concentration resulting in % lethality. For the test organisms described in 8.3-8.4, the criterion concentration would be mg risperidone per liter. This value is about four orders of magnitude greater than the estimated maximum concentration of risperidone in sewage treatment facilities (discussed in Item 6) . Similar statements may be made regarding the animal toxicity studies described in 8.5. In all cases, the toxicity criterion concentration/emission concentration ratio may be expected to increase by at least several more orders of magnitude in surface waters (due to sludge/water partitioning and dilution effects discussed in Item 7). Therefore, the concentrations required to observe toxicological effects are exceedingly high relative to the emitted concentrations due to use. The results summarized in 8.1-8.2 demonstrate that, in most cases, risperidone does not affect the development of alga nor of environmentally important microorganisms that would be found in sewage sludge or aquatic ecosystems. Some growth inhibition is observed with green alga but only at levels which far exceed the expected environmental concentration, especially when it is taken into account that the exceedingly small amount of risperidone released to the receiving waters will be attenuated further by favored sorption onto the sediment. Since risperidone does not effectively volatilize to the atmospheric compartment (as discussed in Item 7), airborne effects of risperidone are not environmentally relevant.

Therefore, the overall conclusion is that emission of risperidone from use of the drug will not result in environmentally adverse effects.

TABLE 8A. SUMMARY OF ENVIRONMENTAL EFFECTS OF RISPERIDONE

STUDY/REF.	RESULTS/CONCLUSIONS
Algal Assay (EA Handbk, 4.01)	Slight effect on growth observed at 10 mg/L risperidone (far above the expected environmental concentration) after 10 days in the green alga; no lasting effect on growth observed at up to 100 mg/L risperidone after10 days in the blue-green alga. Therefore, the effects of risperidone on algal growth are not environmentally significant.
Microbial Toxicity (EA Handbk, 4.02)	No growth inhibition observed at up to 100 ppm risperidone; therefore risperidone is considered practically nontoxic towards sewage and surface water microorganisms
Daphnia Acute Toxicity (EA Handbk, 4.08)	The EC_{50}-48 hr value is 6.0 mg/l; risperidone is considered to be moderately toxic towards related water organisms. [14]
Bluegill Acute Toxicity (EA Handbk, 4.11)	The LC_{50}-96 hr value is 5.8 mg risperidone per liter; therefore, risperidone is considered to be moderately toxic towards related fresh-water fish. [14]
Mouse/Rat/ Dog Acute Toxicity (Appendix F)	The worst case LD_{50} value is 18.3 mg/kg when administered orally; risperidone is considered to be moderately hazardous towards related mammalian life.

9. USE OF RESOURCES AND ENERGY

a. Natural Resources (Land Use, Minerals, Energy) Required To Produce, Transport, Use and/or Dispose of Drug

The estimate of the energy requirement for the manufacture of risperidone for marketing in the US is approximately 0.1 % of the total energy use for drug production.

Detailed information is provided in Confidential Appendix I.

b. Effects, if any, upon Endangered or Threatened Species and upon Property Listed in National Register of Historic Places:

Janssen Pharmaceutica will produce the drug substance and/or product only within the existing facilities in Belgium and Puerto Rico. Hence, there will be no adverse effect on surrounding properties listed in the National Register of Historic Places. Letters of acknowledgement from the Historic Preservation Office and related governmental agencies in Puerto Rico are provided in Appendix 9.

Based on the available information from Fate (Item 7) and Effect (Item 8), resource and energy use will not effect endangered or threatened species.

10. MITIGATION MEASURES

The design and use of facilities, buildings, equipment, and procedures for manufacturing, packaging, distribution, and disposal of the drug substance and drug product meet current standards of operation (building and energy regulations), pharmaceutical production (Good Manufacturing Practices), environmental protection, and occupational exposure.

Occupational standards in Belgium are prescribed in the national "General Regulation for Labor Patronage" (Algemeen Reglement voor Arbeidsbescherming, ARAB). Most of the standards are the TLV's set by ACGIH. The Janssen facilities in Belgium comply with these standards, which are also included in our MSDS for chemical substances.

The controls exercised to mitigate potential adverse environmental impacts associated with operations have been described in Item 6. Internal and External inspections help assure that mitigation practices are maintained.

There is no potential adverse environmental impact from disposal of the drug product by consumers, which would require special disposal instructions in the package circular.

Other practices in place to mitigate potential adverse environmental impacts include:

(a) Spill-control procedures, as required by Federal, State, and local regulation, or company policy, wherever there is potential for adverse effect.

(b) Personnel hygiene and health, safety, and GMP training are monitored regularly.

(c) Waste minimization is practiced in accordance with regulations or when there is an opportunity for resource conservation. Examples include: recovering and redistillation of synthesis solvents; recycling cardboard, paper, glass and metals.

11. ALTERNATIVES TO THE PROPOSED ACTION

In accordance with Council on Environmental Quality (CEQ) regulations, the only alternative to the proposed action would be (a) No Action (Not Approved), i.e. the only alternative would be not effecting the proposed action to approve the marketing of RISPERDAL® tablets. That would deprive persons with severe mental illness of a safe and effective drug, which has been demonstrated to be directly associated with improvement in the quality of life and reduction of the economic burden of the disease.

Furthermore, adverse environmental impacts have not been identified with the proposed action to produce and market RISPERDAL® tablets. Manufacturing, packaging, labeling, quality-control testing and distribution of the product have not been associated with any known environmental impacts. Because of the strict environmental controls and mitigation practices exercised, there is low risk for adverse environmental impact.

12. LIST OF PREPARERS.

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Qualifications : Ref. to Appendix 8.

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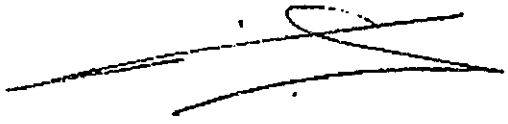
13. CERTIFICATIONS.

" The undersigned official certifies that the information presented is true, accurate, and complete to the best of the knowledge of the firm."

August 6, 1993



Roger Wils

Vice President Environmental Affairs

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