NDA20-243

P9 2 AP Ltr

3. We acknowledge the commitment made in your September 9, 1994 amendment to conduct an adequate and well-controlled relapse prevention trial for fluvoxamine in the maintenance treatment of OCD.

4. We acknowledge the commitment made in your September 9, 1994 amendment to conduct additional studies to clarify the metabolism of fluvoxamine.

5. We acknowledge the commitment made in your September 9, 1994 amendment to complete and submit your study in children and adolescents with OCD.

Pharmacology

We acknowledge the commitment made in your September 9, 1994 amendment to conduct repeat preclinical Segment I and II reproduction studies in the rat based upon your rangefinding and/or toxicokinetic studies. We believe that the original studies did not achieve adequate exposure. If you decide to request that the Agency accept those studies, please provide complete toxicity and/or toxicokinetic data accompanied by a comprehensive discussion to support your position.

Manufacturing and Controls

We acknowledge the commitment made in your September 9, 1994 amendment to have your established name, fluvoxamine maleate, adopted by the USAN Council.

Biopharmaceutics

We acknowledge the commitment made in your September 9, 1994 amendment to accept the following dissolution method and specification for all tablet strengths:

Apparatus:	USP Apparatus 2 (Paddle)
Paddle Speed:	50 RPM
Medium:	900 ml purified water at 37°C ± 0.5°C
Q:	NLT

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 20-243. 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

NDA 20-243

N20-243

APP LTR
LBL

NDA 20-243

DEC 5 1994

Solvay Pharmaceuticals
Attention: J. Greg Perkins, Ph.D.
Vice President, Regulatory Affairs
901 Sawyer Road
Marietta, Georgia 30062

Dear Dr. Perkins:

Please refer to your New Drug Application (NDA) dated December 24, 1991, submitted pursuant to section 505(b) of the Federal Food, Drug, and Cosmetic Act for Luvox® (Fluvoxamine maleate) 25, 50, 100, and 150 mg Tablets, NDA 20-243.

We also refer to an Agency Approvable letter dated August 30, 1994, and we also acknowledge receipt of your additional communications dated September 7, 9, 20, November 4, and December 1, 1994.

Reference is also made to a telephone conversation between Mr. Don Ruggirello of your office and Mr. Paul David of this Agency dated November 1, 1994, in which the Agency notified you by facsimile transmission of the environmental assessment deficiencies contained in your resubmission dated September 9, 1994. We also refer to the November 30, 1994, telephone conference between Mr. Ruggirello and Ms. Nancy Sager, of this Agency, in which Ms. Sager informed you that any changes in the method of disposal of fluvoxamine maleate will require submission of a supplement to the approved NDA.

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 in Obsessive Compulsive Disorder (OCD). Additionally, we refer to a November 9, 1994, conference call between staff from FDA and Solvay during which agreement was reached on final labeling revisions and additional Phase 4 commitments. Accordingly, the application, with these labeling revisions, is approved, effective as of the date of this letter.

Accompanying this letter (ATTACHMENT 1) is the labeling, including the revisions agreed to, that should be used for marketing this drug product. These revisions are terms of the NDA approval. Marketing the product before making the agreed upon revisions in the product's labeling may render the product misbranded and an unapproved new drug.

Please note that the labeling only reflects the strengths which you intend to market, i.e., the 50 and 100 mg tablets.

Below is a listing of Phase 4 commitments and other agreements made between Solvay and the Agency.

Clinical

1. As discussed in our conference call dated November 9, 1994, we note your agreement to study the elimination half-life of fluvoxamine at steady state after multiple oral doses of 300 mg/day.

2. As discussed in our conference call dated November 9, 1994, we note your agreement to conduct a clinical study to explore the possible effect of the combined use of fluvoxamine and terfenadine on parent terfenadine levels and/or QT intervals.

cc:
ORIG 20-243
HF-2/M watch
HFD-2/L pkin
HFD-85
HFD-100/ ple
HFD-102/ Vincent/N
HFD-120/D FI
HFD-120/Pl ber/
/GF zger
/SBl /WRees
HFD-240/SDa e
HFD-344/RYou
HFD-420/RBaw
HFD-638
HFD-713/LNevi /DHoberman
HFD-735
District Offic
Doc # LTRFLUVX 1
NDA APPROVED

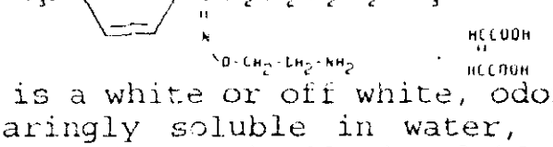
ATTACHMENT

Luvox
(Fluvoxamine Maleate)
Tablets
50 mg and 100 mg

DESCRIPTION

Fluvoxamine maleate is a selective serotonin (5-HT) reuptake inhibitor (SSRI) belonging to a new chemical series, the 2-aminoethyl oxime ethers of aralkylketones. It is chemically unrelated to other SSRIs and clomipramine. It is chemically designated as 5-methoxy-4'-(trifluoromethyl)valerophenone-(E)-O-(2-aminoethyl)oxime maleate (1:1) and has the empirical formula $C_{15}H_{21}O_2N_2F_3 \cdot C_4H_4O_4$. Its molecular weight is 434.4.

The structural formula is:



Fluvoxamine maleate is a white or off white, odorless, crystalline powder which is sparingly soluble in water, freely soluble in ethanol and chloroform and practically insoluble in diethyl ether.

LUVOX™ Tablets are available in 50 mg and 100 mg strengths for oral administration. In addition to the active ingredient, fluvoxamine maleate, each tablet contains the following inactive ingredients: carnauba wax, hydroxypropyl methylcellulose, mannitol, polyethylene glycol, polysorbate 80, pregelatinized starch, silicon dioxide, sodium stearyl fumarate, starch, synthetic iron oxides, and titanium dioxide.

CLINICAL PHARMACOLOGY

Pharmacodynamics

The mechanism of action of fluvoxamine maleate in obsessive compulsive disorder is presumed to be linked to its specific serotonin reuptake inhibition in brain neurons. In preclinical studies, it was found that fluvoxamine inhibited neuronal uptake of serotonin.

In <u>in vitro</u> studies fluvoxamine maleate had no significant affinity for histaminergic, alpha or beta adrenergic, muscarinic or dopaminergic receptors. Antagonism of some of these receptors is

thought to be associated with various sedative, cardiovascular, anticholinergic, and extrapyramidal effects of some psychotropic drugs.

Pharmacokinetics

Bioavailability

The absolute bioavailability of fluvoxamine maleate is 53%. Oral bioavailability is not significantly affected by food.

In a dose proportionality study involving fluvoxamine maleate at 100, 200 and 300 mg/day for 10 consecutive days in 30 normal volunteers, steady state was achieved after about a week of dosing. Maximum plasma concentrations at steady state occurred within 3-8 hours of dosing and reached concentrations averaging 88, 283 and 546 ng/mL, respectively. Thus, fluvoxamine had nonlinear pharmacokinetics over this dose range, i.e., higher doses of fluvoxamine maleate produced disproportionately higher concentrations than predicted from the lower dose.

Distribution/Protein Binding

The mean apparent volume of distribution for fluvoxamine is approximately 25 L/kg, suggesting extensive tissue distribution.

Approximately 80% of fluvoxamine is bound to plasma protein, mostly albumin, over a concentration range of 20 to 2000 ng/mL.

Metabolism

Fluvoxamine maleate is extensively metabolized by the liver; the main metabolic routes are oxidative demethylation and deamination. Nine metabolites were identified following a 5 mg radiolabelled dose of fluvoxamine maleate, constituting approximately 85% of the urinary excretion products of fluvoxamine. The main human metabolite was fluvoxamine acid which, together with its N-acetylated analog, accounted for about 60% of the urinary excretion products. A third metabolite, fluvoxethanol, formed by oxidative deamination, accounted for about 10%. Fluvoxamine acid and fluvoxethanol were tested in an in vitro assay of serotonin and norepinephrine reuptake inhibition in rats; they were inactive except for a weak effect of the former metabolite on inhibition of serotonin uptake (1-2 orders of magnitude less potent than the parent compound). Approximately 2% of fluvoxamine was excreted in urine unchanged. (See PRECAUTIONS -- Drug Interactions).

Elimination

Following a ^{14}C labelled oral dose of fluvoxamine maleate (5 mg), an average of 94% of drug-related products was recovered in the urine within 71 hours.

The mean plasma half-life of fluvoxamine at steady state after multiple oral doses of 100 mg/day in healthy, young volunteers was 15.6 hours.

Elderly Subjects

In a study of LUVOX™ Tablets at 50 and 100 mg comparing elderly (aged 66-73) and young subjects (aged 19-35), mean maximum plasma concentrations in the elderly were 40% higher. The multiple dose elimination half-life of fluvoxamine was 17.4 and 25.9 hours in the elderly compared to 13.6 and 15.6 hours in the young subjects at steady state for 50 and 100 mg doses, respectively.

In elderly patients, the clearance of fluvoxamine was reduced by about 50% and, therefore, LUVOX™ Tablets should be slowly titrated during initiation of therapy.

Hepatic and Renal Disease

A cross study comparison (healthy subjects vs. patients with hepatic dysfunction) suggested a 30% decrease in fluvoxamine clearance in association with hepatic dysfunction. The mean minimum plasma concentrations in renally impaired patients (creatinine clearance of 5 to 45 mL/min) after 4 and 6 weeks of treatment (50 mg bid, N=13) were comparable to each other, suggesting no accumulation of fluvoxamine in these patients. (See PRECAUTIONS, Use in Patients with Concomitant Illness.)

Clinical Trials

The effectiveness of LUVOX™ Tablets for the treatment of Obsessive Compulsive Disorder (OCD) was demonstrated in two 10-week multicenter, parallel group studies of adult outpatients. Patients in these trials were titrated to a total daily fluvoxamine dose of 150 mg/day over the first two weeks of the trial, following which the dose was adjusted within a range of 100-300 mg/day (on a bid schedule), on the basis of response and tolerance. Patients in these studies had moderate to severe OCD (DSM III-R), with mean baseline ratings on the Yale-Brown Obsessive Compulsive Scale (YBOCS, total score) of 23. Patients receiving fluvoxamine maleate experienced mean reductions of approximately 4 to 5 units on the YBOCS total score, compared to a 2 unit reduction for placebo patients.

The following table provides the outcome classification by treatment group on the Global Improvement item of the Clinical Global Impressions (CGI) scale for both studies combined.

Table 1. Outcome Classification (%) on CGI-Global Improvement Item for Completers in Pool of Two OCD Studies		
Outcome Classification	Fluvoxamine (N = 120)	Placebo (N = 134)
Worse	4%	6%
No Change	31%	51%
Minimally Improved	22%	32%
Much Improved	30%	10%
Very Much Improved	13%	2%

Exploratory analyses for age and gender effects on outcomes did not suggest any differential responsiveness on the basis of age or sex.

INDICATIONS AND USAGE

LUVOX™ Tablets are indicated for the treatment of obsessions and compulsions in patients with obsessive-compulsive disorder (OCD), as defined in the DSM-III-R. The obsessions or compulsions cause marked distress, are time-consuming, or significantly interfere with social or occupational functioning.

The efficacy of LUVOX™ was established in two 10-week trials with obsessive-compulsive outpatients with the diagnosis of obsessive compulsive disorder as defined in DSM-III-R. (See Clinical Trials under CLINICAL PHARMACOLOGY).

Obsessive-compulsive disorder is characterized by recurrent and persistent ideas, thoughts, impulses or images (obsessions) that are ego-dystonic and/or repetitive, purposeful, and intentional behaviors (compulsions) that are recognized by the person as excessive or unreasonable.

The effectiveness of LUVOX™ Tablets for long-term use, i.e., for more than 10 weeks, has not been systematically evaluated in placebo-controlled trials. Therefore, the physician who elects to use LUVOX™ Tablets for extended periods should periodically reevaluate the long-term usefulness of the drug for the individual patient. (See DOSAGE AND ADMINISTRATION).

CONTRAINDICATIONS

Coadministration of terfenadine or astemizole with LUVOX™ is contraindicated (see WARNINGS and PRECAUTIONS).

LUVOX™ Tablets are contraindicated in patients with a history of hypersensitivity to fluvoxamine maleate.

WARNINGS

Potential for Interaction with Monoamine Oxidase Inhibitors

In patients receiving another serotonin reuptake inhibitor drug in combination with monoamine oxidase inhibitors (MAOI), there have been reports of serious, sometimes fatal, reactions including hyperthermia, rigidity, myoclonus, autonomic instability with possible rapid fluctuations of vital signs, and mental status changes that include extreme agitation progressing to delirium and coma. These reactions have also been reported in patients who have discontinued that drug and have been started on a MAOI. Some cases presented with features resembling neuroleptic malignant syndrome. Therefore, it is recommended that LUVOX™ Tablets not be used in combination with a MAOI, or within 14 days of discontinuing treatment with a MAOI. After stopping LUVOX™ Tablets, at least 2 weeks should be allowed before starting a MAOI.

Other Potentially Important Drug Interactions
(Also see PRECAUTIONS, Drug Interactions)

Benzodiazepines

Alprazolam - When fluvoxamine maleate (100 mg qd) and alprazolam (1 mg qid) were co-administered to steady-state, plasma concentrations and other pharmacokinetic parameters (AUC, C_{max}, $T_{1/2}$) of alprazolam were approximately twice those observed when alprazolam was administered alone; oral clearance was reduced by about 50%. The elevated plasma alprazolam concentrations resulted in decreased psychomotor performance and memory. This interaction, which has not been investigated using higher doses of fluvoxamine, may be more pronounced if a 300 mg daily dose is co-administered, particularly since fluvoxamine exhibits non-linear pharmacokinetics over the dosage range 100-300 mg. If alprazolam is co-administered with LUVOX™ Tablets, the initial alprazolam dosage should be at least halved and titration to the lowest effective dose is recommended. No dosage adjustment is required for LUVOX™ Tablets.

Similar pharmacokinetic interactions would be expected with some other benzodiazapines, such as triazolam, but are not seen with all, e.g., lorazepam (see Precautions, Drug Interactions). Caution is recommended whenever benzodiazepines are co-administered with LUVOX™ Tablets.

Potential Terfenadine and Astemizole Interactions

Terfenadine and astemizole are both metabolized by the cytochrome P450IIIA4 isozyme, and it has been demonstrated that ketoconazole, a potent inhibitor of IIIA4, blocks the metabolism of terfenadine and astemizole, resulting in increased plasma concentrations of parent drug. Increased plasma concentrations of terfenadine and astemizole cause QT prolongation and torsades de pointes-type ventricular tachycardia, sometimes fatal. As noted above, a substantial pharmacokinetic interaction has been observed for fluvoxamine in combination with alprazolam, a drug that is known to be metabolized by the IIIA4 isozyme. Although it has not been definitively demonstrated that fluvoxamine is a potent IIIA4 inhibitor, it is likely to be, given the substantial interaction of fluvoxamine with alprazolam. Consequently, it is recommended that fluvoxamine not be used in combination with either terfenadine or astemizole (see CONTRAINDICATIONS AND PRECAUTIONS).

Theophylline

The effect of steady-state fluvoxamine (50 mg bid) on the pharmacokinetics of a single dose of theophylline (375 mg as 442 mg aminophylline) was evaluated in 12 healthy non-smoking, male volunteers. The clearance of theophylline was decreased approximately 3-fold. Therefore, if theophylline is co-administered with fluvoxamine, its dose should be reduced to one third of the usual daily maintenance dose and plasma concentrations of theophylline should be monitored. No dosage adjustment is required for LUVOX™ Tablets.

Warfarin

When fluvoxamine maleate (50 mg tid) was administered concomitantly with warfarin for two weeks, warfarin plasma concentrations increased by 98% and prothrombin times were prolonged. Thus patients receiving oral anticoagulants and LUVOX™ Tablets should have their prothrombin time monitored and their anticoagulant dose adjusted accordingly. No dosage adjustment is required for LUVOX™ Tablets.

PRECAUTIONS

General

Activation of Mania/Hypomania

During premarketing studies involving primarily depressed patients, hypomania or mania occurred approximately 1% of patients treated with fluvoxamine. Activation of mania/hypomania has also been reported in a small proportion of patients with major affective disorder who were treated with other marketed antidepressants. As with all antidepressants, LUVOX™ Tablets should be used cautiously in patients with a history of mania.

Seizures

During premarketing studies, seizures were reported in 0.2% of fluvoxamine-treated patients. LUVOX™ Tablets should be used cautiously in patients with a history of seizures. It should be discontinued in any patient who develops seizures.

Suicide

The possibility of a suicide attempt is inherent in patients with depressive symptoms, whether these occur in primary depression or in association with another primary disorder such as OCD. Close supervision of high risk patients should accompany initial drug therapy. Prescriptions for LUVOX™ Tablets 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

Closely monitored clinical experience with LUVOX™ Tablets in patients with concomitant systemic illness is limited. Caution is advised in administering LUVOX™ Tablets to patients with diseases or conditions that could affect hemodynamic responses or metabolism.

LUVOX™ Tablets have 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 systematically excluded from many clinical studies during the product's premarketing testing. Evaluation of the electrocardiograms for patients with depression or OCD who participated in premarketing studies revealed no differences between fluvoxamine and placebo in the emergence of clinically important ECG changes.

In patients with liver dysfunction, fluvoxamine clearance was decreased by approximately 30%. LUVOX™ Tablets should be slowly titrated in patients with liver dysfunction during the initiation of treatment.

Information for Patients

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

Interference with Cognitive or Motor Performance

Since any psychoactive drug may impair judgement, thinking, or motor skills, patients should be cautioned about operating hazardous machinery, including automobiles, until they are certain that LUVOX™ Tablets therapy does not adversely affect their ability to engage in such activities.

Pregnancy

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

Nursing

Patients receiving LUVOX™ Tablets should be advised to notify their physicians if they are breast feeding an infant. (See PRECAUTIONS--Nursing Mothers.)

Concomitant Medication

Patients should be advised to notify their physicians if they are taking, or plan to take, any prescription or over-the-counter drugs, since there is a potential for clinically important interactions with LUVOX™ Tablets.

Alcohol

As with other psychotropic medications, patients should be advised to avoid alcohol while taking LUVOX™ Tablets.

Allergic Reactions

Patients should be advised to notify their physician if they develop a rash, hives, or a related allergic phenomenon during therapy with LUVOX™ Tablets.

Laboratory Tests

There are no specific laboratory tests recommended.

Drug Interactions

Potential Interactions with Drugs that Inhibit or are Metabolized by Cytochrome P450 Isozymes

Multiple hepatic cytochrome P450 (CYP450) enzymes are involved in the oxidative biotransformation of a large number of structurally different drugs and endogenous compounds. The available knowledge concerning the relationship of fluvoxamine and the CYP450 enzyme system has been obtained mostly from pharmacokinetic interaction

studies conducted in healthy volunteers, but some preliminary in vitro data are also available. Based on a finding of substantial interactions of fluvoxamine with certain of these drugs (see later parts of this section and also Warnings for details) and limited in vitro data for the IIIA4 isozyme, it appears that fluvoxamine inhibits the following isozymes that are known to be involved in the metabolism of the listed drugs:

IA2	IIC9	IIIA4
Warfarin	Warfarin	Alprazolam
Theophylline		
Propranolol		

In vitro data suggest that fluvoxamine is a relatively weak inhibitor of the IID6 isozyme.

None of the drugs studied for drug interactions significantly affected the pharmacokinetics of fluvoxamine. However, the metabolism of fluvoxamine has not been fully characterized and the effects of potent inhibitors of IID6, such as quinidine, or of IIIA4, such as ketoconazole, on fluvoxamine metabolism have not been studied.

A clinically significant fluvoxamine interaction is possible with drugs having a narrow therapeutic ratio such as terfenadine or astemizole, warfarin, theophylline, certain benzodiazepines, and phenytoin. If LUVOX™ Tablets are to be administered together with a drug that is eliminated via oxidative metabolism and has a narrow therapeutic window, plasma levels and/or pharmacodynamic effects of the latter drug should be monitored closely, at least until steady-state conditions are reached (See WARNINGS).

CNS Active Drugs

Monoamine Oxidase Inhibitors - See WARNINGS

Alprazolam - See WARNINGS

Lorazepam - A study of multiple doses of fluvoxamine maleate (50 mg bid) in healthy male volunteers (N=12) and a single dose of lorazepam (4 mg single dose) indicated no significant pharmacokinetic interaction. On average, both lorazepam alone and lorazepam with fluvoxamine produced substantial decrements in cognitive functioning; however, the co-administration of fluvoxamine and lorazepam did not produce larger mean decrements compared to lorazepam alone.

Lithium - As with other serotonergic drugs, lithium may enhance the

serotonergic effects of fluvoxamine and, therefore, the combination should be used with caution. Seizures have been reported with the co-administration of fluvoxamine maleate and lithium.

Tryptophan - Tryptophan may enhance the serotonergic effects of fluvoxamine, and the combination should, therefore, be used with caution. Severe vomiting has been reported with the co-administration of fluvoxamine maleate and tryptophan.

Clozapine - Elevated serum levels of clozapine have been reported in patients taking fluvoxamine maleate and clozapine. Since clozapine related seizures and orthostatic hypotension appear to be dose related, the risk of these adverse events may be higher when fluvoxamine and clozapine are co-administered. Patients should be closely monitored when fluvoxamine maleate and clozapine are used concurrently.

Alcohol - Studies involving single 40 g doses of ethanol (oral administration in one study and intravenous in the other) and multiple dosing with fluvoxamine maleate (50 mg bid) revealed no effect of either drug on the pharmacokinetics or pharmacodynamics of the other.

Tricyclic Antidepressants (TCAs) - Significantly increased plasma TCA levels have been reported with the co-administration of fluvoxamine maleate and amitriptyline, clomipramine, or imipramine. Caution is indicated with the co-administration of LUVOX™ Tablets and TCAs.

Carbamazepine - Elevated carbamazepine levels and symptoms of toxicity have been reported with the co-administration of fluvoxamine maleate and carbamazepine.

Methadone - Significantly increased methadone (plasma level:dose) ratios have been reported when fluvoxamine maleate was administered to patients receiving maintenance methadone treatment, with symptoms of opioid intoxication in one patient. Opioid withdrawal symptoms were reported following fluvoxamine maleate discontinuation in another patient.

Other Drugs

Theophylline - See WARNINGS

Propranolol and Other Beta-Blockers - Co-administration of fluvoxamine maleate 100 mg per day and propranolol 160 mg per day in normal volunteers resulted in a mean five-fold increase (range 2 to 17) in minimum propranolol plasma concentrations. In this study, there was a slight potentiation of the propranolol-induced reduction in heart rate and reduction in the exercise diastolic pressure.

One case of bradycardia and hypotension and a second case of orthostatic hypotension have been reported with the co-administration of fluvoxamine and metoprolol.

If propranolol or metoprolol is co-administered with LUVOX™ Tablets, a reduction in the initial beta-blocker dose and more cautious dose titration is recommended. No dosage adjustment is required for LUVOX™ Tablets.

Co-administration of fluvoxamine maleate 100 mg per day with atenolol 100 mg per day (N=6) did not affect the plasma concentrations of atenolol. Unlike propranolol and metoprolol, which undergo hepatic metabolism, atenolol is eliminated primarily by renal excretion.

Warfarin - See WARNINGS

Digoxin - Administration of fluvoxamine maleate 100 mg daily for 18 days (N=8) did not significantly affect the pharmacokinetics of a 1.25 mg single intravenous dose of digoxin.

Diltiazem - Bradycardia has been reported with the co-administration of fluvoxamine maleate and diltiazem.

Effects of Smoking on Fluvoxamine Metabolism

Smokers had a 25% increase in the metabolism of fluvoxamine compared to nonsmokers.

Electroconvulsive Therapy (ECT)

There are no clinical studies establishing the benefits or risks of combined use of ECT and fluvoxamine maleate.

Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis

There is no evidence of carcinogenicity, mutagenicity or impairment of fertility with fluvoxamine maleate.

There was no evidence of carcinogenicity in rats treated orally with fluvoxamine maleate for 30 months or hamsters treated orally with fluvoxamine maleate for 20 (females) or 26 (males) months. The daily doses in the high dose groups in these studies were increased over the course of the study from a minimum of 160 mg/kg to a maximum of 240 mg/kg in rats, and from a minimum of 135 mg/kg to a maximum of 240 mg/kg in hamsters. The maximum dose of 240

mg/kg is approximately 6 times the maximum human daily dose on a mg/m^2 basis.

Mutagenesis

No evidence of mutagenic potential was observed in a mouse micronucleus test, an *in vitro* chromosome aberration test, or the Ames microbial mutagen test with or without metabolic activation.

Impairment of Fertility

In fertility studies of male and female rats, up to 80 mg/kg/day orally of fluvoxamine maleate, (approximately 2 times the maximum human daily dose on a mg/m^2 basis) had no effect on mating performance, duration of gestation, or pregnancy rate.

Pregnancy

Teratogenic Effects - Pregnancy Category C

In teratology studies in rats and rabbits, daily oral doses of fluvoxamine maleate of up to 80 and 40 mg/kg, respectively (approximately 2 times the maximum human daily dose on a mg/m^2 basis) caused no fetal malformations. However, in other reproduction studies in which pregnant rats were dosed through weaning there was (1) an increase in pup mortality at birth (seen at 80 mg/kg and above but not at 20 mg/kg), and (2) decreases in postnatal pup weights (seen at 160 but not at 80 mg/kg) and survival (seen at all doses; lowest dose tested = 5 mg/kg). (Doses of 5, 20, 80, and 160 mg/kg are approximately 0.1, 0.5, 2, and 4 times the maximum human daily dose on a mg/m^2 basis). While the results of a cross-fostering study implied that at least some of these results likely occurred secondarily to maternal toxicity, the role of a direct drug effect on the fetuses or pups could not be ruled out. There are no adequate and well-controlled studies in pregnant women. Fluvoxamine maleate should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Labor and Delivery

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

Nursing Mothers

As for many other drugs, fluvoxamine is secreted in human breast milk. The decision of whether to discontinue nursing or to discontinue the drug should take into account the potential for serious adverse effects from exposure to fluvoxamine in the nursing infant as well as the potential benefits of LUVOX™ Tablets therapy to the mother.

Pediatric Use

Safety and effectiveness of LUVOX™ Tablets in individuals below 18 years of age have not been established.

Geriatric Use

Approximately 230 patients participating in controlled premarketing studies with LUVOX™ Tablets were 65 years of age or over. No overall differences in safety were observed between these patients and younger patients. Other reported clinical experience has not identified differences in response between the elderly and younger patients. However, the clearance of fluvoxamine is decreased by about 50% in elderly compared to younger patients (see Pharmacokinetics under CLINICAL PHARMACOLOGY), and greater sensitivity of some older individuals also cannot be ruled out. Consequently, LUVOX™ Tablets should be slowly titrated during initiation of therapy.

ADVERSE REACTIONS

Associated with Discontinuation of Treatment

Of the 1087 OCD and depressed patients treated with fluvoxamine maleate in controlled clinical trials conducted in North America, 22% discontinued treatment due to an adverse event. The most common events (≥1%) associated with discontinuation and considered to be drug related (i.e., those events associated with dropout at a rate at least twice that of placebo) included:

TABLE 2
ADVERSE EVENTS ASSOCIATED WITH DISCONTINUATION OF TREATMENT IN OCD AND DEPRESSION POPULATIONS

BODY SYSTEM/ ADVERSE EVENT	PERCENTAGE OF FLUVOXAMINE PATIENTS	PERCENTAGE OF PLACEBO PATIENTS
BODY AS A WHOLE		
Headache	3%	1%
Asthenia	2%	<1%
Abdominal Pain	1%	0
DIGESTIVE		
Nausea	9%	1%
Diarrhea	1%	<1%
Vomiting	2%	<1%
Anorexia	1%	<1%
Dyspepsia	1%	<1%
NERVOUS SYSTEM		
Insomnia	4%	1%
Somnolence	4%	<1%
Nervousness	2%	<1%
Agitation	2%	<1%
Dizziness	2%	<1%
Anxiety	1%	<1%
Dry Mouth	1%	<1%

Incidence in Controlled Trials

Commonly Observed Adverse Events in Controlled Clinical Trials:

LUVOX™ Tablets have been studied in controlled trials of OCD (n=320) and depression (n=1350). In general, adverse event rates were similar in the two data sets. The most commonly observed adverse events associated with the use of LUVOX™ Tablets and likely to be drug-related (incidence of 5% or greater and at least twice that for placebo) derived from Table 3 below were: somnolence, insomnia, nervousness, tremor, nausea, dyspepsia, anorexia, vomiting, abnormal ejaculation, asthenia, and sweating. In a pool of two studies involving only patients with OCD, the following additional events were identified using the above rule: dry mouth, decreased libido, urinary frequency, anorgasmia, rhinitis, and taste perversion.

Adverse Events Occurring at an Incidence of 1%:

Table 3 that follows enumerates adverse events that occurred at a

frequency of 1% or more, and were more frequent than in the placebo group, among patients treated with LUVOX™ Tablets in two short-term placebo controlled OCD trials (10 week) and depression trials (6 week) in which patients were dosed in a range of generally 100 to 300 mg/day. This table shows the percentage of patients in each group who had at least one occurrence of an event at some time during their treatment. Reported adverse events were classified using a standard COSTART-based Dictionary terminology.

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 may differ from those that prevailed in the clinical trials. 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 non-drug factors to the side-effect incidence rate in the population studied.

TABLE 3

TREATMENT-EMERGENT ADVERSE EVENT INCIDENCE RATES BY BODY SYSTEM IN OCD AND DEPRESSION POPULATIONS COMBINED[1]

ADVERSE EVENT	Percentage of Patients Reporting Event	
	FLUVOXAMINE N = 892	PLACEBO N = 778
BODY AS WHOLE		
Headache	22	20
Asthenia	14	6
Flu Syndrome	3	2
Chills	2	1
CARDIOVASCULAR		
Palpitations	3	2
DIGESTIVE SYSTEM		
Nausea	40	14
Diarrhea	11	7
Constipation	10	8

ADVERSE EVENT	Percentage of Patients Reporting Event	
	FLUVOXAMINE N = 892	PLACEBO N = 778
Dyspepsia	10	5
Anorexia	6	2
Vomiting	5	2
Flatulence	4	3
Tooth Disorder[2]	3	1
Dysphagia	2	1
NERVOUS SYSTEM		
Somnolence	22	8
Insomnia	21	10
Dry Mouth	14	10
Nervousness	12	5
Dizziness	11	6
Tremor	5	1
Anxiety	5	3
Vasodilatation[3]	3	1
Hypertonia	2	1
Agitation	2	1
Libido Decreased	2	1
Depression	2	1
CNS Stimulation	2	1
RESPIRATORY SYSTEM		
Upper Respiratory Infection	9	5
Dyspnea	2	1
Yawn	2	0
SKIN		
Sweating	7	3
SPECIAL SENSES		

ADVERSE EVENT	Percentage of Patients Reporting Event[1]	
	FLUVOXAMINE N = 892	PLACEBO N = 778
Taste Perversion	3	1
Amblyopia[4]	3	2
UROGENITAL		
Abnormal Ejaculation[5,6]	8	1
Urinary Frequency	3	2
Impotence[6]	4	1
Anorgasmia	2	0
Urinary Retention	1	0

1 Events for which fluvoxamine maleate incidence was equal to or less than placebo are not listed in the table above, but include the following: abdominal pain, abnormal dreams, appetite increased, back pain, chest pain, confusion, dysmenorrhea, fever, infection, leg cramps, migraine, myalgia, pain, paresthesia, pharyngitis, postural hypotension, pruritus, rash, rhinitis, thirst, and tinnitus.

2 Includes "toothache," "tooth extraction and abscess," and "caries."

3 Mostly feeling warm, hot or flushed.

4 Mostly "blurred vision."

5 Mostly "delayed ejaculation."

6 Incidence based on number of male patients.

Adverse Events in OCD Placebo Controlled Studies Which are Markedly Different (defined as at least a two-fold difference in rate) in Rate from the Pooled Event Rates in OCD and Depression Placebo Controlled Studies

The events in OCD studies with a two-fold decrease in rate compared to event rates in OCD and depression studies were dysphagia and amblyopia (mostly blurred vision). Additionally, there was an approximate 25% decrease in nausea.

The events in OCD studies with a two-fold increase in rate compared to event rates in OCD and depression studies were: asthenia, abnormal ejaculation (mostly delayed ejaculation), anxiety, infection, rhinitis, anorgasmia (in males), depression, libido decreased, pharyngitis, agitation, impotence, myoclonus/twitch, thirst, weight loss, leg cramps, myalgia, and urinary retention. These events are listed in order of decreasing rates in the OCD

trials.

Vital Sign Changes

Comparisons of fluvoxamine maleate and placebo groups in separate pools of short-term OCD and depression trials on (1) median change from baseline on various vital signs variables and on (2) incidence of patients meeting criteria for potentially important changes from baseline on various vital signs variables revealed no important differences between fluvoxamine maleate and placebo.

Laboratory Changes

Comparisons of fluvoxamine maleate and placebo groups in separate pools of short-term OCD and depression trials on (1) median change from baseline on various serum chemistry, hematology, and urinalysis variables and on (2) incidence of patients meeting criteria for potentially important changes from baseline on various serum chemistry, hematology, and urinalysis variables revealed no important differences between fluvoxamine maleate and placebo.

ECG Changes

Comparisons of fluvoxamine maleate and placebo groups in separate pools of short-term OCD and depression trials on (1) mean change from baseline on various ECG variables and on (2) incidence of patients meeting criteria for potentially important changes from baseline on various ECG variables revealed no important differences between fluvoxamine maleate and placebo.

Other Events Observed During the Premarketing Evaluation of LUVOX™ Tablets

During premarketing clinical trials conducted in North America and Europe, multiple doses of fluvoxamine maleate were administered for a combined total of 2737 patient exposures in patients suffering OCD or Major Depressive Disorder. Untoward events associated with this exposure were recorded by clinical investigators using descriptive 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 limited (i.e., reduced) number of standard event categories.

In the tabulations which follow, a standard COSTART-based Dictionary terminology has been used to classify reported adverse events. If the COSTART term for an event was too general as to be uninformative, it was replaced with a more informative term. The frequencies presented, therefore, represent the proportion of the 2737 patient exposures to multiple doses of fluvoxamine maleate who experienced an event of the type cited on at least one occasion while receiving fluvoxamine maleate. All reported events are included in the list below, with the following exceptions: 1) those events already listed in Table 3, which tabulates incidence rates of common adverse experiences in placebo controlled OCD and depression clinical trials, are excluded; 2) those events for which a drug cause was considered remote (i.e., neoplasia, gastrointestinal carcinoma, herpes simplex, herpes zoster, application site reaction, and unintended pregnancy) are omitted; and 3) events which were reported in only one patient and judged to not be potentially serious are not included. It is important to emphasize that, although the events reported did occur during treatment with fluvoxamine maleate, a causal relationship to fluvoxamine maleate has not been established.

Events are further classified within body system categories and enumerated in order of decreasing frequency using the following definitions: frequent adverse events are defined as those occurring on one or more occasions in at least 1/200 patients; infrequent adverse events are those occurring between 1/100 and 1/1,000 patients; and rare adverse events are those occurring in less than 1/1,000 patients.

Body as a Whole: Frequent: accidental injury, malaise; Infrequent: allergic reaction, neck pain, neck rigidity, overdose, photosensitivity reaction, suicide attempt; Rare: cyst, pelvic pain, sudden death.

Cardiovascular System: Frequent: hypertension, hypotension, syncope, tachycardia; Infrequent: angina pectoris, bradycardia, cardiomyopathy, cardiovascular disease, cold extremities, conduction delay, heart failure, myocardial infarction, pallor, pulse irregular, ST segment changes; Rare: AV block, cerebrovascular accident, coronary artery disease, embolus, pericarditis, phlebitis, pulmonary infarction, supraventricular extrasystoles.

[illegible] System: Frequent: elevated liver transaminases; [illegible] colitis, eructation, esophagitis, gastritis, [illegible]ritis, gastrointestinal hemorrhage, gastrointestinal gingivitis, glossitis, hemorrhoids, melena, rectal [illegible]ge, stomatitis; Rare: biliary pain, cholecystitis, [illegible]thiasis, fecal incontinence, hematemesis, intestinal [illegible]truction, jaundice.

Endocrine System: Infrequent: hypothyroidism; Rare: goiter.

Hematic and Lymph Systems: Infrequent: anemia, ecchymosis, leukocytosis, lymphadenopathy, thrombocytopenia; Rare: leukopenia, purpura.

Metabolic and Nutritional Systems: Frequent: edema, weight gain, weight loss; Infrequent: dehydration, hypercholesterolemia; Rare: diabetes mellitus, hyperglycemia, hyperlipidemia, hypoglycemia, hypokalemia, lactate dehydrogenase increased.

Musculoskeletal System: Infrequent: arthralgia, arthritis, bursitis, generalized muscle spasm, myasthenia, tendinous contracture, tenosynovitis; Rare: arthrosis, myopathy, pathological fracture.

Nervous System: Frequent: amnesia, apathy, hyperkinesia, hypokinesia, manic reaction, myoclonus, psychotic reaction; Infrequent: agoraphobia, akathisia, ataxia, CNS depression, convulsion, delirium, delusions, depersonalization, drug dependence, dyskinesia, dystonia, emotional lability, euphoria, extrapyramidal syndrome, gait unsteady, hallucinations, hemiplegia, hostility, hypersomnia, hypochondriasis, hypotonia, hysteria, incoordination, increased salivation, libido increased, neuralgia, paralysis, paranoid reaction, phobia, psychosis, sleep disorder, stupor, twitching, vertigo; Rare: akinesia, coma, fibrillations, mutism, obsessions, reflexes decreased, slurred speech, tardive dyskinesia, torticollis, trismus, withdrawal syndrome.

Respiratory System: Frequent: cough increased, sinusitis; Infrequent: asthma, bronchitis, epistaxis, hoarseness, hyperventilation; Rare: apnea, congestion of upper airway, hemoptysis, hiccups, laryngismus, obstructive pulmonary disease, pneumonia.

Skin: Infrequent: acne, alopecia, dry skin, eczema, exfoliative dermatitis, furunculosis, seborrhea, skin discoloration, urticaria.

Special Senses: Infrequent: accomodation abnormal, conjunctivitis, deafness, diplopia, dry eyes, ear pain, eye pain, mydriasis, otitis media, parosmia, photophobia, taste loss, visual field defect; Rare: corneal ulcer, retinal detachment.

Urogenital System: Infrequent: anuria, breast pain,[1] cystitis, delayed menstruation,[1] dysuria, female lactation,[1] hematuria, menopause,[1] menorrhagia,[1] metrorrhagia,[1] nocturia, polyuria, premenstrual syndrome,[1] urinary incontinence, urinary tract infection, urinary urgency, urination impaired, vaginal hemorrhage,[1] vaginitis;[1] Rare: kidney calculus, hematospermia,[2] oliguria.

[1] Based on the number of females.
[2] Based on the number of males.

Non-US Postmarketing Reports

Voluntary reports of adverse events in patients taking LUVOX™ Tablets that have been received since market introduction and are of unknown causal relationship to LUVOX™ Tablets use include: toxic epidermal necrolysis, Stevens-Johnson syndrome, Henoch-Schoenlein purpura, bullous eruption, priapism, agranulocytosis, neuropathy, aplastic anemia, anaphylactic reaction, hyponatremia, acute renal failure, and severe akinesia with fever when fluvoxamine was co-administered with antipsychotic medication.

DRUG ABUSE AND DEPENDENCE

Controlled Substance Class

LUVOX Tablets are not controlled substances.

Physical and Psychological Dependence

The potential for abuse, tolerance and physical dependence with fluvoxamine maleate has been studied in a nonhuman primate model. No evidence of dependency phenomena was found. The discontinuation effects of LUVOX™ Tablets were not systematically evaluated in

controlled clinical trials. LUVOX™ Tablets were not systematically studied in clinical trials for potential for abuse, but there was no indication of drug-seeking behavior in clinical trials. It should be noted, however, that patients at risk for drug dependency were systematically excluded from investigational studies of fluvoxamine maleate. Generally, it is not possible to predict on the basis of preclinical or premarketing clinical experience the extent to which a CNS active drug will be misused, diverted, and/or abused once marketed. Consequently, physicians should carefully evaluate patients for a history of drug abuse and follow such patients closely, observing them for signs of fluvoxamine maleate misuse or abuse (i.e., development of tolerance, incrementation of dose, drug-seeking behavior).

OVERDOSAGE

Human Experience

Worldwide exposure to fluvoxamine maleate includes over 37,000 patients treated in clinical trials and an estimated exposure of 4,500,000 patients treated during foreign marketing experience (circa 1992). Of the 354 cases of deliberate or accidental overdose involving fluvoxamine maleate reported from this population, there were 19 deaths. Of the 19 deaths, 2 were in patients taking fluvoxamine maleate alone and the remaining 17 were in patients taking fluvoxamine maleate along with other drugs. In the remaining 335 patients, 309 had complete recovery after gastric lavage or symptomatic treatment. One patient had persistent mydriasis after the event, and a second patient had a bowel infarction requiring a hemicolectomy. In the remaining 24 patients the outcome was unknown. The highest reported overdose of fluvoxamine maleate involved a non-lethal ingestion of 10,000 mg (equivalent of 1-3 months' dosage). The patient fully recovered with no sequelae.

Commonly observed adverse events associated with fluvoxamine maleate overdose included drowsiness, vomiting, diarrhea, and dizziness. Other notable signs and symptoms seen with fluvoxamine maleate overdose (single or mixed drugs) included coma, tachycardia, bradycardia, hypotension, ECG abnormalities, liver function abnormalities, convulsions, and symptoms such as aspiration pneumonitis, respiratory difficulties or hypokalemia

that may occur secondary to loss of consciousness or vomiting.

Management of Overdose

1. An unobstructed airway should be established with maintenance of respiration as required. Vital signs and ECG should be monitored.

2. Administration of activated charcoal may be as effective as emesis or lavage and should be considered in treating overdose. Since absorption with overdose may be delayed, measures to minimize absorption may be necessary for up to 24 hours post-ingestion.

3. Maintain close observation as clinically indicated.

4. There are no specific antidotes for LUVOX™ Tablets.

5. In managing overdosage, consider the possibility of multiple drug involvement. The physician should consider contacting a poison control center for additional information on the treatment of any overdosage.

6. Dialysis is not believed to be beneficial.

DOSAGE AND ADMINISTRATION

The recommended starting dose for LUVOX™ Tablets is 50 mg, administered as a single daily dose at bedtime. In the controlled clinical trials establishing the effectiveness of LUVOX™ Tablets in OCD, patients were titrated within a dose range of 100 to 300 mg/day. Consequently, the dose should be increased in 50 mg increments every 4 to 7 days, as tolerated, until maximum therapeutic benefit is achieved, not to exceed 300 mg per day. It is advisable that a total daily dose of more than 100 mg should be given in two divided doses. If the doses are not equal, the larger dose should be given at bedtime.

Dosage for Elderly or Hepatically Impaired Patients

Elderly patients and those with hepatic impairment have been observed to have a decreased clearance of fluvoxamine maleate. Consequently, it may be appropriate to modify the initial dose and the subsequent dose titration for these patient groups.

Maintenance/Continuation Extended Treatment

Although the efficacy of LUVOX™ Tablets beyond 10 weeks of dosing for OCD has not been documented in controlled trials, OCD is a chronic condition, and it is reasonable to consider continuation for a responding patient. Dosage adjustments should be made to maintain the patient on the lowest effective dosage, and patients should be periodically reassessed to determine the need for continued treatment.

HOW SUPPLIED

Tablets 50 mg: yellow, elliptical, film-coated (debossed "Solvay" and "4205" on one side and scored on the other)

Bottles of 100	NDC 0032-4205-01
Bottles of 1000	NDC 0032-4205-10
Unit dose pack of 100	NDC 0032-4205-11

Tablets 100 mg: scored, beige, elliptical, film-coated (debossed "Solvay" and "4210" on one side and scored on the other)

Bottles of 100	NDC 0032-4210-01
Bottles of 1000	NDC 0032-4210-10
Unit dose pack of 100	NDC 0032-4210-11

LUVOX™ Tablets should be protected from high humidity and stored at controlled room temperature, 15°-30° C (59°-86° F).

Dispense in tight containers.

Caution: Federal law prohibits dispensing without prescription.

Doc #LABFLUVX.AP4

AE 44

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 20-243

AUG 30 1994

Solvay Pharmaceuticals
Attention: Virginia O. Ackerman
901 Sawyer Road
Marietta, Georgia 30062

Dear Ms. Ackerman:

Please refer to your New Drug Application (NDA) dated December 24, 1991, submitted pursuant to section 505(b) of the Federal Food, Drug, and Cosmetic Act for Luvox® (Fluvoxamine maleate) 25, 50, 100, and 150 mg Tablets, NDA 20-243.

We also acknowledge receipt of your additional communications (see ATTACHMENT 1).

We have completed our review of this application and it is APPROVABLE. Final approval will require your responses to the following issues:

CLINICAL

1. Labeling

Accompanying this letter (ATTACHMENT 2) is the Agency's proposal for the labeling of Luvox®. Our proposal is based on your labeling proposal submitted in an October 27, 1993 amendment. We believe it presents a fair summary of the information available on the benefits and risks of fluvoxamine. Please use the proposed text verbatim.

We have proposed a number of changes to your draft labeling, and explanations for these changes are provided in the bracketed comments embedded within the proposed text. In certain instances, we have asked you to further modify labeling. Division staff would be happy to meet with you to discuss any disagreements you might have with any part of the proposed labeling format or content.

2. Safety Update

Our assessment of the safety of fluvoxamine in the treatment of OCD is based on our review of all safety information submitted up to and including your final safety update (11-23-93). This update focused on serious events with a cutoff date of 10-22-93. Please provide a final serious events update to include serious adverse events up to a more recent cutoff date. In addition, please provide a summary of any additional postmarketing data available since the 11-23-93 safety update, with a focus on serious events. This final safety update may be in the same general format as your November 23, 1993 safety update. Of particular importance, it should include a line listing of previously unreported deaths and other serious events associated with the use of fluvoxamine along with narrative summaries. The safety update should identify any previously unrecognized serious adverse events that appear to be causally related to the use of fluvoxamine.

3. World Literature Update

Please provide a world literature update for fluvoxamine including information available subsequent to the literature update provided in your 11-23-93 amendment. This update should focus on reports of serious adverse events associated with the use of fluvoxamine and can be in the same general format as that utilized in your 11-23-93 literature update.

4. Foreign Regulatory Update

Please provide any new information on the regulatory status of fluvoxamine worldwide, i.e., information available subsequent to the regulatory status update provided in your 11-23-93 amendment.

5. Long-Term Efficacy Data

One deficiency of your development program for fluvoxamine in the treatment of OCD was the absence of adequate relapse prevention data. It is not unreasonable to expect relapse prevention data for treatments of chronic conditions such as OCD, and the PDAC is also increasingly focused on this issue. In managing OCD, the clinician is faced with the question of what to do following response to acute treatment. While there were some data available from open and uncontrolled extensions from studies 5529 and 5534, these data were inadequate for analysis and they do not shed much useful light on this question. In the absence of adequate data bearing on this question, we have proposed in labeling an acknowledgement of the absence of data, along with a suggestion that it would not be unreasonable to continue responding patients beyond the acute treatment phase. However, prior to the final approval of this application, we ask that you commit to conducting, following the approval of this indication, an adequate and well-controlled relapse prevention trial for fluvoxamine in the maintenance treatment of OCD.

6. Pediatric OCD Information

Another important deficiency in your development program for this indication was the absence of safety and efficacy data for children and adolescents. There were only a few adolescents and no children represented in the population of OCD patients that you studied. This is a problem for OCD because of the very early age of onset for this disorder (peak age of onset is 9 for males and 12 for females). Once fluvoxamine is approved for treating adults with OCD, it is likely that many children and adolescents with OCD will be treated with this drug as well. We are aware that you have underway a 10-week trial involving children and adolescents with OCD, and we encourage you to complete this trial in a timely manner so that the labeling can be updated following approval with information pertinent to the treatment of patients in these age groups.

PHARMACOLOGY

1. Pregnancy Category C

The segment III reproduction studies in rats revealed a decrease in pup weight and survival. Because it could not be determined whether or not all of these findings were related to effects of the drug on the developing fetus in utero or were secondary to postnatal drug effects on the dams and/or pups, we have labeled fluvoxamine pregnancy Category C. We would be happy to discuss with you approaches to studying this question. If such a study or studies clearly establish that the adverse effect on pup weight and survival is occurring as a result of postnatal effect rather than an in utero effect of drug on the fetus, the labeling may be changed from pregnancy Category C to pregnancy Category B.

2. Segment I and II Rat Studies

The segment I and II rat reproduction studies were conducted at doses which were too low to provide a valid assessment of the potential of

fluvoxamine to produce adverse effects on these phases of reproduction in this species. We thus request that these studies be repeated post-marketing. Doses used in these studies should be based on rangefinding studies and/or other relevant data to insure adequate exposure.

MANUFACTURING AND CONTROLS

1. Methods Validation

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.

2. Establishment Inspections

Please note that the establishment inspections have not yet been completed. We cannot approve this application until satisfactory Establishment Inspection Reports have been received for all facilities involved in the manufacture and packaging of the bulk drug and the drug product.

3. Nomenclature

The established name, fluvoxamine maleate, has not been adopted by the USAN Council. We request that you submit this name to the council expeditiously.

4. Environmental Assessment

Your environmental assessment has been carefully reviewed. Prior to approving this application, you will need to fully address the following deficiencies:

1. Item 4: Please revise this item to include descriptions of the environments present and adjacent to the manufacturing facility in the Netherlands and the packaging facility in New Jersey.

2. Item 5: Please revise this item to include all impurities in addition to the (Z) isomer and appropriate limits.

3. Regarding Item 6:

   A. Regarding manufacture of the drug substance:

      1. We note that all environmental assessment information regarding the manufacture of the drug substance was submitted in a confidential appendix. The Environmental Assessment (EA) is a public document which will be available for review per 21 CFR 25.31. Information defined in the formats per 21 CFR 25.31a should be contained in the EA. Confidential or proprietary information should be placed in appendices which are clearly marked as confidential at the end of the EA. However, confidential information should be summarized to the extent possible and included as part of the EA in accordance with 21 CFR 25.30(b).

      2. You indicated that limits for the emission of specific organic solvents were included in the applicable permits. The documents submitted did not contain a list

of specific organic solvents or applicable limits. Please submit this information along with certification from the appropriate regulatory authorities confirming the accuracy of the information.

3. Please include, in the assessment, a discussion of controls used to limit gaseous and particulate air emissions.

4. You have indicated that, due to the multiproduct nature of the manufacturing facility, accurate determination of the impact of the action on compliance with wastewater stream limits was not possible. However, the increase in the amount of wastewater along with reasonable assumptions (e.g. the COD/BOD of the influent remains relatively constant over time) may be used to estimate the increase in influent COD/BOD in order to demonstrate that sufficient reserve capacity does exist for wastewater treatment. Please submit this type of estimate along with the appropriate assumptions.

5. Please include, in the assessment, a brief description of the controls used at your wastewater treatment plant.

6. Please include, in the assessment, a brief description of the incineration equipment and process (e.g. two stage, emission controls) used for the disposal of solid and chemical wastes.

7. Please note that all statements of compliance with applicable environmental regulations and laws must be included in the Environmental Assessment and not in confidential appendices.

B. Regarding manufacture of the drug product:

1. Please include, in the assessment, a brief description of the incineration equipment and process (e.g. two stage, emission controls) used at both proposed facilities for the disposal of solid and chemical wastes.

2. Please submit calculations showing the potential impact the action may have on compliance with permit limits for air emissions.

3. Please revise the listings and descriptions of all of permit numbers to include expiration dates and applicable limits. Do not send copies of the actual permits unless specifically requested.

4. Regarding Items 7 and 8:

A. The testing reports submitted in support of this assessment contained significant discrepancies (See Comment 8). The information based on these studies must therefore be considered inadequate to support any conclusions regarding fate of emitted substances and environmental effects of released substances. You have therefore failed to comply with

the regulations for these items per 21 CFR 25.31a(a). Your EA must address all topics included for these items and contain testing results to support any conclusions. The items may reference confidential appendices where necessary, but may not be composed solely of such references.

B. You have stated that the drug substance was not found to be biodegradable by the test model employed and have failed to identify a mechanism for removal of the drug substance from the environment. Failure to identify such a mechanism may necessitate chronic toxicity studies. Please submit estimates of when such studies would be required as well as proposed testing. Please note also that identification of a mechanism for the rapid removal of the drug substance from the environment could possibly negate the need for chronic toxicity studies, and it is strongly recommended that a mechanism be identified if possible.

C. You have referred to the "PMA/FDA Environmental Assessment Technical Test Matrix" and the "PMA/FDA Interim Environmental Assessment Guidance" in your assessment. Please be advised that this interim PMA document is not an FDA document and has not been sanctioned by the Agency. The phraseology used in your assessment should be modified accordingly.

5. Item 10: Please note that the purpose of this item is to address measures taken if available information indicates that adverse environmental impacts may be associated with the proposed action. Should the assessment indicated no adverse impact, please state that it is your conclusion that there will be no adverse impact and that mitigation is therefore not necessary.

6. Item 11: The determination of whether an alternative action is "not warranted" is the decision of the Agency. Please revise your statement to remove this phrase.

7. Item 14: Please revise this item to include all references, including OECD and FDA testing procedures, as well as the PMA interim document.

8. Regarding Item 15:

A. You failed to include Data Summary Charts in your Environmental Assessment. Please note that these charts should be part of the assessment and not placed solely within confidential appendices.

B. The study submitted for the determination of dissociation constants is inadequate.

1. The report was revised to indicate that the constant observed in the range of pH 10 - 12 was due to excess base and not a true inflection point without submitting supporting data.

2. The report indicated that the inflection points at lower pH values were due in part to the protonation of the carboxylate groups on the maleate as well as the primary amine group on fluvoxamine. Data resolving these was not submitted.

3. The report indicated that analysis in aqueous solutions at pH > 8 was complicated by the precipitation of the free base. This observation strongly suggests that the fluvoxamine is dissociated from the maleate, with the potential for precipitation in the environment. Dissociation constant studies should therefore be conducted on fluvoxamine free base and not fluvoxamine maleate.

C. The study submitted for the determination of octanol/water partition coefficients is inadequate.

1. The study indicated that the partition coefficient at differed from that obtained at lower concentrations. However, association or dissociation effects were not addressed as required in the Technical Assistance Document 3.02.

2. The above observation, along with the precipitation of the free base at pH values >8 indicate that the study should have been conducted at pH values of 5, 7 and 9 using fluvoxamine free base instead of at pH 7 using fluvoxamine maleate.

D. The study submitted for the determination of water solubility is inadequate. In view of the above observations, the solubility study should have been conducted at pH values of 5, 7 and 9 using fluvoxamine free base.

E. The study submitted for the determination of vapor pressure is inadequate. In view of the above observations, the study should have been conducted using fluvoxamine free base in order to determine the Henry's Law constant for the molecule.

F. The study submitted for the determination of aerobic biodegradation is inadequate in that significant deviations from OECD Procedure 301E were made without the submission of validation for the changes. The changes included:

1. Storage of soil samples for up to 30 days instead of same day use.

2. Storage of activated sludge for up to 48 hours instead of same day use.

3. The use of raw sewerage in the combined inoculum.

4. The acclimation of the combined inoculum to the test substance for 14 days prior to initiation of the study.

5. The use of sealed biometer flasks containing $Ba(OH)_2$ scrubbers. Note that the OECD procedure requires closure which allows for exchange between the flask and the atmosphere.

In addition, the testing results for CO_2 evolution were described as lower than expected for the control substance. The extent, potential cause and significance of the deviation was not addressed.

G. The study submitted for the determination of microbial inhibition is inadequate.

1. The general protocol submitted did not include detailed information regarding the testing procedure used, to include specific media and preparation, and incubation conditions.

2. The incubation conditions reported in the testing results did not include observed temperature ranges and were not consistent with the time periods shown in the procedure section of the report.

In addition, the study indicated that a % dimethyl sulfoxide solution was needed to reach the required drug substance concentration of ppm, since the sample was not soluble in water at this level. This observation is not consistent with the value of ppm reported in the water solubility study. Please explain the discrepancy.

BIOPHARMACEUTICS

1. Additional Metabolism Studies

On the basis of positive in vivo interaction studies and case reports suggestive of fluvoxamine interactions, it appears that fluvoxamine may inhibit several cytochrome P450 isozymes, i.e., IA2, IIC9, IIIA4, and possibly IID6. The preliminary in vitro data submitted October 29, 1993 support the in vivo findings regarding IIIA4 inhibition, but not for IID6 inhibition. Given the likelihood that fluvoxamine is a potent IIIA4 inhibitor, we have proposed a contraindication for the concomitant use of fluvoxamine and either terfenadine or astemizole because of the potentially very serious risks of such use.

There is a need for more studies to establish definitively the extent to which fluvoxamine may inhibit any of these isozymes. Consequently, we ask that you conduct, subsequent to approval, additional studies to clarify the metabolism of fluvoxamine. We would be happy to discuss with you the design of appropriate studies to achieve this goal.

2. Alprazolam/Fluvoxamine Interaction

We note that in a study involving the coadministration of alprazolam 1 mg qid and fluvoxamine 100 mg qd, the mean fluvoxamine concentration was decreased by about 25% compared to fluvoxamine alone. Although a 25% decrease in fluvoxamine concentration may not represent a clinically important difference, this finding raises a question about a possibly clinically important effect on fluvoxamine concentration at higher doses of fluvoxamine given on a bid schedule, especially since fluvoxamine pharmacokinetics become nonlinear at higher doses. Please comment on this finding.

3. Dissolution Specification

We ask that you agree to the following recommendation by the Division of Biopharmaceutics for a dissolution method and specification for all tablet strengths:

Apparatus:	USP Apparatus (Paddle)
Paddle Speed:	RPM
Medium:	ml purified water at
Q:	NLT % in minutes

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.

Please submit 12 copies of the final printed labeling.

In accordance with the policy described in 21 CFR 314.102(d) and in the Center for Drug Evaluation and Research Staff Manual Guide CDB 4820.6, you may request an informal conference with the Division to discuss what further steps you need to secure approval. The meeting is to be requested at least 15 days in advance. Alternatively, you may choose to receive such a report via a telephone call. Should you wish this conference or a telephone report, or should any questions arise concerning this NDA, please contact Mr. Paul David, Regulatory Management Officer, at (301) 594-2777.

Within 10 days after the date of this letter, you are required to amend the application, or notify us of your intent to file an amendment, or follow one of the other alternatives under 21 CFR 314.110. In the absence of such action on your part, the FDA may proceed to withdraw the application.

This drug may not be legally marketed for the indication provided by this application until you have been notified in writing that the application is approved.

Sincerely yours,

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

ATTACHMENTS

cc: HFD-240/Sbanesc
ORIG NDA 20-243
HFD-2/Medwatch
HFD-85
HFD-100/RTemple
HFD-102/PVincent/CGood
HFD-120/DIV FILE
HFD-120/PLeber/TLaughren/GDubitsky
/GFitzgerald/BRosloff
/SBlum/WRzeszotarski/DDavid
HFD-344/RYoung
HFD-420/RBaweja
HFD-500
HFD-638
HFD-713/ENevius/DHoberman
HFD-735
District Office
Doc # LTRFLUVX.AE1
NDA APPROVABLE

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NDA 20-243

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L: TRADEMARK REVIEW FROM NOMENCLATURE COMMITTEE/ Sponsor committed to obtain USAN name

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ATTACHMENT 1

NDA 20-243
LUVOX® (Fluvoxamine Maleate) Tablets

Amendments and Correspondence submitted to NDA since original submission:

March 16, 1992	March 18, 1992	March 20, 1992
March 24, 1992	March 25, 1992	March 31, 1992
April 9, 1992	April 15, 1992	April 22, 1992
May 18, 1992	June 12, 1992	June 15, 1992
July 17, 1992	July 27, 1992	August 24, 1992
September 01, 1992	September 04, 1992	September 17, 1992
November 24, 1992	December 03, 1992	December 03, 1992
January 15, 1993	February 12, 1993	February 23, 1993
February 24, 1993	February 24, 1993	March 02, 1993
March 05, 1993	April 08, 1993	April 08, 1993
May 03, 1993	May 21, 1993	May 27, 1993
June 07, 1993	July 01, 1993	July 21, 1993
July 30, 1993	July 30, 1993	August 23, 1993
August 25, 1993	September 01, 1993	September 09, 1993
September 28, 1993	September 21, 1993	October 13, 1993
October 27, 1993	November 23, 1993	November 23, 1993
December 20, 1993	January 28, 1994	April 5, 1994

CSO LBL Review

CSO LABELING REVIEW
Comparison of approval letter for Dr. Temple's signature to the approvable letter issued August 30, 1994

I have used ~~strikes~~ to denote text deleted or moved. Shaded text denotes additions or inserted words from elsewhere in your text.

ATTACHMENT

Luvox
(Fluvoxamine Maleate)
Tablets
50 mg and 100 mg

DESCRIPTION

Fluvoxamine maleate is a selective serotonin (5-HT) reuptake inhibitor (SSRI) belonging to a new chemical series, the 2-aminoethyl oxime ethers of aralkylketones. It is chemically unrelated to other SSRIs and clomipramine. It is chemically designated as 5-methoxy-4'-(trifluoromethyl)valerophenone-(E)-O-(2-aminoethyl)oxime maleate (1:1) and has the empirical formula $C_{15}H_{21}O_2N_2F_3 \cdot C_4H_4O_4$. Its molecular weight is 434.4.

The structural formula is:

Fluvoxamine maleate is a white or off white, odorless, crystalline powder which is sparingly soluble in water, freely soluble in ethanol and chloroform and practically insoluble in diethyl ether.

LUVOX™ Tablets are available in : 50 mg and 100 mg strengths for oral administration. In addition to the active ingredient, fluvoxamine maleate, each tablet contains the following inactive ingredients: carnauba wax, hydroxypropyl methylcellulose, mannitol, polyethylene glycol, polysorbate 80, pregelatinized starch, silicon dioxide, sodium stearyl fumarate, starch, synthetic iron oxides, and titanium dioxide.

CLINICAL PHARMACOLOGY

Pharmacodynamics

The mechanism of action of fluvoxamine maleate in obsessive compulsive disorder is presumed to be linked to its specific serotonin reuptake inhibition in brain neurons. In preclinical studies, it was found that fluvoxamine inhibited neuronal uptake of serotonin.

In in vitro studies fluvoxamine maleate had no significant affinity for histaminergic, alpha or beta adrenergic, muscarinic, or dopaminergic receptors. Antagonism of some of these receptors is thought to be associated with various sedative, cardiovascular, anticholinergic, and extrapyramidal effects of some psychotropic drugs.

Pharmacokinetics

Bioavailability

The absolute bioavailability of fluvoxamine maleate is 53%. Oral bioavailability is not significantly affected by food.

In a dose proportionality study involving fluvoxamine maleate at 100, 200 and 300 mg/day for 10 consecutive days in 30 normal volunteers, steady state was achieved after about a week of dosing. Maximum plasma concentrations at steady state occurred within 3-8 hours of dosing and reached concentrations averaging 88, 283 and 546 ng/mL, respectively. Thus, fluvoxamine had nonlinear pharmacokinetics over this dose range, i.e., higher doses of fluvoxamine maleate produced disproportionately higher concentrations than predicted from the lower dose.

Distribution/Protein Binding

The mean apparent volume of distribution for fluvoxamine is approximately 25 L/kg, suggesting extensive tissue distribution.

Approximately 80% of fluvoxamine is bound to plasma protein, mostly albumin, over a concentration range of 20 to 2000 ng/mL.

Metabolism

Fluvoxamine maleate is extensively metabolized by the liver; the main metabolic routes are oxidative demethylation and deamination. Nine metabolites were identified following a 5 mg radiolabelled dose of fluvoxamine maleate, constituting approximately 85% of the urinary excretion products of fluvoxamine. The main human metabolite was fluvoxamine acid which, together with its N-acetylated analog, accounted for about 60% of the urinary excretion products. A third metabolite, fluvoxethanol, formed by oxidative deamination, accounted for about 10%. Fluvoxamine acid and fluvoxethanol were tested in an in vitro assay of serotonin and norepinephrine reuptake inhibition in rats; they were inactive except for a weak effect of the former metabolite on inhibition of serotonin uptake (1-2 orders of magnitude less potent than the parent compound). Approximately 2% of fluvoxamine was excreted in urine unchanged. (See PRECAUTIONS -- Drug Interactions).

Elimination

Following a ^{14}C-labelled oral dose of fluvoxamine maleate (5 mg), an average of 94% of drug-related products was recovered in the urine within 71 hours.

The mean plasma half-life of fluvoxamine at steady state after multiple oral doses of 100 mg/day in healthy, young volunteers was 15.6 hours

Elderly Subjects

In a study of LUVOX™ Tablets at 50 and 100 mg comparing elderly (aged 66-73) and young subjects (aged 19-35), mean maximum plasma concentrations in the elderly were 40% higher. The multiple dose elimination half-life of fluvoxamine was 17.4 and 25.9 hours in the elderly compared to 13.6 and 15.6 hours in the young subjects at steady state for 50 and 100 mg doses, respectively.

In elderly patients, the clearance of fluvoxamine was reduced by about 50% and, therefore, LUVOX™ Tablets should be slowly titrated during initiation of therapy.

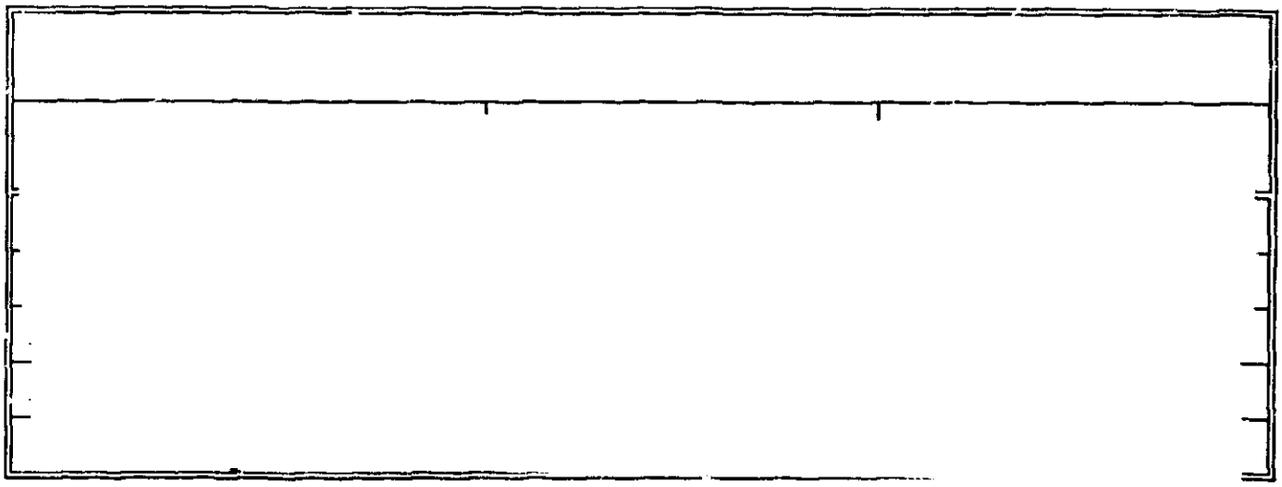
Hepatic and Renal Disease

A cross study comparison (healthy subjects vs. patients with hepatic dysfunction) suggested a 30% decrease in fluvoxamine clearance in association with hepatic dysfunction. The mean minimum plasma concentrations in renally impaired patients (creatinine clearance of 5 to 45 mL/min) after 4 and 6 weeks of treatment (50 mg bid, N=13) were comparable to each other, suggesting no accumulation of fluvoxamine in these patients. (See PRECAUTIONS, Use in Patients with Concomitant Illness.)

Clinical Trials

The effectiveness of LUVOX™ Tablets for the treatment of Obsessive Compulsive Disorder (OCD) was demonstrated in two 10-week multicenter, parallel group studies of adult outpatients. Patients in these trials were titrated to a total daily fluvoxamine dose of 150 mg/day over the first two weeks of the trial, following which the dose was adjusted within a range of 100-300 mg/day (on a bid schedule), on the basis of response and tolerance. Patients in these studies had moderate to severe OCD (DSM III-R), with mean baseline ratings on the Yale-Brown Obsessive Compulsive Scale (YBOCS, total score) of 23. Patients receiving fluvoxamine maleate experienced mean reductions of approximately 4 to 5 units on the YBOCS total score, compared to a 2 unit reduction for placebo

patients.



The following table provides the outcome classification by treatment group on the Global Improvement item of the Clinical Global Impressions (CGI) scale for both studies combined.

Table 1. Outcome Classification (%) on CGI-Global Improvement Item for Completers in Pool of Two OCD Studies

Outcome Classification	Fluvoxamine (N = 120)	Placebo (N = 134)
Worse	4%	6%
No Change	31%	51%
Minimally Improved	22%	32%
Much Improved	30%	10%
Very Much Improved	13%	2%

Exploratory analyses for age and gender effects on outcomes did not suggest any differential responsiveness on the basis of age or sex.

INDICATIONS AND USAGE

LUVOX™ Tablets are indicated for the treatment of obsessions and compulsions in patients with obsessive-compulsive disorder (OCD), as defined in the DSM-III-R. The obsessions or compulsions cause marked distress, are time-consuming, or significantly interfere with social or occupational functioning.

The efficacy of LUVOX™ was established in two 10-week trials with obsessive-compulsive outpatients with the diagnosis of obsessive compulsive disorder as defined in DSM-III-R. (See Clinical Trials under CLINICAL PHARMACOLOGY).

Obsessive-compulsive disorder is characterized by recurrent and persistent ideas, thoughts, impulses or images (obsessions) that are ego-dystonic and/or repetitive, purposeful, and intentional behaviors (compulsions) that are recognized by the person as excessive or unreasonable.

The effectiveness of LUVOX™ Tablets for long-term use, i.e., for more than 10 weeks, has not been systematically evaluated in placebo-controlled trials. Therefore, the physician who elects to use LUVOX™ Tablets for extended periods should periodically reevaluate the long-term usefulness of the drug for the individual patient. (See DOSAGE AND ADMINISTRATION).

CONTRAINDICATIONS

Coadministration of terfenadine or astemizole with LUVOX™ is contraindicated (see WARNINGS and PRECAUTIONS).

LUVOX™ Tablets are contraindicated in patients with a history of hypersensitivity to fluvoxamine maleate.

WARNINGS

Potential for Interaction with Monoamine Oxidase Inhibitors

In patients receiving another serotonin reuptake inhibitor drug in combination with monoamine oxidase inhibitors (MAOI), there have been reports of serious, sometimes fatal, reactions including hyperthermia, rigidity, myoclonus, autonomic instability with possible rapid fluctuations of vital signs, and mental status changes that include extreme agitation progressing to delirium and

coma. These reactions have also been reported in patients who have discontinued that drug and have been started on a MAOI. Some cases presented with features resembling neuroleptic malignant syndrome. Therefore, it is recommended that LUVOX™ Tablets not be used in combination with a MAOI, or within 14 days of discontinuing treatment with a MAOI. After stopping LUVOX™ Tablets, at least 2 weeks should be allowed before starting a MAOI.

Other Potentially Important Drug Interactions

(Also see Precautions, Drug Interactions)

Benzodiazepines

Alprazolam - When fluvoxamine maleate (100 mg qd) and alprazolam (1 mg qid) were co-administered to steady-state, plasma concentrations and other pharmacokinetic parameters (AUC, C_{max}, $T_{1/2}$) of alprazolam were approximately twice those observed when alprazolam was administered alone; oral clearance was reduced by about 50%. The elevated plasma alprazolam concentrations resulted in decreased psychomotor performance and memory. This interaction, which has not been investigated using higher doses of fluvoxamine, may be more pronounced if a 300 mg daily dose is co-administered, particularly since fluvoxamine exhibits non-linear pharmacokinetics over the dosage range 100-300 mg. If alprazolam is co-administered with LUVOX™ Tablets, the initial alprazolam dosage should be at least halved and titration to the lowest effective dose is recommended. No dosage adjustment is required for LUVOX™ Tablets.

Similar pharmacokinetic interactions would be expected with some other benzodiazapines, such as triazolam, but are not seen with all, (e.g., lorazepam, see Precautions,Drug Interactions). Caution is recommended whenever benzodiazepines are co-administered with LUVOX™ Tablets.

Potential Terfenadine and Astemizole Interactions

Terfenadine and astemizole are both metabolized by the cytochrome P450IIIA4 isozyme, and it has been demonstrated that ketoconazole, a potent inhibitor of IIIA4, blocks the metabolism of terfenadine and astemizole, resulting in increased plasma concentrations of parent drug. Increased plasma concentrations of terfenadine and astemizole cause QT prolongation and torsades de pointes-type ventricular tachycardia, sometimes fatal. As noted above, a substantial pharmacokinetic interaction has been observed for fluvoxamine in combination with alprazolam, a drug that is known to be metabolized by the IIIA4 isozyme. Although it has not been definitively demonstrated that fluvoxamine is a potent IIIA4 inhibitor, it is likely to be, given the substantial interaction of fluvoxamine with alprazolam. Consequently, it is recommended that fluvoxamine not be used in combination with either terfenadine or astemizole (see CONTRAINDICATIONS AND PRECAUTIONS).

Theophylline

The effect of steady-state fluvoxamine (50 mg bid) on the pharmacokinetics of a single dose of theophylline (375 mg as 442 mg aminophylline) was evaluated in 12 healthy non-smoking, male volunteers. The clearance of theophylline was decreased approximately 3-fold. Therefore, if theophylline is co-administered with fluvoxamine, its dose should be reduced to one third of the usual daily maintenance dose and plasma concentrations of theophylline should be monitored. No dosage adjustment is required for LUVOX™ Tablets.

Warfarin

When fluvoxamine maleate (50 mg tid) was administered concomitantly with warfarin for two weeks, warfarin plasma concentrations increased by 98% and prothrombin times were prolonged. Thus patients receiving oral anticoagulants and LUVOX™ Tablets should have their prothrombin time monitored and their anticoagulant dose adjusted accordingly. No dosage adjustment is required for LUVOX™ Tablets.

PRECAUTIONS

General

Activation of Mania/Hypomania

During premarketing studies involving primarily depressed patients, hypomania or mania occurred approximately 1% of patients treated with fluvoxamine. Activation of mania/hypomania has also been reported in a small proportion of patients with major affective disorder who were treated with other marketed antidepressants. As with all antidepressants, LUVOX™ Tablets should be used cautiously in patients with a history of mania.

Seizures

During premarketing studies, seizures were reported in 0.2% of fluvoxamine-treated patients. LUVOX™ Tablets should be used cautiously in patients with a history of seizures. It should be discontinued in any patient who develops seizures.

Suicide

The possibility of a suicide attempt is inherent in patients with depressive symptoms, whether these occur in primary depression or in association with another primary disorder such as OCD. Close supervision of high risk patients should accompany initial drug therapy. Prescriptions for LUVOX™ Tablets 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

Closely monitored clinical experience with LUVOX™ Tablets in patients with concomitant systemic illness is limited. Caution is advised in administering LUVOX™ Tablets to patients with diseases or conditions that could affect hemodynamic responses or metabolism.

LUVOX™ Tablets have 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 systematically excluded from many clinical studies during the product's premarketing testing. Evaluation of the electrocardiograms for patients with depression or OCD who participated in premarketing studies revealed no differences between fluvoxamine and placebo in the emergence of clinically important ECG changes.

In patients with liver dysfunction, fluvoxamine clearance was decreased by approximately 30%. LUVOX™ Tablets should be slowly titrated in patients with liver dysfunction during the initiation of treatment.

Information for Patients

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

Interference with Cognitive or Motor Performance

Since any psychoactive drug may impair judgement, thinking, or motor skills, patients should be cautioned about operating hazardous machinery, including automobiles, until they are certain that LUVOX™ Tablets therapy does not adversely affect their ability to engage in such activities.

Pregnancy

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

Nursing

Patients receiving LUVOX™ Tablets should be advised to notify their physicians if they are breast feeding an infant. (See PRECAUTIONS--Nursing Mothers.)

Concomitant Medication

Patients should be advised to notify their physicians if they are taking, or plan to take, any prescription or over-the-counter drugs, since there is a potential for clinically important interactions with LUVOX™ Tablets.

Alcohol

As with other psychotropic medications, patients should be advised to avoid alcohol while taking LUVOX™ Tablets.

Allergic Reactions

Patients should be advised to notify their physician if they develop a rash, hives, or a related allergic phenomenon during therapy with LUVOX™ Tablets.

Laboratory Tests

There are no specific laboratory tests recommended.

Drug Interactions

Potential Interactions with Drugs that Inhibit or are Metabolized by Cytochrome P450 Isozymes

Multiple hepatic cytochrome P450 (CYP450) enzymes are involved in the oxidative biotransformation of a large number of structurally different drugs and endogenous compounds. The available knowledge concerning the relationship of fluvoxamine and the CYP450 enzyme system has been obtained mostly from pharmacokinetic interaction studies conducted in healthy volunteers, but some preliminary *in vitro* data are also available. Based on a finding of substantial interactions of fluvoxamine with certain of these drugs (see later parts of this section and also Warnings for details) and limited *in vitro* data for the IIIA4 isozyme, it appears that fluvoxamine inhibits the following isozymes that are known to be involved in the metabolism of the listed drugs:

IA2	IIC9	IIIA4
Warfarin	Warfarin	Alprazolam
Theophylline		
Propranolol		

In vitro data suggest that fluvoxamine is a relatively weak inhibitor of the IID6 isozyme.

None of the drugs studied for drug interactions significantly affected the pharmacokinetics of fluvoxamine.

However, the metabolism of fluvoxamine has not been fully characterized and the effects of potent inhibitors of IID6, such as quinidine, or of IIIA4, such as ketoconazole, on fluvoxamine metabolism have not been studied.

A clinically significant fluvoxamine interaction is possible with drugs having a narrow therapeutic ratio such as terfenadine or astemizole, warfarin, theophylline, certain benzodiazepines, and phenytoin. If LUVOX™ Tablets are to be administered together with a drug that is eliminated via oxidative metabolism and has a narrow therapeutic window, plasma levels and/or pharmacodynamic effects of the latter drug should be monitored closely, at least until steady-state conditions are reached (See WARNINGS).

CNS Active Drugs

Monoamine Oxidase Inhibitors - See WARNINGS

Alprazolam - See WARNINGS

Lorazepam - A study of multiple doses of fluvoxamine maleate (50 mg bid) in healthy male volunteers (N=12) and a single dose of lorazepam (4 mg single dose) indicated no significant pharmacokinetic interaction. On average, both lorazepam alone and lorazepam with fluvoxamine produced substantial decrements in cognitive functioning; however, the co-administration of fluvoxamine and lorazepam did not produce larger mean decrements compared to lorazepam alone.

Lithium - As with other serotonergic drugs, lithium may enhance the serotonergic effects of fluvoxamine and, therefore, the combination should be used with caution. Seizures have been reported with the co-administration of fluvoxamine maleate and lithium.

Tryptophan - Tryptophan may enhance the serotonergic effects of fluvoxamine, and the combination should, therefore, be used with caution. Severe vomiting has been reported with the co-administration of fluvoxamine maleate and tryptophan.

Clozapine - Elevated serum levels of clozapine have been reported in patients taking fluvoxamine maleate and clozapine. Since clozapine related seizures and orthostatic hypotension appear to be

dose related, the risk of these adverse events may be higher when fluvoxamine and clozapine are co-administered. Patients should be closely monitored when fluvoxamine maleate and clozapine are used concurrently.

Alcohol - Studies involving single 40 g doses of ethanol (oral administration in one study and intravenous in the other) and multiple dosing with fluvoxamine maleate (50 mg bid) revealed no effect of either drug on the pharmacokinetics or pharmacodynamics of the other.

Tricyclic Antidepressants (TCAs) - Significantly increased plasma TCA levels have been reported with the co-administration of fluvoxamine maleate and amitriptyline, clomipramine, or imipramine. Caution is indicated with the co-administration of LUVOX™ Tablets and TCAs.

Carbamazepine - Elevated carbamazepine levels and symptoms of toxicity have been reported with the co-administration of fluvoxamine maleate and carbamazepine.

Methadone - Significantly increased methadone (plasma level:dose) ratios have been reported when fluvoxamine maleate was administered to patients receiving maintenance methadone treatment, with symptoms of opioid intoxication in one patient. Opioid withdrawal symptoms were reported following fluvoxamine maleate discontinuation in another patient.

Other Drugs

Theophylline - See WARNINGS

Propranolol and Other Beta-Blockers - Co-administration of fluvoxamine maleate 100 mg per day and propranolol 160 mg per day in normal volunteers resulted in a mean five-fold increase (range 2 to 17) in minimum propranolol plasma concentrations. In this study, there was a slight potentiation of the propranolol-induced reduction in heart rate and reduction in the exercise diastolic pressure.

One case of bradycardia and hypotension and a second case of orthostatic hypotension have been reported with the co-administration of fluvoxamine and metoprolol. While hypotension is infrequently associated with the use of metoprolol due to a preferential effect on cardiac adrenoreceptors, high doses also inhibit adrenoreceptors in vascular musculature and may result in hypotensive reactions as reported.

If propranolol or metoprolol is co-administered with LUVOX™ Tablets, a reduction in the initial beta-blocker dose and more cautious dose titration is recommended. No dosage adjustment is required for LUVOX™ Tablets.

Co-administration of fluvoxamine maleate 100 mg per day with atenolol 100 mg per day (N=6) did not affect the plasma concentrations of atenolol. Unlike propranolol and metoprolol, which undergo hepatic metabolism, atenolol is eliminated primarily by renal excretion.

Warfarin - See WARNINGS

Digoxin - Administration of fluvoxamine maleate 100 mg daily for 18 days (N=8) did not significantly affect the pharmacokinetics of a 1.25 mg single intravenous dose of digoxin.

Diltiazem - Bradycardia has been reported with the co-administration of fluvoxamine maleate and diltiazem.

Effects of Smoking on Fluvoxamine Metabolism

Smokers had a 25% increase in the metabolism of fluvoxamine compared to nonsmokers.

Electroconvulsive Therapy (ECT)

~~ECT~~

There are no clinical studies establishing the benefits or risks of combined use of ECT and fluvoxamine maleate.

Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis

There is no evidence of carcinogenicity, mutagenicity or impairment of fertility with fluvoxamine maleate.

There was no evidence of carcinogenicity in rats treated orally with fluvoxamine maleate for 30 months or hamsters treated orally with fluvoxamine maleate for 20 (females) or 26 (males) months. The daily doses in the high dose groups in these studies were increased over the course of the study from a minimum of 160 mg/kg to a maximum of 240 mg/kg in rats, and from a minimum of 135 mg/kg to a maximum of 240 mg/kg in hamsters. The maximum dose of 240 mg/kg is approximately 6 times the maximum human daily dose on a mg/m^2 basis.

Mutagenesis

No evidence of mutagenic potential was observed in a mouse

micronucleus test, an *in vitro* chromosome aberration test, or the Ames microbial mutagen test with or without metabolic activation.

Impairment of Fertility

In fertility studies of male and female rats, up to 80 mg/kg/day orally of fluvoxamine maleate, (approximately 2 times the maximum human daily dose on a mg/m^2 basis) had no effect on mating performance, duration of gestation, or pregnancy rate.

Pregnancy

Teratogenic Effects - Pregnancy Category C

In teratology studies in rats and rabbits, daily oral doses of fluvoxamine maleate of up to 80 and 40 mg/kg, respectively (approximately 2 times the maximum human daily dose on a mg/m^2 basis) caused no fetal malformations. However, in other reproduction studies in which pregnant rats were dosed through weaning there was (1) an increase in pup mortality at birth (seen at 80 mg/kg and above but not at 20 mg/kg), and (2) decreases in postnatal pup weights (seen at 160 but not at 80 mg/kg) and survival (seen at all doses; lowest dose tested = 5 mg/kg). (Doses of 5, 20, 80, and 160 mg/kg are approximately 0.1, 0.5, 2, and 4 times the maximum human daily dose on a mg/m^2 basis). While the results of a cross-fostering study implied that at least some of these results likely occurred secondarily to maternal toxicity, the role of a direct drug effect on the fetuses or pups could not be ruled out. There are no adequate and well-controlled studies in pregnant women. Fluvoxamine maleate should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Labor and Delivery

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

Nursing Mothers

As for many other drugs, fluvoxamine is secreted in human breast milk. The decision of whether to discontinue nursing or to discontinue the drug should take into account the potential for serious adverse effects from exposure to fluvoxamine in the nursing infant as well as the potential benefits of LUVOX™ Tablets therapy to the mother.

Pediatric Use

Safety and effectiveness of LUVOX™ Tablets in individuals below 18 years of age have not been established.

Geriatric Use

Approximately 230 patients participating in controlled premarketing studies with LUVOX™ Tablets were 65 years of age or over. No overall differences in safety were observed between these patients and younger patients. Other reported clinical experience has not identified differences in response between the elderly and younger patients. However, the clearance of fluvoxamine is decreased by about 50% in elderly compared to younger patients (see Pharmacokinetics under CLINICAL PHARMACOLOGY), and greater sensitivity of some older individuals also cannot be ruled out. Consequently, LUVOX™ Tablets should be slowly titrated during initiation of therapy.

ADVERSE REACTIONS

Associated with Discontinuation of Treatment

Of the 1087 OCD and depressed patients treated with fluvoxamine maleate in controlled clinical trials conducted in North America, 22% discontinued treatment due to an adverse event. The most common events (≥1%) associated with discontinuation and considered to be drug related (i.e., those events associated with dropout at a rate at least twice that of placebo) included:

[SEE SPECIFIC TABLE REVISIONS FROM APPROVABLE AND APPROVAL LETTERS; P.DAVID, CSO]

TABLE 2
ADVERSE EVENTS ASSOCIATED WITH DISCONTINUATION OF TREATMENT IN OCD AND DEPRESSION POPULATIONS

BODY SYSTEM/ ADVERSE EVENT	PERCENTAGE OF FLUVOXAMINE PATIENTS	PERCENTAGE OF PLACEBO PATIENTS
Body as a Whole	Fluvoxamine	Placebo
BODY AS A WHOLE		
Headache	3%	1%
Asthenia	2%	<1%
Abdominal Pain	1%	0
DIGESTIVE		
Nausea	9%	1%
Diarrhea	1%	<1%
Vomiting	2%	<1%
Anorexia	1%	<1%
Dyspepsia	1%	<1%
NERVOUS SYSTEM		

Insomnia	4%	1%
Somnolence	4%	<1%
Nervousness	2%	<1%
Agitation	2%	<1%
Dizziness	2%	<1%
Anxiety	1%	<1%
Dry Mouth	1%	<1%

Incidence in Controlled Trials

Commonly Observed Adverse Events in Controlled Clinical Trials:

LUVOX™ Tablets have been studied in controlled trials of OCD (n=320) and depression (n=1350). In general, adverse event rates were similar in the two data sets. The most commonly observed adverse events associated with the use of LUVOX™ Tablets and likely to be drug-related (incidence of 5% or greater and at least twice that for placebo) derived from Table 3 below were: somnolence, insomnia, nervousness, tremor, nausea, dyspepsia, anorexia, vomiting, abnormal ejaculation, asthenia, and sweating. In a pool of two studies involving only patients with OCD, the following additional events were identified using the above rule: dry mouth, decreased libido, urinary frequency, anorgasmia, rhinitis, and taste perversion.

Adverse Events Occurring at an Incidence of 1%:

Table 3 that follows enumerates adverse events that occurred at a frequency of 1% or more, and were more frequent than in the placebo group, among patients treated with LUVOX™ Tablets in two short-term placebo controlled OCD trials (10 week) and depression trials (6 week) in which patients were dosed in a range of generally 100 to 300 mg/day. This table shows the percentage of patients in each group who had at least one occurrence of an event at some time during their treatment. Reported adverse events were classified using a standard COSTART-based Dictionary terminology.

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 may differ from those that prevailed in the clinical trials. 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 non-drug factors to the side-effect incidence rate in the population studied.

[SEE APPROVAL AND APPROVABLE LETTERS FOR SPECIFIC TABLE REVISIONS; P.DAVID, CSO]

TABLE 3
TREATMENT-EMERGENT ADVERSE EVENT INCIDENCE RATES BY BODY SYSTEM IN OCD AND DEPRESSION POPULATIONS COMBINED[1]

ADVERSE EVENT

	Reporting Event	
BODY SYSTEM/ADVERSE EVENT	FLUVOXAMINE N= 892	PLACEBO N= 778
BODY AS WHOLE		
Headache	22	20
Asthenia	14	6
Flu Syndrome		2
Chills	2	10
CARDIOVASCULAR		
Palpitations	3	2
DIGESTIVE SYSTEM		
Nausea	40	14
Diarrhea	11	7
Constipation	10	8
Dyspepsia	10	5
Anorexia		2
Vomiting	5	2
Flatulence	4	3
Tooth Disorder[2]	1	1
Dysphagia	2	1

ADVERSE EVENT	Percentage of Patients Reporting Event	
	FLUVOXAMINE N= 892	PLACEBO N= 778
		SYSTEM
Somnolence	22	8 14
Insomnia	21	10 10
Dry Mouth	14	10 6
Nervousness	12	5 3
Dizziness	11	6 8
	5	1
Tremor		
Anxiety	5	3
Vasodilatation[3]	3	1
Hypertonia	2	1
Agitation	2	1
Libido Decreased	2 6	
		1
Depression	2	1 4
CNS Stimulation	2	1
RESPIRATORY SYSTEM		
Upper Respiratory Infection	9	5
	2	1
Dyspnea		
Yawn	2	0
SKIN		

ADVERSE EVENT

	Percentage of Patients Reporting Event	
	FLUVOXAMINE N=	PLACEBO N= 778
Sweating	7	3
SPECIAL SENSES		
Taste Perversion	3	1
Amblyopia[4]	3	2
UROGENITAL		
Abnormal Ejaculation[5,6]	8	1
	3	2
Impotence[6]	2	1
Anorgasmia	2	0
Urinary Retention	1	0

[1] Events for which fluvoxamine maleate incidence was equal to or less than placebo are not listed in the table above, but include the following: abdominal pain, abnormal dreams, appetite increased.

back pain, chest pain, confusion, dysmenorrhea, fever, infection, leg cramps,

migraine, myalgia,

pain

paresthesia, pharyngitis, postural hypotension, pruritus, rash, rhinitis, thirst, and tinnitus.

[2] Includes "toothache," "tooth extraction and abscess," and "caries."

[3] Mostly feeling warm, hot or flushed.

[5] Mostly "blurred vision."
[6] Mostly "delayed ejaculation."
[7] Incidence based on number of male patients.

Adverse Events in OCD Placebo Controlled Studies Which are Markedly Different (defined as at least a two-fold difference in rate) in Rate from the Pooled Event Rates in OCD and Depression Placebo Controlled Studies

The events in OCD studies with a two-fold decrease in rate compared to event rates in OCD and depression studies were dysphagia and amblyopia (mostly blurred vision). Additionally, there was an approximate 25% decrease in nausea.

The events in OCD studies with a two-fold increase in rate compared to event rates in OCD and depression studies were: asthenia, abnormal ejaculation (mostly delayed ejaculation), anxiety, infection, rhinitis, anorgasmia (in males), depression, libido decreased, pharyngitis, agitation, impotence, myoclonus/twitch, thirst, weight loss, leg cramps, myalgia, and urinary retention. These events are listed in order of decreasing rates in the OCD trials.

Vital Sign Changes

Comparisons of fluvoxamine maleate and placebo groups in separate pools of short-term OCD and depression trials on (1) median change from baseline on various vital signs variables and on (2) incidence of patients meeting criteria for potentially important changes from baseline on various vital signs variables revealed no important differences between fluvoxamine maleate and placebo.

Laboratory Changes

Comparisons of fluvoxamine maleate and placebo groups in separate pools of short-term OCD and depression trials on (1) median change from baseline on various serum chemistry, hematology, and urinalysis variables and on (2) incidence of patients meeting criteria for potentially important changes from baseline on various serum chemistry, hematology, and urinalysis variables revealed no important differences between fluvoxamine maleate and placebo.

ECG Changes

Comparisons of fluvoxamine maleate and placebo groups in separate pools of short-term OCD and depression trials on (1) mean change from baseline on various ECG variables and on (2) incidence of patients meeting criteria for potentially important changes from baseline on various ECG variables revealed no important differences between fluvoxamine maleate and placebo.

Other Events Observed During the Premarketing Evaluation of LUVOX™ Tablets

During premarketing clinical trials conducted in North America and Europe, multiple doses of fluvoxamine maleate were administered for a combined total of 2737 patient exposures in patients suffering OCD or Major Depressive Disorder.

Untoward events associated with this exposure were recorded by clinical investigators using descriptive 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 limited (i.e., reduced) number of standard event categories.

In the tabulations which follow, a standard COSTART-based Dictionary terminology has been used to classify reported adverse events. If the COSTART term for an event was so general as to be uninformative, it was replaced with a more informative term. The frequencies presented, therefore, represent the proportion of the 2737 patient exposures to multiple doses of fluvoxamine maleate who experienced an event of the type cited on at least one occasion while receiving fluvoxamine maleate. All reported events are included in the list below, with the following exceptions: 1) those events already listed in Table 3, which tabulates incidence rates of common adverse experiences in placebo controlled OCD and depression clinical trials, are excluded; 2) those events for which a drug cause was considered remote (i.e., neoplasia, gastrointestinal carcinoma, herpes simplex, herpes zoster, application site reaction, and unintended pregnancy) are omitted; and 3) events which were reported in only one patient and judged to not be potentially serious are not included. It is important to emphasize that, although the events reported did occur during treatment with fluvoxamine maleate, a causal relationship to fluvoxamine maleate has not been established.

Events are further classified within body system categories and enumerated in order of decreasing frequency using the following definitions: frequent adverse events are defined as those occurring on one or more occasions in at least 1/100 patients; infrequent adverse events are those occurring between 1/100 to at least 1/1,000 patients; rare adverse events are those occurring in less than 1/1,000 patients.

Body as a Whole: Frequent:

accidental injury, malaise; Infrequent: allergic reaction,

neck pain, neck rigidity, overdose, photosensitivity reaction, suicide attempt; Rare: cyst, pelvic pain, sudden death.

Cardiovascular System: Frequent:

hypertension, hypotension, syncope,

tachycardia; Infrequent: angina pectoris,

bradycardia, cardiomyopathy, cardiovascular disease, cold extremities, conduction delay,

heart failure, myocardial infarction,

pallor, pulse irregular, ST segment changes; Rare: AV block,

cerebrovascular accident, coronary artery disease, embolus, pericarditis, phlebitis, pulmonary infarction, supraventricular extrasystoles.

Digestive System: Frequent: elevated liver transaminases; Infrequent: colitis,

eructation, esophagitis, gastritis,

gastroenteritis

gastrointestinal hemorrhage, gastrointestinal ulcer, gingivitis, glossitis, hemorrhoids, melena,

rectal hemorrhage, stomatitis; Rare: biliary pain,

cholecystitis, cholelithiasis, fecal incontinence,

hematemesis, intestinal obstruction, jaundice.

Endocrine System: Infrequent: hypothyroidism; Rare: goiter.

Hematic and Lymph Systems: Infrequent: anemia, ecchymosis, leukocytosis, lymphadenopathy, thrombocytopenia; Rare:

leukopenia, purpura.

Metabolic and Nutritional Systems: Frequent: edema, weight gain, weight loss; Infrequent: dehydration, hypercholesterolemia; Rare:

diabetes mellitus, hyperglycemia, hyperlipidemia, hypoglycemia, hypokalemia, lactate dehydrogenase increased.

Musculoskeletal System: Infrequent: arthralgia,

bursitis, generalized muscle spasm,

myasthenia, tendinous contracture, tenosynovitis; Rare: arthrosis,

myopathy, pathological fracture.

Nervous System: Frequent: amnesia,

apathy,

hyperkinesia, hypokinesia,

manic reaction, myoclonus, psychotic reaction; Infrequent: agoraphobia, akathisia,

ataxia,

CNS depression, convulsion, delirium, delusions,

depersonalization, drug dependence, dyskinesia, dystonia,

emotional lability, euphoria, extrapyramidal syndrome, gait unsteady, hallucinations,

hemiplegia,

hostility, hypersomnia, hypochondriasis, hypotonia,

hysteria, incoordination

increased salivation, libido increased, neuralgia, paralysis, paranoid reaction, phobia, psychosis, sleep disorder, stupor, twitching, vertigo; Rare: akinesia, coma, fibrillations, mutism, obsessions, reflexes decreased, slurred speech, tardive dyskinesia, torticollis, trismus, withdrawal syndrome.

Respiratory System: Frequent: cough increased, sinusitis; Infrequent:

asthma, bronchitis,

epistaxis, hoarseness, hyperventilation; Rare: apnea, congestion of upper airway, hemoptysis, hiccups, laryngismus, obstructive pulmonary disease,
pneumonia.

Skin: Infrequent: acne,

alopecia, dry skin, eczema,
exfoliative dermatitis,
furunculosis, seborrhea, skin discoloration,
urticaria.

Special Senses: Infrequent: accomodation abnormal,

conjunctivitis, deafness, diplopia,

dry eyes, ear pain,

eye pain, mydriasis, otitis media, parosmia, photophobia, taste loss, visual field defect; Rare: corneal ulcer, retinal detachment.

Urogenital System: Infrequent: anuria,

breast pain, cystitis, delayed menstruation,[1] dysuria, female lactation,[1] hematuria, menopause,[1] menorrhagia,[1] metrorrhagia,[1] nocturia, premenstrual syndrome,[1] urinary incontinence, urinary tract infection, urinary urgency, urination impaired, vaginal hemorrhage, vaginitis;[1] Rare: kidney calculus, hematospermia,[2] oliguria.

[1] Based on the number of females.
[2] Based on the number of males.

Non-US Postmarketing Reports

Voluntary reports of adverse events in patients taking LUVOX™ Tablets that have been received since market introduction and are of unknown causal relationship to LUVOX™ Tablets use include: toxic epidermal necrolysis, Stevens-Johnson syndrome, Henoch-Schoenlein purpura, bullous eruption, priapism, agranulocytosis, neuropathy, aplastic anemia, anaphylactic reaction, hyponatremia, acute renal failure, and severe akinesia with fever when fluvoxamine was co-administered with antipsychotic medication.

DRUG ABUSE AND DEPENDENCE

Controlled Substance Class

LUVOX Tablets are not controlled substances.

Physical and Psychological Dependence

The potential for abuse, tolerance and physical dependence with fluvoxamine maleate has been studied in a nonhuman primate model. No evidence of dependency phenomena was found. The discontinuation effects of LUVOX™ Tablets were not systematically evaluated in controlled clinical trials. LUVOX™ Tablets were not systematically studied in clinical trials for potential for abuse, but there was no indication of drug-seeking behavior in clinical trials. It should be noted, however, that patients at risk for drug dependency were systematically excluded from investigational studies of

fluvoxamine maleate. Generally, it is not possible to predict on the basis of preclinical or premarketing clinical experience the extent to which a CNS active drug will be misused, diverted, and/or abused once marketed. Consequently, physicians should carefully evaluate patients for a history of drug abuse and follow such patients closely, observing them for signs of fluvoxamine maleate misuse or abuse (i.e.- development of tolerance, incrementation of dose, drug-seeking behavior).

OVERDOSAGE

Human Experience

Worldwide exposure to fluvoxamine maleate includes over 37,000 patients treated in clinical trials and an estimated exposure of 4,500,000 patients treated during foreign marketing experience (circa 1992). Of the 354 cases of deliberate or accidental overdose involving fluvoxamine maleate reported from this population, there were 19 deaths. Of the 19 deaths, 2 were in patients taking fluvoxamine maleate alone and the remaining 17 were in patients taking fluvoxamine maleate along with other drugs. In the remaining 335 patients, 309 had complete recovery after gastric lavage or symptomatic treatment. One patient had persistent mydriasis after the event, and a second patient had a bowel infarction requiring a hemicolectomy. In the remaining 24 patients the outcome was unknown. The highest reported overdose of fluvoxamine maleate involved a non-lethal ingestion of 10,000 mg (equivalent of 1-3 months' dosage). The patient fully recovered with no sequelae.

Commonly observed adverse events associated with fluvoxamine maleate overdose included drowsiness, vomiting, diarrhea, and dizziness. Other notable signs and symptoms seen with fluvoxamine maleate overdose (single or mixed drugs) included coma, tachycardia, bradycardia, hypotension, ECG abnormalities, liver function abnormalities, convulsions, and symptoms such as aspiration pneumonitis, respiratory difficulties or hypokalemia that may occur secondary to loss of consciousness or vomiting.

Management of Overdose

1. An unobstructed airway should be established with maintenance of respiration as required. Vital signs and ECG should be monitored.

2. Administration of activated charcoal may be as effective as emesis or lavage and should be considered in treating overdose. Since absorption with overdose may be delayed, measures to minimize absorption may be necessary for up to 24 hours post-ingestion.

3. Maintain close observation as clinically indicated.

4. There are no specific antidotes for LUVOX™ Tablets

5. In managing overdosage, consider the possibility of multiple drug involvement. The physician should consider contacting a poison control center for additional information on the treatment of any overdosage.

6. Dialysis is not believed to be beneficial.

DOSAGE AND ADMINISTRATION

The recommended starting dose for LUVOX™ Tablets is 50 mg, administered as a single daily dose at bedtime. In the controlled clinical trials establishing the effectiveness of LUVOX™ Tablets in OCD, patients were titrated within a dose range of 100 to 300 mg/day. Consequently, the dose should be increased in 50 mg increments every 4 to 7 days, as tolerated, until maximum therapeutic benefit is achieved, not to exceed 300 mg per day. It is advisable that a total daily dose of more than 100 mg should be given in two divided doses. If the doses are not equal, the larger dose should be given at bedtime.

Dosage for Elderly or Hepatically Impaired Patients

Elderly patients and those with hepatic impairment have been observed to have a decreased clearance of fluvoxamine maleate. Consequently, it may be appropriate to modify the initial dose and the subsequent dose titration for these patient groups.

Maintenance/Continuation Extended Treatment

Although the efficacy of LUVOX™ Tablets beyond 10 weeks of dosing for OCD has not been documented in controlled trials, OCD is a chronic condition, and it is reasonable to consider continuation for a responding patient. Dosage adjustments should be made to maintain the patient on the lowest effective dosage, and patients should be periodically reassessed to determine the need for continued treatment.

HOW SUPPLIED

Tablets 50 mg: yellow, elliptical, film-coated (debossed "Solvay" and "4205" on one side and scored on the other)

Tablets 50 mg - yellow, elliptical, film-coated (debossed "Solvay"
and "4205" on one side and scored on the other)

Bottles of 100	NDC 0032-4205-01
Bottles of 1000	NDC 0032-4205-10
Unit dose pack of 100	NDC 0032-4205-11

Tablets 100 mg:———scored, beige, elliptical, film-coated (debossed "Solvay" and "4210" on one side and scored on the other)

Bottles of 100	NDC 0032-4210-01
Bottles of 1000	NDC 0032-4210-10
Unit dose pack of 100	NDC 0032-4210-11

LUVOX™ Tablets should be protected from high humidity and stored at controlled room temperature, 15°-30° C (59°-86° F).

Dispense in tight containers.

Caution: Federal law prohibits dispensing without prescription.

Doc #LABFLUVX.AP4

mORS

REVIEW AND EVALUATION OF CLINICAL DATA

Application Information

NDA #:	20,243
Sponsor:	Solvay Pharmaceuticals
Clock Date:	December 30, 1991

Drug Name

Generic Name:	Fluvoxamine Maleate
Proposed Trade Name:	Luvox

Drug Categorization

Pharmacological Category:	Selective Serotonin Reuptake Inhibitor
Proposed Indication:	Obsessive Compulsive Disorder
NDA Classification:	1S
Dosage Forms, Strengths, and Route of Administration:	25mg, 50mg, 100mg, and 150mg film-coated tablets.

Reviewer Information

Clinical Reviewer:	Gregory M. Dubitsky, M.D.
Review Completion Date:	October 22, 1993

CONTENTS

VOLUME 1

VOLUME 2

Appendices

1.0 Material Reviewed

1.1 NDA Material

The following items were examined in the process of preparing this review.

NDA VOLUME(S)	SUBMISSION DATE	MATERIAL
1.25	December 24, 1991	Human pharmacokinetics
1.40	December 24, 1991	Summary and draft labeling.
1.41	December 24, 1991	Background, special interest studies
1.42	December 24, 1991	Clinical pharmacology studies
1.49	December 24, 1991	Study report (5529)
1.49-1.52	December 24, 1991	Appendices to study report (5529)(Reference only)
1.52	December 24, 1991	Study report (5534)
1.52-1.56	December 24, 1991	Appendices to study report (5534)(Reference only)
1.62	December 24, 1991	Table of studies and Integrated Summary of Efficacy.
1.63-1.65	December 24, 1991	Integrated Safety Summary (Strata I)
1.66-1.85	December 24, 1991	Strata I ISS Appendices (Reference only)
1.86-1.87	December 24, 1991	Integrated Safety Summary (Strata II)
1.88-1.95	December 24, 1993	Strata II ISS Appendices (Reference only)
1.97-1.99	December 24, 1991	Integrated Safety Summary (Strata III)
1.100-1.123	December 24, 1993	Strata III ISS Appendices (Reference only)

NDA VOLUME(S)	SUBMISSION DATE	MATERIAL
1.124	December 24, 1991	Integrated Safety Summary (Strata IV), "Acute Fluvoxamine Poisoning Report"
1.125-1.128	December 24, 1991	Strata IV Patient Profiles (Reference only)
1.129	December 24, 1991	Overdose & Drug Abuse Information, Benefit to Risk Statement
1.130-1.141	December 24, 1991	Master Bibliography (predominantly summaries)
1.307	December 24, 1991	Index to NSR's & CRF's (Reference only)
1.308-1.324	December 24, 1991	NSR's (Deaths, serious AE's, & dropouts) (Reference only)
1.325-1.423	December 24, 1991	CRF's (Deaths & serious AE's) (Reference only)
-	January 15, 1993	Suicidality meta-analysis
-	February 12, 1993	Updated COSTART Dictionary & revised AE tables
-	February 23, 1993	Strata III Safety Update (to July 1992)
-	April 8, 1993	Strata IV Safety Update (to July 1992)
-	June 3, 1993	Reports of 4 new human pharmacokinetic studies

NDA VOLUME(S)	SUBMISSION DATE	MATERIAL
-	April 4, 1992 May 12, 1992 May 13, 1992 July 17, 1992 October 12, 1992 October 26, 1992 October 30, 1992 January 27, 1993 January 29, 1993 February 2, 1993 February 5, 1993 February 8, 1993 February 10, 1993 March 5, 1993 April 8, 1993 May 3, 1993 May 4, 1993 May 19, 1993 May 27, 1993 July 1, 1993 July 9, 1993 July 22, 1993 July 26, 1993 August 8, 1993 August 12, 1993 August 19, 1993 August 23, 1993 August 26, 1993 September 2, 1993 September 9, 1993	Responses to requests for additional safety information.

1.2 IND Material

The division file for IND the sponsor's IND for fluvoxamine, was consulted during the course of the NDA review. In addition, the following material pertaining to IND was reviewed.

SUBMISSION DATE	MATERIAL
February 11, 1992	IND Annual Report
May 24, 1993	IND Annual Report
July 2, 1992 July 15, 1992 July 24, 1992 August 6, 1992 August 13, 1992 August 21, 1992 August 28, 1992 Sept. 17, 1992 October 2, 1992 October 22, 1992 November 6, 1992 November 20, 1992 December 1, 1992 December 14, 1992 December 17, 1992 January 15, 1993 January 22, 1993 February 4, 1993 February 22, 1993 March 2, 1993 March 17, 1993 March 26, 1993 April 13, 1993 April 19, 1993 May 5, 1993 May 17, 1993 May 27, 1993 June 22, 1993 July 2, 1993 July 22, 1993	"10-Day Reports" of serious adverse events.

2.0 Background

2.1 Indication

The only other drug currently approved by the FDA for treatment of OCD is clomipramine (Anafranil), which was approved in 1990 on the basis of demonstrated moderate effectiveness in treating obsessions and compulsions in patients with moderate to severe DSM-III OCD in controlled clinical trials. It is claimed that fluvoxamine has a side effect profile which is superior to that of clomipramine, most notably a low incidence of anticholinergic side effects, no clinically significant cardiotoxicity and an extremely low seizure rate.

Fluoxetine (Prozac), another selective serotonin reuptake inhibitor which is approved for depression, has also been shown to be helpful in treating some patients with OCD in investigational trials and was recommended for approval for this indication by the Psychopharmacologic Drugs Advisory Committee in July 1993.

Other available drugs, such as tricyclic antidepressants, have not demonstrated consistent efficacy in OCD.

2.2 Related IND's and NDA's

Other selective serotonin reuptake inhibitors currently approved in the U.S. are summarized below.

Trade Name	Generic Name	NDA #	Indication
Prozac	Fluoxetine	18,936	Depression
Zoloft	Sertraline	19,839	Depression
Paxil	Paroxetine	20,031	Depression

IND (sponsored by Lawrence H. Price, M.D. of Yale University) and IND (sponsored by Daniel Winstead, M.D. of Tulane University) are IND's in addition to the sponsor's IND which have been filed for the investigational use of fluvoxamine in the United States and are currently active. Records indicate that 10 other IND's for the investigational use of fluvoxamine have been filed over the past several years; these appear to have been cancelled or withdrawn or are inactive at this time.

2.3 Administrative History

Fluvoxamine maleate is a novel unicyclic compound which was first synthesized in The Netherlands in the early 1970's. It was

discovered to selectively inhibit the reuptake of serotonin into presynaptic neurons both in vitro and in vivo and, given this property, fluvoxamine was investigated with the intention of ultimately seeking marketing approval for the treatment of depression.

IND was submitted to the FDA on October 15, 1975 for the initiation of trials of fluvoxamine in the treatment of depression. Studies commenced and a patent was issued for fluvoxamine maleate on April 18, 1978, to expire in 1995. A pre-NDA meeting convened on May 19, 1983, to discuss required data and the format to be used for the NDA submission.

NDA for the use of fluvoxamine in depression was submitted on December 20, 1983, and included a total of 71 separate studies and 1,172 subjects treated with fluvoxamine over an 8 year period in Europe and North America. After a thorough review of this submission, a not-approvable letter was sent to the sponsor based primarily on failure to adequately demonstrate efficacy. Also, data contained in the Pharmacology, Chemistry, and Biopharmaceutics sections was considered to be deficient. On October 3, 1985, the sponsor informed the FDA of its intent to file an amendment to the NDA but an adequate amendment had not been filed as of October 2?. 1990, and the NDA was considered to be withdrawn.

In the meanwhile, the sponsor elected to pursue studies to demonstrate the efficacy and safety of fluvoxamine for the treatment of obsessive-compulsive disorder based on the theory that CNS serotonergic dysfunction was implicated in the biology of OCD. On September 18, 1987, an amendment to the original IND was filed for the initiation of studies 5529 and 5534, two adequate and well-controlled studies which, together with safety data accumulated over the previous several years, were intended to provide the basis for the eventual approval of fluvoxamine for OCD.

Given the vast safety database that had been accumulated to that time, the sponsor proposed a stratification of safety data to pool studies of comparable completeness and reliability. A meeting was held on May 21, 1990, to consider the sponsor's proposal. A pre-NDA meeting occurred on May 4, 1991, during which stratification of safety studies into 3 levels was detailed and presentation formats were further delineated.

NDA #20,243 for the use of fluvoxamine in OCD was received on December 30 1991; the initial submission presented all data available as of December 31, 1990. A determination to file this NDA was made on February 18, 1992.

2.4 Directions for Use

The following recommendations are proposed by the sponsor:

Initial therapy should consist of fluvoxamine 50mg qHS for 4 days, then 100mg qHS for another 4 days. Subsequent doses should be titrated by 50mg increments, with 3-4 days at each dose level until maximum therapeutic effect is attained. The recommended daily dosage range is 100-300mg. Tablets should be swallowed with water and without chewing. Total daily doses of greater than 100mg should be taken in two equally divided doses. If unequal doses are taken, the larger dose should be taken at bedtime. Recommended duration of therapy for OCD is unclear. It is reasonable to consider continued treatment for a responding patient with periodic assessment of drug usefulness.

Since fluvoxamine is extensively metabolized by the liver, this being the major route of excretion, it will be important to consider recommendations for use in patients with hepatic impairment. Likewise, specific directions for use in the elderly may be warranted given decrements in hepatic and renal function with age.

Particular attention should be paid to drug-drug interactions which may need to be mentioned as contraindications or warnings in labeling, such as the contraindicated use of concurrent MAOI therapy with other SSRI's.

Finally, the potential for hepatotoxicity must be assessed to formulate any recommendation for monitoring liver function during therapy.

2.5 Foreign Marketing

Fluvoxamine was first approved for marketing in Switzerland in 1983 and has since been approved in 40 other foreign countries for the treatment of depressive disorders; the estimated worldwide exposure as of early 1993 is about million patients. There have been no foreign marketing withdrawals to date. Below are the 36 countries where fluvoxamine is marketed (as of May 1993).

Austria	Hungary	Saudi Arabia
Belgium	Ireland	Singapore
Canada	Israel	Slovenia
Croatia	Italy	Spain
Cyprus	Jordan	Sweden
Czechoslovakia	Luxembourg	Switzerland
Denmark	Malta	Taiwan
Finland	Netherlands	Thailand
France	Netherlands Antilles	Turkey
Germany	Norway	U A. E.
Greece	Pakistan	United Kingdom
Hong Kong	Portugal	Yugoslavia

3.0 Chemistry

Chemistry data has been reviewed separately. There are no outstanding chemistry concerns relevant to the clinical use of fluvoxamine.

4.0 Animal Pharmacology

The mechanism of action of fluvoxamine in obsessive-compulsive disorder is not specifically known but is felt to be related to its selective serotonin reuptake inhibition in CNS neuronal synapses. Fluvoxamine binds in a highly selective manner to presynaptic receptors which mediate serotonin reuptake. There is no significant affinity for histaminergic, dopaminergic, alpha or beta adrenergic, or muscarinic receptors. Animal studies have produced no data which would preclude its clinical use in man at the maximum recommended dose, 300mg/day, corresponding to approximately 4-6mg/kg/day.

Autonomic signs, to include constipation and mydriasis, were noted at a doses of 5-80 mg/kg in dogs.

The following renal abnormalities were observed in animal studies: kidney lymphocytic infiltration in rats exposed to 40-240 mg/kg/day

for 18 months, renal tubular changes in hamsters exposed to 9-432 mg/kg/day for 4 weeks, and glomerular atrophy in dogs treated with 62.5 mg/kg/day for 52 weeks.

Fluvoxamine administration to mice (up to 21 weeks) and hamsters (up to 13 weeks) demonstrated an association with hypolipidemia at oral doses ≥80 mg/kg/day in mice and ≥9 mg/kg/day in hamsters; there was accumulation of lipids in the liver of the mice and, only at the highest doses (230 and 432 mg/kg/day), in the hamsters. Fluvoxamine 160-200 mg/kg/day given for 1 year to rats was associated with a mild form of phospholipidosis. When dogs were exposed for 7 months and one year to 60 mg/kg/day, foamy macrophages were observed in the intestinal and mesenteric lymph nodes and the spleen: these cells were found to consist mainly of phospholipid. Although this possibly indicated a disturbance in fat metabolism, the significance of this finding for humans is not known.

In vitro studies indicate that fluvoxamine can prolong the elimination of drugs which are metabolized by oxidation in the liver.

Fluvoxamine was not considered mutagenic in the micronucleus test, the chromosome aberration test, or the Ames test with and without metabolic activation.

There are no documented effects on mutagenic or carcinogenic potential. Reproductive studies in rats revealed lower mean values for litter size and litter weight with occasional statistical significance at doses of 5-80mg/kg/day. Also, rat offspring exposed to the milk of dams treated with 160mg/kg/day showed decreased survival during the early post partum period.

Fluvoxamine was administered to drug-naive monkeys (n=4) for two 28-day periods to assess for physical dependence liability, using diazepam as a control (n=2). During the first period, the dose was increased to 67.5 mg/kg PO bid and, during the second period, 90 mg/kg PO bid. A benzodiazepine antagonist, Ro 15-1788, was given on days 24 and 59 four hours after the morning dose, producing withdrawal symptoms (mild hyperirritability, apprehension) in only 1 of 4 fluvoxamine monkeys on day 24 and moderate to severe withdrawal signs in the diazepam-treated animals on both days. Following drug discontinuation after the first period, 2 fluvoxamine animals exhibited piloerection and apprehension on single occasions with none of the 3[1] surviving fluvoxamine animals showing any such signs after the second period; mild to severe signs were observed after both periods in the diazepam monkeys.

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[1]One monkey died of an accidental lung dose during the second period.

Fluvoxamine was thus felt to be devoid of physical dependence liability.

Potential for psychological dependence was assessed in 4 drug-naive monkeys in a self-administration test[2]. After single doses of 1, 2, and 4 mg/kg, 3 of 4 monkeys showed no evidence of drug-seeking behavior above control levels. A further period of dosing with fluvoxamine 4 mg/kg every 3 hours failed to initiate lever-pressing. The fourth monkey did demonstrate a desire to self-administer fluvoxamine after a 4 mg/kg dose. However, when the fixed ratio of lever presses to doses was increased from 1 press:1 dose to 3 presses:1 dose, lever pressing immediately regressed, which was not felt to be typical of drug-seeking behavior.

[2]In this test, monkeys received a dose of Fluvoxamine by intragastric cannula in response to lever pressing.

5.0 Description of Clinical Data Sources

The clinical safety data for fluvoxamine derives from over 175 clinical trials and a post-marketing surveillance database generated by an estimated 4.5 million patient exposures since it was first introduced in Switzerland in 1983. Given the variable reliability and completeness of this clinical information in this immense database, a decision was made by the sponsor to organize the Phase 2-3 data into 4 Strata (I-IV) so that data within each Strata is of comparable completeness and reliability:

> Strata I consists of 13 North American controlled studies.
>
> Strata II is comprised of 70 North American uncontrolled and European controlled and uncontrolled studies.
>
> Strata III is composed of 92, generally uncontrolled, worldwide post-marketing studies.
>
> Strata IV consists of the worldwide post-marketing surveillance database maintained by the sponsor.

The cutoff date for Phase 1 data was May 1993. The cutoff date for Strata I and Strata II data was December 31, 1990; Strata III and Strata IV data have been updated to July 1, 1992. Additionally, serious adverse events, to include deaths, which have been submitted to the agency as of July 1993[1] have been monitored for cases which were felt to be clinically significant and possibly drug related.

Also mentioned in this submission is Strata V, a residual category which the sponsor has reserved for studies which have produced incomplete or unverifiable data, investigations which had not been initiated by the cutoff date for inclusion in the original NDA database (December 1990), or individual patient data which was incomplete or inadvertently omitted from the original NDA database. For these subjects, this submission does include a Narrative Summary Report (NSR) and a Case Report Form (CRF) for each subject who died during or after study (5 deaths) and for each subject who experienced a serious adverse event (29 patients).

The only Strata IV and Strata V data addressed in this review are deaths and serious adverse events. Reasonably accurate population sizes for these two Strata are not known.

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[1]This data is compiled in two IND Annual Reports (February 1992 and May 1993) and, for events reported since the end of the period covered by the last Annual Report (October 1992), as separate 10-Day Reports of serious adverse events.

5.1 Primary Development Program

Strata I, II, and III studies are depicted in the Table of Studies in **Appendix 5.1.**

Table 5.1 displays a summary enumeration of participants in the various trials of the sponsor's primary development program for fluvoxamine.

TABLE 5.1
SUMMARY OF ALL STUDIES

	Enumeration by Treatment Group		
	N_{fluv}	N_{plac}	N_{other}
PHASE 1 (CLINICAL PHARMACOLOGY & PHARMACOKINETICS)			
Single Dose	269	79	69
Multiple Dose	382	179	180
SUBTOTAL	651	258	249
PHASES 2-3 (CLINICAL STUDIES)			
Strata I			
Placebo Controlled			
Outpatient			
Fixed Dose	226	114	0
Dose Titration	795	793	493
Inpatient			
Dose Titration	66	49	65
SUBTOTAL	1087	956	558
Strata II			
Placebo Controlled			
Outpatient			
Dose Titration	177	50	98
Inpatient			
Dose Titration	115	86	50
Active Controlled			

TABLE 5.1
SUMMARY OF ALL STUDIES

	Enumeration by Treatment Group		
	N_{fluv}	N_{plac}	N_{other}
Outpt			
Dose Titration	135	0	119
Inpatient			
Fixed Dose	34	0	33
Dose Titration	177	0	176
Uncontrolled			
Outpatient			
Short-Term	6	0	0
Long-Term	962	20	24
Inpatient	278	6	7
SUBTOTAL *	1923	428	581
Strata III			
Placebo Controlled			
Outpatient			
Dose Titration	92	58	0
Active Controlled			
Outpatient			
Dose Titration	761	0	508
Inpatient			
Dose Titration	218	0	215
Uncontrolled			
Outpatient			
Short-Term	32813	0	0
Long-Term	151	0	0
Unknown	45	0	0
Inpatient	150	0	0

TABLE 5.1 SUMMARY OF ALL STUDIES			
	Enumeration by Treatment Group		
	N_{fluv}	N_{plac}	N_{other}
Unknown	357	0	0
SUBTOTAL	34587	58	723
SINGLE DOSE TOTAL	269	79	69
MULTIPLE DOSE TOTAL	37706	1292	1882
GRAND TOTAL **	37975	1371	1951

* Patients within each treatment group are unique.
** Note that the grand total is less than the sum of the Phase 1 and Phase 2-3 study totals: this reflects elimination of double enumeration for 765 Strata I patients who continued treatment in Strata II extension trials and who were counted in the enumerations for both individual Strata; the grand total equals the number of unique patients in each treatment group.

5.1.1 Phase 1

Study Type and Design/Patient Enumeration

Phase 1 studies within the sponsor's development include 14 miscellaneous clinical pharmacology studies, 28 pharmacokinetic studies, and 13 drug interaction studies as of May 1993; these are listed and briefly described in **Appendix 5.1.** Subjects in these studies were distributed among treatment groups as follows: fluvoxamine = 651, placebo= 258, and other active control= 249.

Demographics

The demographic profile of Phase 1 study participants is depicted in **Table 5.1.1.1** below. (Percentages are based on patients with available demographic data.)

Extent of Exposure (Dose/Duration)

Exposure and mean daily dose data for the Phase 1 study population is presented in **Table 5.1.1.2** below. (Percentages are based on patients with available dose and duration data.)

these 2 patients were removed from the analyses, these interactions were no longer significant at the α= 0.10 level.

Additionally, a responder analysis was performed using CGI improvement item scores to examine the percentage of patients experiencing a significant response during the study. Responders were defined as those subjects rated as "much improved" (score= 2) or "very much improved" (score= 1) at each evaluation point. Displayed is the percentage of responders over time using the observed cases sample and at Week 10 using the LOCF dataset.

Miscellaneous Issues (Studies 5529 and 5534)

The Y-BOCS total score was broken down into obsession and compulsion subscores and changes in these subscores from baseline were examined for the treatment groups from studies 5529 and 5534 combined (i.e. all fluvoxamine treated patients were pooled and all placebo treated patients were pooled). This data is presented at the end of **Appendix 7.2.1.**

Mean subscores were comparable at baseline. Mean changes from baseline for each subscore over time using the OC dataset and at endpoint using the LOCF dataset were likewise similar, suggesting that both components of the disorder responded about equally. There is a hint that improvement in obsessions may occur earlier than that for compulsions.

David Hoberman, Ph.D., the Statistical Reviewer for this NDA, performed the following analysis to enumerate the fluvoxamine patients by baseline level of illness in terms of outcome level of illness for the pooled "observed cases" datasets of the pivotal trials (N_{fluv}= 120, N_{plac}= 134). The level of illness was defined according to the NIMH-OC categories: Normal= 1-3, Subclinical= 4-6, Clinical= 7-9, Severe= 10-12, and Very Severe= 13-15. The enumerations of fluvoxamine patients are shown in **Table 7.2.1.2.**

There was a slight tendency for patients with higher baseline levels of illness to improve in greater numbers. Specifically, the percentages of completers in each baseline category who experienced improvement by at least one NIMH-OC category by Week 10 are: subclinical 0%, clinical 51%, severe 63%, and very severe 67%.

TABLE 5.1.1.1
Demographic Profile for Phase 1 Studies

	Fluvoxamine (N_{tot}= 651)	Placebo (N_{tot}= 258)	Active-Control (N_{tot}= 249)
AGE			
Mean (yrs)	32.9	29.9	28.8
Range (yrs)			
Groups (%)			
<40 yrs	76%	82%	85%
40-64 yrs	14%	17%	14%
≥65 yrs	10%	1%	1%
SEX (%)			
Female	19%	19%	17%
Male	81%	81%	83%
MEAN WEIGHT (kg)	72.8	71.3	71.7

TABLE 5.1.1.2

Number (Percent) of all Volunteers Receiving Fluvoxamine According to Mean Daily Dose and Duration in Phase 1 Studies (N = 634) *

Duration (Days)	≤50mg	50<mg≤100	100<mg≤150	150<mg≤200	200<mg≤250	>250mg
1	512	153	43	15	1	3
2-7	154	183	77	33	16	50
8-14	24	68	4	1	7	0
15-21	0	21	3	3	1	0
22-28	0	17	0	1	0	0
29-39	1	17	0	0	0	0

* Subjects were enumerated at each dose level received by the duration of exposure at that level; thus, many subjects were enumerated in multiple cells within a column and/or in multiple columns.

5.1.2 Strata I Studies

Study Type and Design/Patient Enumeration

Strata I involved a total of 2601 patients, of whom 1087 were exposed to fluvoxamine, and consists of 13 studies: 2 OCD trials and 11 trials in depression. The two OCD studies, 5529 and 5534, were ten week, flexible-dose trials of fluvoxamine in patients with DSM-III-R Obsessive Compulsive Disorder and form the basis for the demonstration of fluvoxamine efficacy in the treatment of OCD. The remaining 11 studies were trials of fluvoxamine in patients with depression and lasted from 4 to 12 weeks. Planned dose range for all these trials was 100-300 mg/day generally given on a bid schedule. Nine of these depression studies used an active control (desipramine or imipramine 100-300 mg/day) in addition to a placebo control.

Demographics

The Strata I patient population is described demographically in **Table 5.1.2.1** below. Females predominated in the Strata I depression trials but, for the 2 Strata I OCD studies, the sexes were about equally represented; this reflects the epidemiology of these conditions. Overall, most fluvoxamine patients were Caucasian and between the ages of 31 and 50 years old; about 6% were age 65 or older.

Extent of Exposure (Dose/Duration)

Table 5.1.2.2 displays the duration of exposure vs modal daily dose of fluvoxamine for Strata I subjects. Approximately 85% received a modal daily dose in the range recommended in proposed labeling, 100-300 mg/day: 80% of these patients were treated for 3 weeks or longer.

TABLE 5.1.2.1 DEMOGRAPHICS - STRATA I						
	TOTAL	OCD Studies		Depression Studies		
	N_{fluv}	N_{fluv}	N_{plac}	N_{fluv}	N_{plac}	N_{other}
Number Pts.	1087	160	160	927	796	558
Sex						
% Male	38.5	48.7	49.4	36.7	40.8	38.9
% Female	61.5	51.2	50.6	63.3	59.2	61.1
M/F Ratio	.62	.95	.98	.58	.69	.64
Race						
% White	74.1	97.5	95.6	70.0	79.0	91.6
% Black	2.8	.6	0	3.1	4.0	5.4
% Other	2.3	1.9	4.4	2.4	2.6	3.0
% Unknown	20.9	0	0	24.5	14.3	0
Age						
% 18-30	25.9	32.5	37.5	24.7	25.5	22.0
% 31-50	53.6	55.6	50.0	53.3	49.2	48.7
% 51-64	14.9	9.4	8.7	15.9	19.2	21.1
% >=65	5.6	2.5	3.7	6.1	6.0	8.1

TABLE 5.1.2.2 DOSE vs EXPOSURE - STRATA I FLUVOXAMINE PATIENTS *						
Exposure	Modal Dose (mg/day)					
	<=50	100	200	250-300	TOTAL	(%)
<=2 wks.	88	127	50	1	266	(25)
3-6 wks.	62	245	136	146	589	(55)
7-10 wks.	4	60	24	90	178	(17)
>=11 wks.	0	9	4	17	30	(3)
TOTAL	154	441	214	254	1063	(100)
(%)	(14)	(41)	(20)	(24)	(100)	

* Total excludes 24 subjects for whom Dose/Exposure data is unknown.

5.1.3 Strata II Studies

Study Type and Design/Patient Enumeration

Strata II is composed of a total of 70 North American uncontrolled and European controlled and uncontrolled studies: 60 of these studies were trials of fluvoxamine in depressed patients, 4 were OCD studies, and the remaining 6 studies were for other indications: panic disorder (2), alcoholism (2), renal impairment (1), and migaine (1). Ten of the depression studies and 2 of the OCD studies were long-term extensions of Strata 1 trials (see below). A total of 2546 patients were involved in Strata II studies, with 1923 exposed to fluvoxamine. The range of duration for these trials was 4-52 weeks with a planned dose range of 100-300 mg/day.

Demographics

The Strata II patient demographic characteristics are shown in **Table 5.1.3.1** below. Treatment group totals consist of all patients who were ever exposed to that treatment for any period of time. Females predominated in these trials, most of which studied depressed patients. Almost 10% of the fluvoxamine patients were elderly (>= age 65).

TABLE 5.1.3.1 DEMOGRAPHICS - STRATA II			
	N_{fluv}	N_{plac}	N_{other}
Number Pts.	1923	428	581
Sex			
% Male	37.5	41.8	31.8
% Female	60.8	53.2	67.6
% Unknown	1.7	4.9	0.5
M/F Ratio	.62	.79	.47
Race			
% White	57.6	89.7	55.4
% Black	1.1	1.6	2.1
% Other	1.4	3.7	1.2
% Unknown	39.8	4.9	41.3
Age			
% <18	0	0	0.3
% 18-30	16.9	23.1	13.8
% 31-50	46.4	50.5	46.6
% 51-64	22.5	17.8	25.8
% >=65	9.3	3.7	9.8
% Unknown	5.0	4.9	3.6

Extent of Exposure (Dose/Duration)

Table 5.1.3.2 depicts exposure vs duration for the Strata II patient population. Almost one third of the Strata II fluvoxamine patients were treated for 25 weeks or longer. About 80% of the fluvoxamine patients received a modal daily dose in the range 100-300 mg/day generally given on a bid schedule, with 89% of these exposed for 3 weeks or longer.

TABLE 5.1.3.2 DOSE vs EXPOSURE - STRATA II FLUVOXAMINE PATIENTS *							
	Modal Dose (mg/day)						
Exposure (weeks)	<=50	100-150	200	250-300	>300	**TOTAL**	(%)
<=2	114	105	41	13	0	273	(15)
3-8	84	291	128	147	2	652	(35)
9-24	55	99	58	124	0	336	(18)
25-48	27	73	35	87	0	222	(12)
49-96	86	101	28	98	1	314	(17)
>96	9	14	9	51	0	83	(4)
TOTAL	375	683	299	520	3	1880	(100)
(%)	(20)	(36)	(16)	(28)	(0)	(100)	

* Excludes 43 patients for whom Dose/Exposure data is unknown.

There were 765 Strata I patients who continued treatment into a Strata II extension trial. The **combined** Strata I/II database encompasses 4382 unique patients, of which 2737 were exposed to fluvoxamine. This population was used to search for specific, uncommon adverse events, when a larger database was desirable. In order to adjust adverse event incidence rates for differences in treatment exposure duration when this pool was utilized, the sponsor computed the exposure for each treatment group within this database in terms of patient-exposure-years (PEY's), with 1 PEY being equivalent to one patient exposed to that treatment for one year or two patients exposed for 6 months and so on. PEY statistics for the combined Strata I/Strata II database are:

Fluvoxamine 940 PEY
Placebo 133 PEY
Active-Control 132 PEY

Table 5.1.3.3 and **Table 5.1.3.4** depict the demographic characteristics and dose vs. duration data, respectively, for Strata I/Strata II. Treatment group totals, above, consist of all patients ever exposed to a given treatment for any period of time.

TABLE 5.1.3.3 DEMOGRAPHICS - STRATA I/II (combined)			
	N_{fluv}	N_{plac}	N_{other}
Number Pts.	2737	1055	979
Sex			
% Male	37.8	41.0	34.6
% Female	61.0	57.0	65.1
% Unknown	1.2	2.0	0.3%
M/F Ratio	0.62	0.72	0.53
Race			
% White	60.8	81.3	69.8
% Black	1.6	3.1	3.9
% Other	1.8	2.8	1.8
% Unknown	35.8	12.8	24.5
Age			
% <18	0	0	0.2
% 18-30	19.7	26.5	17.8
% 31-50	48.2	48.5	45.5
% 51-64	20.3	17.7	24.6
% >=65	8.3	5.2	9.8
% Unknown	3.5	2.0	2.2

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TABLE 5.1.3.4 DOSE vs EXPOSURE - STRATA I/II FLUVOXAMINE PATIENTS *							
	Modal Dose (mg/day)						
Exposure (weeks)	<=50	100-150	200	250-300	>300	**TOTAL**	**(%)**
<=2	139	303	89	15	0	546	(20)
3-8	52	582	221	258	2	1115	(42)
9-24	21	147	62	166	0	396	(15)
25-48	9	87	34	89	0	219	(8)
49-96	20	164	26	98	1	309	(12)
>96	6	21	8	53	0	88	(3)
TOTAL	247	1304	440	679	3	2673	(100)
(%)	(9)	(49)	(16)	(25)	(0)		

* Totals exclude 64 patients for whom dose/duration data is unknown.

5.1.4 Strata III Studies

Study Type and Design/Patient Enumeration

Strata III is composed of 92 worldwide marketing studies conducted in Europe and Pakistan which were completed as of July 1, 1992. The range of planned duration for Strata III studies was 4-52 weeks with doses in the range 50-300 mg/day. None of these studies were planned or conducted according to consistent guidelines and safety data was frequently incomplete or inconsistent. Sixty-six of these studies make up the "dedicated safety database" in which a total of 35,368 subjects were involved, with 34,587 were exposed to fluvoxamine; about 96% of the fluvoxamine subjects participated in uncontrolled, depression trials.

The remaining 26 investigations are excluded from this database because of deficiencies, particularly lack of any CRF's, which render the data clearly inferior to the data in the dedicated database. These excluded studies involved 1089 patients with 951 exposed to fluvoxamine; these subjects are excluded from the tabulations in this section and were discussed only in a separate "Medical Report" in the ISS of this NDA. Only deaths and serious adverse events occurring in this database will be addressed in this review.

Demographics

Table 5.1.4.1 below shows the demographic profile of the Strata III dedicated database. Again, females predominate in this population. Elderly patients (>= age 65) make up 14% of Strata III fluvoxamine patients. Racial statistics were not reported for Strata III.

TABLE 5.1.4.1 DEMOGRAPHICS - STRATA III

	N_{flux}	N_{plac}	N_{other}	N_{TOTAL}
Number Pts.	34587	58	723	35368
Sex				
% Male	28.9	37.9	30.2	28.9
% Female	69.2	60.3	67.9	69.2
% Unknown	1.9	1.7	1.9	1.9
M/F Ratio	.42	.63	.44	.42
Age				
% <18	0.1	0	0.1	0.1
% 18-30	13.6	22.4	12.6	13.6
% 31-50	44.3	51.7	47.4	44.4
% 51-64	26.2	24.1	25.2	26.2
% >=65	14.0	0	12.7	14.0
% Unknown	1.8	1.7	1.9	1.8

Extent of Exposure (Dose/Duration)

Dose vs duration data for Strata III is displayed in **Table 5.1.4.2.** About 84% of the fluvoxamine treatment group received a modal daily dose in the range 100-300 mg/day generally given on a bid schedule with over 90% of these patients being exposed for 3 weeks or longer.

TABLE 5.1.4.2 DOSE vs EXPOSURE - STRATA III FLUVOXAMINE PATIENTS *							
Exposure (weeks)	Modal Dose (mg/day) <=50	100-150	200	250-300	>300	**TOTAL**	**(%)**
<=2	1556	2232	92	27	0	3907	(12)
3-7	3029	15193	3073	794	7	22096	(70)
8-25	349	3480	1089	368	11	5297	(17)
26-51	8	129	27	14	1	179	(1)
>=52	13	49	20	10	1	93	(0)
TOTAL*	4955	21083	4301	1213	20	31572	(100)
(%)	(16)	(67)	(14)	(4)	(0)	(100)	

* Total excludes 3015 subjects for whom dose and/or exposure data is unknown.

5.2 Secondary Clinical Data Sources

5.2.1 Non-IND Studies

This submission includes references to 12 non-IND studies reported in the literature: 7 Phase 1 studies and, under IND 5 Phase 2/3 studies. These studies are listed and briefly described in **Appendix 5.1.**

5.2.2 Post-Marketing Experience

Strata IV of the Integrated Safety Summary data embraces post-marketing information accrued since the initial introduction of fluvoxamine in Switzerland in 1983, to include safety monitoring reports from the United Kingdom. There has been no action by any regulatory agency to withdraw approval of fluvoxamine. Based on typical patterns of use and the amount of fluvoxamine sold since that time, it is estimated that million individuals have been treated with this drug worldwide. The sponsor has within its organization an Adverse Drug Experience Unit (ADEU) which is responsible for the monitoring of adverse events related to the use of Solvay compounds worldwide. All known information from spontaneous reporting and the literature and submitted by regulatory authorities to the sponsor is transferred to the ADEU and entered into a database regardless of event severity or causality.

As of June 30, 1992, 1426 cases had been received by the ADEU at Solvay: 525 of these are classified as serious[2], 897 as not serious, and 4 as indeterminate. Sixty-seven deaths were reported: 30 deaths were due to suicide and, of these, 19 were due to an overdose; only 2 of the overdose deaths appeared to involve fluvoxamine alone.

5.2.3 Literature

A Master Bibliography, which consists of 12 volumes of literature data, was reviewed for evidence of fluvoxamine-associated safety issues. There was no indication of any safety concerns which had not been addressed elsewhere in this submission.

6.0 Summary of Human Pharmacokinetics

Absorption: Oral doses of fluvoxamine are virtually completely absorbed as shown by radioactive excretion: an average of 94% of a C-14 labelled dose was recovered in urine within 71 hours. The mean oral absolute bioavailability in 17 subjects was 53% (90% C.I.= 44-662%); it appears that fluvoxamine undergoes an moderate degree of hepatic extraction. Absorption is not significantly affected by the presence of food. After a single 50mg tablet dose, C_{max} is achieved in 3-8 hours (mean 5 hrs.) and is in the range ng/ml (mean 17.6 ng/ml). A study of single oral doses of 25mg, 50mg, and 100mg indicates essentially linear pharmacokinetics over this dose range. However, a dose proportionality study involving multiple doses at 100, 200, and 300 mg/day (given on a bid schedule for 1 week at each level) in 30 normal males indicated nonlinear pharmacokinetics with greater than proportional increases in C_{ss} and AUC over this dose range. Steady state concentrations were achieved after (at most) 6 days of dosing at the 2 higher doses and after 4 days at 100 mg/day.

Distribution: Plasma protein binding is about 80% in humans over the plasma concentration range of ng/ml. Fluvoxamine appears to have a high volume of distribution in humans (~20 L/kg), consistent with pronounced tissue binding.

Metabolism: Fluvoxamine is extensively metabolized by the liver, the main route being oxidative demethylation of the aliphatic

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[2]Cases were classified according to FDA criteria at the time of classification; when severity, and not seriousness, was documented for an event, all cases rated as "severe" or as "very severe" were classified as serious.

methoxyl group and yielding the corresponding carboxylic acid. Nine urinary metabolites have been identified. Fluvoxamine acid and N-acetylated fluvoxamine acid make up 60% of the excretion products. A third metabolite, flovoxethanol, makes up 10% of the urinary excretion products. Fluvoxamine acid and fluvoxethanol have shown no serotonin reuptake inhibitory activity. Fluvoxamine shows little isomerization of the active trans isomer to the inactive cis isomer during metabolism. The maximum rate of metabolism, 330 mg/12 hrs., is about double the maximum recommended dosing rate (300 mg/24 hours).

Elimination: The mean plasma half-life after a single 50 mg oral dose in healthy volunteers was 13 hours compared to 16 hours under steady-state conditions with 100 mg/day dosing. Elimination follows Michaelis-Menten kinetics. Only about 4% of an orally administered dose is excreted unchanged in the urine.

See **Section 8.8** for a summary of drug interaction studies and case reports.

7.0 Efficacy Findings

7.1 Overview of Studies Pertinent to Efficacy

This NDA contains the results of 2 pivotal trials in support of the claim of efficacy in the treatment of DSM-III-R Obsesssive-Compulsive Disorder (OCD): H.114.5529 and H.114.5534, referrred to hereafter as 5529 and 5534.

Also briefly mentioned in this submission are 14 other trials of fluvoxamine in OCD:

-three placebo controlled trials, 2 of which were conducted under non-sponsor IND's [2] with the third being a foreign post-marketing study conducted under the sponsor's IND (FR.009).

-one active-controlled trial conducted under IND

-one-year, uncontrolled humanitarian extensions to 5529 and 5534: 5529E and 5534E.

-two uncontrolled trials conducted under the sponsor's compassionate use program: 5533 and 5540-O.

-six uncontrolled trials conducted under IND , 2 of which were ongoing at the time of NDA submission.

Since most of these 14 studies cannot contribute definitive efficacy data, this review will focus on the 2 pivotal studies, 5529 and 5534, which were submitted as primary support for the claim of efficacy.

7.2 Summary of Studies Pertinent to Efficacy

7.2.1 Short-Term Placebo Controlled Trials

The 2 placebo-controlled pivotal studies, 5529 and 5534, have identical overall study plans. Common elements will be presented first followed by information specific to each study, with appendices of tabulated data corresponding to each study found in **Appendix 7.2.1.**

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[1] Sponsored by Merck, Sharp, and Dohme.

[2] Individual investigator IND sponsored by George Heninger, M.D. (Yale University).

Common Elements: Study Plan

Objectives

Assessment of the relative effectiveness and safety of fluvoxamine and placebo in the treatment of OCD.

Population

Criteria for inclusion were:

- Outpatients with DSM-III-R Obsessive-Compulsive Disorder.
- Age: 18 years or older.
- Diagnosis of OCD for at least 12 months pre-study.
- NIMH OC Global Rating Scale score of ≥7 at screening and at baseline.

Criteria for exclusion were:

- Met DSM-III-R criteria for a major affective disorder, had a pre-study HAMD total score ≥20, or an HAMD item 1 score of >2.
- A history of other psychiatric disorders including schizophrenia, psychotic symptoms, bipolar disorder, dementia, psychosurgery, personality disorders which might interfere with compliance, Tourette's syndrome, panic disorder, agoraphobia, eating disorders, or, within the prior year, substance abuse or alcoholism.
- Clinically unstable medical illness or not euthyroid. Patients with cardiovascular, hepatic, renal, gastrointestinal, pulmonary, metabolic, endocrine, hematologic, or systemic disease that could interfere with diagnosis, treatment, or assessment of OCD were excluded.
- Necessary medication with any drug that might obscure the action of or interact with fluvoxamine.
- Any clinically important ECG or laboratory study abnormality.
- Multiple drug allergies.
- Treatment with an MAOI, anxiolytic, antipsychotic, or lithium within 4 weeks of trial participation or another antidepressant drug within 2 weeks.
- Exposure to any experimental medication or depot neuroleptic within 3 months of trial participation.
- ECT, insulin shock, or psychiatric hospitalization within 6 months of study initiation.

Design

Studies 5529 and 5534 were 10 week, randomized, double-blind, placebo-controlled, parallel group trials, each involving 4 U.S. centers with a total of 320 patients, 160 per treatment group.

Potential participants were evaluated during a 14 to 30 day screening period[3] during which placebo (one capsule each evening) was given and patients were assessed with clinical examinations, laboratory studies, and an ECG. On the last day of screening, baseline evaluations were performed[4] and eligible patients were assigned a patient identification number in order of study qualification; patient numbers were obtained from a randomization schedule of 160 consecutive patient identification numbers that had been prepared by the sponsor so that 40 patients, 20 per treatment group, were enrolled at each site. Patients who dropped out were not replaced.

Based on the results of a previous double-blind, placebo-controlled, cross-over study[5], a target dose range of 100-300 mg/day was chosen, with an initial dose of 25 mg bid and titration to a maximum of 150 mg bid depending on clinical response and tolerance.

Treatment was conducted under double-blind conditions with identical gelatin opaque capsules; the blind was broken for only two patients, one in each study; these were placebo patients who were terminated due to worsening of OCD symptomatology.

Patients were titrated to a daily dose of 150 mg/day over the first 2 weeks of the trial. After this, each investigator was permitted to increase the dose to a maximum of 300 mg/day if the patient had not adequately responded or suffered any dose-limiting symptoms. Doses were given on a bid schedule in matching capsules containing either fluvoxamine 50 mg or placebo; if the number of capsules for a given day was uneven, the greater number was taken in the evening. For those subjects experiencing adverse experiences, the dose could be adjusted within the range of 100-300 mg/day. The minimum allowed dose was 100 mg/day.

The schedule for efficacy and safety measures is provided in **Table 7.2.1.1.** In the case of patients prematurely terminating, week 10 assessments were to be done at the time of termination. Laboratory studies consisted of hematology, biochemistry, and urinalysis evaluations. Also, thyroid hormone levels (T_3 and T_4) were obtained at screening.

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[3]Duration of the washout was dependent on prior medication use.

[4]Y-BOCS, 17-item HAMD, CGI, NIMH OC scale, and vital signs.

[5]Perse et al. Am J Psychiatry 1987; 144(12): 1543-1548 (Protocol MSD-17 done under IND .

TABLE 7.2.1.1 - SCHEDULE OF EFFICACY & SAFETY ASSESSMENTS: 5529 & 5534							
	Screen	Day 0	End of Week:				
			2	4	6	8	10
Diagnostic Criteria	X						
Prior Medication	X						
Inclusion/Exclusion		X					
HAMD		X					
Randomization		X					
Baseline Assessment		X					
Y-BOCS	X	X	X	X	X	X	X
NIMH OC scale	X	X	X	X	X	X	X
CGI	X	X	X	X	X	X	X
Dosage Record		X	X	X	X	X	X
Concomitant Meds		X	X	X	X	X	X
Drug Plasma Assay							X
Physical Examination	X						X
Vital Signs	X	X	X	X	X	X	X
Lab Studies	X						X
12-Lead ECG	X						X
Adverse Experiences		X	X	X	X	X	X

Additional psychoactive medication, ECT, and behavioral therapy were prohibited except for sleeping medication when deemed unavoidable[6]. Other drugs were to be taken only if unavoidable provided that the investigator was satisfied that the medication would not interact with or obscure the action of fluvoxamine.

Analysis Plan

The intent-to-treat population, consisting of all patients who had, at a minimum, one dose of study medication and one evaluation after this dose, was used for efficacy analysis. Separate analyses were performed for an LOCF dataset, in which last observations for dropouts were carried forward to Week 10, as well as for a visit-wise dataset, which utilized data from all patients remaining in the trial at each assessment point and excluded data from patients who had dropped out prior to that point.

For both studies, primary efficacy measures were change from baseline in the Yale-Brown Obsessive-Compulsive Scale (Y-BOCS) and the NIMH Global OC Scale (NIMH OC) scores at the last available assessment, or endpoint; a secondary measure of efficacy was the Clinical Global Improvement item of the Clinical Global Impression scale (CGI)[7].

A 2-way ANOVA model which assessed for treatment, center, and treatment-by-center effects, was used for hypothesis testing. For a study to be considered "positive," a statistically significant difference in at least one of the primary variables in favor of fluvoxamine over placebo was to be observed, with a 2-tailed significance level set at $\alpha = 0.025$ (2-tailed) to correct for multiplicity. Additonally, to explore the nature of any treatment effects, changes from baseline in the Y-BOCS, NIMH OC, and the CGI improvement score would be examined at weeks 4, 6, 8, and 10.

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[6]Either chloral hydrate 1-2 gm or lorazepam 1-2 mg HS.

[7]The **Y-BOCS** is a 10 item scale which rates, for obsessions and compulsions separately, the following 5 features, each on a scale of 0 (none) to 4 (extreme): time consumed, interference, distress, resistance, and control over the obsessions/compulsions.
The **NIMH-OC** is a global rating of the present clinical state on a categorical scale, with specific clinical definitions of each category: 1-3 (minimal/normal), 4-6 (subclinical symptoms), 7-9 (clinical symptoms), 10-12 (severe), and 13-15 (very severe).
The **CGI** rates severity of illness and global improvement separately, each on a scale of 1 (normal and very much improved, respectively) to 7 (extremely ill and very much worse, respectively); the third rated parameter is an efficacy index, which cross-rates therapeutic effect and degree of side effects.

Study 5529

Investigators/Locations

The following individuals were the principal investigators for each center in this study.

Center number/Investigator	Location
1/ John H. Greist, M.D.	University of Wisconsin Madison, Wisconsin
2/ Michael Jenike, M.D.	Massachusetts General Hospital Boston, Massachusetts
3/ Jeffrey Lieberman, M.D.	Hillside Hospital Division of Long Island Jewish Medical Center Glen Oaks, New York
4/ Steven Rasmussen, M.D.	Butler Hospital Providence, Rhode Island

Baseline Demographics

Mean ages for the 2 treatment groups were very close, 35.4 for the fluvoxamine group and 35.8 for placebo. There were roughly equal numbers of males and females and most subjects were Caucasian. There were no significant between-group imbalances at baseline with respect to sex, race, or age.

Baseline Illness Severity

There were no substantial differences between treatment groups in mean baseline scores on the Y-BOCS, NIMH OC, or CGI severity of illness rating.

Patient Disposition

Eighty patients were randomized to each treatment group; the intent-to-treat sample consisted of 79 fluvoxamine patients and 80 placebo patients; 20% of the fluvoxamine group dropped out, most of these due to adverse experiences, whereas only 5% of the placebo group prematurely terminated.

Dosing Information

The mean daily dose for patients in the study gradually increased over time, with a relative plateau after Week 6. The average dose of the completers at Week 10 was roughly 250 mg/day.

Use of Concomitant Medications

Fifty-three fluvoxamine and 54 placebo patients in the ITT sample used concomitant medication during the study. The most commonly used medications among the fluvoxamine subjects were: aspirin, lorazepam, acetaminophen, ibuprofen, and chloral hydrate. One fluvoxamine patient continued chronic Limbitrol therapy throyghout the study for depressive symptomatology, which remained unchanged.

Efficacy Results

Appendix 7.2.1 presents a summary of the efficacy results: fluvoxamine is compared with placebo on mean change from baseline for the Y-BOCS, NIMH-OC, and the CGI improvement item for the observed cases (OC) dataset at each visit during the study. Also displayed is a summary of changes from baseline at Week 10 for these 3 variables using an LOCF dataset. Reported p-values are based on 2-tailed significance testing for treatment effect as described under Analysis Plan. Analysis for treatment-by-center interaction was non-significant for all variables using both datasets at the $\alpha = 0.10$ level.

Additionally, a responder analysis was performed using CGI improvement item scores to examine the percentage of patients experiencing a significant response during the study. Responders were defined as those subjects rated as "much improved" (score= 2) or "very much improved" (score= 1) at each evaluation point. Displayed is the percentage of responders over time using the observed cases sample and at Week 10 using the LOCF dataset.

Study 5534

Investigators/Locations

The following individuals were the principal investigators for each center in this study.

Center number/Investigator	Location
1/ Michael Kozak, M.D.	Medical College of Pennsylvania Philadelphia, Pennsylvania
2/ Wayne Goodman, M.D.	Yale University New Haven, Connecticut
3/ Michael Liebowitz, M.D.	New York State Psychiatric Institute New York, New York
4/ Kerrin White, M.D.	McLean Hospital Belmont, Massachusetts

Baseline Demographics

Mean ages for the 2 treatment groups were very close, 36.7 for the fluvoxamine group and 36.6 for placebo. There were equal numbers of males and females and most subjects were Caucasian. There were no significant between-group imbalances at baseline with respect to sex, race, or age.

Baseline Illness Severity

There were no substantial differences between treatment groups in mean baseline scores on the Y-BOCS, NIMH OC, or CGI severity of illness rating.

Also, there were no important differences in mean demographic variables or baseline clinical rating scale scores between studies 5529 and 5534.

Patient Disposition

Eighty patients were randomized to each treatment group; the intent-to-treat sample consisted of 78 fluvoxamine patients and 78

placebo patients: 26% of the fluvoxamine group dropped out, most of these due to adverse experiences, whereas 20% of the placebo group prematurely terminated.

It should be noted that a packaging error occurred during this trial which involved 20 patients from Center 4: the final bottle of capsules dispensed at Week 8 to seven fluvoxamine patients contained placebo and to eight placebo patients contained fluvoxamine; the other 5 patients, who would have received mislabeled medication, had prematurely terminated before Week 8 and were not effected. For purposes of efficacy analysis, the affected 15 patients were considered to have competed the trial at Week 8, prior to receiving the mispackaged medication.

Dosing Information

The mean daily dose for patients in the study gradually increased over time, reaching a maximum at the end of the study: the average dose of the completers at Week 10 was, as for 5529, roughly 250 mg/day.

Use of Concomitant Medications

Fifty-four fluvoxamine and 54 placebo patients in the ITT sample used concomitant medication during the study. The most commonly used medications among the fluvoxamine subjects were: aspirin, lorazepam, acetaminophen, ibuprofen, and chloral hydrate. One fluvoxamine patient used imipramine for one day due to increased depressive symtomatology and subsequently dropped out. A placebo patient used cannabis throughout the study, a protocol violation; no effect on OCD symptoms was seen.

Efficacy Results

Appendix 7.2.1 presents a summary of the efficacy results: fluvoxamine is compared with placebo on mean change from baseline for the Y-BOCS, NIMH-OC, and the CGI improvement item for the observed cases (OC) dataset at each visit during the study. Also shown is a summary of changes from baseline at Week 10 for these 3 variables using an LOCF dataset. Reported p-values are based on 2-tailed significance testing for treatment effect as described under Analysis Plan.

There were significant treatment-by-center interactions for the Y-BOCS at Weeks 8 and 10 using the OC sample and at Week 10 using the LOCF sample and for the NIMH-OC at Week 10 using the LOCF sample. These interactions are attributed by the sponsor to 2 placebo patients in Center 3 who experienced a dramatic remission of symptoms during the second half of the trial: when the scores of

these 2 patients were removed from the analyses, these interactions were no longer significant at the α= 0.10 level.

Additionally, a responder analysis was performed using CGI improvement item scores to examine the percentage of patients experiencing a significant response during the study. Responders were defined as those subjects rated as "much improved" (score= 2) or "very much improved" (score= 1) at each evaluation point. Displayed is the percentage of responders over time using the observed cases sample and at Week 10 using the LOCF dataset.

Miscellaneous Issues (Studies 5529 and 5534)

The Y-BOCS total score was broken down into obsession and compulsion subscores and changes in these subscores from baseline were examined for the treatment groups from studies 5529 and 5534 combined (i.e. all fluvoxamine treated patients were pooled and all placebo treated patients were pooled). This data is presented at the end of **Appendix 7.2.1.**

Mean subscores were comparable at baseline. Mean changes from baseline for each subscore over time using the OC dataset and at endpoint using the LOCF dataset were likewise similar, suggesting that both components of the disorder responded about equally. There is a hint that improvement in obsessions may occur earlier than that for compulsions.

David Hoberman, Ph.D., the Statistical Reviewer for this NDA, performed the following analysis to enumerate the fluvoxamine patients by baseline level of illness in terms of outcome level of illness for the pooled "observed cases" datasets of the pivotal trials (N_{fluv}= 120, N_{plac}= 134). The level of illness was defined according to the NIMH-OC categories: Normal= 1-3, Subclinical= 4-6, Clinical= 7-9, Severe= 10-12, and Very Severe= 13-15. The enumerations of fluvoxamine patients are shown in **Table 7.2.1.2.**

There was a slight tendency for patients with higher baseline levels of illness to improve in greater numbers. Specifically, the percentages of completers in each baseline category who experienced improvement by at least one NIMH-OC category by Week 10 are: subclinical 0%, clinical 51%, severe 63%, and very severe 67%.

TABLE 7.2.1.2 - ENUMERATION OF FLUVOXAMINE COMPLETERS BY LEVEL OF ILLNESS AT BASELINE VS. WEEK 10						
Baseline		NIMH-OC Category at Week 10				
NIMH-OC Category	# of Pts.	Normal	Sub-clinical	Clinical	Severe	Very Severe
Subclinical	1	0	1	0	0	0
Clinical	78	6	34	34	4	0
Severe	38	1	9	14	14	0
Very Severe	3	0	0	1	1	1

This analysis was repeated for the placebo patients and results are displayed in Table 7.2.1.3. Here, 22% of those in the baseline "clinical" category improved by at least one category versus 39% in the severe category. Thus, it seems that greater spontaneous improvement among more ill patients may account in part for the observed trend in the fluvoxamine group.

TABLE 7.2.1.3 - ENUMERATION OF PLACEBO COMPLETERS BY LEVEL OF ILLNESS AT BASELINE VS. WEEK 10						
Baseline NIMH-OC Category	# of Pts.	NIMH-OC Category at Week 10				
		Normal	Sub-clinical	Clinical	Severe	Very Severe
Clinical	85	1	18	60	6	0
Severe	49	0	2	17	29	1

Additionally, Dr. Hoberman expanded on the "responder analysis" done by the sponsor using the CGI improvement item as previously described: the numbers of patients who experienced categories of improvement in total Y-BOCS score were evaluated using the same dataset used above.

Table 7.2.1.4 displays the results of this enumeration. While substantial numbers of patients in both groups showed no or small (≤25%) decrease in Y-BOCS score at endpoint (52% of the fluvoxamine vs. 81% of the placebo patients), clearly a greater percentage of fluvoxamine patients experienced a substantial decrease (≥26%) in Y-BOCS score compared to placebo patients (48% vs. 19%). Also, 18% of the fluvoxamine patients versus only 6% of the placebo patients had a greater than 50% decrease in Y-BOCS.

TABLE 7.2.1.4 - ENUMERATION OF FLUVOXAMINE VS. PLACEBO PATIENTS BY CATEGORY OF DECREASE IN Y-BOCS FROM BASELINE TO WEEK 10: 5529/5534 (OC DATASET)				
% Decrease in Total Y-BOCS Score	Fluvoxamine		Placebo	
	N	%	N	%
≤ 0%	29	24%	52	39%
1-25%	34	28%	57	42%
26-50%	39	33%	19	14%
51%-75%	15	13%	5	4%
76-100%	3	2%	1	1%
TOTAL	120	100%	134	100%

A total of 21 fluvoxamine and 33 placebo patients in Studies 5529 and 5534 used concomitant psychotropic medication during the trials. The numbers of responders (as defined under Efficacy Results above) and non-responders at endpoint was calculated for concomitant psychotropic medication users in each treatment group for the 2 studies combined: results are summarized in **Table 7.2.1.5** below. Most of the concomitant psychotropic medication use occurred among non-responders in both treatment groups. Thus, it does not appear that the use of other psychotropic agents affected the observed efficacy of fluvoxamine in favor of drug or increased the rate of remission among placebo patients.

TABLE 7.2.1.5 - CONCOMITANT PSYCHOTROPIC MEDICATION USE IN RESPONDERS VS. NON-RESPONDERS: STUDIES 5529/5534 COMBINED		
	Fluvoxamine	Placebo
TOTAL USING CONCOMITANT PSYCHOTROPICS	21	33
Responders	2	9
Non-Responders	19	24

Efficacy Conclusions (Studies 5529 and 5534)

The results of each study consistently favored fluvoxamine over placebo for both primary efficacy variables beyond 6-8 weeks of

treatment using the observed cases analysis and at endpoint using the LOCF dataset. Also, the between-group comparisons of the percentages of patients with a significant response at endpoint as rated by the CGI improvement item as well as by the percentage change on the Y-BOCS support the efficacy of fluvoxamine over placebo in the short-term treatment of outpatients with OCD.

7.2.2 Other Trials Pertinent to Efficacy Evaluation

There are 14 other trials of fluvoxamine in the treatment of OCD which are briefly discussed in this NDA: 1 placebo-controlled foreign post-marketing study, 2 placebo-controlled studies and 1 active-control study not conducted under the sponsor's IND, and 10 uncontrolled studies. The 3 placebo controlled studies of fluvoxamine in OCD will be briefly described.

MSD-17[8], conducted under IND was a placebo-controlled, double-blind crossover study with 8 week treatment periods and a 2 week inter-period washout. Twenty patients with DSM-III OCD were enrolled and 16 completed the study. Flexible dosing was used in the range of 25mg bid to 150mg bid. Four patients met the criteria for major depression. Using the completer dataset, there were statistically significant changes from baseline (α= 0.05) with fluvoxamine treatment versus placebo for 4 of the 5 obsessive-compulsive measures[9], with at least 25% improvement on most measures. There were also significant changes on measures of depression and anxiety. Improvement in obsessive-compulsive measures correlated with improvement in depressive symptoms.

A double-blind, placebo-controlled, parallel group trial conducted under IND enrolled 50 patients with DSM-III OCD; 42 of these (21 per treatment group) completed at least 2 weeks of treatment and were included in the efficacy analysis. Active treatment consisted of fluvoxamine 50-300 mg/day for either 6 or 8 weeks. Decreases in the mean Y-BOCS scores for the fluvoxamine group were significantly greater than for the placebo group at weeks 2, 3, 5, 6, 7, and 8 (α= 0.01). Also, there were

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[8]Perse T et al. Fluvoxamine Treatment in Obsessive-Compulsive Disorder. Am J Psychiatry 1987; 144(12): 1543-1548.

[9]SCL-90 obsessive-compulsive scale, General Rating Scale-obsessions, General Rating Scale-compulsions, and the Maudsley Obsessive-Compulsive Inventory. The mean change on the Obsessive-Compulsive Checklist was not significant (p=0.10).

[10]Goodman W et al. Efficacy of Fluvoxamine in Obsessive-Compulsive Disorder. Arch Gen Psychiatry 1989; 46(1): 36-44.

significantly more responders[11] in the fluvoxamine compared to the placebo group (α= 0.01) at endpoint. Improvements in obsessions and compulsions were roughly equal.

FR.009[12], a Strata III post-marketing study, randomly assigned outpatients with DSM-III OCD to one of three treatment groups for 24 weeks: fluvoxamine with anti-exposure (F_a)[13], fluvoxamine with exposure (F_e), or placebo with exposure (P_e). Fluvoxamine was administered in evening doses up to 300mg. Of the 60 patients entering the trial, 44 completed treatment to week 24. Clinical assessments were made at weeks 8, 24, and 48 (post-treatment follow-up). Rituals were self-rated and rated by a blinded assessor according to time and discomfort as well as the total duration of rituals each day, the latter taken as a global measure of treatment effectiveness. At week 24, the number of "successes[14]" by treatment group were: F_e= 11/16, F_a= 7/13, and P_e= 6/15; pairwise comparisons of F_e versus F_a and F_e versus P_e revealed no statistically significant differences. Overall, holding fluvoxamine exposure constant (F_a versus F_e), there was no difference between anti-exposure and exposure in terms of variables measuring ritual behavior at any timepoint. Holding exposure constant (F_e versus P_e), fluvoxamine was better than placebo on rituals only at week 8; this inter-group difference disappeared by week 24.

While these studies generally lend support to the claim of efficacy of fluvoxamine in the treatment of OCD, they cannot provide primary evidence of efficacy because of lack of a placebo control and/or small sample size. These studies are summarized in **Appendix 7.2.2.**

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[11]"Responder" was defined as previously described in this section.

[12]Cottraux J et al. A Controlled Study of Fluvoxamine and Exposure in Obsessive-Compulsive Disorder. International Clinical Psychpharm. 1990; 5: 17-30.

[13]Exposure patients were assigned homework and flooding in fantasy for 8 weeks and guided exposure with response prevention for another 16 weeks; anti-exposure patients were requested to avoid any exposure to feared situations and to not resist rituals and/or compulsions.

[14]"Success" is defined by a ≥30% reduction in the total duration of rituals per day.

7.3 Summary of Data Perinent to Important Clinical Issues

7.3.1 Predictors of Response

The relationships between therapeutic response and each of the demographic variables, age and sex, were examined by Dr. Hoberman. This analysis included all fluvoxamine patients from both studies and considered response as the changes from baseline in the Y-BOCS score or NIMH-OC score at the last assessment. A regression of response on age indicated a statistically non-significant slope. Similarly, the distributions of responses at endpoint by sex were nearly identical. Thus, there did not appear to be any clear correlation between therapeutic effect and age or between therapeutic effect and sex.

Dr. Hoberman performed the following analyses to examine potential predictors of response. Only those patients in the "observed cases" datasets of the pivotal trials were included in these assessments (N_{fluv}= 120, N_{plac}= 134).

First, patients were subgrouped according to baseline total Y-BOCS scores; those in the upper and lower quartiles of the distributions of baseline scores were then evaluated in terms of Week 10 Y-BOCS and NIMH-OC scores to assess the relationship between level of illness at baseline and response. **Table 7.3.1.1** displays the results of this investigation. There is no consistent difference between these 2 subgroups.

TABLE 7.3.1.1 - BASELINE Y-BOCS VS. RESPONSE

Baseline Y-BOCS	Number of Patients	Mean Change from Baseline (Y-BOCS)	Mean Change from Baseline (NIMH-OC)
≥ 27	32	-6.7	-1.5
≤ 20	39	-4.6	-1.9

Next, a similar analysis was performed according to baseline HAMD scores to examine the relationship between baseline degree of depressive symptomatology and outcome at Week 10. **Table 7.3.1.2** depicts the results of this examination. As above, there appears to be no significant difference between these subgroups.

TABLE 7.3.1.2 - BASELINE HAMD VS. RESPONSE			
Baseline HAMD	Number of Patients	Mean Change from Baseline (Y-BOCS)	Mean Change from Baseline (NIMH-OC)
≥ 13	32	-4.8	-1.7
≤ 5	32	-5.6	-1.7

Due to the flexible dosing used in these studies, a dose-response relationship cannot be addressed. Nonetheless, this issue was explored in a preliminary manner by examining the relationship between final fluvoxamine dose and Week 10 therapeutic response was assessed. **Table 7.3.1.3** depicts the outcome of this analysis. There is no clear evidence of a dose-response relationship based on this data.

TABLE 7.3.1.3 - FINAL FLUVOXAMINE DOSE VS. RESPONSE			
Final Fluvoxamine Dose (mg/day)	Number of Patients	Mean Change from Baseline (Y-BOCS)	Mean Change from Baseline (NIMH-OC)
50	4	-6.5	-3.3
100	12	-6.5	-2.2
150	15	-6.2	-1.3
200	13	-7.5	-2.5
250	10	-10.8	-3.7
300	66	-4.0	-1.4

Post-hoc subgroup analyses were performed by the sponsor examining the effects of marital status, previous "resistance" to SSRI treatment, and "secondary depressive symptomatology" on the therapeutic effects of fluvoxamine. While these analyses showed no substantial interaction between each of these variables and efficacy, any conclusions drawn from these analyses, particularly from the latter 2 analyses, are of questionable validity: regarding efficacy in treatment resistant patients, treatment resistance was not well defined and the adequacy of previous SSRI trials is in doubt; regarding the effect of depressive symptomatology on efficacy, conclusions about an antidepressant component to the total therapeutic effect cannot be drawn since only baseline HAMD scores were collected.

Fluvoxamine plasma levels were performed for all participants at the final assessment timepoint as a measure of compliance. However, there was no consistency in the timing of blood sample collection (≥12 hours after the last dose) and, as expected, no correlation was seen between fluvoxamine plasma levels and therapeutic response (i.e. change from baseline in the Y-BOCS and the improvement item of the CGI).

7.3.2 Size of the Treatment Effect

There are no studies comparing the OCD efficacy of fluvoxamine to that of other agents approved or pending approval for this indication with the same patient population. However, a rough comparison was made by the following method.

The treatment effect size observed with fluvoxamine was compared to that seen with 2 other drugs used in the treatment of OCD: Anafranil, currently approved for the treatment of OCD, and Prozac, recommended for approval for the treatment of OCD by the Psychopharmacologic Drugs Advisory Committee on July 20, 1993. This evaluation was accomplished by comparing the mean changes from baseline to endpoint in the total Y-BOCS score for the active drug patients in the short-term pivotal trials submitted to support efficacy in each NDA.

For each drug, 2 such studies were submitted. Since the Prozac trials were dose comparison trials, results for each dose level are provided (20, 40, and 60 mg/day). Results are presented in **Table 7.3.2** below.

The mean baseline total Y-BOCS scores across these populations were comparable, with a slightly higher score among the Anafranil patients. While any definitive statement about comparable efficacy mandates a comparison of fluvoxamine with another active agent in a well-controlled clinical trial, in these studies the effect size observed with fluvoxamine was comparable to that seen with Prozac, which was substantially less than that seen with Anafranil. Although the presented data is based on "Observed Cases" datasets, a similar pattern holds true for the corresponding LOCF datasets.

TABLE 7.3.2 - COMPARISON OF TREATMENT EFFECT SIZES FOR FLUVOXAMINE, ANAFRANIL, & PROZAC IN PIVOTAL SHORT-TERM OCD STUDIES (OC ANALYSIS)

Drug	Duration of Trials	Dose Range	Trials	Baseline Number of Pts.	Mean Y-BOCS at Baseline	Endpoint Number of Pts.	Mean Δ in Y-BOCS from Baseline
Fluvoxamine	10 weeks	100-300	5529	79	23.3	67	-5.8
			5534	78	22.6	53	-5.2
Anafranil	10 weeks	100-300	59	118	26.3	102	-10.1
			61	134	26.2	120	-11.5
Prozac	13 weeks	20	HCEP#1	47	23.0	42	-5.3
			HCEP#2	39	24.4	33	-3.7
		40	HCEP#1	45	22.4	35	-4.3
			HCEP#2	41	25.4	32	-7.1
		60	HCEP#1	47	23.1	37	-5.0
			HCEP#2	42	26.0	31	-10.0

7.3.3 Choice of Dose

Since no adequate and well-controlled fixed dose trials have been conducted, a definitive statement about a dose-therapeutic response relationship cannot be made. Based on the dosing strategy used in the dose titration studies which provide primary support for the claim of efficacy, it seems that an initial dose of 25 mg b with increases in dose to 150 mg bid as tolerated and over a week period is appropriate, at least in healthy adults.

7.3.4 Duration of Treatment

While long-term, uncontrolled humanitarian extension trials do suggest maintenance of efficacy in OCD patients for one year, this issue has not been studied using well-controlled trials. To date, efficacy up to only 10 weeks has been adequately studied.

7.4 Conclusions Regarding Efficacy Data

Overall, the data from studies conducted in this development program provide support for the efficacy of fluvoxamine in the acute treatment of outpatients with DSM-III-R OCD with doses in the range of 50-150 mg bid (or 100-300 mg/day) for periods up to 10 weeks.

Patients with significant depression were excluded from the pivotal trials to eliminate improvement in depression as a confounding variable in the determination of OCD efficacy; efficacy in a depressed OCD population has not been well studied to date. Also, efficacy in OCD patients who have been refractory to other agents has not been established.

8.0 Safety Findings

8.1 Methods

The general [illegible] to assessing the safety data from this immense, com[illegible]se was two-pronged:

1) An effor[illegible] to identify important, serious adverse events which coul[illegible]ally linked to fluvoxamine exposure. Since these event[illegible] expected to be uncommon, this search tended to encompass mo[illegible] the NDA database. Specifically, this entailed: a) a review of individual clinical data for each patient who died while exposed or shortly after exposure to fluvoxamine, including those involving an overdose of fluvoxamine, in the entire NDA database (Strata I through V) up to July 1993; b) a review of individual clinical information for certain serious adverse events[1] in the total database up to July 1993, those adverse events being selected on the basis of judged potential to represent a clinically significant anatomical or physiological change which could lead to death or serious and/or permanent alteration in bodily functioning; c) a specific search for clinical symptoms related to drug-induced bleeding symptoms, allergic events, serotonin syndrome, and zimelidine syndrome, generally utilizing the combined Strata I/Strata II database; d) a review of available data regarding abuse potential or any withdrawal phenomena seen with discontinuation of fluvoxamine therapy and outcome of pregnancy for women exposed to fluvoxamine during gestation; and e) a survey of drug-demographic, drug-disease, and drug-drug interaction studies and case reports which might portend dangerous clinical events related to these interactions.

2) An assessment of the common adverse event profile, laboratory study changes, vital sign alterations, and electrocardiogram changes commonly associated with fluvoxamine use, to include events usually seen with fluvoxamine overdose. In addition, the potential for a relationship between fluvoxamine treatment and suicidality as well as hostile/aggressive behavior was explored. An examination of particular events which appeared to be associated with premature termination was performed. With the exception of ECG changes, these parameters were examined in both OCD and depression populations. Since these events were commonly observed, populations used for these investigations came mainly from the high-quality, but relatively small, Strata I studies.

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[1]Serious defined as per 21 CFR 312.32: any adverse event that is fatal, life-threatening, permanently disabling, requiring inpatient hospitalization, or represents a congenital anomaly, overdose, or cancer.

A summary of potentially important adverse events considered to be related to fluvoxamine use are summarized as well as important events not felt to be related to fluvoxamine.

The following findings are based on a review of the safety database as outlined above. Since several different pools of studies were used to examine the safety areas noted above, each pool will be described in its corresponding section. Note that discussions of individual patients are referenced by (Strata/Protocol Number/Patient Number), except for Strata IV cases, which do not have protocol designations.

8.2 Assessment of Deaths

Narrative Summary Reports for all Strata I, II, and V deaths that occurred up to December 31, 1990 and all Strata III and IV deaths up to July 1, 1992 were examined. A line listing of each fluvoxamine death is presented in **Appendix 8.2.1** and of each Placebo and Other Active Drug death in **Appendix 8.2.2**. Treatment group assignment is the treatment at the time of death or, in the case of post-study deaths, the last treatment received.

Table 8.2.1 enumerates all 146 deaths in fluvoxamine-treated patients that occurred in all 5 Strata for the above timeframes.

TABLE 8.2.1 - ENUMERATION OF ALL DEATHS

Strata	Fluvoxamine	Placebo	Other Active	TOTAL
I	0	0	1	1
II	18	1	1	20
III	58	0	5	63
IV	67	N/A	N/A	67
V	3	0	2	5
TOTAL	146	1	9	156

Deaths from the Strata I/II pre-marketing studies will be presented first, then data from the lower quality, Strata III trials will be considered. Lastly, death information from post-marketing surveillance (Strata IV) and the miscellaneous safety database (Strata V) will be discussed.

Strata I/II Deaths

Within this database, the crude incidence rates death are: fluvoxamine 0.7% (18/2737), placebo 0.1% (1/1055), and active-control 0.2% (2/979). When these rates are adjusted for different exposure durations across treatment groups, the rates (per 100 PEY) are not substantially different: fluvoxamine 1.9, placebo 0.8, and active-control 1.5.

The identified causes of death among the 18 fluvoxamine patients are categorized in **Table 8.2.2.**

Among fluvoxamine patients, the most common cause of death by far was suicide (7/18 deaths or 39%). This is not surprising given that the vast majority of these subjects suffered from a depressive illness. Deaths due to overdose are discussed further in **Section 8.5.8.** The death rate due to cardiac events is 0.1% (4/2737). Other events were evenly distributed among 6 other known causes. There was one placebo death due to suicide and 2 deaths on active-control agents (imipramine and clomipramine), both due to suicide.

TABLE 8.2.2 - CAUSES OF DEATH: STRATA I/II FLUVOXAMINE PATIENTS

	N
Suicide	7
Unknown	1
Cardiac Events *	4
Infection	1
Cancer/Neoplasm	1
Stroke	1
Accidental Injury	1
Pulmonary Embolism	1
Hemorrhagic Pleurisy	1
TOTAL	18

* 3 heart attacks nd 1 case of cardiac failure.

Strata III

The crude death rates within Strata III are: fluvoxamine 0.2% (58/34,587), placebo 0.0% (0/58), and active-control 0.7% (5/723). The identified causes of death among the 58 Strata III fluvoxamine patients are categorized in **Table 8.2.3.**

Again, suicide was the leading known cause of death (22/58 deaths or 38%), followed by cancer/neoplasm (8/58 or 14%), and infection (7/58 or 12%), usually pneumonia or bronchopneumonia (5 of the 7 cases). The 8 cancers and neoplasms are distributed among 5 different organ systems: CNS (3), gastrointestinal (2), and uterine, breast, and lymphoma (1 each).

There were 5 deaths on active-control agents: dothiepin (2 suicides) and mianserin (2 myocardial infarctions and one cause unknown).

TABLE 8.2.3 - CAUSES OF DEATH: STRATA III FLUVOXAMINE PATIENTS

	N
Suicide	22
Unknown	9
Cancer/Neoplasm	8
Infection	7
Cardiac Events *	4
Stroke	3
Accidental Injury	3
Pulmonary Embolism	1
Ruptured Aneurysm (Unspec.)	1
TOTAL	58

* 2 heart attacks and 2 cases of cardiac arrest.

Strata IV/V

There is no reasonably accurate denominator for this population. There were 67 reports of death in the sponsor's post-marketing surveillance database (Strata IV) and 3 deaths in Strata V fluvoxamine patients. Two active-control patients (both taking imipramine) in Strata V died, one of suicide and one secondary to choking. Causes of death are depicted in **Table 8.2.4.**

TABLE 8.2.4 - CAUSES OF DEATH: STRATA IV/V FLUVOXAMINE PATIENTS	
	N
Suicide	30
Cardiac Events *	11
Unknown	11
Infection	4
Cancer/Neoplasm	1
Stroke	2
Accidental Injury	1
Pulmonary Embolism	1
Sudden Death	3
G.I. Hemorrhage	2
Pancreatitis	2
Ruptured Aortic Aneurysm	1
Leuko/Thrombocytopenia	1
TOTAL	70

* 6 heart attacks, 2 cardiac arrests, and 3 cases of cardiac failure.

There were 3 cases described as "sudden death": one patient suffered from cerebral palsy and epilepsy and, for the other 2 patients, phenothiazines were felt to play a role in the sudden death. The case of leukopenia and thrombocytopenia occurred in an 80 y.o. male who received 100 mg/day of fluvoxamine for 3 days with markedly abnormal hematology studies one day after drug discontinuation. Leukemia was felt to be a more likely etiology than a drug reaction although a bone marrow biopsy was not performed. The patient died 3 days after stopping fluvoxamine. (IV/ FL629)

In addition to the above, 10-day reports of all serious adverse events submitted since the corresponding cutoff dates to July 1993 were screened for deaths which could be related to fluvoxamine exposure: no death among these reports was judged to be reasonably attributable to fluvoxamine.

The assessment of the potential role of fluvoxamine in contributing to a fatal outcome was often complicated by predisposing medical

conditions, concurrent medications, and incomplete data, making any definitive statement about causality very difficult in some cases. As will be discussed in **Section 8.5.8**, there are 2 overdose deaths which may have involved ingestion of fluvoxamine alone.

Otherwise, it is concluded that there is no evidence that the use of fluvoxamine was likely to play a significant etiologic role in any of these deaths in the judgement of this medical reviewer.

8.3 Assessment of Dropouts

8.3.1 Overall Pattern of Dropouts

In the course of the studies in Strata I, II, and III, there were a total of 13,148 patients who prematurely terminated for a variety of reasons. **Table 8.3.1.1** enumerates these dropouts by treatment group according to treatment at the time of dropout.

TABLE 8.3.1.1 - PREMATURE TERMINATIONS *

Strata	Fluvoxamine (N_{tot}=37324)	Placebo (N_{tot}=1113)	Other (N_{tot}=1702)
I	450	309	242
II	1048	80	170
III	10655	15	178
TOTAL	12154	404	590

* N_{tot}= the number of unique patients per treatment group for all 3 Strata combined.

Strata I

Table 8.3.1.2 depicts the percentages of enrolled Strata I subjects by treatment group who completed studies and who dropped out for 5 major categories of reasons: 1) ineffective medication, 2) adverse experiences (includes adverse events, suicide attempts, deaths due to suicide, and deaths due to other causes), 3) intercurrent illness (used only if a condition was clearly not related to drug treatment), 4) improvement, or 5) administrative reasons (includes lost to follow-up, protocol violations, or other non-drug related reasons). Dropout rates in the fluvoxamine group for all categories of reasons were comparable to those in the group treated with other active drugs, with slightly fewer fluvoxamine subjects dropping out for adverse events (21.7% vs. 27.8%, respectively).

TABLE 8.3.1.2 - STRATA I TERMINATIONS			
	Fluvoxamine	Placebo	Other
# Exposed	1087	956	558
% Total Dropouts	42%	33%	43%
% Dropout By Reason			
- Lack of Effect	8%	14%	6%
- Adverse Experience	22%	7%	28%
- Intercurrent Illness	0%	1%	0%
- Improvement	0%	0%	0%
- Administrative	12%	11%	9%

Strata II

For purposes of these enumerations, treatment group is determined by the treatment (i.e. fluvoxamine, placebo, or other active drug) received at the time of trial discontinuation. **Table 8.3.1.3** presents the percentages of enrolled Strata II patients who dropped out for the 5 general categories of reasons described under Strata I. Over one-half of the fluvoxamine patients dropped out of Strata II studies, primarily due to adverse experiences, administrative reasons, and lack of effect, with the rates for each of these categories higher than the corresponding rates for patients treated with other active drugs.

TABLE 8.3.1.3 - STRATA II TERMINATIONS			
	Fluvoxamine	Placebo	Other
# Exposed	1923	428	581
% Total Dropouts	54%	19%	29%
% Dropout By Reason			
- Lack of Effect	14%	9%	8%
- Adverse Exp.	20%	2%	10%
- Intercurrent Illness	0%	0%	0%
- Improvement	6%	2%	3%
- Administrative	14%	6%	8%

Strata III

The data in this section derives only from the 66 studies in the dedicated database in Strata III. **Table 8.3.1.4** presents the percentages of patients who enrolled in studies and prematurely terminated for the 5 major categories of reasons described above. Fluvoxamine-treated patients demonstrated a high completion rate (>2/3) with the most frequent reason for dropout being adverse events. The dropout rate due to adverse experiences in the fluvoxamine group was comparable to the rates in the placebo and other active control populations.

TABLE 8.3.1.4 - STRATA III TERMINATIONS

	Fluvoxamine	Placebo	Other
# Exposed	34587	58	723
% Total Dropouts	31%	26%	24%
% Dropout By Reason			
- Lack of Effect	2%	7%	3%
- Adverse Exp.	14%	12%	13%
- Intercurrent Illness	0%	0%	0%
- Improvement	2%	0%	2%
- Administrative	13%	7%	6%

8.3.2 Adverse Events Associated with Dropout

During clinical studies in Strata I, II, and III, a total of 5,995 subjects dropped out due to adverse experiences. **Table 8.3.2.1** enumerates these dropouts by treatment group according to treatment at the time of termination and Strata.

TABLE 8.3.2.1 - PREMATURE TERMINATIONS DUE TO ADVERSE EVENTS

Strata	Fluvoxamine	Placebo	Other	TOTAL
I	236	67	155	458
II	383	7	56	446
III	4989	7	95	5091
TOTAL	5608	81	306	5995

Strata I

In Strata I studies, the most frequent body systems involved in adverse events leading to dropout were the nervous sytem, the digestive system, and body as a whole. For purposes of comparing dropout rates across treatment groups, the two 10 week pivotal studies in Obsessive Compulsive Disorder, 5529 and 5534, were pooled to examine dropout rates in patients with OCD; **Table 8.3.2.2** displays the incidence rates for dropout in this pool by these body systems.

Table 8.3.2.3 presents dropout data for specific adverse events in the pooled OCD studies for events cited by at least 1.0% of the fluvoxamine dropouts. For this table and subsequent analogous tables, the figures provided are the percentages of patients who prematurely terminated and cited an adverse event in that body system as a reason for dropout.

TABLE 8.3.2.2 - DROPOUT RATES (%) BY BODY SYSTEM IN STRATA I OCD STUDIES

	FLUV (N=160)	PLAC (N=160)
Nervous	8.8	1.9
Digestive	3.8	0.6
Body as a Whole	5.6	1.9
Any Body System	15.6	3.8

TABLE 8.3.2.3 - SPECIFIC AE'S LEADING TO DROPOUT IN STRATA I OCD STUDIES

Body System	Adverse Event	FLUV (N=160)	PLAC (N=160)
Nervous	Insomnia	3.1	0.0
	Somnolence	2.5	0.0
	Anxiety	1.9	0.0
Digestive	Nausea	2.5	0.6
Body as a Whole	Asthenia	3.1	0.0
	Infection	1.3	0.6

Likewise, the following placebo controlled, depression studies of equal, short duration (6 weeks) were pooled: 5506, 5508, 5510, 5520, 5522, 5525, 5526, 5527, and 5528. **Table 8.3.2.4** displays the rates of premature termination by major body system for this pool of studies for body systems implicated in at least 5% of the fluvoxamine dropouts: nervous, digestive, and body as a whole. In each of the above mentioned body systems as well as for all adverse events combined, patients in these studies dropped out at a higher rate than patients in OCD studies.

TABLE 8.3.2.4 - DROPOUT RATES (%) BY BODY SYSTEM IN SHORT-TERM DEPRESSION DROPOUT POOL

	FLUV (N=879)	PLAC (N=746)	OTH (N=505)
Nervous	14.9	3.9	18.0
Digestive	12.5	1.6	7.1
Body as a Whole	6.7	2.6	5.5
Any Body System	22.3	7.5	26.3

Table 8.3.2.5 depicts the frequency of premature termination by specific event for events cited by at least 1.0% of the fluvoxamine dropouts in this study pool. All listed adverse experiences occurred more often in fluvoxamine patients than in placebo recipients. Nausea was associated with dropout at a sustantially higher rate among the fluvoxamine subjects compared to those receiving other standard antidepressants (imipramine or desipramine). Also, nausea was seen in 11% of the depressed fluvoxamine patients at the time of dropout but was implicated in premature termination for only about 3% of the OCD fluvoxamine patients. Dry mouth, given as a reason for dropout in 4.8% of the active control drop outs and the most common event leading to termination in this treatment group, occurred in only 0.9% of the fluvoxamine dropouts.

TABLE 8.3.2.5 - SPECIFIC AE'S LEADING TO DROPOUT IN SHORT-TERM DEPRESSION DROPOUT POOL

Body System	Adverse Event	FLUV (N=879)	PLAC (N=746)	OTHER (N=505)
Nervous	Insomnia	4.2	1.6	2.6
	Somnolence	4.0	0.4	4.2
	Nervousness	2.8	0.4	2.6
	Dizziness	2.4	0.4	2.8
	Agitation	1.9	0.1	2.2
	Anxiety	1.0	0.1	0.8
Digestive	Nausea	10.6	1.1	4.0
	Vomiting	2.6	0.3	2.0
	Diarrhea	1.7	0.5	0.4
	Anorexia	1.3	0.4	1.0
	Dyspepsia	1.3	0.1	0.8
Body as a Whole	Headache	3.0	0.9	1.4
	Asthenia	1.5	0.5	1.8
	Abd. Pain	1.0	0.0	0.0

Strata II

For purposes of evaluating dropout rates seen with extended exposure to fluvoxamine, the following Strata II placebo controlled, depression studies of about equal, long duration (46-52 weeks) were pooled: 5508E, 5525E, 5526E, and 5527E. Protocol 5508E employed a target dose range of 50-300 mg/day; the other 3 trials used 100-300 mg/day. The most frequent body systems involved for dropouts were, as in Strata I, the nervous sytem, the digestive system, and body as a whole. The rates of association of these systems with premature termination is shown in **Table 8.3.2.6.** Treatment group assignment is determined by the treatment received at the time of trial discontinuation.

TABLE 8.3.2.6 - DROPOUT RATES (%) BY BODY SYSTEM IN LONG-TERM DEPRESSION STUDY POOL			
	FLUV (N=197)	PLAC (N=63)	OTH (N=116)
Nervous	11.2%	1.6%	6.9%
Digestive	7.1%	0.0%	5.2%
Body as a Whole	6.1%	1.6%	8.6%
Any Body System	19.3%	4.8%	17.2%

Table 8.3.2.7 displays the incidences of specific AE's leading to dropout which were noted in at least 1.0% of the fluvoxamine terminators. With the exception of psychotic depression, none of these events caused placebo subjects to dropout.

Of the 37 fluvoxamine patients dropping out due to adverse events in the course of these 4 extension trials, 26 dropped out in the first 10 weeks of the extension trials, 7 terminated during the second 10 week period, and 4 during the third 10 week period. No patient in any treatment group dropped out due to an adverse event after 30 weeks of participation in this pool. It must be noted, however, that the attrition rate during the first 10 weeks in all 3 treatment groups was high and highest in the fluvoxamine group, of which about 40% prematurely terminated by week 10; less than 20% of the fluvoxamine group continued participation in these trials beyond week 30 with similar figures for the placebo and active-control groups. Thus, this data is not felt to be very useful for the assessment of significant adverse events seen with long-term use of fluvoxamine and the incidence rates noted in **Table 8.3.2.7** are weighted toward events associated with dropout with short-term use. Examination of the 11 fluvoxamine dropouts that occurred with longer-term exposure (i.e. beyond week 10 of the extension trial) showed that the adverse events reported at dropout were very diverse and there was no clear pattern of adverse experiences associated with these dropouts.

TABLE 8.3.2.7 - SPECIFIC AE'S LEADING TO DROPOUT IN LONG-TERM DEPRESSION STUDY POOL

Body System	Adverse Event	FLUV (N=197)	PLAC (N=63)	OTHER (N=116)
Nervous	Insomnia	2.5%	0.0%	0.9%
	Dry Mouth	2.0%	0.0%	1.7%
	Somnolence	2.0%	0.0%	0.9%
	Nervousness	1.5%	0.0%	0.9%
	Tremor	1.5%	0.0%	0.0%
	Manic Reaction	1.0%	0.0%	0.9%
	Psychotic Depression	1.0%	1.6%	0.0%
Digestive	Nausea	4.1%	0.0%	4.3%
	Constipation	1.0%	0.0%	0.9%
	Diarrhea	1.0%	0.0%	0.0%
Body as a Whole	Headache	4.1%	0.0%	5.2%
Urogenital	Impotence *	3.1%	0.0%	0.0%
	Prostatic Disorder *#	1.5%	0.0%	0.0%
Cardiovascular	Tachycardia	2.0%	0.0%	1.7%
Skin	Sweating	1.5%	0.0%	3.5%

* Rate denominators corrected for sex.
# Prostate infection.

Strata III

Most Strata III studies used a target dose range of 50-300 mg/day. Planned duration of these trials varied widely, from 4 to 52 weeks. In these studies, 14.4% of the fluvoxamine subjects discontinued trials due to adverse experiences. **Table 8.3.2.8** shows dropout rates by body system in Strata III studies and **Table 8.3.2.9** displays the incidence of adverse experiences in the fluvoxamine group which contributed to premature termination in at least 1.0% of the fluvoxamine patients. Since the vast majority of Strata III patients were in the fluvoxamine treatment group, comparisons across treatment groups are not presented in the latter table. Qualitatively, this adverse event profile is not substantially

different from those in the Strata I and Strata II study pools. Quantitatively, these incidence rates appear to be somewhat lower, perhaps a reflection of less complete adverse event documentation in these lower quality studies and/or exposure to lower doses (**16%** of all Strata III fluvoxamine patients received a modal dose of >=200 mg/day whereas about **43%** of both Strata I and Strata II patients received a modal dose in this range.) (Note: The denominators in these 2 tables exclude subjects for whom CRF documentation regarding adverse events leading to dropout was incomplete and judged by the sponsor to be unreliable; this involved 855 fluvoxamine patients, 3 placebo patients, and 44 patients treated with another active control.)

TABLE 8.3.2.8 - DROPOUT RATES (%) BY BODY SYSTEM IN STRATA III

	FLUV (N=33,732)	PLAC (N=55)	OTH (N=679)
Digestive	6.9	1.8	2.7
Nervous	6.5	1.8	4.4
Body as a Whole	3.9	5.5	2.1
Any Body System	12.3	7.3	7.5

TABLE 8.3.2.9 - ADVERSE EVENTS LEADING TO DROPOUT IN STRATA III FLUVOXAMINE PATIENTS

Body System	Adverse Event	Incidence (%) (N=33,732)
Digestive	Nausea	4.6
	Vomiting	1.7
Nervous	Dizziness	1.5
	Somnolence	1.2
Body as a Whole	Headache	1.2
	Abdominal Pain	1.1

8.4 Safety Findings Discovered with Other Specific Search Strategies

8.4.1 Search for Serious Adverse Events

The sponsor used a specific search strategy to screen all 5 Strata for "serious" adverse events; for Strata III and Strata IV, this includes the July 1992 updates. The criteria used to define a serious adverse event were in accordance with the FDA definition: any adverse event that was fatal, life-threatening, permanently disabling, requiring inpatient hospitalization, or represented a congenital anomaly, overdose, or cancer. For purposes of this section, only non-fatal serious adverse events will be discussed unless otherwise noted; all deaths were addressed in **Section 8.2.** Causality judgement was not a factor in the sponsor's report of these events.

There were 33 fluvoxamine patients in Strata I, 152 in Strata II, and 702 in Strata III[1] who reported serious adverse events. The sponsor's review of spontaneous adverse event reports (Strata IV) revealed 483 serious events. Also, 16 fluvoxamine patients in Strata V experienced serious adverse events.

In Strata I, Strata II, Strata III, and Strata V, the most common reason for designating an event as serious among fluvoxamine patients was hospitalization; also, in all 4 of these Strata, the most common reason for hospitalization was worsening of depression. Within the world-wide post-marketing surveillance database (Strata IV), the most common non-fatal, serious event was intentional overdose.

Serious adverse events, including those associated with death, seen in the combined Strata I/Strata II population at an incidence rate of at least 1/1,000 among the fluvoxamine patients are displayed in **Table 8.4.1**, along with the placebo and active-control rates. All rates in the fluvoxamine group approximate the placebo rates with the exceptions of those for suicidality and non-suicidal depression. However, when these rates are adjusted for different exposure durations among the treatment groups, the adjusted fluvoxamine rates (per 100 PEY) are less than the placebo rates: suicidalality: fluvoxamine 5.9, placebo 6.0, and active-control 9.8; non-suicidal depression: fluvoxamine 5.2, placebo 7.5, and active-control 0.8.

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[1]Excluding one serious adverse event in a fluvoxamine patient in the non-dedicated database of Strata III: a 37 year old male with depression took an overdose of diazepam after 54 days of fluvoxamine therapy; apparently there were no adverse sequelae of this event since the patient completed the 6 month study.

TABLE 8.4.1 - SERIOUS ADVERSE EVENTS OCCURRING AT AN INCIDENCE ≥ 1/1,000: STRATA I/STRATA II			
Adverse Event	FLUV (N=2737)	PLAC (N=1055)	CONTROL (N=979)
Suicidality *	2.0%	0.8%	1.3%
Non-Suicidal Depression **	1.8%	0.9%	0.1%
Accidental Injury	0.3%	0.1%	0.2%
Infection	0.3%	0.1%	0.1%
Allergic Reaction	0.2%	0.0%	0.1%
Myocardial Infarction	0.2%	0.0%	0.2%
Neurosis	0.2%	0.2%	0.1%
Syncope	0.2%	0.0%	0.1%
Cerebrovascular Accident	0.1%	0.0%	0.0%
Mania	0.1%	0.0%	0.4%
Seizure	0.1%	0.2%	0.4%

* Includes events coded as suicide, suicide attempt, overdose, or suicidal ideation.
** Includes only those patients with depression or psychotic depression **and** none of the terms included under suicidality.

Serious event listings for all clinical trials (Strata I, II, III, and V) were examined by the reviewer to search for adverse event terms which were felt to possibly represent clinically significant, drug-related events. Serious events which prompted review of individual Narrative Summary Reports were: allergic reaction, anemia, arrhythmia, atrial tachycardia, bowel infarction, carcinoma/neoplasm, cataract, cerebrovascular accident, coma, delirium, dementia, drug level increased, dyspnea, gastrointestinal bleeding, goiter, hematuria, hemoptysis, hepatitis, hypertension, hyponatremia, hypotension, hypothyroidism, intestinal obstruction, jaundice, liver necrosis, lung edema, mesenteric occlusion, myocardial infarction, pancreatitis, paralysis, pericarditis, peritonitis, postural hypotension, pulmonary embolism, renal caculus, retinal detachment/disorder, sepsis, shock, stupor, tachycardia, thrombocytopenia, and withdrawal syndrome.

Events classified as serious in this database but not selected for individual case review are listed in **Appendix 8.4.1:** for some events, the number of observed cases was clearly not unusual given the sample size (N_{fluv}> 37,000); for other events, the terms were deemed less likely to represent truly hazardous experiences; the remainder of these events are adequately addressed in other sections of this review and a case-by-case review as part of this search was not felt to be critical (i.e. convulsions, mania, abortion, pregnancy, ecchymosis, suicidal ideation/attempt, overdose, and hostility).

Additionally, listings of serious adverse events for Strata IV were screened for events which: 1) were identified in the other Strata and felt to be clinically important and possibly drug related[2] OR 2) events which were felt to represent a potentially serious drug effect and were not seen in the other Strata[3]. This database included 10-day Reports of serious adverse events up to July 1993.

Based on the above selection of specific events for review, a total of 149 cases of non-fatal, serious adverse events were reviewed: 26 cases were felt to be clinically significant and attributable to fluvoxamine[4]. These events are as follows:

Allergic reaction, bradycardia, epidermal necrolysis, Stevens-Johnson syndrome, hepatitis, hyponatremia, dystonia, extrapyramidal symptoms, and thrombocytopenia. (Only an isolated case was identified for each of 2 events: thrombocytopenia and bradycardia which was not due to a drug interaction. These are presented in **Section 8.5.2.2** and **Section 8.5.3**, respectively. The other cases will be discussed in **Section 8.6**.)

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[2]Events seen in Strata I, II, III, and V which were felt to be important and possibly drug-related, including isolated findings, include the following: allergic reaction, bradycardia, drug interaction, hyponatremia, liver toxicity, movement disorders, and thrombocytopenia. Other events which were classified in this category were: nausea, sexual dysfunction, mania, and seizure; it was felt that data regarding these events was adequate to permit discussion in **Section 8.6** and thus these were not sought in the search of Strata IV.

[3]Important events not previously observed were: cerebellar syndrome, epidermal necrolysis, marrow depression, and Stevens-Johnson syndrome.

[4]Causality was based on the judgement of the reviewer and included the following factors: timing of the event relative to Fluvoxamine therapy, likelihood of alternative etiologies, approximate incidence of the event in the general population, and results of rechallenge with the drug.

Also clinically significant and attributable to fluvoxamine were the following, which are thought to be related to drug-drug interactions: increased anticoagulant effect due to possible interaction with a hepatically metabolized Vitamin K antagonist, bradycardia due to a possible interaction with propranolol, bradycardia due to a possible interaction with diltiazem, orthostatic hypotension due to a possible interaction with metoprolol, increased theophylline levels with toxicity, and increased levels of tricyclic antidepressants (amitriptyline and clomipramine) - these cases will be presented in **Section 8.8.3.**

8.4.2 Suicidality

Emergence/Worsening of Suicidal Ideation

The emergence of suicidal ideation was assessed by conducting a meta-analysis of 12 clinical studies[3] in depression using item #3 (Suicide) of the Hamilton Depression Rating Scale (HDRS). All studies were either 4 weeks or 6 weeks in duration. Emergence of suicidal ideation was defined as a change from an item 3 score of 0 or 1 at baseline to 3 or 4 at any time post-baseline; only patients with a baseline score of 0 or 1 were included in this analysis. Emergence rate differences across treatment groups were primarily tested for statistical significance using the Mantel-Haenszel adjusted incidence difference with secondary analysis using Pearson's Chi-Square test. **Table 8.4.2.1** presents the rates for emergence by treatment group.

Statistical analysis of this data reveals no significant difference for fluvoxamine vs placebo or for fluvoxamine vs active control using both the Mantel-Haenszel adjusted incidence difference and Pearson's Chi-Square. The Breslow-Day test was not significant for lack of homogeneity of the odds ratios across the 12 studies at the 0.10 level for fluvoxamine vs placebo nor for fluvoxamine vs Active Control. It is concluded that fluvoxamine treatment was not associated with an increased risk of emergence of substantial suicidal ideation among these depressed patients compared to placebo or tricyclic control groups.

[3]The database consisted of 3 placebo-controlled studies (5076, 5522, and 5528) and 9 placebo- and active-controlled studies (5045, 5505, 5506, 5508, 5510, 5520, 5525, 5526, and 5527). Active controls were imipramine or desipramine 50-300 mg/day.

TABLE 8.4.2.1 - INCIDENCE OF EMERGENCE OF SUICIDAL IDEATION IN 12 PLACEBO-CONTROLLED TRIALS: A META-ANALYSIS

	FLUVOXAMINE (N=478)	PLACEBO (N=376)	ACTIVE CONTROL (N=250)
Number (%)	8 (1.7%)	12 (3.2%)	7 (2.8%)
M.H. Adj. Incidence Difference *	---	-1.4%	-1.1%
95% C.I. for Difference	---	-3.5, 0.6	-3.4, 1.3
M.H. p-value for Difference	---	0.17	0.36
Pearson's Chi-Square p-value for Difference	---	0.15	0.31

* Difference of fluvoxamine rate minus placebo/active-control rate. Negative values for the adjusted incidence difference indicate that the fluvoxamine rate was less than the Placebo/Active Control rate.

The incidence of worsening of suicidal ideation was evaluated using the same study pool and analysis as described above. Worsening was defined as an increase in the item 3 score from baseline at any time; patients with a baseline score of 4 (the highest possible score) were excluded from this analysis. **Table 8.4.2.2** presents the rates for worsening by treatment group.

Statistical analysis of this data reveals no significant difference for fluvoxamine vs placebo or fluvoxamine vs active control comparisons of rates of suicidal ideation worsening. The Breslow-Day test was not significant for lack of homogeneity of the odds ratios across the 12 studies at the 0.10 level. It is concluded that fluvoxamine treatment was not associated with an increased risk of worsening of suicidal ideation among depressed patients relative to placebo or tricyclic control groups.

TABLE 8.4.2.2 - NUMBER OF PATIENTS WITH WORSENING OF SUICIDAL IDEATION IN 12 PLACEBO-CONTROLLED TRIALS: A META-ANALYSIS

	FLUVOXAMINE (N=886)	PLACEBO (N=789)	ACTIVE CONTROL (N=542)
Number (%)	147 (16.6%)	137 (17.4%)	82 (15.1%)
M.H. Adj. Incidence Difference *	---	-.60%	2.1%
95% C.I. for Difference	---	-4.2, 3.0	-2.2, 6.3
M.H. p-value for Difference	---	0.74	0.34
Pearson's Chi-Square p-value for Difference	---	0.67	0.47

* Difference of fluvoxamine rate minus placebo/active-control rate. Negative values for the adjusted incidence difference indicate that the fluvoxamine rate was less than the placebo/active control rate.

Suicidal Ideation/Behavior

The occurrence of events associated with suicidality was examined in the combined Strata I/Strata II population. Investigator terms which were the focus of this search are classified as follows: suicidal ideation, suicide attempts and gestures, and completed suicides. **Table 8.4.2.3** displays the incidence rates of these events within this dataset. The only difference between the fluvoxamine and placebo incidence rates which is significant is that for suicide attempts[4]; however, when these rates are corrected for the difference in exposure duration between these 2 treatment groups, the adjusted rates (per 100 PEY) are: fluvoxamine 1.6 and placebo 0.8. These rates are not substantially different.

In summary, fluvoxamine treatment does not appear to be related to the emergence or worsening of suicidal ideation or suicidal behavior.

[4]Using the 2-tailed Fisher's exact test with $\alpha = 0.10$; $p = 0.054$.

TABLE 8.4.2.3 - INCIDENCE OF EVENTS RELATED TO SUICIDALITY: STRATA I/II			
	FLUV (N=2737)	PLACEBO (N=1055)	OTHER (N=979)
Suicidal Ideation	0.6%	0.2%	0.3%
Suicide Attempts*	0.5%	<0.1%	0.2%
Suicides	0.2%	<0.1%	0.2%
All Events	1.1%	0.3%	0.5%

* Includes gestures and completed suicides.

8.4.3 Events Related to Aggression or Hostility

The listings of adverse events for Strata I and Strata II was searched for investigator terms which suggested the emergence of aggression or hostility during treatment with fluvoxamine, placebo, or an active-control drug. The percentages of patients with these events are: fluvoxamine 0.6% (17/2737), placebo 0.3% (3/1055), and active-control 0.2% (4/979). If adjustment is made for the difference in exposure duration among the 3 treatment groups, the rates (per 100 PEY) are: fluvoxamine 1.8, placebo 2.3, and active-control 3.0. It does not appear that fluvoxamine exposure is related to the emergence of aggression or hostility.

8.4.4 Bleeding Symptoms

Ecchymosis was observed in 1.3% (2/160) of the Strata I OCD fluvoxamine patients, 0.7% (5/732) of the Strata I short-term depression pool patients, and in none (0/778) of the placebo patients in either pool. To estimate the incidence of all bleeding events in a larger database, adverse events in the Strata I/Strata II population were searched for investigator terms which suggested bleeding. Events identified were: hemorrhage, anemia, decreased hematocrit, melena, hematochezia, epistaxis, hematuria, menorrhagia, metrorrhagia, hematospermia, bleeding gums, ecchymosis, bruising, hematoma, and purpura. Incidence rates[5] for all identified bleeding events in this dataset were: fluvoxamine 2.0% (55/2737), placebo 1.0% (11/1055), and active-controls 1.5%

[5]For a given patient, multiple occurrences of bleeding or simultaneous bleeding from multiple sites was counted as a single numerator event for purposes of computing an overall bleeding event incidence rate.

(15/979). Exposure-adjusted rates (per 100 PEY) are: fluvoxamine 5.9, placebo 8.3, and active-control 11.4.

One fluvoxamine patient in this population died with a bleeding event listed as a cause of death: a 70 year old male who had been treated with fluvoxamine up to 150 mg/day for over 31 weeks died, with the documented causes of death being myocardial infarction and perforated duodenal ulcer. Of note, this patient appears to have been treated chronically for arthritis with piroxicam, with which gastrointestinal perforation has been observed. It is unlikely that fluvoxamine played a role in this death. (II/5066/2533)

Six other fluvoxamine patients in Strata I and Strata II dropped out with a bleeding event reported at the time of dropout. These cases are summarized in **Table 8.4.4** below. In two of these cases, predisposing conditions are noted: chronic gastritis and diverticular disease. The possibility of exacerbation of these conditions by fluvoxamine exposure and the etiologic role of fluvoxamine in the other four cases is unclear but a drug relationship is not suggested given the wide range of exposure durations prior to dropout.

TABLE 8.4.4 - DROPOUTS WITH BLEEDING EVENTS: STRATA I/II

Strata/Study/ Pt.	Age	Sex	Dose (mg/day)	Duration (days)	Event	Comments
I/5534/62898	38	F	250	65	Fe Deficiency Anemia	"Mild": slight ↓ in H/H, using ASA PRN; improved with Fe TX.
II/5508E/ 5392	37	F	300	199	Bleeding Ulcer	TX'd with cimetidine during trial.
II/5520E/657	34	F	300	235	Gastric Bleeding	"Long H/O gastritis."
II/5066/3352	43	M	75	3	Hematemesis	Vomited blood ×2 with epigastric pain, nausea.
II/5529E/ 62719	39	F	200	66	Rectal Bleeding	Felt to be D/T diverticular disease.
II/5526E/ 61453	30	F	300	68	↑ Menstrual Bleeding	Occurred during 2 periods without D/C after first episode, no labs.

The search for serious adverse events revealed 2 cases of bleeding ulcers, 1 case of rupture of esophageal varices, and 1 case of hemoptysis which were not felt to be related to fluvoxamine exposure[6].

Overall, evidence to date does not support an association between fluvoxamine and bleeding events.

8.4.5 Serotonin Syndrome

To investigate the possible emergence of serotonin syndrome in fluvoxamine-treated patients, it was requested that the sponsor search the available clinical trial database for patients concurrently exposed to fluvoxamine and at least one other serotonergic agent; the clinical data pertaining to these patients was then assessed for the emergence of serotonin syndrome as defined by diagnostic criteria suggested by Sternbach[7]. Since considerable data necessary for proper analysis was missing for Strata III patients, only Strata I, Strata II, and Strata V search results were reported. Additionally, data for 30 Strata IV patients who experienced adverse events and had been exposed to combined fluvoxamine/lithium therapy was submitted for review. Altogether, clinical data for 81 unique patients with concomitant exposure to fluvoxamine and other serotonergic agents[8] was examined. Examination of the reported symptom clusters for these patients revealed no case that met the aforementioned criteria for serotonin syndrome.

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[6]Bleeding ulcers: II/5508E/5392 and III/CH.950/09_013; ruptured varices: III/FR.019/1504210; and hemoptysis: III/UK.921/GG_Y126.

[7]Sternbach H: The Serotonin Syndrome. Am J Psychiatry 1991; 148:705-713. The suggested Diagnostic criteria are: **A.** At least 3 of the following coincident with the addition of or increase in a known serotonergic agent to an established regimen - mental status changes, agitation, myoclonus, hyperreflexia, diaphoresis, shivering, tremor, diarrhea, incoordination, or fever; **B.** Other etiogies have been ruled out; **and C.** No preceding initiation or increased dose of a neuroleptic. These criteria were suggested on the basis of a review of 38 human cases of serotonin syndrome from 12 literature reports cited in the above article.

[8]Lithium, L-tryptophan, trazodone, imipramine, amoxapine, amitriptyline, clomipramine, triazolam, buspirone, and fenfluramine.

8.4.6 Allergic Reactions

Adverse events associated with dropout in the combined Strata I/ Strata II population were searched for investigator terms that suggested an allergic reaction, namely: allergic reaction, eosinophilia, rash, and urticaria. The incidence rates for allergic events at the time of premature termination were equal for fluvoxamine (16/2737, 0.6%) and placebo (5/1055, 0.5%) and considerably higher in the active control group (24/979, 2.5%).

A search of all 5 Strata was performed for allergic events classified as serious or associated with dropout, clinically important, and reasonably attributable to fluvoxamine. Four serious adverse events were identified. A case in Strata I involved urticaria and acute dyspnea during fluvoxamine therapy and is possibly related to fluvoxamine: this case is presented in **Section 8.6.4.** A case from Strata IV involved anaphylaxis; clinical information about this case is not adequate to determine the exact nature or seriousness of the event: a 93 year old female experienced "anaphylaxis" following one day of treatment with fluvoxamine 100 mg/day; fluvoxamine was discontinued and the patient had a complete recovery. (IV/FL765) The other 2 cases were not felt to be related to fluvoxamine exposure[9].

8.4.7 Zimelidine Syndrome

The 4 most common manifestations of the zimelidine syndrome are fever, arthralgia, myalgia, rash, and liver enzyme elevations. The adverse events associated with dropout in the Strata I/Strata II fluvoxamine-exposed population (N_{total}=2737) were searched for investigator terms consistent with one of these manifestations as well as flu syndrome. Then, among the patients prematurely terminating and experiencing at least one of the above at the time of dropout, a search was performed to identify patients who had a combination of 2 or more of these manifestations at dropout. Only one patient was identified: a 23 year old male who had been treated with fluvoxamine for 24 weeks at doses up to 300 mg/day and dropped out because of a flu syndrome with fever; it is highly unlikely that this case represents zimelidine syndrome given the duration of exposure prior to onset and the patient's report of a "head cold" at the time of dropout. (II/5509E/6214)

There is a Strata IV case of Guillain-Barre syndrome following fluvoxamine exposure: a 48 year old male had been treated for depression for 6 months with fluvoxamine 150 mg/day; then fluvoxamine was discontinued and fluoxetine was taken for 2 months, at which time he was hospitalized with a several day history of right facial weakness, intermittent diplopia, and distal numbness

[9] II/5066/2611 and IV/FLUV1920060.

in his extremities. Two weeks before, he had experienced an episode of "gastric flu". Based on a complete neurological work-up, the diagnosis of Guillain-Barre was made and he was treated with plasmapheresis. Eventually, all symptoms completely cleared. It is felt that this event was most likely related to the preceding "flu" illness and not likely related to fluvoxamine. (IV/FL742)

8.5 Other Safety Findings

8.5.1 ADR Incidence Tables

Treatment emergent signs and symptoms (TESS) were defined as those signs and symptoms which occurred after initiation of double-blind treatment or those present prior to drug administration but which increased in severity during double-blind treatment; this definition is independent of causality judgement. For Strata I and II, coding of TESS was performed using a modified COSTART dictionary (3rd Edition). This dictionary was modified once by the sponsor following submission of the original NDA to reconcile coding inconsistencies that were detected and to document all terms associated with any given adverse event in lieu of coding each adverse event to one term.

For purposes of comparing the fluvoxamine rates of common adverse events with corresponding placebo rates, only data in the highest quality Strata (Strata I) was examined. Two Strata I study pools were formed for this purpose such that studies within each pool were of equal duration: the **OCD Pool** consisted of 5529 and 5534 (10 week trials) and the **Short-Term Depression Pool** consisted of 5520, 5522, 5525, 5526, 5527, and 5528 (6 week trials). **Appendix 8.5.1.1** and **Appendix 8.5.1.2** list adverse event incidence rates that occurred at an incidence of 1% or more among fluvoxamine-treated patients in the OCD Pool and the Short-Term Depression Pool, respectively.

Common and Drug-Related Adverse Events

Based on the above tables, events commonly seen with the use of fluvoxamine (incidence ≥ 5%) and not observed at a comparable incidence among placebo-treated patients (fluvoxamine incidence ≥ 2× Placebo incidence) in either of the 2 study pools are shown in **Table 8.5.1.1** in order of decreasing frequency.

TABLE 8.5.1.1 - COMMON & DRUG-RELATED ADVERSE EXPERIENCES

OCD POOL	DEPRESSION POOL
Insomnia	Nausea
Nausea	Somnolence
Somnolence	Insomnia
Asthenia	Nervousness
Abnormal Ejaculation	Asthenia
Nervousness	Dyspepsia
Dry Mouth	Sweating
Thinking Abnormal	Anorexia
Rhinitis	Vomiting
Tremor	
Anorexia	
Anorgasmia (Males)	
Sweating	
Libido Decreased	
Taste Perversion	
Urinary Frequency	

Evidence of Dose-Relatedness for Certain Adverse Events

No adequate fixed dose study was available to systematically analyze the relationship of dose to certain adverse events.

Evidence of Adaptation for Certain Adverse Events

The likelihood that patients will adapt to common, drug-related adverse experiences over time was investigated by pooling the short-term depression pool (5520, 5522, 5525, 5526, 5527, and 5528) with the 2 Strata I OCD trials (5529 and 5534). Then, from this pool of 8 studies, those patients who completed their respective studies and experienced a given adverse event during the first week of the study were taken as a cohort and the incidence of that adverse event in that cohort was computed for each week to week 6. This was done for each of the 18 common and drug-related events in the Strata I pools. These incidence rates over time are displayed in **Appendix 8.5.1.3.** For the following adverse events, patients did show evidence of tolerance over the first 6 weeks: anorexia, asthenia, dyspepsia, insomnia, nausea, nervousness, somnolence, sweating, taste perversion, thinking abnormal, tremor, urinary frequency, and vomiting. A substantial proportion of patients with dry mouth and rhinitis at Week 1 still had these experiences at Week 6. The small sample sizes for sexual events (abnormal ejaculation, male anorgasmia, and decreased libido) reflect the fact that most of these events had an onset after the first week of treatment and were thus excluded from this analysis.

Other Events Noted During Pre-Marketing Evaluation

In the course of the pre-marketing assessment of fluvoxamine, multiple doses were administered to a total of 2112 patients in the Strata I and Strata II studies which collected adverse event data by spontaneous reporting. In the tabulations that follow, the revised COSTART dictionary, as described above, was used to classify the investigator terms for these adverse events. The frequencies presented represent the proportion of these 2112 patients who experienced the given event on at least one occasion while receiving fluvoxamine. Those events already listed in **Appendices 8.5.1.1** and **8.5.1.2** are not listed here. It must be noted that the following tabulations are independent of any judgement of causality, i.e. although the events occurred during treatment, they were not necessarily caused by the treatment.

Events were further categorized by body system and listed in order of decreasing frequency as follows: frequent events occurred on one or more occasions in at least 1/100 patients; infrequent events occurred at a frequency of 1/100 to 1/1000 patients; rare events occurred in fewer than 1/1000 patients.

Body as a Whole - Frequent: infection, pain; Infrequent: malaise, neck pain, face edema, allergic reaction, hangover effect, neck rigidity, overdose, suicide attempt, photosensitivity reaction; Rare: hernia, abnormal lab test, abdomen enlarged, cyst, halitosis, intentional overdose, neoplasm, pelvic pain.

Cardiovascular - Frequent: tachycardia; Infrequent: hypotension, migraine, hypertension, syncope, abnormal ECG, peripheral vascualar disease, cardiovascular disorder, angina pectoris, pallor; Rare: arrhythmia, cerebrovascular accident, cerebrovascular disorder, hemorrhage, AV block, bradycardia, cardiomyopathy, heart failure, supraventricular extrasystole, supraventricular tachycardia, varicose veins.

Digestive - Infrequent: abnormal liver function tests, colitis, eructation, gastrointestinal disorder, esophagitis, gastroenteritis, gingivitis, melena, Rare: cholecystitis, cholelithiasis, gastritis, gastrointestinal hemorrhage, glossitis, rectal hemorrhage, ulcerative stomatitis, biliary pain, duodenal ulcer, gastrointestinal carcinoma, hematemesis, ileitis, jaundice, liver damage, malabsorption syndrome, peptic ulcer syndrome, stomach ulcer, tongue disorder, tongue edema, tooth caries.

Endocrine - Rare: hypothyroidism.

Hematic and Lymphatic - Infrequent: anemia, lymphadenopathy; Rare: iron deficiency anemia, thrombocytopenia, leukopenia, purpura.

Metabolic and Nutritional - Frequent: weight gain; Infrequent: edema, peripheral edema; Rare: dehydration, diabetes mellitus, hypercholesterolemia, hypoglycemia, hypokalemia.

Musculoskeletal - Infrequent: myasthenia, arthralgia, leg cramps, arthritis, bursitis, rheumatoid arthritis, tenosynovitis; Rare: tendinous contracture, joint disorder, muscle hemorrhage, myopathy, pathological fracture.

Nervous - Frequent: amnesia; Infrequent: neurosis, ataxia, apathy, manic reaction, vertigo, akathisia, psychotic depression, hypokinesia, depersonalization, emotional lability, increased salivation, sleep disorder, dyskinesia, paranoid reaction, hallucinations, hyperkinesia, speech disorder, hostility, neuralgia, abnormal gait, libido increased, stupor, euphoria, extrapyramidal syndrome, hypotonia, psychosis; Rare: convulsions, delusions, dystonia, hemiplegia, hysteria, reflexes decreased, akinesia, CNS depression, cogwheel rigidity, hyperesthesia, incoordination, personality disorder, torticollis, withdrawal syndrome.

Respiratory - Frequent: cough increased; Infrequent: sinusitis, yawn, bronchitis, epistaxis, hyperventilation, voice alteration; Rare: asthma, lung disorder, pneumonia, apnea, hiccup, laryngitis, nasal septal defect, pleural disorder, respiratory disorder.

Skin - Infrequent: dry skin, acne, urticaria, herpes simplex, skin disorder, alopecia, maculopapular rash; Rare: exfoliative dermatitis, furunculosis, skin discoloration, application site reaction, eczema, herpes zoster, hirsutism, nail disorder, psoriasis, seborrhea, skin granuloma.

Special Senses - Frequent: tinnitus; Infrequent: abnormal vision, abnormality of accomodation, eye disorder, ear disorder, ear pain, mydriasis, conjunctivitis, photophobia, dry eyes; Rare: deafness, diplopia, eye pain, otitis media, parosmia, taste loss, corneal ulcer, eye hemorrhage, retinal detachment, visual field defect.

Urogenital* - Infrequent: vaginitis, menstrual disorder, metrorrhagia, urinary tract infection, menorrhagia, polyuria, urinary urgency, cystitis, nocturia, dysuria, female lactation, urinary incontinence, menopause; Rare: breast pain, hematuria, urination impaired, urine abnormality, breast enlargement, unintended pregnancy, uterine disorder, vaginal hemorrhage, anuria, kidney pain.

* Incidence rates of sex-specific adverse events were based on the number of females or males at risk, as appropriate.

8.5.2 Laboratory Findings

In Strata I, approximately 144 fluvoxamine patients in the 2 pivotal OCD studies and 757 fluvoxamine patients in the 11 depression studies had evaluable laboratory data (i.e. both baseline and post-baseline laboratory values) for clinical biochemistry, hematology, and urinalysis studies. About 160 Strata II fluvoxamine patients who participated in the OCD extension trials 5529E and 5534E (with or without further participation in the open-ended trial 5540-O) had evaluable labs. In the original Strata III dedicated database, only 17 of 54 studies collected laboratory data, yielding 1630 fluvoxamine patients with at least one lab value. Given that most Strata II and Strata III lab data is uncontrolled, only Strata I laboratory data was examined in detail; data is presented for the OCD pool[1] and the depression pool[2] separately in each subsection below. For Strata II and III, only dropouts due to abnormal lab assessments were addressed.

8.5.2.1 Serum Chemistry

Median changes from baseline to last visit in chemistry parameters are depicted in **Appendix 8.5.2.1.1** and **Appendix 8.5.2.1.2** for the OCD pool and the depression pool, respectively. The small median increases in SGOT and SGPT compared to placebo were not felt to be clinically significant but, given past foreign labeling changes related to transient, mild increases in LFT's seen with fluvoxamine, these changes were explored in more detail as follows. Box plots of the distributions of changes from baseline to week 10 for the Strata I OCD pool and from baseline to weeks 2, 4, and 6 for the Strata I depression pool were examined. Visual inspection of these plots suggested a tendency for slightly higher changes from baseline in the fluvoxamine group versus placebo for both enzymes in the OCD pool but negligible differences between treatment groups in the depression pool. The 90% levels (i.e. the value which equals or exceeds the change from baseline for 90% of the patients for each enzyme at each timepoint) are presented in **Appendix 8.5.2.1.2a.** There is a hint that fluvoxamine may be associated with slight elevations in SGOT and SGPT compared to placebo, as noted by the increased changes from baseline at Week 10 in the OCD pool. However, increases of this magnitude are not likely to have clinical significance. Patients with larger changes in transaminase levels will be discussed in the next section.

Comparison of the median changes by treatment group for the other chemistry variables reveals no or negligible differences.

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[1]Two OCD studies: 5529 and 5534.

[2]Eleven depression studies: 5505, 5506, 5508, 5510, 5520, 5522, 5525, 5526, 5527, 5528, and 5531.

Table 8.5.2.1 presents the criteria that were used to identify patients in Strata I studies with clinically significant serum chemistry values:

TABLE 8.5.2.1
CRITERIA FOR IDENTIFYING PATIENTS WITH POTENTIALLY CLINICALLY SIGNIFICANT CHANGES IN CLINICAL CHEMISTRY VARIABLE

	LOW	HIGH
Albumin	≤2.5 g/dl	
Alkaline Phosphatase		≥390 U/L
BUN		>30 mg/dl
Calcium	≤8.2 mg/dl	≥12 mg/dl
Chloride	≤90 meq/L	≥118 meq/L
Cholesterol		≥600 mg/dl
Creatinine		>2 mg/dl
Globulin	≤1 g/dl	
Glucose	<30 mg/dl	≥175 mg/dl
LDH		>750 u/ml
Phosphorous	≤1.7 mg/dl	
Potassium	≤2.5 meq/L	≥6.5 meq/L
SGOT		>150 U/L
SGPT		>165 U/L
Sodium	≤126 meq/L	>156 meq/L
Total Bilirubin		>2 mg/dl
Uric Acid		
Female		>8.5 mg/dl
Male		>10.5 mg/dl

Appendix 8.5.2.1.3 and **Appendix 8.5.2.1.4** provide the proportions of patients who met these criteria at some time during double-blind treatment in the OCD pool and in the depression pool, respectively. Note that these tables include patients with abnormal as well as normal baseline values. In both study pools, the incidence of elevated serum glucose was slightly higher among fluvoxamine

patients compared to placebo. Most of these abnormalities are in patients with poorly controlled diabetes mellitus and these differences across treatment groups were not statistically significant[3]. Differences between fluvoxamine and placebo for all other chemistry variables were not significant[3].

Seven fluvoxamine patients had a significant increase in SGPT levels during treatment, the highest elevation being 6X ULN (I/5529/62681); none of these cases was classified as serious using FDA criteria, none was associated with jaundice or liver failure, and only one of these patients dropped out, a 54 year old male who dropped out due to severe anxiety after 3 100mg doses of fluvoxamine and had elevations of SGOT and SGPT to 91 and 194 U/L, respectively, post-study with normal values one week later (I/5520/404). Of the remaining 6 cases, one abnormality substantially decreased toward the normal range with continued treatment, 3 substantially decreased within 2 weeks after fluvoxamine exposure stopped, and 2 had abnormal values at study termination with no follow-up data[4].

If the transaminase data for both pools are combined, 0% (0/918) of the fluvoxamine patients and 0.2% (2/842) of the placebo patients met the above criteria for SGOT abnormalities; 0.8% (7/906) of the fluvoxamine patients and 0.6% (5/829) of the placebo patients had SGPT abnormalities. Neither difference is statistically significant[5].

The combined Strata I/Strata II population was reviewed for patients who prematurely terminated and for whom a chemistry abnormality was documented at the time of termination. The vast majority of these abnormalities consisted of abnormal liver function tests, which occurred at incidence rates of 0.4% (12/2737), 0.1% (1/1055), and 0.7% (7/979) in the fluvoxamine, placebo, and active-control groups, respectively. The 12 fluvoxamine patients who dropped out due to elevated LFT's were individually assessed: 4 had mild (<2X ULN) or moderate (2-3X ULN) changes which normalized after discontinuation, 3 had abnormal baseline values without significant change during treatment, 2 had moderate changes (3X ULN) which decreased with continued drug exposure, 1 had a mild change without follow-up, 1 had hepatitis B, and 1 had marked elevation of LFT's (7X ULN) which normalized after

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[3] α= 0.10, 2-tailed Fisher's exact test.

[4] Decreased with treatment: I/5508/5401; decreased after drug D/C: I/5522/9520, I/5525/61175, and I/5528/62309; no F/U: I/5527/61841 and I/5529/62681.

[5] Using the 2-tailed Fisher's exact test, p= 0.23 for the SGOT comparison and p= 0.78 for the SGPT comparison.

fluvoxamine discontinuation[6]. All cases occurred within the first 6 weeks of exposure to fluvoxamine except for one patient from study 5529, who was noted to have increased transaminases at Week 10, at the first post-baseline laboratory assessment[7]. In all cases of treatment-emergent LFT elevation possibly related to fluvoxamine and with follow-up data, the abnormality was reversible. One patient, who experienced normalization of LFT's after fluvoxamine discontinuation, was rechallenged with no recuurence of the abnormality (II/5529E/62681).

In this population, only 2 other patients dropped out with a related lab abnormality: a poorly controlled diabetic patient dropped out with hyperglycemia (II/5540-D/61433) and another patient was noted to have hypokalemia during an E.R. visit for a sprained ankle (potassium level not provided) (II/5534E/62856).

Strata III was reviewed for dropouts and serious adverse events with associated chemistry abnormalities. Events which were felt to be clinically important and possibly related to fluvoxamine are 2 cases of jaundice and 1 case of hyponatremia. These cases will be discussed in **Section 8.6.**

The search for serious adverse events revealed a total of 15 cases of hepatitis: 5 of these are felt to be possibly related to fluvoxamine treatment and are discussed in **Section 8.6.** Of the other 10 cases, assessment of drug relatedness in 6 was confounded by the concomitant exposure to alcohol and/or other drugs with the potential for hepatic effects and the remaining 4 cases were not felt to be related to fluvoxamine exposure[8]. Also, there were 4 cases cases of jaundice classified as serious: 2 of these were felt to be attributable to fluvoxamine and are presented in **Section 8.6.** The other 2 cases were unlikely to be related to fluvoxamine[9].

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[6]Abnormal baseline without significant change: I/5525/61119, II/5532/4, and II/5533/90081; mild-moderate increase, normal after drug D/C: II/5004/5, II/5015/130, II/5091/8290, and II/5532/5; decreased with treatment: II/5091/8283 and II/5520E/203; no F/U: II/5525E/61327; Hepatitis B: II/5520E/511; and marked increase, normal after drug D/C: II/5529E/62681.

[7]It should be noted that, within the Strata I/Strata II database, 616 patients were exposed to fluvoxamine for 25 weeks or longer.

[8]Confounded cases: III/FR.024/426123, IV/FL446, IV/FL643, IV/FL1136, IV/FLUV1920029, and IV/FLUV7920003; cases probably not drug related: III/EU.901/879, III/FR.003/4606, IV/FL755, IV/FLUV1920075.

[9]III/UK.921/UN_X163 and IV/FL1519.

It appears that infrequent mild to moderate elevations in liver function tests may occur with fluvoxamine exposure; these changes generally appear to be reversible with discontinuation of the drug. Otherwise, there is no evidence to suggest a pattern of chemistry abnormalities which could be reasonably attributed to fluvoxamine.

8.5.2.2 Hematology

Median changes from baseline to last visit in hematology variables are depicted in **Appendix 8.5.2.2.1** and **Appendix 8.5.2.2.2** for the OCD pool and the depression pool, respectively. Comparison of the median changes between the fluvoxamine and placebo treatment groups for each hematology parameter reveals no or negligible differences. **Table 8.5.2.2** presents the criteria that were used to identify patients in Strata I studies with clinically significant hematology values:

TABLE 8.5.2.2
CRITERIA FOR IDENTIFYING PATIENTS WITH POTENTIALLY CLINICALLY SIGNIFICANT CHANGES IN HEMATOLOGY VARIABLES

	LOW	HIGH
Hemoglobin		
Female	< 9.5 g/dl	
Male	< 11.5 g/dl	
Hematocrit		
Female	< 32%	
Male	< 37%	
Red Blood Cells	≤ 3 x 10^3/cmm	
White Blood Cells	< 2.8 x 10^3/cmm	> 16 x 10^3/cmm
Neutrophils	< 15%	
Lymphocytes		≥ 75%
Monocytes		≥ 15%
Eosinophils		> 10%
Basophils		≥ 10%
Platelets	< 75 x 10^3/cmm	> 700 x 10^3/cmm
Mean Corpuscular Volume (MCV)	≤ 65 fl	≥ 110 fl

Mean Corpuscular Hemoglobin (MCH)	≤ 20 pg	
Mean Corpuscular Hemoglobin Content (MCHC	≤ 20%	

Appendix 8.5.2.2.3 and **Appendix 8.5.2.2.4** provide the proportions of patients who met these criteria at some time during double-blind treatment in the OCD pool and in the depression pool, respectively. Note that these tables include patients with abnormal as well as normal baseline values. Overall, only changes in the total WBC count in the depression pool approached statistical significance[10]: fluvoxamine patients experienced a higher incidence of low WBC counts than placebo patients (1.0% vs. 0.3%) but placebo patients had a higher incidence of high WBC counts than the fluvoxamine group (0.6% vs. 0%). All 9 fluvoxamine cases of low WBC counts were examined: in none of these did the WBC count fall below 2,000/mm^3. It is interesting to note that all 9 patients were female and 6 of the 9 were in the age range 25-36. One of the 9 patients continued fluvoxamine despite this abnormality and experienced normalization of this finding. Five of the 9 abnormalities were discovered at the end of treatment or shortly after discontinuation and subsequently resolved. In the other 3 cases, the abnormality was noted at the end of treatment and no follow-up information was available[11].

The search for adverse events identified 2 cases of anemia and one case of pancytopenia, which were not felt to be related to fluvoxamine treatment[12].

The Strata I/Strata II database was searched for dropouts with documentation of a hematology abnormality at the time of termination. Only 3 fluvoxamine patients met these criteria: a 38 year old female was found to have an iron deficiency anemia at final visit which resolved with iron supplementation (I/5534/62898); a 50 year old female experienced a drop in platelet count to 8,000 with bruising following 21 months of exposure which

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[10] α= 0.10, 2-tailed Fisher's exact test.

[11] Normalized with treatment: I/5505/5015; detected at or shortly after drug discontinuation and subsequently resolved: I/5520/143, I/5520/732, I/5525/61030, I/5525/61369, and I/5534/62930; and no F/U: I/5522/9110, I/5526/61463, and I/5534/62864.

[12] Anemia: III/UK.905/C154 and III/UK.905/C155; pancytopenia: IV/FL637.

normalized following drug discontinuation and splenectomy: final diagnosis was not provided (II/5540-D/61417); and the third patient, a 41 year old female, experienced a decreased platelet count to 69,000 after 2 months of continuous fluvoxamine exposure which increased to 176,000 within 3 days of drug discontinuation, thus appearing to be drug related. Prior platelet counts were not provided (II/5520E/169). An additional case of thrombocytopenia and one of purpura, both from Strata IV and identified from the search for serious adverse events, were not felt to be fluvoxamine related (IV/FL412 and IV/FL1934, respectively).

Thrombocytopenia was seen in all 3 treatment groups in the Strata I/II population, with incidence rates of 0.1% (3/2737), <0.1% (1/1055), and 0.1% (1/979) in the fluvoxamine, placebo, and active-control groups, respectively. Incidence rates adjusted for exposure duration were 0.3, 0.8, and 0.8 per 100 patient-years, respectively.

A special search was done for bleeding symptoms in 2 Strata I and one Strata II pools of studies: see **Section 8.4.3.** There was little evidence to suggest an association between fluvoxamine treatment and bleeding events.

It is premature to draw any conclusions based on the slightly increased incidence of decreased WBC counts noted in fluvoxamine versus placebo patients in the Strata I pools. It does seem that this finding is infrequent (≤1/100), not associated with any clinically significant events, and reversible. There was only one case of marked thrombocytopenia which could be attributed to fluvoxamine. Overall, there is no evidence that fluvoxamine treatment is associated with a pattern of significant hematology variable abnormalities.

8.5.2.3 Urinalysis

Appendix 8.5.2.3.1 and **Appendix 8.5.2.3.2** display median changes from baseline to last visit in urinalysis variables for the OCD pool and the depression pool, respectively. No differences across any treatment groups were noted in the median changes in either pool.

Table 8.5.2.3 presents the criteria that were used to identify patients in Strata I studies with clinically significant urinalysis values:

TABLE 8.5.2.3
CRITERIA FOR IDENTIFYING PATIENTS WITH POTENTIALLY CLINICALLY SIGNIFICANT CHANGES IN URINALYSIS VARIABLES

	LOW	HIGH
pH	≤4	≥9
Protein		An increase of at least 2 units from BL
Ketone		4 +
Glucose		An increase of at least 2 units from BL
Blood (Dipstick)		4 +

Appendix 8.5.2.3.3 and **Appendix 8.5.2.3.4** provide the proportions of patients who met these criteria at some time during double-blind treatment in the OCD pool and in the depression pool, respectively. Note that these tables include patients with abnormal as well as normal baseline values. There are no statistically significant differences[13] between fluvoxamine and placebo on any urinalysis variable.

No patients in the combined Strata I/Strata II population or in the Strata III database dropped out with an associated urinalysis abnormality.

The search for serious adverse events revealed 3 cases of hematuria and 2 cases of renal calculi which did not appear to be related to fluvoxamine[14].

8.5.3 Vital Signs

Median changes from baseline to last visit in vital sign variables are depicted in **Appendix 8.5.3.1** and **Appendix 8.5.3.2** for the pool of the 2 Strata I OCD trials and the pool of the 11 Strata I Depression trials, respectively. Comparison of the median changes between the fluvoxamine and placebo treatment groups reveals no or negligible differences.

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[13] α= 0.10, 2-tailed Fisher's exact test.

[14] Hematuria: III/BE.903/I_87, III/FR.003/4412, III/UK.904/G077; renal calculi: I/5510/5709 and III/SP.914/52.

Table 8.5.3.1 displays the criteria used to define a significant vital sign abnormality:

TABLE 8.5.3.1 - CRITERIA FOR IDENTIFYING PATIENTS WITH POTENTIALLY CLINICALLY SIGNIFICANT CHANGES IN VITAL SIGNS VARIABLES *
FEBRUARY 1, 1993

	LOW	HIGH
Pulse	≤50 bpm and a decrease of 15 bpm	≥120 bpm and an increase of 15 bpm
Systolic Blood Pressure (SBP)	≤90 mm Hg and a decrease of 20 mm Hg	≥180 mm Hg and an increase of 20 mm Hg
Diastolic Blood Pressure (DBP)	≤50 mm Hg and a decrease of 15 mm Hg	≥105 mm Hg and an increase of 15 mm Hg
Temperature	≥101 degrees F and a decrease of at least 2 degrees F	≥101 degrees F and an increase of at least 2 degrees F
Weight	A change from baseline of at least -7%	A change from baseline of at least +7%

* All changes are relative to baseline.

Appendix 8.5.3.3 and **Appendix 8.5.3.4** provide the proportions of patients who met these criteria at some time during double-blind treatment in the OCD pool and in the Depression pool, respectively. A comparison of fluvoxamine and placebo incidence rates for vital sign abnormalities indicates no statistically significant differences[15].

The incidence rates of premature termination associated with vital sign abnormalities among fluvoxamine patients in the Strata I/ Strata II database were all < 0.3% and are displayed in **Appendix 8.5.3.5** with the corresponding rates for the placebo and active-control groups.

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[15] α= 0.10, 2-tailed Fisher's exact test.

A review of the fluvoxamine dropouts and serious adverse events in Strata I and Strata II for clinically important events related to vital sign changes revealed only 2 cases.

> A 67 year old female dropped out due to a substantial increase in systolic and diastolic blood pressures which seemed to be associated with fluvoxamine exposure (baseline: 160/90 standing, 186/94 supine; Day #7: 192/112 standing, 218/120 supine) and which returned to pre-study levels after fluvoxamine discontinuation and increase in the dose of pindolol, which had been started concurrently with initiation of fluvoxamine treatment. This patient had pre-existing hypertension. (I/5506/5210)
>
> The second patient, a 47 year old female, dropped out due to bradycardia (standing pulse 44 bpm, supine pulse 40 bpm) noted on Day#8 which improved on follow-up (standing pulse 64 bpm, supine pulse 58 bpm 8 days after drug discontinuation); bradycardia was noted pre-study but pulse rate was not provided. (II/5011/7)

Since both cases involved abnormalities which existed pre-study, it is difficult to gauge the significance of these events.

The search for serious adverse events revealed 3 cases of significant vital sign changes probably related to fluvoxamine therapy; since all 3 events were likely due to the interaction of fluvoxamine and another agent (bradycardia with fluvoxamine + propranolol, bradycardia with fluvoxamine + diltiazem, and orthostatic hypotension with fluvoxamine + metoprolol), these cases will be presented in **Section 8.8.3.** This search also identified 3 cases of hypotension, one with bradycardia, which were not felt to be fluvoxamine related[16].

A 10-day report, submitted 11/20/92, involved a 70 year old female who received fluvoxamine 50 mg bid for 2 days and experienced dizziness and weakness; examination revealed a pulse of 35 bpm (blood pressure not indicated). There were no concomitant medications and no known predisposing medical conditions. The patient recovered after atropine administration and fluvoxamine was discontinued. (IV/FLUV1920217)

To search for other cases of significant bradycardia, the entire NDA database was searched for dropouts with bradycardia: this revealed only one case of clinical importance which could be reasonably attributed to fluvoxamine - a 63 year old male who had bradycardia most likely due to an interaction between fluvoxamine and metoprolol. This case is presented in **Section 8.8.3.**

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[16] II/5083/3717, III/FR.004/0824 and IV/FLUV14920012.

Thus, the former case is the only identified case of significant bradycardia which was not due to a possible interaction of fluvoxamine with another medication. Future adverse event surveillance may elucidate the potential for fluvoxamine to cause bradycardia.

Overall, only isolated cases of important vital sign changes which could be related to fluvoxamine exposure were seen. It does not appear that fluvoxamine treatment is linked with a pattern of significant vital sign abnormalities.

8.5.4 ECG's

This section will address ECG findings observed with both short-term and long-term use of fluvoxamine in OCD and depression. [Note: ECG information for the 2 Strata I OCD studies (5529 and 5534) and for the Strata II extension of these trials (5529E, 5534E, and 5540-O) was submitted by the sponsor as part of this NDA. Data and analyses for the 11 Strata I depression trials and their Strata II extensions as of December 31, 1991 were submitted as part of NDA 20,350, currently pending review for the use of fluvoxamine in the treatment of depression. Information presented in this section regarding ECG findings in depression studies was extracted from the latter NDA.]

The medical review procedure which was applied to the coding and evaluation of ECG tracings was performed by an independent consultant who is an experienced clinician and clinical researcher in electrocardiography; this consisted of 2 stages: 1) identification of abnormalities in the study population as a whole under blinded conditions and 2) assessment of identified abnormalities in the context of the patient's pre-study condition, treatment assignment, and clinical course.

Short-Term Effects

A total of 277 patients in the Strata I OCD studies had both a baseline and at least one follow-up ECG recording: 139 fluvoxamine patients and 138 placebo patients[17]. A deteriorated ECG is defined as an ECG in which the overall sum of findings since the previous tracing could possibly point to a change in patient status that could require investigation. Specific criteria used to determine

[17]In total, 320 patients were enrolled in the 2 OCD trials. Of these, 43 were excluded from the short-term ECG analysis for the following reasons: drug packaging error in 5534 (14 patients), no follow-up ECG (20 patients), follow-up ECG done after initiation of extension trial participation (9 patients).

deterioration included a PR interval >0.21 sec, QRS interval >0.12 sec, and QT_c >0.45 sec. Among Strata I OCD fluvoxamine patients, 28/138 (20%) were judged to have experienced a deterioration in their ECG tracings relative to baseline versus 20/138 (14%) in the placebo group; this difference is not statistically significant[18]. **Appendix 8.5.4.1** provides the numbers of patients within this study pool who had follow-up ECG's which were judged by the consultant to be deteriorated relative to baseline for various ECG characteristics. There are no statistically significant differences in the incidence of specific findings or of classes of findings associated with deteriorated ECG's between fluvoxamine and placebo patients with ECG deterioration[19]. There were no cases of second degree AV block or complete heart block. No ECG was considered to be deteriorated to the extent that the patient's cardiac condition was compromised or at risk for compromise. All deteriorations were felt to be clinically benign by the consultant.

ECG waveform measurements were made from matched pairs of baseline and "end-of-treatment" ECG's; changes were compared across treatment groups. The mean changes and standard deviation of each distribution of changes are presented in **Table 8.5.4.1.** Changes were very small and no substantial differences between the 2 treatment groups were noted.

TABLE 8.5.4.1 - CHANGES IN WAVEFORM MEASUREMENTS FROM BASELINE TO END OF TREATMENT: STRATA I OCD STUDIES

	FLUVOXAMINE			PLACEBO		
	N	Mean Δ	S.D.	N	Mean Δ	S.D.
Ventricular/ Atrial Rate	139	-0.8	11.3	138	+0.8	11.5
PR Interval	139	-0.002	0.015	138	+0.002	0.016
QRS Interval	139	-0.001	0.007	138	0.000	0.006
QT_c Interval	139	-0.002	0.029	138	0.000	0.032

[18] α= 0.10, 2-tailed Fisher's exact test.

[19] α= 0.10, 2-tailed Fisher's exact test comparing the following proportion between treatment groups: (number of patients in that group manifesting an ECG deterioration with a given finding)/(number of patients in that group manifesting an ECG deterioration with any of the other findings). Note that each patient in this analysis had only one deteriorated ECG.

A total of 1840 patients in the Strata I depression studies[20] had both a baseline and at least one follow-up ECG recording and were included in an analysis of ECG deteriorations: 740 fluvoxamine patients, 648 placebo patients, and 452 patients on active-control agents (imipramine or desipramine). Among Strata I depression fluvoxamine patients, 146/740 (20%) were judged to have experienced a deterioration in their ECG tracings relative to baseline versus 129/648 (20%) in the placebo group and 186/452 (41%) in the active-control group (imipramine or desipramine). **Appendix 8.5.4.2** provides the numbers of patients within this study pool who had follow-up ECG's which were judged by the consultant to be deteriorated relative to baseline with various ECG characteristics.

There was a statistically significant difference[21] in the incidence rates of 6 findings when the fluvoxamine and placebo treatment groups were compared. For 4 of these findings (total of all rhythm disturbances, sinus tachycardia, PVC's, and first degree AV block), the placebo rate was higher than the fluvoxamine rate.

There was a higher incidence of deteriorated ECG's with a short PR interval in the fluvoxamine group compared to the placebo group (3.9% versus 1.4%, p=0.10); the clinical significance of this finding is not known. Among the fluvoxamine patients with a deteriorated ECG and a short PR interval, 1 patient experienced a serious adverse experience and 1 dropped out. These 2 cases[22] were reviewed: neither case appeared to involve a cardiac adverse event that could be attributed to fluvoxamine.

Also, there was a higher incidence of T-wave flattening among the fluvoxamine patients compared to the placebo patients (6.3% versus 2.3%, p=0.04). Of the fluvoxamine patients with a deteriorated ECG who had flat T-waves, 3 experienced a serious adverse event and 2 dropped out. However, a review of these 5 cases[23] indicated that none of the serious events or adverse experiences associated with

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[20] 5505, 5506, 5508, 5510, 5520, 5522, 5525, 5526, 5527, 5528, and 5531.

[21] α= 0.10, 2-tailed Fisher's exact test comparing the following proportion between treatment groups: (number of deteriorated ECG's manifesting a specific ECG finding)/(the total number of deteriorated ECG's associated with all other findings in that treatment group).

[22] I/5528/62202 and I/5531/62611.

[23] I/5510/5803, I/5520/651, I/5522/9312, I/5522/9443, and I/5528/62202.

dropout could be reasonably attributed to cardiac effects of fluvoxamine.

Overall, no ECG was considered to be deteriorated to the extent that the patient's cardiac condition was compromised or at risk for compromise with the exception of one patient, who experienced an acute myocardial infarction related to coronary artery disease following 9 days of fluvoxamine treatment (I/5526/61745).

ECG waveform measurements were examined from matched pairs of baseline and "end-of-treatment" ECG's and changes were compared across the fluvoxamine and placebo treatment groups. The mean changes and standard deviation of each distribution of changes are presented in **Table 8.5.4.2.** As with the OCD pool, changes were very small and no clinically meaningful differences between the 2 treatment groups were noted.

TABLE 8.5.4.2 - CHANGES IN WAVEFORM MEASUREMENTS FROM BASELINE TO END OF TREATMENT: STRATA I DEPRESSION STUDIES

	FLUVOXAMINE			PLACEBO		
	N	Mean Δ	S.D.	N	Mean Δ	S.D.
Atrial Rate	740	-1.0	11.8	648	-0.5	11.4
Ventricular Rate	740	-1.0	11.8	648	+0.5	29.5
PR Interval	740	-0.002	0.016	648	+0.001	0.017
QRS Interval	740	0.000	0.009	648	0.000	0.041
QT_c Interval	740	-0.002	0.030	648	0.000	0.027

Long-Term Effects

A total of 185 patients from the Strata I OCD trials received fluvoxamine treatment in the corresponding one year Strata II open-label extension study (5529E or 5534E); patients completing one of these extension trials were then eligible to continue treatment in 5540-O, an open-ended humanitarian extension trial. For these patients, the baseline ECG was the baseline ECG prior to core study treatment for Strata I fluvoxamine patients and the final Strata I ECG for Strata I placebo patients.

As for the Strata I pool, ECG waveform measurements were made from matched pairs of baseline and "end-of-treatment" ECG's and changes

were compared across treatment groups[24]. The mean changes and standard deviation of each distribution of changes are presented in **Table 8.5.4.3.** With the exception of ventricular rate, changes were again very small and comparable to those seen in the shorter duration studies. There is a larger mean change in ventricular rate compared to the Strata I data: a mean decrease of about 2.6 bpm. This is likely to have little clinical significance.

TABLE 8.5.4.3 - CHANGES IN WAVEFORM MEASUREMENTS FROM BASELINE TO END OF TREATMENT: STRATA II OCD STUDIES

	FLUVOXAMINE		
	N	Mean Δ	SEM
Ventricular/ Atrial Rate	158	-2.57	11.973
PR Interval	157	+0.001	0.017
QRS Interval	158	+0.002	0.010
QT$_c$ Interval	158	-0.002	0.031

A total of 388 patients from the Strata 1 depression trials received treatment with fluvoxamine in a long-term Strata II extension study[25]; patients completing one of these extension trials were then eligible to continue treatment in 5540-D, an open-ended humanitarian extension trial. Duration of the extension studies ranged from 24 to 52 weeks. As above, the baseline ECG was the ECG just prior to core study treatment for Strata I fluvoxamine patients and the final Strata 1 ECG for Strata 1 placebo patients. There were 311 fluvoxamine patients in long-term Strata II depression studies who had both a baseline and at least least one follow-up ECG and who were eligible for inclusion in the following analysis.

The mean changes in various waveform parameters from baseline to last available ECG and the standard deviation of each distribution of changes are presented in **Table 8.5.4.4.** As above, changes were very small and comparable to those seen in the short duration studies; there was no decrease in ventricular rate comparable to that seen in the long-term OCD pool.

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[24]The long-term ECG analysis includes only 158 patients; 27 Strata II patients were excluded: 11 due to the packaging error in 5534 and 16 who had no Strata II follow-up ECG.

[25]5505E, 5506E, 5508E, 5510E, 5520E, 5522E, 5525E, 5526E, 5527E, and 5531E.

TABLE 8.5.4.4 - CHANGES IN WAVEFORM MEASUREMENTS FROM BASELINE TO END OF TREATMENT: STRATA II DEPRESSION STUDIES			
	FLUVOXAMINE		
	N	Mean Δ	SEM
Ventricular/ Atrial Rate	311	+0.4	11.9
PR Interval	311	-0.002	0.017
QRS Interval	311	+0.004	0.055
QT$_c$ Interval	311	+0.001	0.036

There was a 28 year old female in a long-term depression study (II/5525E/61335) who was found to have an asymptomatic Mobitz I (Wenckebach) second-degree heart block following 5 months of fluvoxamine treatment. However, a follow-up ECG 2 weeks later did not demonstrate persistence of this finding; also, her baseline ECG was abnormal (first-degree AV block). This patient was using iron supplementation at the time of the Mobitz I block, a factor which was felt by the cardiology consultant to possibly contribute to this finding. Overall, it is unlikely that fluvoxamine played a role in the etiology of this event.

The combined Strata I/Strata II population was screened for dropouts with associated ECG abnormalities. For each of the following ECG findings, one fluvoxamine patient prematurely terminated and manifested the finding at termination: sinus arrest (II/5041/847), sinus tachycardia (I/5508/6351), supraventricular tachycardia (II/5100/10630), atrial ectopic rhythm (I/5527/61897), ventricular extrasystole (II/5503/9), non-specific ST-T changes (II/5059/20), and T-wave inversion (II/5015/155). The case of sinus arrest occurred in a 66 year old female who experienced palpitations, dyspnea on exertion, diaphoresis, and weakness pre-study but unfortunately did not have a baseline ECG. She was found to have an irregular pulse about 9 days after starting fluvoxamine and was referred for cardiology consultation; she was hospitalized, found to have ischemic heart disease, and underwent permanent pacemaker placement. Clinical summaries of the other 6 cases were reviewed: in 3 cases, a causal relationship between the event and fluvoxamine was doubtful[26]; in the other 3, the events were not deemed clinically important[27].

[26] II/5015/155, II/5100/10630, and II/5503/9.

[27] I/5508/6351, I/5527/61897, and II/5059/20.

The search of all Strata for serious adverse events revealed 8 cases of myocardial infarction[28], 3 cases of cardiac arrhythmia[29], and cardiogenic pulmonary edema[30] which were not felt to be reasonably attributable to fluvoxamine exposure.

In summary, the above data does not suggest a pattern of significant ECG abnormalities associated with fluvoxamine therapy.

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[28] I/5526/61745, II/5005/8, III/FR.019/1706108, III/FR.024/76141, III/UK.904/P080, III/UK.905/C170, III/UK.905/Q075, and III/UK.921/RW_G202.

[29] II/5100/10630, III/WG.900/1091_02, and III/G.915/711_01.

[30] III/FR.012/0329 and III/FR.019/1502202.

8.5.5 Special Studies

Studies of Effects on Sleep, EEG, and Cognitive Functioning

H.114.5501: This study was a randomized, double-blind, placebo-controlled, crossover study to examine the effects of fluvoxamine on sleep. Eight healthy males received, at weekly intervals, single oral doses of fluvoxamine 25mg, 50mg, 100mg, 150mg, and placebo in random order 20 minutes prior to sleep. Fluvoxamine showed a tendency to increase REM latency and to shorten REM time.

H.114.5502: This was a randomized, double-blind, placebo- and active-controlled, crossover study to assess the EEG effects of fluvoxamine. Twelve healthy subjects were treated with single oral doses of fluvoxamine 10mg, 25mg, 50mg, and 75mg; imipramine 75mg; and placebo on 6 occasions in random order. The EEG's of subjects receiving fluvoxamine 75mg resembled those of subjects who received imipramine except that the former lacked the slow wave activity characteristic of imipramine, suggesting that perhaps fluvoxamine was less sedating than imipramine.

H.114.5016: This double-blind, placebo-controlled, crossover study examined the influence of fluvoxamine on the EEG and attention span. Ten healthy volunteers received single, oral doses of fluvoxamine 75mg; clovoxamine 50mg, 75mg, and 125mg; imipramine 75mg; and placebo in random order at weekly intervals. Both fluvoxamine and imipramine produced an increase in slow wave activity (imipramine > fluvoxamine) with a concomitant increase in fast β activity and a decrease in α activity. Psychometric testing showed an improvement in attention and concentration with fluvoxamine compared to placebo.

H.114.5088: This was a double-blind, placebo- and active-controlled, crossover study of the EEG and memory effects of multiple dose fluvoxamine. Nine healthy participants were administered fluvoxamine (50mg bid), mianserin (20mg bid), and placebo (bid), each for an 8 day period in random order with 1 week washouts. Fluvoxamine was found to have no effect on memory performance or EEG; it did impair performance in the symbol copying test compared to placebo but not compared to mianserin.

Studies of Autonomic Effects

H.114.5512: This was a randomized, double-blind, placebo-controlled, crossover study of the autonomic effects of fluvoxamine. Seventeen normal volunteers received single oral doses at weekly intervals of fluvoxamine (50mg, 75mg, and 100mg), doxepin (50mg and 75mg), and amitriptyline (50mg and 75mg) in a Latin Square design. At all 3 doses, fluvoxamine demonstrated no distinguishable difference from placebo in its effect on salivary flow, pupil diameter, and palpebral fissure size; the other 2 drugs showed clear differences from placebo in these areas. All 3 drugs

were associated with small, clinically insignificant changes in vital signs.

H.114.930/UK: This randomized, double-blind, placebo- and active-controlled, crossover study investigated the autonomic effects of single doses of fluvoxamine. Ten healthy volunteers received fluvoxamine (50mg or 100mg), amitriptyline (50mg or 100mg), and placebo. Fluvoxamine was indistinguishable from placebo with respect to supine and standing blood pressures and heart rates, resting pupil diameter, and miotic responses to pilocarpine and light flashes; there was a slight reduction in salivary flow and a small but dose related reduction in carbachol-induced sweating. Amitriptyline was associated with strong anticholinergic effects.

Studies of Cardiovascular Effects

H.114.5030: This was a double-blind, placebo- and active-controlled, 3-way crossover study of the cardiovascular effects of fluvoxamine in 27 healthy volunteers. Treatments were administered using a Latin Square design and consisted of 9 day treatment periods for fluvoxamine, clovoxamine, and placebo with 5 day washouts between periods; active drug dosing was as follows: days 1-2= 50mg tid, days 3-7= 100mg tid, days 8-9= 50mg tid. Both drugs showed a prolongation of the R-R interval, equivalent to a decrease in heart rate of up to 7 bpm, compared to placebo. There were no other systematic, relevant findings.

Studies of Endocrine Effects

H.114.5515: This was a randomized, double-blind, placebo-controlled, parallel group study in 10 healthy males to evaluate the influence of fluvoxamine on hypothalamic-pituitary function. Participants (5/group) were assigned to receive oral dose of fluvoxamine 50mg or placebo every 8 hours for 4 doses. Endocrine responses to insulin-induced hypoglycemia and to TRH were then measured. Prolactin, GH, and cortisol response to hypoglycemia as well as the prolactin and TSH response to TRH administration were unchanged before and after fluvoxamine treatment.

H.114.5103: This double-blind, 3-way crossover study investigated the effects of fluvoxamine on melatonin secretion in 8 healthy males. Single 100mg doses of fluvoxamine and desipramine as well as placebo were given, with 1 week washout periods between the 3 treatments. Fluvoxamine, but not desipramine, greatly increased the quantity and duration of melatonin secretion relative to placebo; there was no evidence of a secretory phase shift with fluvoxamine although desipramine advanced the onset of secretion by 3-4 hours.

Studies of Miscellaneous Physiological Effects

H.114.5024: This double-blind, crossover study investigated certain physiological effects of fluvoxamine in 11 healthy subjects. Participants received either 10mg or 25mg of fluvoxamine tid for 7 days followed by a 2 week washout; the alternate dose of fluvoxamine was then given for 7 days. At these doses, fluvoxamine had no demonstrable effect on blood serotonin, platelet monoamine oxidase, urinary phenolic acids, or catecholamines. There was a slight inhibition of platelet aggregation. A slight increase in serum creatinine, a fall in systolic blood pressure, and a dose related increase in diastolic blood pressure with the higher dose was found. None of these changes were deemed clinically significant.

Published Studies Outside the Sponsor's IND

Seven special studies were conducted outside the sponsor's IND: 1) effect of fluvoxamine on the sleep EEG in depressed inpatients[1], 2) effect of fluvoxamine on CSF 5-HIAA and cognition in alcoholics with organic brain syndromes[2], 3) safety of fluvoxamine in patients with liver disease[3], 4-7) 4 published studies of the effect of fluvoxamine on melatonin secretion[4].

8.5.6 Withdrawal Phenomena/Abuse Potential

As described in **Section 4.0**, monkey studies to assess for physical dependence liability and abuse potential did not provide clear evidence of a distinct symptom cluster associated with fluvoxamine discontinuation nor evidence of abuse potential. There are no human clinical trials specifically designed to evaluate withdrawal symptoms associated with fluvoxamine discontinuation or abuse

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[1]Kupfer DL et al. Fluvoxamine versus Desipramine: Comparative Polysomnographic Effects. Biol. Psychiatry. 1991; 29: 23-40.

[2]Martin PR et al. Fluvoxamine Treatment of Alcoholic Chronic Organic Brain Syndromes. Clin. Pharmacol. Ther. 1987; 41(2): 211.

[3]Holm E et al. Safety of Fluvoxamine for Patients with Chronic Liver Disease. Adv. Pharmacother. 1986; 2: 151-165.

[4]Demisch K. et al. The Influence of Acute and Subchronic Administration of Various Antidepressants on Early Morning Melatonin Plasma Levels in Healthy Subjects: Increases Following Fluvoxamine. J. Neural. Transm. 1987; 68: 257-270. (3 studies) and Demisch K. et al. Melatonin and Cortisol Increase After Fluvoxamine. Br. J. Clin. Pharmac. 1986; 22: 620-622.

potential. However, the sponsor did submit the following data regarding possible clinical effects of fluvoxamine discontinuation.

Two patients who participated in sponsored clinical trials developed symptoms upon fluvoxamine discontinuation which could represent withdrawal phenomena. One patient (II/5540-0/62904) experienced withdrawal symptoms which were likely related to the surreptitious use of clonazepam. Also, eight cases of possible withdrawal effects were spontaneously reported to the sponsor with an additional case reported in the literature. All 11 cases are presented in **Table 8.5.6.1.** Incomplete data and lack of a control limit the usefulness of this data.

Also, there is one published study describing potential withdrawal phenomena following abrupt discontinuation of fluvoxamine in 14 Panic Disorder patients who had been treated for up to 8 months with doses up to 300 mg/day[5]. Symptomatology on the day of discontinuation (Day 0) was assessed and these patients were subsequently contacted 5 and 10 days after discontinuation and evaluated in persor on Day 14 for spontaneously reported adverse events. In summary, 9 of the 14 patients experienced symptoms including dizziness/incoordination. headaches, sleep disturbances, and irritability which began within 24 hours of discontinuation and were reported 5 days after stopping fluvoxamine; symptoms were reduced in severity by Day 10 and were essentially resolved by Day 14. With the exception of 1 patient with sleep disturbance at baseline, none of these symptoms were present on Day 0. Two other patients experienced an occurrence of anxiety of sufficient severity to warrant treatment. It must be noted, however, that: 1) this was not a random sampling of patients, 2) there was no control for comparison, 3) monitoring for the use of other medication was <u>not</u> performed during the withdrawal period, 4) the sample size was small, 5) the incidences of 3 of 4 of the above mentioned symptoms was well under 50% at Day 5 even after exclusion of the 2 subjects requiring treatment (92% for dizziness/incoordination, 42% for headaches, 17% for sleep disturbances, and 33% for irritability), and 6) a line listing of symptoms by subject was not available so that the actual clustering of symptoms could not be assessed. Thus, this data is also felt to be of limited value.

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[5]Black DW, et al. The Abrupt Discontinuation of Fluvoxamine in Patients with Panic Disorder. J Clin Psychiatry 1993; 54: 146-149.

8.8 Summary of Drug Interactions

8.8.1 Drug-Demographic Interactions

Three demographic variables were studied regarding their predictive value for the occurrence of the 18 common and drug-related adverse events which were identified in **Section 8.5.1**: sex (male versus female), age (<65 versus ≥65 years old), and race (Caucasian versus non-Caucasian). The 18 identified events are: anorgasmia (among males), abnormal ejacualation, anorexia, asthenia, dry mouth, dyspepsia, insomnia, libido decreased, nausea, nervousness, rhinitis, somnolence, sweating, taste perversion, abnormal thinking, tremor, urinary frequency, and vomiting. For these analyses, the dataset used consisted of all patients in the combined Strata I/Strata II population who participated in studies which used spontaneous reporting to collect adverse experience data (N_{fluv}= 2112, N_{plac}= 821). Excluded from the respective analyses were 5 patients with sex designation missing, 32 patients with missing age data, and 887[1] patients with no indication of race.

The method used to explore for demographic interactions was as follows, using the sex variable as an example. For each identified adverse event, the relative risks for males (RR_m) and females (RR_f) with reference to placebo were computed, then the ratio of the relative risks of females to males (RR_f/RR_m) was calculated. Next, the odds ratios for each subgroup and also a common odds ratio (using the Mantel-Haenszel method) were calculated. Finally, the homogeneity of the odds ratios between the subgroups was tested for each selected adverse event using the Breslow-Day Chi-Square test. This was then repeated using the age and race subgroupings.

No significant interactions were seen for sex and race. Two events were more common in the younger age group (<65) than in the older age group (≥65), with a third event being of borderline significance: nausea, somnolence, and taste perversion, respectively. However, these findings must be interpreted with caution since they arose out of multiple comparisons. Also note that these analyses may be underpowered to detect subtle differences.

Three studies and one report compared the pharmacokinetics of fluvoxamine in elderly subjects with the corresponding parameters in young volunteers.

Study 5090 involved 8 subjects between the ages of 63 and 82 years old and used a 50 mg dose of fluvoxamine to compare single dose kinetics between young and elderly subjects. When compared to 8 young adults from Study 5087, there were no significant differences

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[1]Eighteen studies did not collect race data, accounting for 855 of these patients.

TABLE 8.5.6.1 - POTENTIAL FLUVOXAMINE WITHDRAWAL SYNDROMES

Protocol	Patient	Age	Sex	Fluvoxamine Dose (mg/day)	Duration of TX (days)	Observations/Comments
CLINICAL TRIAL REPORTS						
01.01[6]		26	F	100	42	Headache & nightmares X 3 nights beginning 1 day after D/C.
5529		42	F	Unknown	70	Nausea, weakness X 5 days; vivid dreams, nightmares, paresthesia, & depression X 2 weeks after D/C.
POST-MARKETING SURVEILLANCE REPORTS						
		29	F	50/Unk[7]	~180/30	Anxiety & agitation within 2 days of D/C, resolved with restarting fluvoxamine; same SX after second trial following more gradual taper.
		43	F	200	60	Headache, anxiety, light-headedness, tearfulness, weepiness X 4 days.

[6]Study RH.114.01.01 is included in the sponsor's pivotal depression program as part of their recent NDA for depression, which was submitted in June 1993; this study is not otherwise mentioned in the OCD NDA.

[7]Patient received Fluvoxamine treatment during 2 time periods.

TABLE 8.5.6.1 - POTENTIAL FLUVOXAMINE WITHDRAWAL SYNDROMES

Protocol	Patient	Age	Sex	Fluvoxamine Dose (mg/day)	Duration of TX (days)	Observations/Comments
		Unk	M	250	Unk	W/D phenomena noted but not described.
		Unk	F	100	174	W/D phenomena noted but not described.
		Unk	F	200	67	Diarrhea, abdominal pain, syncope, headache of unk. duration.
		70	F	200	~165	W/D phenomena noted but not described.
		Unk	M	100	90	W/D phenomena noted but not described.
		12	M	12.5	~250	Nausea & headache beginning 3 days after D/C, resolved with restarting fluvoxamine.
LITERATURE REPORTS						
British Journal of Psychiatry, 160: 283-284, February 1992.		30	F	100/150[3]	365/Unk	Feelings of aggression after first D/C; elation, hypomania, aggressive feelings/thoughts after second D/C.

To further investigate the possibility of discontinuation phenomena in humans, the 7 Strata 1 depression trials which used spontaneous reporting to collect adverse event data[8] were pooled as were the 2 Strata I OCD studies (5529 and 5534). Duration of these trials ranged from 6 to 12 weeks. Only patients with adequate data during taper or after discontinuation of fluvoxamine were included in this analysis: the depression pool consisted of 459 fluvoxamine patients and 455 placebo patients and the OCD pool included 138 fluvoxamine patients and 152 placebo patients. Newly emergent adverse events which occurred during the 2 week period following discontinuation of fluvoxamine were then enumerated for both treatment groups in the 2 pools. For those patients who underwent a taper of fluvoxamine, newly emergent events while medication was being decreased during the 10 day period before total discontinuation were counted as well. For purposes of this analysis, a newly emergent event was one that was not noted for a given patient during the 3 week period prior to taper or discontinuation; this definition was intended to exclude events which may not have been associated with the discontinuation of fluvoxamine. The incidence rates of these events among fluvoxamine patients could then be examined and compared to the corresponding placebo rates.

There were no significant differences between the fluvoxamine and the placebo treatment groups with respect to adverse event incidence rates for any adverse event. Among the 597 fluvoxamine patients included in this analysis, 567 (95%) experienced no adverse experiences during taper or post-discontinuation phases and no adverse event was noted at an incidence rate of 1% or higher. It is concluded that this analysis demonstrated no adverse events related to the discontinuation of fluvoxamine.

[8]Studies 5520, 5522, 5525, 5526, 5527, 5528, and 5531.

8.5.7 Human Reproduction Data

An unpublished Prescription Event Monitoring (PEM) study conducted in Britain by the CSM provides data on 18 women who were exposed to fluvoxamine during pregnancy. Seventeen women were exposed during the first trimester with the following outcome: 7 live births of presumably normal newborns (including a pair of normal twins); 5 spontaneous abortions; 4 terminated pregnancies; and 1 ectopic pregnancy. The one patient exposed during the second or third trimester had a normal live birth. The same study reports the results of follow-up on 57 women exposed to fluvoxamine prior to the last menstrual period: 32 live births (including 1 infant with gross abnormalities who lived 3 hours and 1 infant with an absent kidney); 8 pregnancies terminated (including one termination following detection of a genetic defect by amniocentesis in a woman who was exposed to phentermine in addition to fluvoxamine); 7 spontaneous abortions; 2 ectopic pregnancies; and 8 with outcome unknown. These results are summarized in **Table 8.5.7.**

There have been no adequate and well-controlled trials to study the effects of fluvoxamine in pregnant women. As of April 1993, the sponsor had received reports of 34 patients who took fluvoxamine during pregnancy or became pregnant while taking fluvoxamine (these reports likely overlay cases from the PEM study). The outcomes of these pregnancies are as follows: 20 normal deliveries with normal newborns; 3 pregnancies terminated; 2 spontaneous abortions; 2 pending delivery; 1 normal delivery with severe jaundice in the infant and normal LFT's (mother also received fluoxetine during the first trimester); 1 premature delivery with tachypnea, apnea, bradycardia, and hypoglycemia noted in the infant (consistent with prematurity); and 5 with no information available.

TABLE 8.5.7 - OUTCOME OF PREGNANCIES FROM PEM STUDY

Timeframe for Fluvoxamine Exposure	Total Pregnancies	Pregnancy Outcome (%)[1]				
		Live Births	Ectopic Pregnancy	Spontaneous Abortion	Pregnancy Terminated	Outcome Unknown
Before LMP	57	32 (56%)	2 (4%)	7 (12%)	8 (14%)	8 (14%)
First Trimester	17	7 (41%)	[illegible]	5 (29%)	4 (24%)	0 (0%)
Second/Third Trim.	1	1 (100%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)

[1] Percentages of the row totals.

8.5.8 Overdose Experience

Table 8.5.8.1 displays the demographic characteristics of the 354 overdoses which were reported as of October 1991 for Strata I, II, and V and as of July 1992 for Strata III and IV. The preponderance of the overdoses were in females (70%) and in patients under the age of 51 (82%). As expected, most reports were in Strata IV (spontaneous post-marketing reports), which reflects the total patient population exposed worldwide.

TABLE 8.5.8.1 FLUVOXAMINE OVERDOSE DEMOGRAPHICS

	STRATA					
	I	II	III	IV	V	TOTAL
# Overdoses	4	9	51	271	19	354
SEX						
Male	1	0	18	73	8	100
Female	3	9	32	194	11	249
Unknown	0	0	1	4	0	5
AGE						
<18	0	0	0	16	0	16
18-30	1	2	18	106	7	134
31-50	3	5	24	98	10	140
51-64	0	1	3	13	1	18
>=65	0	1	4	14	0	19
Unknown	0	0	2	24	1	27

There were 19 overdose deaths which involved fluvoxamine in Strata IV as of July 1992 (no overdose deaths were reported in the other Strata). In only 2 cases was fluvoxamine judged to have been taken alone:

> A 55 y.o. female with a medical history remarkable for seizure, cerebral infarction, renal dysfunction, gastritis, and an ulcer took an estimated >5,000 mg fluvoxamine which produced a blood level of 0.3 mg/100 ml (C_{max} is 0.03-0.07 mg/100ml after repeated doses of 300mg/day) and an extremely elevated liver concentration of fluvoxamine. However, diazepam 5mg iv had been

administered upon hospital admission and may have contributed to demise; the timing of the diazepam dose relative to the time of death is unclear, however. Also, this patient was using temazepam prior to death and this drug may have been involved in the overdose. (IV/FL1778)

A spontaneous adverse event report submitted to the FDA on April 1, 1992, describes a female in her 50's or 60's who apparently took an unknown amount of fluvoxamine and subsequently died; post-mortem examination revealed a fluvoxamine blood concentration of .35 mg/100ml, about 5 times the maximum therapeutic level. No other drugs were detected. (IV/FLUV14920013)

All 19 overdose deaths are summarized in **Appendix 8.5.8.1.**

In the remaining 335 patients, only 2 are known to have complicated recoveries:

A 3 y.o. female who took 4,000 mg of fluvoxamine with amitriptyline 750 mg and naproxen experienced a bowel infarction and underwent a hemicolectomy, with subsequent uneventful recovery. (II/5526E/61665)

A 19 year old female who took an overdose of fluvoxamine 1400mg, prazepam 60mg, and alcohol; bilateral dilated pupils were noted and this finding was still present 3 months later. This finding is questionably related to drug toxicity given the persistence of this finding over time. (IV/FL152)

The outcome for 24 patients is unknown. The other 309 patients were considered to have complete recoveries.

Also, a 63 year old female with no hepatic disease who ingested an overdose of fluvoxamine 1500mg and flunitrazepam 40mg (typical flunitrazepam dose= 2mg) experienced hepatitis marked by elevations in LFT's up to 60X ULN. Since flunitrazepam was felt to have very weak hepatoxic effects and other causes were ruled out, fluvoxamine was felt to be the probable cause for the hepatitis. This patient completely recovered. (IV/FL448)

An analysis of 2 collections of overdose cases is presented in this NDA. The Paris Poison Centre (PPC) received reports of 221 cases of deliberate fluvoxamine overdose from July 1985 to June 1988 (overdose range 150-9000mg) and the International Safety Department of Duphar BV collected data on 78 cases up to December 31, 1990. These bodies of information have been somewhat useful in characterizing the experience with fluvoxamine overdose.

Correlation of overdose signs and symptoms with fluvoxamine ingestion is difficult and uncertain due to the frequent ingestion

of concomitant medications, individual subject variability, and imprecision in estimating the amounts of drug consumed. Both the PPC Study and the Duphar Study sought to identify signs and symptoms associated with overdoses which could be attributed to fluvoxamine alone.

Among the 194 overdose cases in the PPC database which manifested toxicity, symptoms were identified in the study analysis as probably due to fluvoxamine, after symptoms which could be adequately explained by the ingestion of the other agents taken in each case were excluded. **Appendix 8.5.8.2** displays these symptoms, the number of cases displaying each symptom, and the amount of fluvoxamine ingested.

Among the 56 overdose cases in the Duphar Study which were symptomatic, 20 appeared to have taken fluvoxamine alone. **Appendix 8.5.8.3** presents the symptoms displayed in these 20 cases with the amount of fluvoxamine assumed to have been taken in each case.

Overall, symptoms observed were consistently benign with fluvoxamine ingestions under 1000 mg in these patients: drowsiness, tremor, nausea, vomiting, abdominal pain, bradycardia, and anticholinergic effects (dry mouth, mydriasis, sinus tachycardia, and urinary retention) were seen. Bradycardia was not serious and required no treatment. Most of the seizures occurred with ingestions ≥1500 mg.

Plasma assays were performed in 46 subjects in the PPC study and in 7 patients from the Duphar database. Results indicated no meaningful correlation between plasma levels and clinical manifestations, with the most clinically benign cases often having very high levels and some of the most serious cases having only moderate levels. Also, there did not appear to be a correlation between plasma levels and prognosis. The highest known non-lethal plasma level is 0.27 mg/100 ml following a 4800 mg overdose, which ended in complete recovery. The highest known non-lethal dose is ~10,000 mg, which also ended in complete recovery. Patients have survived untreated overdoses up to 2500 mg.

Treatment of fluvoxamine overdose is symptomatic. Absorption may be delayed beyond 24 hours; thus, gastric lavage and administration of charcoal is recommended up to 24 hours post-overdose and, given possible delayed onset of symtomatology, it is recommended that patients be monitored for at least 48 hours post-overdose regardless of initial clinical presentation. Due to a large volume of distribution, elimination by dialysis is not recommended.

In summary, it appears that 2 overdose deaths were due to fluvoxamine taken alone, although one of these may have involved the use of CNS depressants in addition to fluvoxamine. Of the non-fatal fluvoxamine overdoses, only 2 patients are known to have experienced complicated recoveries from an overdose involving

fluvoxamine (bowel infarction/hemicolectomy and persistent mydriasis); however, both cases involved other drugs in addition to fluvoxamine and one, mydriasis, is doubtfully overdose related.

Given the low incidence of fatal outcome in overdoses which involved fluvoxamine as well as high incidence of complete recovery from fluvoxamine overdose, it is concluded that fluvoxamine is reasonably safe when taken in overdose.

8.6 Summary of Potentially Important Adverse Events Considered Possibly or Probably Drug Related

8.6.1 Nausea

Nausea was very commonly reported as an adverse event in both the Strata I OCD and short-term depression pools, being the most common adverse experience reported and the event most frequently associated with premature termination in the latter pool; see **Table 8.6.1.1** and **Table 8.6.1.2** below. Of fluvoxamine-treated patients with nausea, about 25% dropped out in the depression pool versus only 9% in the OCD pool, suggesting poorer tolerance and/or increased severity of this adverse event in depressed patients. However, examination of a completer cohort analysis (see **Section 8.5.1**) indicates that adaptation to nausea did occur in those patients who did not dropout, with a cohort of 246 patients reporting nausea at week 1, 130/246 at week 2, 45/246 at week 4, and only 17/246 at week 6. There were no serious adverse events in Strata I associated with nausea.

TABLE 8.6.1.1 - INCIDENCE OF NAUSEA IN STRATA I STUDY POOLS

	FLUVOXAMINE	PLACEBO
OCD POOL	29.4%	6.9%
SHORT-TERM DEPRESSION POOL	42.2%	16.0%

TABLE 8.6.1.2 - INCIDENCE OF NAUSEA ASSOCIATED WITH DROPOUT IN STRATA I DROPOUT POOLS

	FLUVOXAMINE	PLACEBO
OCD POOL	2.5%	0.6%
SHORT-TERM DEPRESSION DROPOUT POOL	10.6%	1.1%

8.6.2 Sexual Dysfunction

Sexual dysfunction, especially ejaculation disturbance, has been reported with other SSRI's. In the Strata I OCD pool, the incidence of abnormal ejaculation was particularly common among fluvoxamine males compared to placebo males, as depicted in **Table 8.6.2.1** below; it was less frequent in the short-term depression pool. Similar but less noticeable interpool differences were seen for male anorgasmia and impotence. Abnormal ejaculation and

anorgasmia appear tc be common, drug-related among males treated for OCD and more prevalent in the OCD patients compared to the depressed patients.

TABLE 8.6.2.1 - INCIDENCE OF SEXUAL DYSFUNCTION IN STRATA I STUDY POOLS *

	FLUVOXAMINE	PLACEBO
OCD POOL		
Abnormal Ejaculation	17.9%	0.0%
Anorgasmia (Males)	7.7%	0.0%
Impotence	3.8%	1.3%
Anorgasmia (Females)	2.4%	0.0%
SHORT-TERM DEPRESSION POOL		
Abnormal Ejaculation	4.5%	0.8%
Impotence	1.9%	0.8%
Anorgasmia (Males)	1.9%	0.0%
Anorgasmia (Females)	0.6%	0.0%

* Incidence denominators corrected for gender as appropriate.

Despite the frequency of sexual side effects in these Strata I pools, these events were associated with dropout for relatively few patients as shown in **Table 8.6.2.2.**

In summary, fluvoxamine does appear to be associated with the frequent occurrence of sexual dysfunction, particularly delayed ejaculation and male anorgasmia. These events seem to occur at higher frequencies in patients with OCD compared to depression. These events were infrequently associated with premature termination.

TABLE 8.6.2.2 - INCIDENCE OF SEXUAL DYSFUNCTION ASSOCIATED WITH DROPOUT IN STRATA I DROPOUT POOLS *		
	FLUVOXAMINE	PLACEBO
OCD POOL		
Abnormal Ejaculation	0.0%	0.0%
Anorgasmia (Males)	0.0%	0.0%
Impotence	0.0%	0.0%
Anorgasmia (Females)	0.0%	0.0%
SHORT-TERM DEPRESSION DROPOUT POOL		
Impotence	0.6%	0.0%
Abnormal Ejaculation	0.3%	0.0%
Anorgasmia (Males)	0.0%	0.0%
Anorgasmia (Females)	0.0%	0.0%

* Incidence denominators corrected for gender as appropriate.

8.6.3 Liver Dysfunction

The search for serious adverse events revealed 5 cases of hepatitis from Strata IV which were felt to be reasonably attributable to fluvoxamine exposure. These cases are summarized in **Table 8.6.3.1** below.

TABLE 8.6.3.1 - HEPATITIS CASES REPORTED AS SERIOUS ADVERSE EVENTS AND PROBABLY DUE TO FLUVOXAMINE					
Patient#	Age	Sex	Dose (mg/day)	Duration* (days)	Comments
	46	M	300	18	With jaundice, no LFT data, resolved 2 wks. after D/C.
	39	F	100	?	LFT's 4-6X ULN, concurrent alprazolam, resolved after D/C.
	32	F	100	7	With jaundice, LFT's 20X ULN, resolved 3 wks. after D/C.
	49	F	150	28	With jaundice, SGPT 12X ULN, resolved 2 wks. after D/C.
	30	F	100	10	With pruritis + abdominal pain, no LFT data, resolved 20 days after D/C.

*Time to the onset of hepatitis from the initiation of fluvoxamine therapy.

Additionally, there were 6 other cases[1] of hepatitis reported as serious events in which assessment of the role of fluvoxamine was complicated by the use of alcohol and/or other drugs which could have contributed to liver toxicity.

A search for dropouts with hepatitis and/or jaundice among fluvoxamine-exposed patients in the total NDA database revealed only 2 cases in which clinically important events could be reasonably attributed to fluvoxamine. Although both patients were taking concomitant benzodiazepines, there had been no changes in medication or dosing within at least 6 weeks of starting fluvoxamine. Both cases presented with jaundice but no laboratory data was provided.

> A 76 year old male with hepatic cirrhosis was treated with fluvoxamine 50 mg/day for depression for 19 days when he experienced jaundice and malaise; fluvoxamine was

[1] III/FR.024/426123, IV/FL446, IV/FL643, IV/FL1136, IV/FLUV1920029, and IV/FLUV7920003.

discontinued 2 days later and the jaundice resolved over the next 2 weeks, with full recovery (III/UK.905/K066).

A 65 year old female with anxiety neurosis and no known medical problems was treated with fluvoxamine 50 mg/day for 7 days, then 100 mg/day for 3 days when she experienced jaundice, nausea, and vomiting; fluvoxamine was discontinued 4 days later. No follow-up data was given (III/UK.905/N004).

There is a literature report of hepatitis in a 63 year old female, with LFT elevation up to 60X ULN, which was observed following an overdose of fluvoxamine 1500mg and flunitrazepam 40mg; evaluation, to include a hepatitis screen, indicated no evident cause for the hepatitis and it was concluded that the most probable cause was the fluvoxamine ingestion (IV/FL448).

To investigate the incidence of more subtle changes in liver function, the incidence of all events related to liver dysfunction was examined in the Strata I/Strata II database. The overall occurrence of events related to possible hepatic dysfunction within this population is: fluvoxamine 1.9% (53/2737), placebo 1.8% (19/1055), and other control 3.6% (35/979). The incidence of specific events by COSTART term is displayed in **Table 8.6.3.2** below.

Little is known about the case of liver damage: this event was described by the investigator as "liver acting up again", occurred after 176 days of fluvoxamine exposure, was not considered serious, and did not lead to premature termination (II/5079/9526). The case of jaundice lasted only one week, apparently resolving following fluvoxamine dosage adjustment (I/5534/62822).

In summary, this data suggests that fluvoxamine may be associated with rare cases of hepatitis and/or jaundice which seem to occur within the first 4 weeks of treatment and resolve upon discontinuation of fluvoxamine; there is no known case of permanent liver damage which could be attributed to fluvoxamine.

TABLE 8.6.3.2 - INCIDENCE OF LIVER DYSFUNCTION: STRATA I/II						
	FLUVOXAMINE (N=2737)		PLACEBO (N=1055)		OTHER (N=979)	
	#	%	N	%	N	%
LFT's Abnormal	51	1.9	19	1.8	35	3.6
Liver Damage	1	0.04	0	0.0	0	0.0
Jaundice	1	0.04	0	0.0	0	0.0
SGOT Incr.	1	0.04	0	0.0	0	0.0
SGPT Incr.	1	0.04	0	0.0	0	0.0

8.6.4 Skin Disorders

Three spontaneous post-marketing reports of serious skin reactions associated with fluvoxamine therapy were identified:

A 15 year old female was treated for depression with fluvoxamine 100 mg/day, with concurrent clorazepate. After 9 days of treatment, she developed a widespread bullous eruption which included the mucous membranes as well as ocular and genital lesions and eventually progressed to cover 60% of her body surface. She became febrile (104°F) and had respiratory impairment, requiring artificial ventilation. Skin biopsy was consistent with toxic epidermal necrolysis. At one month follow-up, skin pigmentary changes and photophobia persisted. (submitted 6/22/93: IV/FLUV1930086)

A 68 year old male was treated with fluvoxamine 50mg/day as well as lorazepam, meprobamate, alprazolam, and clonidine. After 4 days, he experienced perioral erythema, urethral ulceration, and several erythematous plaques on his buttocks and arms; Stevens-Johnson syndrome was diagnosed. There was a past history of bullous eruption with sulfonamide treatment. He was treated with steroids and fully recovered. (submitted 2/4/91: IV/FL674)

A 26 year old female received fluvoxamine at unknown dose for one month with partial clinical respose; lithium was added to her regimen and, 2 weeks later, she developed a rash which progressed to Stevens-Johnson syndrome. Drugs were stopped and she was treated with prednisone and improved. (submitted May 18, 1987:IV/FL337)

Although the second reaction may be ascribed to meprobamate, with which Stevens-Johnson syndrome has been rarely reported, the timing and duration of meprobamate use is not known and this may be an unlikely etiology. Likewise, in the other 2 cases, a causative role for fluvoxamine cannot be ruled out.

A serious adverse event was identified in Strata I which involved urticaria and dyspnea:

> A 58 year old female with depression, sinus problems, hypertension, and a history of allergy to penicillin and shrimp experienced urticaria following 8 days of fluvoxamine at a dose of 150 mg/day. Fluvoxamine was continued and urticaria persisted; 3 days later, she experienced acute dyspnea and hoarseness and this was treated in an emergency room as an allergic reaction, presumed secondary to fluvoxamine. Fluvoxamine was discontinued and the events resolved over the next 3 days without sequelae. Although she received multiple other medications during the trial, the dates of administration for these drugs could not be reasonably linked to the reported symptoms (I/5526/61695).

The November 1992 issue of Signal, published by the WHO Collaborative Centre For International Drug Monitoring, reported seven cases of photosensitivity during fluvoxamine therapy. These reactions occurred in both sexes and the ages varied from 34 to 64 years old. Time to onset of the reaction was 2 days to 3 months. Two patients took no concomitant medication and the concurrent medication in the other 5 patients is reportedly not known to produce photosensitivity. In 6 patients, fluvoxamine was discontinued and patients recovered. In one of these patients, later rechallenge resulted in a photosensitivity reaction. Further clinical information on these patients is not available. The NDA database contains 6 cases of photosensitivity, 3 in Strata II and 3 in Strata IV[2]. (Overlap of these patients with those referenced in Signal is likely.) These 6 cases were reviewed and an etiologic role for fluvoxamine cannot be ruled out for 5 of the patients; the sixth case is questionably related to fluvoxamine due to an initial onset after more than 3 months of therapy and an adequate rechallenge without recurrence of photosensitivity.

Rash and pruritis were commonly seen in the Strata I OCD (N_{fluv}=160) and short-term depression study pools (N_{fluv}=732) as shown in **Table 3.6.4.1** below:

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[2]II/5520E/176, II/5520E/653, II/5534E/62911, IV/FL373, IV/FL972, and IV/FL1195.

TABLE 8.6.4.1 - INCIDENCE OF RASH AND PRURITIS IN STRATA I STUDY POOLS		
	FLUVOXAMINE	PLACEBO
OCD POOL		
Rash	2.5%	3.1%
Pruritis	2.5%	0.0%
SHORT-TERM DEPRESSION POOL		
Rash	2.0%	1.9%
Pruritis	2.0%	3.1%

Among the fluvoxamine patients in these pools combined (N=892), 15 reported rash, 15 reported pruritis, and 4 reported both rash and pruritis. Based on a comparison with placebo rates, it is difficult to draw any firm conclusions regarding an association of rash or pruritis with fluvoxamine. Time to event onset in the fluvoxamine-treated patients who experienced rash and who experienced pruritis was examined to determine any temporal clustering that might suggest a drug relationship for these 2 events; **Table 8.6.4.2** displays this data. Clustering is not evident for pruritis but two-thirds of the rashes occurred within the first 15 days of therapy. Although this increases the likelihood that rash is drug related, this data must be considered inconclusive.

Among the 19 patients with rash, only 2 dropped out: one developed a rash after 36 days of therapy and the other a rash after 15 days; both events resolved without sequelae within 2 weeks of fluvoxamine discontinuation (I/5522/9331 and I/5525/61098, respectively).

TABLE 8.6.4.2 - INCIDENCE OF RASH AND PRURITIS OVER TIME: FLUVOXAMINE PATIENTS IN THE STRATA I OCD/SHORT-TERM DEPRESSION STUDY POOLS		
Time to Event Onset (days)	Rash (n=19)	Pruritis (n=19)
0-5	4	7
6-10	5	0
11-15	4	3
16-20	1	0
21-25	0	0
26-30	2	3
31-35	0	1
36-40	1	3
>40	2	2

In summary, while fluvoxamine use may be associated with severe skin reactions and photosensitivity, these events have been very rare to date. Rash has been commonly seen with fluvoxamine exposure but was infrequently is associated with dropout.

8.6.5 Hyponatremia

Several cases of hyponatremia have been reported with the use of other selective serotonin reuptake inhibitors, namely fluoxetine and paroxetine. There were no cases of "hyponatremia" reported as an adverse event in the combined Strata I/Strata II database among fluvoxamine patients. However, a review of serious adverse events and premature terminations due to adverse events in all 5 Strata revealed 2 cases of significant hyponatremia, one in Strata III and one in Strata IV.

> A 64 year old female inpatient with bipolar depression, moderate hypertension, hypercholesterolemia, and hyperlipidemia took fluvoxamine 50 mg/day for 3 days during a Strata III study. Two days after stopping fluvoxamine, the patient became febrile, severely hypertensive (systolic blood pressure 190-240), and went into a coma; her serum sodium was 116 mEq/L (sodium at baseline was 141 mEq/L). Final examination 12 days later revealed no abnormality. (III/FR.012/147)

> A 54 year old male outpatient with depression who received fluvoxamine 200 mg/day and, after 7 days of

> exposure, experienced a convulsion and was found to be hyponatremic (serum sodium not given). He was diagnosed with syndrome of inappropriate ADH secetion but no cause for this condition was determined. He was recovered 3 weeks after drug discontinuation. (IV/FL240)

Additionally, a third case of hyponatremia was submitted to the FDA as a 10-day report on May 26, 1993:

> A 70 year old depressed female was treated with fluvoxamine 100 mg/day for 5 days and found to have a serum sodium of 114 mEq/L. SIADH was diagnosed. Fluvoxamine was continued for 5 days following hospital admission and serum sodium levels remained low. Fluvoxamine was then discontinued and, within 3 days, serum sodium rose to 129 mEq/L and continued to rise for the next 7 days. (IV/FLUV1930112)

Although the role of fluvoxamine in the first case is not clear, the latter 2 cases do suggest that fluvoxamine may be associated with the rare occurrence of clinically significant hyponatremia.

8.6.6 Seizure

Since seizures have been infrequently associated with the use of marketed SSRI's, the incidence of this event was examined in the larger StrataI/Strata II dataset. Seizures[3] were observed in the Strata I/Strata II population at the following incidence rates: fluvoxamine 0.2% (6/2737), placebo 0.09% (1/1055), and active-control[4] 0.5% (5/979).

Seizures may be an infrequent complication of fluvoxamine therapy and appeared, in this dataset, to occur at a rate not much higher than the placebo rate and at a rate similar to that seen with other approved antidepressants[5].

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[3]Includes all investigator terms coded into the COSTART term convulsion. Since many of the investigator terms questionably represent an actual seizure (e.g. attacks of cataplexy, pseudo-convulsive attacks, and fits), the rates of true seizures may be overestimated.

[4]Desipramine, imipramine, clomipramine, maprotiline, lithium, and amineptine.

[5]Seizure rates according to current labeling: paroxetine 0.1%, fluoxetine 0.2%, and buproprion 0.4%.

8.6.7 Mania

Since mania is a relatively infrequent but important adverse experience with antidepressant use, the Strata I/Strata II population was reviewed for the incidence of this event. The Strata I/Strata II database includes several cases of mania[6] with the following incidence rates: fluvoxamine 1.1% (29/2737), placebo 0.8% (8/1055), and active-control 1.4% (14/979). Mania associated with dropout occurred at the following rates in this population: fluvoxamine 0.5%, placebo 0.1%, and active-control 0.5%.

The occurrence of mania with fluvoxamine use seems to be infrequent and only slightly higher than the placebo rate. Mania was associated with dropout at a rate equal to that for the active control agents in this population.

8.6.8 Movement Disorders

Although SSRI's are not generally thought to be associated with movement disorder symptoms, such cases have been uncommonly reported with fluoxetine, sertraline, and paroxetine. The search for serious adverse events revealed 5 cases of movement disorders which were felt to be reasonably attributable to fluvoxamine: 4 cases of extrapyramidal symptoms and one case of dystonia[7]. None of these patients was known to have been receiving a concurrent dopamine blocking agent and, in fact, 2 of the patients with EPS had pre-existing Parkinsonism which was exacerbated following exposure to fluvoxamine. Four of the five events resolved following discontinuation of fluvoxamine and the fifth resolved after a decrease in fluvoxamine dose. Additionally, this search revealed 2 other cases of extrapyramidal symptoms, a case of choreoathetosis, and a case of neuroleptic malignant syndrome which were not felt to be related to fluvoxamine[8].

Given these cases, the Strata I/Strata II population was screened for occurrences of related treatment-emergent signs and symptoms during treatment. The incidence rates of these events are displayed in **Table 8.6.8**[9].

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[6]Hypomania is coded as the COSTART term mania.

[7]EPS: IV/FL153, IV/FL158, IV/FL172, and IV/FL2130; Dystonia: IV/FLUV1930050.

[8]EPS: IV/FL177 and IV/FL1521; choreoathetosis: IV/FL173; and NMS: IV/FL611.

[9]Enumerations for these statistics exclude 1 fluvoxamine and 1 active-control patient known to have been administered a dopamine-blocking agent at the time of movement disorder onset.

TABLE 8.6.8 - MOVEMENT DISORDER TESS: STRATA I/STRATA II			
	FLUVOXAMINE (N=2737)	PLACEBO (N=1015)	OTHER (N=979)
Akathisia	0.6%	0.2%	0.6%
Dystonia	0.2%	<0.1%	0.2%
EPS	0.2%	0.0%	0.0%
Dyskinesia	0.3%	0.0%	0.2%
TOTAL	1.3%	0.3%	0.9%

The difference between fluvoxamine and placebo total rates is statistically significant[10] (p=0.003) while that between fluvoxamine and the active-control group is not (p=0.397). Very few of these patients were taking a concomitant dopamine blocker.

Of the 37 fluvoxamine patients with movement disorder symptoms in this database, only 9 dropped out of treatment; 7 of the 9 experienced akathisia.

Thus, it seems that fluvoxamine may be associated with the infrequent occurrence of movement disorder symptoms typically seen with dopamine-blocking agents; however, these do not seem to be substantially more frequent than with the other non-neuroleptic psychotropics used in this population (desipramine, imipramine, clomipramine, maprotiline, lithium, and amineptine), generally do not lead to dropout, and are rarely serious.

8.7 Summary of Other Serious Adverse Events Considered Unlikely to be Drug Related

A serious adverse event, for purposes of this NDA, is defined according to the FDA definition, i.e. one that is fatal, life-threatening, permanently disabling, requiring inpatient hospitalization, or is a congenital anomaly, cancer, or overdose.

Deaths which occurred in fluvoxamine patients in all Strata are considered in **Section 8.2** and are listed by patient in **Appendix 8.2.1**[11]: it is felt that no death could reasonably be attributed

[10]Fisher's exact test, 2-tailed.

[11]As of July 1992.

to fluvoxamine with the exception of the 2 overdose deaths which reportedly involved only fluvoxamine (see **Section 8.5.8**).

Serious adverse experiences involving bleeding symptoms, allergic reactions, and symptoms of zimelidine syndrome were presented in **Section 8.4** under the corresponding special searches.

Serious events associated with laboratory abnormalities, vital sign changes, or ECG manifestations are discussed in **Section 8.5.2**, **8.5.3**, and **8.5.4**, respectively. Overdose experiences are discussed in **Section 8.5.8** and available human reproductive experience is presented in **Section 8.5.7**.

Events which were classified as serious, felt to be clinically important, and reasonably attributed to fluvoxamine[12] are discussed in **Section 8.6**; those which involved probable drug-drug interactions are presented in **Section 8.8.3**.

Appendix 8.7.1 presents a listing of the serious, treatment-emergent adverse experiences among fluvoxamine patients from the search for serious adverse events (**Section 8.4.1**) which were felt to be clinically important but which could not be reasonably considered etiologically related to fluvoxamine and which were not discussed in other sections of this review.

Using the same search procedure in the placebo and active-control groups within Strata I, II, III, and V, 6 other clinically important, treatment-emergent serious adverse events were identified which were felt to be unrelated to drug exposure. (No such events were identified for the placebo group.) These are listed in **Appendix 8.7.2**.

[12]Based on a review of clinical data from a selected sample of serious adverse event cases in all 5 Strata as described in **Section 8.4.1**.

8.8 Summary of Drug Interactions

8.8.1 Drug-Demographic Interactions

Three demographic variables were studied regarding their predictive value for the occurrence of the 18 common and drug-related adverse events which were identified in **Section 8.5.1**: sex (male versus female), age (<65 versus ≥65 years old), and race (Caucasian versus non-Caucasian). The 18 identified events are: anorgasmia (among males), abnormal ejacualation, anorexia, asthenia, dry mouth, dyspepsia, insomnia, libido decreased, nausea, nervousness, rhinitis, somnolence, sweating, taste perversion, abnormal thinking, tremor, urinary frequency, and vomiting. For these analyses, the dataset used consisted of all patients in the combined Strata I/Strata II population who participated in studies which used spontaneous reporting to collect adverse experience data (N_{fluv}= 2112, N_{plac}= 821). Excluded from the respective analyses were 5 patients with sex designation missing, 32 patients with missing age data, and 887[1] patients with no indication of race.

The method used to explore for demographic interactions was as follows, using the sex variable as an example. For each identified adverse event, the relative risks for males (RR_m) and females (RR_f) with reference to placebo were computed, then the ratio of the relative risks of females to males (RR_f/RR_m) was calculated. Next, the odds ratios for each subgroup and also a common odds ratio (using the Mantel-Haenszel method) were calculated. Finally, the homogeneity of the odds ratios between the subgroups was tested for each selected adverse event using the Breslow-Day Chi-Square test. This was then repeated using the age and race subgroupings.

No significant interactions were seen for sex and race. Two events were more common in the younger age group (<65) than in the older age group (≥65), with a third event being of borderline significance: nausea, somnolence, and taste perversion, respectively. However, these findings must be interpreted with caution since they arose out of multiple comparisons. Also note that these analyses may be underpowered to detect subtle differences.

Three studies and one report compared the pharmacokinetics of fluvoxamine in elderly subjects with the corresponding parameters in young volunteers.

Study 5090 involved 8 subjects between the ages of 63 and 82 years old and used a 50 mg dose of fluvoxamine to compare single dose kinetics between young and elderly subjects. When compared to 8 young adults from Study 5087, there were no significant differences

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[1]Eighteen studies did not collect race data, accounting for 855 of these patients.

H.114.5026	Randomized, DB, comparison with imipramine; inpatients with depressive symptoms (n_f=8, n_m=8); fluvoxamine dose 75-225mg/day; 4 weeks.
H.114.5026E	Extension of 5026; n_f=4, n_m=3; fluvoxamine dose 150-225mg/day; 52 weeks.
H.114.5029	DB comparison with clomipramine; inpatients, bipolar or unipolar depression (n_f=15, n_m=15); fluvoxamine dose 150-300mg/day; 4 weeks.
H.114.5029E	Extension of 5029; n_f=5, n_m=1; fluvoxamine dose 75-300mg/day; 52 weeks.
H.114.5035	Randomized, DB comparison with clomipramine; inpatients, primary depressive symptoms (n_f=2, n_m=3); fluvoxamine dose 150-300mg/day; 4 weeks.
H.114.5037	Randomized, DB comparison with imipramine; outpatients, primary depressive syndrome (n_f=18, n_m=22); fluvoxamine dose 75-300mg/day; 4 weeks.
H.114.5038	Randomized, DB comparison with imipramine; inpatients, primary depressive symptoms (n_f=5, n_m=3); fluvoxamine dose 50-300mg/day; 4 weeks.
H.114.5041	Randomized, DB comparison with imipramine; outpatients, primary depressive symptoms (n_f=22, n_m=22); fluvoxamine dose 50-300mg/day; 4 weeks.
H.114.5043	Randomized, DB, long-term comparison with lithium; outpatients, chronic unipolar depression (n_f=17, n_m=12); fluvoxamine dose 50-300mg/day; 24 weeks.
H.114.5052	Randomized, DB comparison with imipramine; inpatients, primary depression (n_f=1, n_m=1); fluvoxamine dose 50-300mg/day; 4 weeks.
H.114.5060	Randomized, DB comparison with clomipramine; outpatients, endogenous depression (n_f=22, n_m=21); fluvoxamine dose 50-200mg/day; 6 weeks.
H.114.5060E	Extension of 5060; n_f=10, n_m=12; fluvoxamine dose 100-400mg/day; 52 weeks.
H.114.5067	Randomized, DB comparison with clomipramine; inpatients, depressive syndromes (n_f=20, n_m=20); fluvoxamine dose 100-400mg/day; 4 weeks.
H.114.5068	Randomized, parallel group comparison with amineptine; inpatients, marked depressive syndrome (n_f=20, n_m=20); fluvoxamine dose 100-300mg/day; 4 weeks.
H.114.5091	Randomized, parallel group comparison with maprotiline; geriatric outpatients, depression (n_f=43, n_m=45); fluvoxamine dose 50-300mg/day; 6 weeks.
H.114.5102	Single-blind, parallel group comparison with maprotiline; inpatients/outpatients, depression (n_f=31,n_m=29); fluvoxamine dose 50-300mg/day; 6 weeks.

H.114.5505E	Extension of 5505; n_1=2, n_2=3; fluvoxamine dose 50-300mg/day; 24 weeks.
H.114.5507	Randomized, DB, comparison with imipramine; inpatients/outpatients, primary depression (n_1=22, n_2=22); fluvoxamine dose 100-300mg/day; 6 weeks.
H.114.5509	Randomized, DB, multicenter comparison with imipramine; outpatients, primary depression (n_1=44, n_2=42); fluvoxamine dose 100-300mg/day; 6 weeks.
H.114.5509E	Extension of 5509; n_1=6, n_2=8; fluvoxamine dose 50-300mg/day; 52 weeks.
UNCONTROLLED STUDIES (DEPRESSION)(STRATA II)	
H.114.5004	Open label study; inpatients, depressive illness (n=13); fluvoxamine dose 4[illegible]-225mg/day; 6 weeks.
H.114.5005	Open label study; inpatients, depressive illness (n=13); fluvoxamine dose 4[illegible]-225mg/day; 5 weeks.
H.114.5006	Open label study; inpatients, depressive illness (n=13); fluvoxamine dose 60-300mg/day; 5 weeks.
H.114.5007	Open label study; inpatients, depressive illness (n=12); fluvoxamine dose 60-300mg/day; 5 weeks.
H.114.5008	Open label study; inpatients, depressive illness (n=10); fluvoxamine dose 60-300mg/day; 5 weeks.
H.114.5009	Baseline-controlled study; inpatients, depressive syndromes (n=2); fluvoxamine dose 90-300mg/day; 4 weeks.
H.114.5010	Open label, early phase II study; inpatients, depressive syndromes (n=7); fluvoxamine dose 150-300mg/day; 5 weeks.
H.114.5011	Baseline-controlled study; inpatients, depressive syndromes (n=11); fluvoxamine dose 90-300mg/day; 4 weeks.
H.114.5012	Open label, early phase II study; inpatients, depressive syndromes (n=7); fluvoxamine dose 75-300mg/day; 4 weeks.
H.114.5013	Early, open label study; outpatients, depressive syndromes (n=6); fluvoxamine dose 75-300mg/day; 4 weeks.
H.114.5019	Open label, long-term study; outpatients, depressive syndromes (n=30); fluvoxamine dose 25-225mg/day; 52 weeks.

H.114.5020	Open label, long-term study; inpatients/outpatients, depressive syndromes (n=31); fluvoxamine dose 50-225mg/day; 52 weeks.
H.114.5034	Baseline-controlled study; inpatients, depression (n=5); fluvoxamine dose 150-300mg/day; 4 weeks.
H.114.5044	Baseline-controlled study; inpatients, depression (n=6); fluvoxamine dose 150-300mg/day; 4 weeks.
H.114.5046	Baseline-controlled study; inpatients, depressive syndromes (n=7); fluvoxamine dose 90-150mg/day; 4 weeks.
H.114.5059	Baseline-controlled, long-term, multicenter study; outpatients, depression (n=31); fluvoxamine dose 50-300mg/day; 51 weeks.
H.114.5066	Baseline-controlled, long-term study in general practice; outpatients, depression (n=222); fluvoxamine dose 25-300mg/day; 52 weeks.
H.114.5079	Baseline-controlled, long-term study; outpatients, depression (n=30); fluvoxamine dose 75-300mg/day; 51 weeks.
H.114.5080	Baseline-controlled study; outpatients, depression (n=7); fluvoxamine dose 50-300mg/day; 4 weeks.
H.114.5082	Long-term, uncontrolled study; depression, (n=19); fluvoxamine dose 50-400mg/day; 52 weeks.
H.114.5100	Baseline-controlled, long-term, multicenter study; outpatients, depression (n=52); fluvoxamine dose 100-300mg/day; 52 weeks.
H.114.5101	Baseline-controlled, long-term, multicenter study; geriatric outpatients, depression (n=39); fluvoxamine dose 50-300mg/day; 52 weeks.
H.114.5503	Open label, early phase II study; inpatients, depressive syndromes (n=12); fluvoxamine dose 100-300mg/day; 4 weeks.
H.114.5504	Open label, early phase II study; inpatients, depressive syndromes (n=11); fluvoxamine dose 50-300mg/day; 4 weeks.
H.114.5520E	Extension of 5520; n=157; fluvoxamine dose 100-300mg/day; 48 weeks.
H.114.5522E	Extension of 5522; n=13; fluvoxamine dose 25-300mg/day; 46 weeks.
H.114.5531E	Extension of 5531; n=7; fluvoxamine dose 100-300mg/day; 52 weeks.

in mean AUC, C_{max}, T_{max}, $t_{½}$, or renal clearance, although there was a hint of a slightly lower renal clearance in the elderly group (mean renal clearance 0.8 L/hr with 95% CI of .05-1.8 vs. 1.6 L/hr with 95% CI 0.4-3.8).

Study 5098 studied 14 healthy volunteers (age ranges not given) to compare steady-state pharmacokinetics between young and elderly patients. Fluvoxamine 50 mg bid was administered for 28 days with multiple blood samples collected on days 14 and 28 for PK analysis and with trough levels on days 5, 10, 14, and 28. There was no difference between the Day 14 and Day 28 AUC's, C_{max}'s, or T_{max}'s. When compared to 8 young adults from Study 5087, there were no significant differences in mean AUC, C_{max}, or $t_{½}$, although there was a hint of a slightly decreased AUC and C_{max} in the elderly.

Report H.114.62 was a retrospective review of data collected from patients age 60 and older who participated in European and North American clinical trials in depression to compare plasma levels with those found in the general study population. Plasma levels selected for analysis were those obtained after patients had been on the same dose for at least 6 days. Mean plasma trough levels were compared at dosages of 100, 150, 200, and 300 mg between 70 elderly subjects and the general population. Mean trough levels and level ranges at each dose were comparable between the 2 groups.

Study RH.114.01.08, the most recently completed study, enrolled 12 young (ages 18-35) and 11 elderly (ages 65-75) subjects to compare single- and multiple-dose pharmacokinetics between the 2 age groups. Fluvoxamine was administered as follows: 25mg on Day 1, 50mg/day on Days 3-13, and 100mg/day on Days 14-20. Multiple blood samples were obtained following dosing on Days 1, 3, 13, and 20 and trough levels were obtained just prior to dosing on Days 11-13 and Days 18-20. Mean pharmacokinetic parameters after single 25 mg doses in the elderly subjects were higher than those in the young population: mean C_{max} (+6%), AUC_{0-48} (+38%), and $T_{½}$ (+52%). A comparison of these parameters at steady state (Day 20) following 100 mg daily dosing is illustrated in **Table 8.8.1.1**. There were no serious adverse events or drug related changes in physical examinations, laboratory studies, or ECG's during this study. While age related PK changes are observed at steady state, the wide range of many of the values limits the ability to draw definitive conclusions from this data.

In summary, nausea, somnolence, and possibly taste perversion may be more common in younger versus older patients. There is a suggestion that clearance of the parent compound may be decreased in the elderly versus younger patients.

TABLE 8.8.1.1 - A COMPARISON OF PHARMACOKINETIC PARAMETERS AT STEADY STATE WITH 100 MG/DAY DOSING IN YOUNG AND ELDERLY SUBJECTS		
	Mean ± SD	
	Young	Elderly
C_{max} (ng/mL)	77.8 ± 51.3	113.7 ± 65.6
AUC_{0-24} (ng x hr/mL)	1328 ± 1054	2036 ± 1288
$T_{½}$ (hrs)	15.6 ± 9.8	25.9 ± 11.5
T_{max} (hrs)	6.1 ± 1.0	7.0 ± 1.2
C_{min} (ng/mL)	38.8 ± 35.9	64.4 ± 50.5

8.8.2 Drug-Disease Interactions

Study 5097 was conducted to assess the influence of renal impairment on the safety and tolerance of fluvoxamine; a subset of the study population provided blood and urine samples for kinetic data. Twenty-five patients with chronic renal impairment (i.e. creatinine clearance <60 ml/min; patients requiring dialysis were excluded) were enrolled at 2 centers to participate in this open-label, baseline-controlled study during which fluvoxamine was given as follows: 50 mg/day X 3 days, then 50 mg bid X 39 days. No serious clinical events were observed. Examination of blood sample data obtained during weeks 4 and 6 from nine patients revealed a range of fluvoxamine trough levels similar to those observed in subjects with normal renal function, also, week 6 levels were comparable to week 4 levels, suggesting that accumulation does not occur in patients with renal impairment once steady-state is achieved.

Study 11.85 examined the effects of liver failure on the pharmacokinetics of fluvoxamine given in a single 100 mg oral dose in 13 patients with a history of alcoholic liver failure[2]. C_{max}, $t_{½}$, and AUC were then calculated for each patient and compared with the mean pharmacokinetic parameters obtained in healthy subjects from 4 similar studies[3]. Overall, results indicated a 60% increase in

[2]Defined by steatosis or steatofibrosis confirmed by biopsy, elevated γ glutamyl transferase, decreased elimination of Bromsulphalein from the bloodstream, and abnormal values for at least 2 other liver laboratory parameters.

[3]114.614, 56654/22/76, 114.607 (capsules), and 114.607 (tablets).

$t_{½}$ and a 76% increase in AUC in the liver patients compared to the normals, indicative of lower clearance in the former; there was little difference in the C_{max} between these populations.

In summary, based on the above studies, it appears that renal impairment has little effect on the pharmacokinetics of fluvoxamine but that hepatic impairment can be expected to prolong the elimination of fluvoxamine. No studies of the pharmacokinetic behavior of fluvoxamine metabolites have been completed to date.

8.8.3 Drug-Drug Interactions

There were 11 studies performed under the sponsor's drug development program to examine pharmacokinetic and/or pharmacodynamic drug interactions involving fluvoxamine.

Digoxin (5087) A double-blind, placebo controlled study in 8 volunteers examining the effects of fluvoxamine 50 mg bid X 18 days on the kinetics of a single dose of digoxin 0.125 mg IV. There were no effects on the volume of distribution, elimination half-life, or AUC of digoxin. It was concluded that chronic fluvoxamine dosing does not influence the kinetics of digoxin.

Propranolol (5092) A double-blind crossover study of the effects of enteric-coated fluvoxamine 50mg bid X 12 days in 12 volunteers who had been stabilized on propranolol sustained release 160 mg/day. In subjects treated with fluvoxamine, plasma levels of propranolol were increased about five-fold. Pharamacodynamic manifestations of this interaction were small but statistically significant decreases in diastolic blood pressure (seen only with exercise) and heart rate (-3 bpm at rest and -8 bpm during exercise).

Propranolol (5095) An identical study to 5092 with the exception that the immediate release form of propranolol was used. Again, fluvoxamine-treated subjects demonstrated a five-fold increase in plasma propranolol levels.

Atenolol (5096) A double-blind crossover study of the effects of enteric-coated fluvoxamine 50mg bid X 12 days in 12 volunteers who had been stabilized on atenolol 100 mg/day. There was no influence of fluvoxamine on plasma levels of atenolol.

Warfarin ((5094) A double-blind crossover study investigating the effect of enteric-coated fluvoxamine 50 mg tid X 2 weeks in 10 volunteers who had been stabilized on warfarin 3-7 mg/day (as needed to produce a 50% increase in prothrombin time). Fluvoxamine appeared to produce a statistically significant increase in warfarin plasma levels (about 60% increase) with associated increases in prothrombin times.

Cytochrome P450 Activity (6003) An open label crossover study of the comparative influence of fluvoxamine 50 mg bid, clovoxamine 50 mg tid, imipramine 50 mg bid, and no treatment on antipyrine AUC and half-life in 8 volunteers. All drugs were administered for 3 days with antipyrine plasma level measurements on the second day. Both fluvoxamine and clovoxamine were associated with significant increases in antipyrine AUC and half-life compared to no treatment; imipramine had no effect on these parameters. There was no indication of a carryover effect during the 2 week washout perious betweeen treatments.

Bromazepam/Lorazepam (6004) A double-blind crossover study of the effect of multiple fluvoxamine dosing (50 mg/day X 4 days, then 100 mg/day X 21 days) on the cognitive effects of single doses of bromazepam 12 mg and lorazepam 4 mg. In the presence of fluvoxamine plus benzodiazepine, peak impairment in attention span and vigilance was markedly reduced with no effect on peak impairment of memory or subjective sedation compared to benzodiazepine alone. Fluvoxamine did appear to prolong impairments in all these areas, which remained significant 40 hours post-dose vs 12 hours post-dose in the absence of fluvoxamine.

Alcohol (6002) A randomized, double-blind, placebo-controlled crossover study examining the effect of single dose fluvoxamine (50 mg) and multiple dose fluvoxamine (50 mg/day X 3 days, then 100 mg/day X 9 days, then 50 mg on Day 13) on the kinetics and clinical effects (labs, vital signs, and cognitive functioning) of single doses (40g) of orally administered ethanol in 12 volunteers. Additionally, the effect of alcohol administration on fluvoxamine kinetics was assessed. There were no significant effects of single dose or multiple dose fluvoxamine on the AUC, C_{max}, or T_{max} of alcohol.

Alcohol (6001) A partially blind crossover study of the effects of fluvoxamine on the kinetics of IV alcohol in 12 volunteers. Two hours after a dose of fluvoxamine 50 mg or placebo, IV alcohol was administered; this was repeated 1 week later after crossover. Then, multiple doses of fluvoxamine (50 mg/day X 3 days, then 50 mg bid X 10 days) were given to all subjects followed by a dose of alcohol. Again, alcohol kinetics were not significantly affected by fluvoxamine.

Alcohol (5538) A randomized, double-blind, placebo-controlled crossover study of of the effects of 2 fluvoxamine dose levels (50 or 100 mg) on memory (word recognition test) in 10 young male social drinkers. There was no significant pharmacodynamic interaction with alcohol.

Alcohol (5074) A double-blind, placebo-controlled parallel group study assessing the effects of fluvoxamine alone and of combined fluvoxamine and alcohol on fitness to drive in 48 volunteers. Subjects were assigned to receive multiple doses of fluvoxamine (25

mg tid X 1 week, then 50 mg tid X 1 week) OR placebo X 2 weeks; in both treatment groups, subgroups were tested with and without alcohol. Fluvoxamine alone produced no impairment in motor performance compared to placebo. The effects of combined fluvoxamine 150 mg/day and alcohol were more pronounced than the effects of either substance taken alone with regard to vigilance, orientation capacity, and continuous attention span.

Alprazolam (P-200-92-016) A randomized parallel group study using 3 arms (fluvoxamine, alprazolam, and fluvoxamine/alprazolam combined) was conducted to assess the effects of multiple dose fluvoxamine use on alprazolam pharmacokinetics. Sixty young, healthy males were evenly assigned among the 3 groups, with assignment controlled for smoker/non-smoker status of the subjects. Study duration was 10 days with fluvoxamine doses of 50mg/day for 3 days and 100mg/day for 7 days; alprazolam was given as 1.0 mg QID on days 7-10. The coadministration of fluvoxamine and alprazolam resulted in a 100% increase in mean alprazolam levels with an increase in mean alprazolam $t_{\frac{1}{2}}$ from 20 hours to 34 hours. The increased plasma levels of alprazolam were associated with significantly increased psychomotor performance decrements, especially on day 10.

Theophylline (6008) A non-randomized crossover study using 12 healthy male volunteers examined the effects of multiple dose fluvoxamine use on theophylline plasma levels following a single dose of oral aminophylline. Study duration was 20 days: aminophylline 442mg was given on day 1 and on day 17; fluvoxamine was administered as 50mg/day on days 4-6 and 50mg bid on days 7-19. The AUC_{∞} of theophylline increased by a factor of 2.67 after coadministration of fluvoxamine; this was attributed to a proportionate decrease in theophylline clearance. C_{max} was not changed. Fluvoxamine plasma levels did not change with the coadministation of theophylline in this study.

As of June 1993, no formal studies of the effect of fluvoxamine on the $P450_{IID6}$ isoenzyme have been completed by the sponsor. There is one published in vitro study which compared the effects of a series of SSRI's on cytochrome $P450_{IID6}$ activity in human liver microsomes[4]: all SSRI's were seen to have potent inhibitory effects on $P450_{IID6}$, with fluvoxamine having relatively less cytochrome inhibition than the other SSRI's tested (paroxetine, fluoxetine, norfluoxetine, sertraline, and citalopram).

Conclusions which may be drawn from the above studies are as follows:

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[4]Crewe HK et al. The Effect of Selective Serotonin Re-uptake Inhibitors on Cytochrome $P450_{2D6}$ Activity in Human Liver Microsomes. Br. J. Clin. Pharmac. (1992), 34:262-265.

1) There is no evidence of an effect of chronic fluvoxamine use on single dose IV digoxin kinetics.

2) Multiple dose fluvoxamine use leads to an five-fold increase in plasma levels of propranolol, suggesting a reduction in hepatic elimination. This is not the case with another β-blocker, atenolol, a drug that is mainly excreted unchanged via the kidneys.

3) Multiple dose use fluvoxamine increases mean plasma warfarin levels by about 60% and prolongs prothrombin times.

4) Fluvoxamine may inhibit the enzyme activity of cytochrome P450 in the liver as demonstrated by decreased antipyrine clearance. This finding may be due to simple competitive inhibition, however, and this inhibition is likely to be reversible.

5) Multiple dose fluvoxamine may prolong cognitive impairments seen with single dose benzodiazepine use.

6) Single and multiple dose fluvoxamine does not appear to affect the pharmacokinetics of alcohol.

7) The combined use of fluvoxamine and alcohol may impair vigilance and attention span significantly more than the use of either substance alone.

8) The combined use of alprazolam and fluvoxamine may result in significantly increased alprazolam levels with concurrent decrements in psychomotor performance.

9) The concurrent administration of fluvoxamine and theophylline may result in significantly increased theophylline levels due to decreased theophylline clearance.

Individual case reports, both from the literature and from the sponsor's database, provide additional data regarding possible drug -drug interactions with fluvoxamine. Unfortunately, lack of complete clinical data and/or follow-up information in some cases limits the usefulness of this data.

Two patients from studies in Strata III experienced cardiovascular compromise when fluvoxamine was used with metoprolol, a β-blocker metabolized by the liver:

> A 47 year old male was being treated with metoprolol 200 mg/day for tachycardia when he began fluvoxamine 100 mg/day for depression. Baseline blood pressure was 135/95 and pulse was 68 bpm. Although vital signs were unchanged after 7 days, he presented with orthostatic hypotension on day 17 of therapy (BP 110/80 supine, 60/40 erect); pulse was not reported. (III/EU.901/840)

> A 63 year old male with depression and hypertensive cardiomyopathy was receiving Moduretic (hydrochlorothiazide 50mg/amiloride 5 mg), captopril 25 mg tid, and metoprolol 300 mg/day when he began fluvoxamine 100 mg/day. After 8 days of therapy, he presented with severe hypotension and bradycardia (BP not provided, pulse= 44 bpm; baseline vital signs were not given). (III/BE.907/38)

Additionally, two Strata IV patients experienced bradycardia, one receiving fluvoxamine with propranolol and one fluvoxamine with diltiazem, a hepatically metabolized calcium channel blocker:

> A 60 year old female was being treated for migraine with propranolol (dose unknown) when treatment was begun with fluvoxamine 100 mg/day. After one day of fluvoxamine exposure, she experienced bradycardia (pulse= 50 bpm, pre-fluvoxamine pulse not given). Both drugs were discontinued with subsequent complete recovery. (IV/FL304)

> A 45 year old male had been treated with diltiazem for Prinzmetal's angina and, following one 50 mg dose of fluvoxamine, experienced bradycardia (pulse= 40 bpm, no pre-fluvoxamine pulse provided). Atropine was administered and fluvoxamine was discontinued; bradycardia did not reoccur. (Bradycardia is associated with diltiazem overdose.) (IV/FL591)

An 81 year old male in a Strata III study who was receiving fluorindione, a hepatically metabolized anticoagulant, experienced a 10% increase in prothrombin time after 12 days of treatment with fluvoxamine 100 mg/day for depression. Treatment was discontinued. (III/FR.012/201)

Theophylline is a drug eliminated primarily by hepatic metabolism. There are 2 case reports of theophylline toxicity possibly related to fluvoxamine use:

> A 80 year old male with COPD and heart failure who was being treated with theophylline began fluvoxamine treatment for depression as a subject in a Strata I study. About one week later (at a fluvoxamine dose of 100 mg/day), he was hospitalized because of a "toxic confusional state" with a theophylline level of 32 mg/L; his pre-fluvoxamine level had been 26.2 mg/L/. No further levels are available. (I/5531/62562)

> An 83 year old male hospitalized for bronchitis had been receiving theophylline with levels of 10.7, 14.6, and 12.7 mg/L in the previous month. Following 13 days of fluvoxamine therapy (100 mg/day) for depression, he

became agitated and developed tachycardia and atrial fibrillation; the theophylline level had increased to 39.8 mg/L. (IV/FL1127)

There are 3 published foreign reports of a possible pharmacokinetic interaction between fluvoxamine and tricyclic antidepressants. One report describes 3 patients taking benzodiazepines (flunitrazepam for one and chlorazepate and prazepam for the other two) as well as the following tricyclics at steady state: clomipramine 150 mg/day, amitriptyline 125 mg/day, and amitriptyline 150 mg/day[5]. Fluvoxamine (100-300 mg/day) was then co-administered for 10 days and plasma TCA/TCA metabolite levels were measured. There were marked increases in the levels of parent drug as well as in the parent:metabolite ratios.

The second report discusses 4 patients on amitryptyline therapy and 4 patients on clomipramine therapy, all at steady state, who then received fluvoxamine augmentation[6]. Again, marked increases in parent TCA levels and parent:metabolite ratios were observed.

The most recent report was submitted to the agency in September 1992[7]. Two patients were being treated with imipramine (100 and 125 mg/day) and two with desipramine (both 100 mg/day) prior to augmentation with fluvoxamine 100 mg/day. All experienced dramatic increases in levels of parent compound (with less impressive changes in desipramine levels in the 2 patients receiving imipramine) compared to pre-fluvoxamine levels and three of the four developed clinical symptoms consistent with TCA toxicity: seizure (1 case), tremor, confusion, and anticholinergic effects.

Since fluvoxamine produces increased synaptic levels of serotonin and lithium potentiates this effect by increasing serotonin synthesis, it has been postulated that a combination of these 2 drugs would produce an increased incidence or severity of serotonergic adverse events. However, a published pilot study in which 6 patients with bipolar disorder or recurrent unipolar depression received both fluvoxamine (100-150 mg/day) and lithium (600-3000 mg/day) for 3 to 23 weeks (total combined exposure was 59 weeks) did not reveal any significant clinical toxicity or evidence

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[5]Bertschy G, et al: Fluvoxamine-tricyclic antidepressant interaction. European J Clin Pharmacol 1991; 40: 119-120.

[6]Vandel S, et al: Fluvoxamine tricyclic antidepressant interaction. Therapie 1990; 45(1): 58.

[7]Spina E, et al. Interaction Between Fluvoxamine and Imipramine/Desipramine in Four Patients. Therapeutic Drug Monitoring 1992; 14: 194-196.

of an effect of fluvoxamine on lithium levels[8]. Randomized, double-blind studies of lithium augmentation for 2 weeks in 11 patients with fluvoxamine-resistant OCD and for 4 weeks in 5 similar patients revealed no increased incidence of adverse events[9]. In yet another study, 9 OCD patients refractory to fluvoxamine monotherapy were treated with a combination of fluvoxamine, lithium, and a neuroleptic concurrently[10]. This regimen was well tolerated. Finally, 52 patients from Strata I, II, IV, and V, who were identified in the process of searching for cases of serotonin syndrome, were exposed concurrently to fluvoxamine and lithium: although there was no pattern of adverse events evident among these patients that might be attributed to a drug interaction, there was one case of hypotension (IV/FL291) and 2 cases of convulsions (IV/FL454 and IV/FL458) which occurred within the first week of fluvoxamine/lithium coadministration which could be attributed to combined therapy.

A unpublished pilot study in Germany was conducted to assess for interaction between fluvoxamine and L-tryptophan: over a period of 4 weeks, 5 patients were administered fluvoxamine 100 mg/day and L-tryptophan 3 g/day. Severe vomiting did occur in one patient at the onset of exposure and led to her discontinuation from the trial. However, nausea did not seem to increase in the other subjects.

Thus, this additional clinical data further supports the possibility that fluvoxamine may raise serum theophylline levels and levels of certain other hepatically metabolized agents, such as metoprolol, propranolol, diltiazem, and anticoagulants; additionally, it suggests that tricyclic antidepressant levels may also be increased by fluvoxamine, probably as a result of decreased metabolism of the parent drug. Isolated reports of seizures and hypotension with concurrent lithium and severe vomiting with concomitant L-tryptophan administration have been reported.

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[8]Hendrickx B and Floris M: A Controlled Pilot Study of the Combination of Fluvoxamine and Lithium. Curr Ther Res 1991; 49(1): 106-110.

[9]McDougle CJ, et al: A Controlled Trial of Lithium Augmentation in Fluvoxamine-Refractory Obsessive-Compulsive Disorder: Lack of Efficacy. J Clin Psychopharmacol 1991; 11:175-184.

[10]McDougle CJ, et al: Neuroleptic Addition in Fluvoxamine-Refractory Obsessive-Compulsive Disorder. Am J Psychiatry 1990; 147: 652-654.

9.0 Labeling Review

The clinical sections of the draft labeling (submitted on 9/28/93) were reviewed. The following modifications to those sections are suggested.

PHARMACOKINETICS

Clinical Trials in Patients with Obsessive Compulsive Disorder (OCD): This paragraph should be inserted under **INDICATIONS AND USAGE** as opposed to this section since it describes the pivotal efficacy studies in suppport of this indication. Furthermore, the following modifications are recommended: 1) this paragraph should mention the numbers of patients studied (160 fluvoxamine and 160 placebo); 2) there is no mention of treatment effect size; this might be addressed by adding the following: "Study completers taking fluvoxamine experienced mean reductions in Y-BOCS total scores of 5.2 and 5.8, representing an average improvement on this scale of approximately 25%. Mean decreases on the NIMH-OC were 2.0 and 1.7 for these patients. Approximately 43% of these patients were rated as 'much improved' or 'very much improved' at the end of treatment as measured by the Clinical Global Impressions improvement item score." 3) the last sentence describes improvement seen in one measure (CGI) in only one study for responders versus non-responders. Significant differences over placebo were not seen this early on the NIMH-OC scale or the Y-BOCS. It is felt that this statement suggests an underestimated latency of therapeutic response and it should be deleted.

INDICATIONS AND USAGE

Obsessive Compulsive Disorder: The second paragraph is essentially duplicates the first sentence of the paragraph discussed above and should be deleted.

PRECAUTIONS

Activation of Mania/Hypomania: This incidence is based on the 6 pivotal depression studies from which has not yet been reviewed. One problem with using this database is that the maximum daily dose was 150 mg. It is suggested that the pre-marketing study database from this NDA be used for incidence calculation (incidence of 1.1%) since the dose range used in the pre-marketing database (maximum of 00 mg/day) is the same as that recommended for the treatment of OCD.

Suicide: The referenced meta-analysis did not show significant improvement in suicidal ideation among fluvoxamine-treated patients when compared to placebo - this statement should be deleted.

Seizures: It is suggested that the incidence of seizures be based on the pre-marketing study database, in which the incidence was 0.2%. The low quality of the Strata III studies casts doubt on the accuracy of the given incidence. The incidence in the post-marketing surveillance database should not be included since a reasonably accurate denominator for this population is not known and since the numerator is based only on reported cases; this rate likely underestimates the true incidence.

Use in Patients with Concomitant Illness: The second paragraph, which describes clinical ECG findings, mentions 1453 depressed patients treated with fluvoxamine in short-term studies; this refers to the combined short-term pool of 139 OCD patients in Strata I as well as 740 patients from the 11 Strata I depression studies and 575 patients from the pivotal depression studies in . The inclusion of OCD patients in addition to depressed patients should be indicated. However, a possible complication is the inclusion of data from a separate, later NDA which has not yet been fully reviewed. Additionally, the maximum dose in this latter database was only 150 mg/day. Also, the last sentence in that paragraph may mention sinus tachycardia and prolonged QT_c **only** since the other findings (PVC's, IVCD, and ST-T changes) were not substantially more frequent in the TCA patients compared to the fluvoxamine patients.

Drug Interactions
Benzodiazepines: The two-fold elevation in alprazolam levels and prolonged alprazolam half-life observed in the formal interaction study should be specifically mentioned to complement the stated PD effects.

Clinical Events Suggesting a Drug Interaction: Mention should be made of the following case reports of important adverse events when the indicated medication was used concurrently with fluvoxamine: bradycardia and hypotension with metoprolol; bradycardia with diltiazem; significantly increased TCA levels with amitriptyline, clomipramine, desipramine, and imipramine; elevated anticonvulsant levels with symptoms of toxicity with carbamazepine; seizures with lithium; and severe vomiting with L-tryptophan.

Nursing Mothers: Based on an animal study in rats which showed that the offspring exposed only to the milk of females treated with 160 mg/kg/day had decreased survival during the first 4 days post-partum, consideration should be given to including an explicit recommendation that fluvoxamine not be administered to nursing mothers unless potential clinical benefits were felt to be preponderant.

ADVERSE REACTIONS
Associated with Discontinuation of Treatment: Pools of Strata I studies of equal duration, one for the OCD trials and one for the depression trials, were used to examine the incidence of adverse

events associated with dropout in the process of reviewing this NDA. Nonetheless, the general incidence rates and patterns of events associated with dropout observed in these pools are similar to those in the presented pool and there are no strong objections to including the data as proposed by the sponsor.

Incidence in Controlled Trials

Table 1: Three modifications are indicated: 1) the presented incidence rates for rhinitis are incorrect; this line should read: Rhinitis 8.8% (fluvoxamine) 3.1% (placebo). 2) the presented incidence for anorgasmia is for males only; this should be so indicated. 3) the incidence for anorgasmia among females was omitted: 2.4% (fluvoxamine) 0.0% (placebo).

Other events observed during the pre-marketing evaluation of LUVOX (fluvoxamine maleate) Tablets: The number of patients exposed to fluvoxamine during pre-marketing trials which documented adverse events by spontaneous reporting is incorrect; the correct number is 2,112. In the listing of other events which follows, the following 3 events should be added: under **Digestive System**, ulcerative stomatitis (rare) and, under **Musculoskeletal System**, myasthenia and leg cramps (both infrequent).

Other Clinical Studies: The section would be better designated as **Foreign Post-Marketing Studies**. Also, it might be worth mentioning that one case of serious hyponatremia possibly related to fluvoxamine treatment was reported in this database.

A section titled **Post Introduction Reports** or **Post Marketing Surveillance Reports** could be added and mention spontaneous reports of the following serious adverse events which may be related to fluvoxamine exposure: 5 cases of hepatitis, a case of toxic epidermal necrolysis, 2 cases of Stevens-Johnson syndrome, and 2 cases of hyponatremia.

OVERDOSAGE

Human Experience

In the sentence discussing the outcome for the 335 non-fatal overdoses, the case in which a bowel infarction occurred and necessitated a hemiclectomy should be mentioned in the same vein as the case of persistent mydriasis, i.e. 309 with complete recovery, one with mydriasis, one with bowel infarction/ hemicolectomy, and 24 with outcome unknown.

In the paragraph describing the signs and symptoms seen with overdose, perhaps it would be more useful to present those events which were commonly seen after an overdose of fluvoxamine (supposedly) alone: drowsiness, vomiting, diarrhea, and dizziness.

Management of Overdose

It is probably worth mentioning the fact that absorption in the overdose situation can be delayed beyond 24 hours and lavage/charcoal should be administered up to 24 hours post-ingestion.

10.0 Conclusions

Overall, there appears to be sufficient evidence to support the efficacy of fluvoxamine in the short-term treatment of OCD. Additionally, fluvoxamine seems to be reasonably safe under the conditions of use recommended in labeling.

11.0 Recommendations

It is recommended that fluvoxamine be approved for use in the treatment of OCD. However, to further support the safe and effective use of fluvoxamine, it is recommended that the following issues be explored by the sponsor.

1) The long-term efficacy of fluvoxamine in the treatment of OCD should be examined by an adequate trial of at least one year duration, such as a relapse prevention trial.

2) Fixed dose studies should be conducted to elucidate the dose-response relationship in OCD, particularly to identify the minimum effective dose.

3) Since OCD not infrequently begins in childhood or adolescence, trials to examine the safety and efficacy of fluvoxamine in the treatment of OCD in these populations should be completed.

4) The interaction of fluvoxamine with the P450 enzyme system should be formally studied to elucidate the specific isoenzymes affected by fluvoxamine administration.

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Medical Reviewer
Psychiatric Drug Products Group

cc: NDA 20-243
HFD-120
HFD-120/TLaughren
/GDubitsky
/PDavid

APPENDIX 5.1 - TABLE OF ALL STUDIES	
PHASE 1 STUDIES	
MISCELLANEOUS CLINICAL PHARMACOLOGY STUDIES	
H.114.5001	Open-label, multiple dose, rising dose tolerance trial; healthy volunteers (n=10); fluvoxamine dose range 5-75mg PO tid; up to 35 days.
H.114.5002	Open label, rising dose tolerance trial; healthy volunteers (n=10); fluvoxamine dose up to 300mg/day; unknown duration.
H.114.5003	DB, PC, multiple dose, crossover tolerance trial; healthy volunteers (n=10); fluvoxamine dose 50mg PO tid; 28 days.
H.114.5018	DB, PC, crossover tolerance trial with enteric-coated capsules in multiple doses; healthy volunteers (n=13); fluvoxamine dose 50mg tid; 28 days.
H.114.5501	Randomized, DB, 5-way crossover study using 4 doses of fluvoxamine & placebo in single doses; effects on sleep; healthy volunteers (n=8); fluvoxamine dose range 25-150mg.
H.114.5502	Randomized, DB, 6-way crossover study using 4 fluvoxamine doses, imipramine 75mg, & placebo in single doses; EEG effects; healthy volunteers (n=12); fluvoxamine dose range 10-75mg.
H.114.5016	DB, 6-way crossover study using 1 dose of fluvoxamine, 3 doses of clovoxamine, 1 dose of imipramine, & placebo in single doses; effects on EEG and attention span; healthy volunteers (n=10); fluvoxamine dose 75mg.
H.114.5088	DB, multiple dose, 3-way crossover study using fixed doses of fluvoxamine, mianserin, & placebo; effect on EEG and memory; healthy volunteers (n=11); fluvoxamine dose = 50mg bid; 38 days.
H.114.5024	DB, 2-way crossover study of 2 dose levels of fluvoxamine; effect on blood serotonin, platelet MAO, platelet aggregation, and urinary catecholamines; healthy volunteers (n=11); fluvoxamine doses 10mg tid or 25mg tid; 14 days.
H.114.5512	Randomized, DB, single dose, Latin square crossover using 3 doses of fluvoxamine, 2 doses of doxepin, 2 doses of amitriptyline, & placebo; autonomic effects: normal volunteers (n=17); fluvoxamine doses 50, 75, and 100mg.
H.114.930/UK	DB, single dose, 5-way crossover study using 2 fluvoxamine doses, 2 amitriptyline doses, & placebo; autonomic effects; healthy volunteers (n=10); fluvoxamine doses 50mg & 100mg.

H.114.5030	DB, 3-way Latin square crossover study using fluvoxamine, clovoxamine, & placebo; cardiovascular effects; healthy volunteers (n=27); fluvoxamine dose: 50mg tid X 2 days, 100mg tid X 5 days, then 50mg tid X 2 days.
H.114.5515	Randomized, DB, PC, parallel group study; effect on hypothalamic-pituitary function; healthy volunteers (5/group); fluvoxamine dose 50mg q 8 hours X 4 doses.
H.114.5103	DB, 3-way crossover study using single doses of fluvoxamine, desipramine, and placebo; effect on melatonin secretion; healthy males (n=8); fluvoxamine dose 100mg.
PHARMACOKINETIC STUDIES	
Study # Unavailable	Open label, single dose absorption study using ^{14}C labeled fluvoxamine; healthy volunteers, n=5; fluvoxamine doses 1mg (1 subject), 5mg (4 subjects).
H.114.6501	Open label, single dose, 2-way crossover study of the effect of food on bioavailability; healthy volunteers, n=12; fluvoxamine dose 50mg.
H.114.615 (report #)	Study of fluvoxamine adsorption by medicinal charcoal.
56630/54/77 (report #)	Study of protein binding in human plasma.
H.114.630 (report #)	Study of protein binding in human plasma.
56654/16/74 (report #)	Determination of metabolites.
56630/114/77 (report #)	Determination of metabolites.
H.114.5099	Open label, single dose study of in vivo isomerization; healthy volunteers, n=5; fluvoxamine doses 50mg q4 hours X 3.
P 61-11	Early, single dose PK study; healthy volunteers, n=10; fluvoxamine dose 100mg.
H.114.5073	Single dose, 3-way crossover dose proportionality study; healthy volunteers, n=12; fluvoxamine doses 25, 50, & 100mg.
RH.114.02.02	Multiple dose, dose proportionality study using the proposed formulation for the U.S. market; healthy volunteers, n=30; fluvoxamine dose: titration to steady state doses of 50mg bid, 100mg bid, & 150mg bid.

H.114.5087	Open label, multiple dose PK study; healthy volunteers, n=6; fluvoxamine dose: 50mg on day 1, 50mg bid on days 4-31, 50mg on day 32.
H.114 5085	Open label study of PK in depressed patients; n=4; fluvoxamine dose: 100mg/day on day 1, 100mg bid on days 4-31, 100mg/day day 32.
H.114.620 (report #)	DB, multiple dose trial; PK in depressed patients compared to healthy volunteers; N. American subgroup: n=102 depressed patients on same dose for at least 6 days, European subgroup: n=42 patients on same dose for at least 4 weeks; fluvoxamine doses to 300mg/day.
H.114.5090	Single dose PK study in elderly volunteers; n=8; fluvoxamine dose 50mg.
H.114.5098	Multiple dose PK study in elderly volunteers; n=14; fluvoxamine dose 50mg bid for 27 days, 50mg on day 28.
H.114.623 (report #)	DB, multiple dose trial; PK in elderly vs young depressed patients; n=69 (subset of H.114.620); fluvoxamine doses to 300mg/day.
H.114.5097	Open label PK study in renally-impaired patients; n=25; fluvoxamine dose: 50mg/day for 3 days then 100mg/day over 6 weeks.
H.114.011	Open label, single dose study; PK in patients with chronic liver disease, n=13; fluvoxamine dose 100mg.
RH.114.00.02	Single dose, pilot bioequivalence study comparing 50mg tablet, 50mg capsule, & 50mg solution; healthy volunteers, n= 6.
RH.114.00.03	Single dose bioequivalence study comparing the 50mg tablet, 50mg capsule, and 50mg solution; healthy volunteers, n=24.
H.114.5064	2-way crossover formuiation study comparing 50mg enteric-coated tablets & 50mg capsules; healthy volunteers, n=8; fluvoamine dose 100mg.
H.114.5517	2-way crossover formulation study comparing enteric-coated tablets vs aqueous solution; healthy volunteers, n=22; fluvoxamine dose 25mg.
H.114.5086	3-way crossover formulation study comparing 50mg film-coated tablets, 50mg capsules, & 50mg aqueous solution; healthy volunteers, n=12; fluvoamine dose 50mg.
H.114.5093	Open label, 2-way crossover formulation study comparing film-coated tablets vs solution; healthy volunteers, n= 12; fluvoxamine dose 50mg.
Study # Unavailable	DB, PC single dose PK study of the Japanese small tablet formulation; healthy volunteers, n=24; fluvoxamine doses 25, 50, 75, 100, & 200mg.

RH.114.01.08	Open-label, parallel group study to compare the single- and multiple-dose pharmacokinetics of fluvoxamine between young and elderly healthy male subjects; n=12 (young), n=11 (elderly); fluvoxamine dosing: 25mg on Day #1, 50mg on Day #3, 50mg daily on Days 3-13, & 100mg on Days 14-20.
H.114.6006	Randomized, 3-way crossover study to compare the pharmacokinetics of 1 oral dose and 2 IV infusions of fluvoxamine; healthy male volunteers, n=18; fluvoxamine doses: 50mg PO, 10mg IV, and 30mg IV.
DRUG INTERACTION STUDIES	
H.114.5083	DB, PC interaction study of the effect of chronic fluvoxamine dosing on IV digoxin kinetics; healthy volunteers, n=8; fluvoxamine dose 50mg bid for 18 days, digoxin dose 0.125mg IV.
H.114.5092	DB crossover PK interaction study of fluvoxamine & propranolol slow release; healthy volunteers, n=12; fluvoxamine dose 50mg bid days 4-15, propranolol dose 160mg/day days 1-15.
H.114.5095	DB crossover PK interaction study of fluvoxamine & propranolol intermediate release; healthy volunteers, n=5; fluvoxamine dose 50mg bid days 4-15, propranolol dose 160mg/day days 1-15.
H.114.5096	DB crossover PK interaction study of fluvoxamine & atenolol; healthy volunteers, n=12; fluvoxamine dose 50mg bid days 4-15, atenolol dose 100mg/day days 1-15.
H.114.5094	DB crossover PK/PD interaction study of fluvoxamine & warfarin; healthy volunteers, n=10; fluvoxamine dose 50mg tid, warfarin dose 3-7mg/day.
H.114.6003	[illegible] PK interaction study comparing the effects of fluvoxamine vs [illegible]amine on the metabolism of antipyrine; healthy volunteers, n=8; [illegible], clovoxamine dose 50mg tid, imipramine dose 50mg bid.
H.114.6004	[illegible] study of single doses of bromazepam and lorazepam in [illegible] of multiple doses of fluvoxamine; effect of fluvoxamine on [illegible] bromazepam and lorazepam; healthy male volunteers (n=12); fluvoxamine [illegible] for 4 days then 100mg for 21 days.
H.114.6002	Random[illegible] ossover study; influence of single & multiple dose fluvoxamine [illegible]nical effects and PK of alcohol; healthy male volunteers (n=12); fluvoxamine dosing: 50mg for 3 days, 100mg for 9 days, then 50mg for 1 day with alcohol on day 1 and alcohol/placebo on days 10 & 13.

H.114.6001	Partially blind crossover PK interaction study of fluvoxamine & IV alcohol; healthy volunteers, n=12; fluvoxamine dose 50mg on day 1 with ethanol 40g IV, 50mg/day days 9-11, 50mg bid with 40g ethanol days 12-21.
H.114.5538	Randomized, [illegible], single dose, crossover, PD interaction study of 2 different doses of fluvoxamine or placebo combined with alcohol or placebo; effect on memory, young male social drinkers, n=10; fluvoxamine doses 50mg & 100mg.
H.114.5074	DB, PC, multiple dose, parallel group, PD interaction study; effects on fitness to drive and interaction with alcohol; healthy volunteers (n=48); fluvoxamine dose 25mg tid X 1 week then 50mg tid X 1 week.
P-2000-0476	DB, parallel group study of the potential interaction between alprazolam and fluvoxamine under multiple dose conditions; healthy male volunteers, n=60; fluvoxamine dose 50mg once daily X3 days then 100mg once daily X7 days, alprazolam dose 1.[illegible] QID.
H.114.6008	Non-randomized, 2-way crossover study of the effect of multiple-dose fluvoxamine on the pharmacokinetic parameters of single-dose oral aminophylline; healthy male volunteers, n=12; fluvoxamine dose 50mg once daily X6 days then 50mg bid X13 days, aminophylline doses of 442mg given in the presence and absence of multiple dose fluvoxamine.
PHASE 2 - 3 STUDIES (OCD)	
STRATA I: NORTH AMERICAN PLACEBO CONTROLLED STUDIES (OCD)	
H.114.5529	DB, parallel group, 4-center, 10 week, flexible dose trial of fluvoxamine vs placebo; outpatients, OCD (n_1=80, n_2=80); fluvoxamine dose range 50-150mg bid.
H.114.5534	DB, parallel group, 4-center, 10 week, flexible dose trial of fluvoxamine vs placebo; outpatients, OCD (n_1=80, n_2=80); fluvoxamine dose range 50-150mg bid.
STRATA II: N. AMERICAN UNCONTROLLED/EUROPEAN CONTROLLED & UNCONTROLLED/SPECIAL & PILOT STUDIES (OCD)	
H.114.5529E	Open-label, humanitarian extension of 5529; outpatients, OCD (n=73); fluvoxamine dose 50-150mg bid; 42 weeks.
H.114.5534E	Open-label, humanitarian extension of 5534; outpatients, OCD (n=47); fluvoxamine dose 50-150mg bid; 42 weeks.
H.114.5533	Open-label, compassionate use protocol; outpatients, OCD (n=153); fluvoxamine dose 50-400mg/day; one year.

H.114.5540-O	Open-label compassionate use protocol for patients completing 5529E, 5533, or 5534E; outpatients, OCD (n=124); fluvoxamine dose 100-300mg/day; open ended.
STRATA III: WORLD-WIDE POST-MARKETING STUDIES (OCD)	
H.114.009/84FR	PC, parallel group trial with behavioral intervention (exposure vs anti-exposure) in OCD; n_t=40, n_p=20; fluvoxamine dose range 100-300mg/day; 26 weeks.
PHASE 2 - 3 STUDIES (DEPRESSION)	
STRATA I NORTH AMERICAN PLACEBO CONTROLLED STUDIES (DEPRESSION)	
H.114	Randomized, DB, PC flexible dose comparison of fluvoxamine & imipramine; outpatients, primary depression (n_f=21, n_p=22, n_i=26); fluvoxamine dose 50-300mg/day; 4 weeks.
H.114.5506	Randomized, DB, PC multicenter, flexible dose comparison of fluvoxamine and imipramine; outpatients, primary depression (n_f=35, n_p=30, n_i=29); fluvoxamine dose 50-300mg/day; 4 weeks.
H.114.5508	Randomized, DB, PC multicenter, flexible dose comparison of fluvoxamine and imipramine; outpatients, primary depression (n_f=81, n_p=79, n_i=84); fluvoxamine dose 50-300mg/day; 4 weeks.
H.114.5510	Randomized, DB, PC flexible dose comparison of fluvoxamine and imipramine; inpatients, primary depression (n_f=31, n_p=19, n_i=36); fluvoxamine dose 50-300mg/day; 6 weeks.
H.114.5520	DB, PC, multicenter, flexible dose comparison of fluvoxamine and imipramine; outpatients, major depression (n_f=159, n_p=157 n_i=79); fluvoxamine dose 100-300mg/day; 6 weeks.
H.114.5522	PC, multicenter, flexible dose comparison of 2 dosing regimens; outpatients, major depression (n_f=226, n_p=114); fluvoxamine dose 25-100mg/day; 6 weeks.
H.114.5525	DB, PC, multicenter, flexible dose comparison of fluvoxamine with imipramine; outpatients, depression (n_f=106, n_p=105, n_i=106); fluvoxamine dose 100-300mg/day; 6 weeks.
H.114.5526	DB, PC, multicenter, flexible dose comparison of fluvoxamine with desipramine; outpatients, depression (n_f=95, n_p=95, n_d=98); fluvoxamine dose 75-300mg/day; 6 weeks.

H.114.5527	DB, PC, multicenter, flexible dose comparison of fluvoxamine with desipramine; outpatients, depression (n_f=71, n_p=72, n_d=73); fluvoxamine dose 100-300mg day; 6 weeks.
H.114.5528	DB, PC, single-center, flexible dose comparison; outpatients, depression (n_f=75,n_p=75); fluvoxamine dose 100-300mg/day; 6 weeks.
H.114.5531	DB, PC, multicenter, flexible dose comparison of fluvoxamine with desipramine; geriatric outpatients, depression (n_f=27, n_p=28, n_d=27); fluvoxamine dose 100-300mg/day; 12 weeks.
STRATA II: N. AMERICAN UNCONTROLLED/EUROPEAN CONTROLLED & UNCONTROLLED/SPECIAL & PILOT STUDIES (DEP.)	
PLACEBO CONTROLLED STUDIES (DEPRESSION)(STRATA II)	
H.114.5045	Randomized, DB, PC, multicenter comparison with imipramine; inpatients, primary depression (n_f=54, n_p=43, n_i=48); fluvoxamine dose 50-300mg/day; 4 weeks.
H.114.5076	Randomized, DB, PC study; inpatients/outpatients, primary depression (n_f=34, n_p=34); fluvoxamine dose 50-300mg/day; 4 weeks.
H.114.5506E	Extension of 5506; n_f=9, n_p=4, n_i=3; fluvoxamine dose 50-300mg/day; 24 weeks.
H.114.5508E	Extension of 5508; n_f=26, n_p=20, n_i=21; fluvoxamine dose 50-300mg/day; 52 weeks.
H.114.5510E	Extension of 5510; n_f=4, n_p=2, n_i=4; fluvoxamine dose 50-300mg/day; 24 weeks.
H.114.5525E	Extension of 5525; n_f=35, n_p=14, n_i=28; fluvoxamine dose 100-300mg/day; 46 weeks.
H.114.5526E	Extension of 5526; n_f=74, n_p=17, n_d=43; fluvoxamine dose 100-300mg/day; 46 weeks.
H.114.5527E	Extension of 5527; n_f=62, n_p=12, n_d=24; fluvoxamine dose 100-300mg/day; 46 weeks.
ACTIVE CONTROLLED STUDIES (DEPRESSION)(STRATA II)	
H.114.5015	DB comparison with clomipramine; inpatients, depressive syndromes (n_f=17,n_c=18); fluvoxamine dose 50mg/day; 4 weeks.
H.114.5017	DB comparison with clomipramine; inpatients, depressive syndromes (n_f=17,n_c=15); fluvoxamine dose 50mg/day; 4 weeks.
H.114.5021	Randomized, DB, comparison with imipramine; inpatients, depressive syndrome (n_f=10, n_i=10); fluvoxamine dose 50-225mg/day; 4 weeks.

H.114.5026	Randomized, DB, comparison with imipramine; inpatients with depressive symptoms (n_f=8, n_i=8); fluvoxamine dose 75-225mg/day; 4 weeks.
H.114.5026E	Extension of 5026; n_f=4, n_i=3; fluvoxamine dose 150-225mg/day; 52 weeks.
H.114.5029	DB comparison with clomipramine; inpatients, bipolar or unipolar depression (n_f=15, n_i=15); fluvoxamine dose 150-300mg/day; 4 weeks.
H.114.5029E	Extension of 5029; n_f=5, n_i=1; fluvoxamine dose 75-300mg/day; 52 weeks.
H.114.5035	Randomized, DB comparison with clomipramine; inpatients, primary depressive symptoms (n_f=2, n_i=3); fluvoxamine dose 150-300mg/day; 4 weeks.
H.114.5037	Randomized, DB comparison with imipramine; outpatients, primary depressive syndrome (n_f=18, n_i=22); fluvoxamine dose 75-300mg/day; 4 weeks.
H.114.5038	Randomized, DB comparison with imipramine; inpatients, primary depressive symptoms (n_f=5, n_i=3); fluvoxamine dose 50-300mg/day; 4 weeks.
H.114.5041	Randomized, DB comparison with imipramine; outpatients, primary depressive symptoms (n_f=22, n_i=22); fluvoxamine dose 50-300mg/day; 4 weeks.
H.114.5043	Randomized, DB, long-term comparison with lithium; outpatients, chronic unipolar depression (n_f=17, n_i=12); fluvoxamine dose 50-300mg/day; 24 weeks.
H.114.5052	Randomized, DB comparison with imipramine; inpatients, primary depression (n_f=1, n_i=1); fluvoxamine dose 50-300mg/day; 4 weeks.
H.114.5060	Randomized, DB comparison with clomipramine; outpatients, endogenous depression (n_f=22, n_i=21); fluvoxamine dose 50-200mg/day; 6 weeks.
H.114.5060E	Extension of 5060; n_f=10, n_i=12; fluvoxamine dose 100-400mg/day; 52 weeks.
H.114.5067	Randomized, DB comparison with clomipramine; inpatients, depressive syndromes (n_f=20, n_i=20); fluvoxamine dose 100-400mg/day; 4 weeks.
H.114.5068	Randomized, parallel group comparison with amineptine; inpatients, marked depressive syndrome (n_f=20, n_i=20); fluvoxamine dose 100-300mg/day; 4 weeks.
H.114.5091	Randomized, parallel group comparison with maprotiline; geriatric outpatients, depression (n_f=43, n_m=45): fluvoxamine dose 50-300mg/day; 6 weeks.
H.114.5102	Single-blind, parallel group comparison with maprotiline; inpatients/outpatients, depression (n_f=31,n_m=29); fluvoxamine dose 50-300mg/day; 6 weeks.

H.114.5505E	Extension of 5505; n_f=2, n_i=3; fluvoxamine dose 50-300mg/day; 24 weeks.
H.114.5507	Randomized, DB, comparison with imipramine; inpatients/outpatients, prima depression (n_f=22, n_i=22); fluvoxamine dose 100-300mg/day; 6 weeks.
H.114.5509	Randomized, DB, multicenter comparison with imipramine; outpatients, prima depression (n_f=44, n_i=42); fluvoxamine dose 100-300mg/day; 6 weeks.
H.114.5509E	Extension of 5509; n_f=6, n_i=8; fluvoxamine dose 50-300mg/day; 52 weeks.
UNCONTROLLED STUDIES (DEPRESSION)(STRATA II)	
H.114.5004	Open label study; inpatients, depressive illness (n=13); fluvoxamine dose 45-225mg/day; 6 weeks.
H.114.5005	Open label study; inpatients, depressive illness (n=13); fluvoxamine dose 45-225mg/day; 5 weeks.
H.114.5006	Open label study; inpatients, depressive illness (n=13); fluvoxamine dose 60-300mg/day; 5 weeks.
H.114.5007	Open label study; inpatients, depressive illness (n=12); fluvoxamine dose 60-300mg/day; 5 weeks.
H.114.5008	Open label study; inpatients, depressive illness (n=10); fluvoxamine dose 60-300mg/day; 5 weeks.
H.114.5009	Baseline-controlled study; inpatients, depressive syndromes (n=2); fluvoxamine dose 90-300mg/day; 4 weeks.
H.114.5010	Open label, early phase II study; inpatients, depressive syndromes (n=7); fluvoxamine dose 150-300mg/day; 5 weeks.
H.114.5011	Baseline-controlled study; inpatients, depressive syndromes (n=11); fluvoxamine dose 90-300mg/day; 4 weeks.
H.114.5012	Open label, early phase II study; inpatients, depressive syndromes (n=7); fluvoxamine dose 75-300mg/day; 4 weeks.
H.114.5013	Early, open label study; outpatients, depressive syndromes (n=6); fluvoxamine dose 75-300mg/day; 4 weeks.
H.114.5019	Open label, long-term study; outpatients, depressive syndromes (n=30); fluvoxamine dose 25-225mg/day; 52 weeks.

H.114.5020	Open label, long-term study; inpatients/outpatients, depressive syndromes (n=31); fluvoxamine dose 50-225mg/day; 52 weeks.
H.114.5034	Baseline-controlled study; inpatients, depression (n=5); fluvoxamine dose 150-300mg/day; 4 weeks.
H.114.5044	Baseline-controlled study; inpatients, depression (n=6); fluvoxamine dose 150-300mg/day; 4 weeks.
H.114.5046	Baseline-controlled study; inpatients, depressive syndromes (n=7); fluvoxamine dose 90-150mg/day; 4 weeks.
H.114.5059	Baseline-controlled, long-term, multicenter study; outpatients, depression (n=31); fluvoxamine dose 50-300mg/day; 51 weeks.
H.114.5066	Baseline-controlled, long-term study in general practice; outpatients, depression (n=222); fluvoxamine dose 25-300mg/day; 52 weeks.
H.114.5079	Baseline-controlled, long-term study; outpatients, depression (n=30); fluvoxamine dose 75-300mg/day; 52 weeks.
H.114.5080	Baseline-controlled study; outpatients, depression (n=7); fluvoxamine dose 50-300mg/day; 4 weeks.
H.114.5082	Long-term, uncontrolled study; depression, (n=19); fluvoxamine dose 50-400mg/day; 52 weeks.
H.114.5100	Baseline-controlled, long-term, multicenter study; outpatients, depression (n=52); fluvoxamine dose 100-300mg/day; 52 weeks.
H.114.5101	Baseline-controlled, long-term, multicenter study; geriatric outpatients, depression (n=39); fluvoxamine dose 50-300mg/day; 52 weeks.
H.114.5503	Open label, early phase II study; inpatients, depressive syndromes (n=12); fluvoxamine dose 100-300mg/day; 4 weeks.
H.114.5504	Open label, early phase II study; inpatients, depressive syndromes (n=11); fluvoxamine dose 50-300mg/day; 4 weeks.
H.114.5520E	Extension of 5520; n=157; fluvoxamine dose 100-300mg/day; 48 weeks.
H.114.5522E	Extension of 5522; n=13; fluvoxamine dose 25-300mg/day; 46 weeks.
H.114.5531E	Extension of 5531; n=7; fluvoxamine dose 100-300mg/day; 52 weeks.

H.114.5536	Open label, compassionate use protocol; outpatients, depression (n=20); fluvoxamine dose 100-300mg/day; 52 weeks.
H.114.5540-D	Open-label, compassionate use protocol for patients completing 5525E, 5526E, 5527F, or 5536; outpatients, depression (n=8); fluvoxamine dose 100-300mg/day; open ended.
STRATA III: WORLD-WIDE POST-MARKETING STUDIES (DEPRESSION)	
CONTROLLED STUDIES	
H.114.938/NL	PC trial in depression; n_f=15, n_c=15; fluvoxamine dose range 50-300mg/day; 8 weeks.
H.114.006/83FR	AC trial in depression; n_f=30, n_{ctrl}=30; fluvoxamine dose range 100-300mg/day; 6 weeks.
H.114.010/84FR	AC trial in depression; n_f=85, n_{ctrl}=41; fluvoxamine dose range 100-200mg/day; 6 weeks.
H.114.015/86FR	AC trial in depression; n_f=366, n_{ctrl}=163; fluvoxamine dose range 100-300mg/day; 8 weeks.
H.114.016/86FR	AC trial in depression; n_f=21, n_{ctrl}=18; fluvoxamine dose range 100-300mg/day; 4 weeks.
H.114.902/IT	AC trial in depression; n_f=10, n_{ctrl}=10; fluvoxamine dose range 100-150mg/day; 4 weeks.
H.114.906/NL	Depression trial (protocol unavailable); n_f=28, n_{ctrl}=28.
H.114.909/UK	AC trial in depression; n_f=34, n_{ctrl}=33; fluvoxamine dose range 100-300mg/day; 6 weeks.
H.114.910/UK	AC trial in depression; n_f=41, n_{ctrl}=37; fluvoxamine dose range 100-300mg/day; 6 weeks.
H.114.914/UK	AC trial in depression; n_f=28, n_{ctrl}=28; fluvoxamine dose range 50-200mg/day; 6 weeks.
H.114.915/UK	AC trial in depression; n_f=29, n_{ctrl}=28; fluvoxamine dose range 50-200mg/day; 6 weeks.
H.114.917/UK	AC trial in depression; n_f=29, n_{ctrl}=31; fluvoxamine dose range 50-150mg/day; 26 weeks.
H.114.918/UK	AC trial in depression; n_f=35, n_{ctrl}=35; fluvoxamine dose range 100-150mg/day, 6 weeks.

H.114.919/UK	AC trial in depression; n_f=31, n_{cntrl}=31; fluvoxamine dose range 100-300mg/day; 6 weeks.
H.114.922/UK	AC trial in depression; n_f=30, n_{cntrl}=17; fluvoxamine dose range 50-150mg/day; 6 weeks.
H.114.905/WG	AC trial in depression; n_f=21, n_{cntrl}=21; fluvoxamine dose range 100-300mg/day; 4 weeks.
UNCONTROLLED STUDIES	
H.114.901.AU	Uncontrolled depression trial; n=37; dose range 100-300mg/day; 6 weeks.
H.114.903/BE	Uncontrolled depression trial; n=151; dose range 100-300mg/day; 52 weeks.
H.114.907/BE	Uncontrolled depression trial; n=46; dose range 100-200mg/day; 8 weeks.
H.114.950/CH	Uncontrolled depression trial (no protocol available); n=317.
H.114.952/CH	Uncontrolled depression trial; n=54; dose range 100-300mg/day; 4 weeks.
H.114.957/CH	Uncontrolled depression trial; n=89; dose range 100-300mg/day; 6 weeks.
H.114.901/EU	Uncontrolled depression trial; n=1133; dose range 100-300mg/day; 6 weeks.
H.114.003/81FR	Uncontrolled depression trial; n=502; dose range 100-300mg/day; 4-6 weeks.
H.114.004/83FR	Uncontrolled depression trial; n=136; dose range 100-300mg/day; 6 weeks.
H.114.005/83FR	Uncontrolled depression trial; n=45; dose 100mg/day; 6 weeks.
H.114.007/83FR	Uncontrolled depression trial; n=477; dose range 100-300mg/day; 6 weeks.
H.114.012/85FR	Uncontrolled depression trial; n=134; dose range 50-300mg/day; 6 weeks.
H.114.019/87FR	Uncontrolled depression trial; n=1918; dose range 100-300mg/day; 6 weeks.
H.114.024/88FR	Uncontrolled depression trial; n=8422; dose range 100-300mg/day; 6 weeks.
H.114.915/G	Uncontrolled depression trial; n=3685; dose range 50-300mg/day; 6 weeks.
H.114.902/NL	Uncontrolled depression trial; n=387; dose range 100-300mg/day; 6(?) weeks.
H.114.904/NL	Uncontrolled depression trial; n=173; dose range 100-300mg/day; 6 weeks.
H.114.920/NL	Uncontrolled depression trial; n=45; dose range 100-300mg/day; duration unknown.
H.114.940/NL	Uncontrolled depression trial; n=60; dose range 100-300mg/day; 6 weeks.

H.114.901/PA	Uncontrolled depression trial; n=30; dose range 50-300mg/day; 6 weeks.
H.114.901/PO	Uncontrolled depression trial (protocol unavailable); n=40.
H.114.9010/PO	Uncontrolled depression trial; n=244; dose range 100-300mg/day; 12 weeks.
H.114.903/PO	Uncontrolled depression trial; n=1451; dose range 100-300mg/day; 6 weeks.
H.114.912/SP	Uncontrolled depression trial; n=2084; dose range 100-300mg/day; 12 weeks.
H.114.913/SP	Uncontrolled depression trial; n=415; dose range 50-300mg/day; 12 weeks.
H.114.914/SP	Uncontrolled depression trial; n=1503; dose range 50-300mg/day; 12 weeks.
H.114.8503/SP	Uncontrolled depression trial; n=109; dose range 100-200mg/day; 6 weeks.
H.114.901/UK	Uncontrolled depression trial; n=62; dose 100mg/day; 6 weeks.
H.114.903/UK	Uncontrolled depression trial; n=352; dose range 100-300mg/day; 6 weeks.
H.114.904/UK	Uncontrolled depression trial; n=2078; dose range 50-300mg/day; 6 weeks.
H.114.905/UK	Uncontrolled depression trial; n=720; dose range 50-300mg/day; 6 weeks.
H.114.907/UK	Uncontrolled depression trial; n=495; dose range 50-300mg/day; 6 weeks.
H.114.908/UK	Uncontrolled depression trial; n=324; dose range 50-150mg/day; 6 weeks.
H.114.920/UK	Uncontrolled depression trial; n=355; dose range 50-100mg/day; 6 weeks.
H.114.921/UK	Uncontrolled depression trial; n=2505; dose range 50-300mg/day; 6 weeks.
H.114.926/UK	Uncontrolled depression trial; n=432; dose range 100-300mg/day; 6 weeks.
H.114.900/WG	Uncontrolled depression trial; n=2296; dose range 100-300mg/day; 6 weeks.
PHASE 2 - 3 STUDIES (MISCELLANEOUS INDICATIONS)	
STRATA II: N. AMERICAN UNCONTROLLED/EUROPEAN CONTROLLED & UNCONTROLLED/SPECIAL & PILOT STUDIES (MISC.)	
H.114.5541	PC trial of fluvoxamine as an adjunct to relapse prevention in alcoholism; inpatients/outpatients, (n_1=10,n_2=9); fluvoxamine dose 50-200mg/day; 12 weeks.
H.114.5532	Uncontrolled study of fluvoxamine as an adjunct to relapse prevention in alcoholism; inpatients, (n=16); fluvoxamine dose 75-150mg/day; 52 weeks.

H.114.MSD-12	Open label, pilot study; inpatients/outpatients with panic attacks and/or agoraphobia (n=2); fluvoxamine dose 100-200mg/day; 6 weeks.
H.114.MSD-12E	Open label, long-term extension of MSD-12; panic attacks, (n=9); fluvoxamine dose 100-200mg/day; 6 weeks.
H.114.5051	Open label study; migraine prophylaxis, outpatients, n=12; fluvoxamine dose 50-300mg/day; 26 weeks.
H.114.5524	Uncontrolled study of fluvoxamine in renal impairment; n=3; fluvoxamine dose 50-300mg/day; 6 weeks.
STRATA III: WORLD-WIDE POST-MARKETING STUDIES (MISC. INDICATIONS)	
CONTROLLED STUDIES	
H.114.902/BE	PC trial in pain control; n_a=17, n_p=18; dose range 50-150mg/day; 8 weeks.
H.114.925/UK	PC, crossover trial in pain control; n_a=20, n_p=5; dose range 100-200mg/day; 12 weeks.
H.114.914/85FR	AC trial in anxious depression; n_a=52, n_{ref}=58; dose range 100-250mg/day; 4 weeks.
H.114.924/UK	AC trial in anxious depression; n_a=60, n_{ref}=61; dose range 100-300mg/day; 6 weeks.
H.114.903/NL	AC trial in emotional instability; n_a=24, n_{ref}=28; dose range 100-300mg/day; 6 weeks.
H.114.013/85FR	AC trial in alcoholism; n_a=25, n_{ref}=25; dose range 100-300mg/day; 4 weeks.
UNCONTROLLED STUDIES	
H.114.020/87FR	Uncontrolled trial in alcoholism; n=83; dose range 100-300mg/day; 13-26 weeks.
H.114.021/87FR	Uncontrolled trial in bulimia; n=18; dose range 100-300mg/day; 8 weeks.
H.114.904.SP	Uncontrolled trial in bulimia; n=20; dose 150mg/day; 8 weeks.
H.114.927/UK	Uncontrolled trial in bulimia; n=17; dose range 100-200mg/day; 8 weeks.
H.114.901/GD	Uncontrolled trial in cardiovascular disease & depression; n=64; dose 100mg/day; 4 weeks.
H.114.937/NL	Uncontrolled trial in PMS; n=8; dose range 50-300mg/day; 12 weeks.
STRATA III: WORLD-WIDE POST-MARKETING STUDIES EXCLUDED FROM THE DEDICATED DATABASE	

H.114.902/AU	Open, baseline-controlled study in patients with panic attacks; n=20; 50-300mg/day; 6 weeks.
H.114.903/AU	DB, PC crossover study of fluvoxamine/placebo added to behavior TX or dietary management in the treatment of obesity; n=62; fluvoxamine dose 100mg/day; 16 weeks.
H.114.901/BE	Open, baseline-controlled tolerance trial of fluvoxamine combined with lithium in bipolar disorder or recurrent endogenous depression; n=6; fluvoxamine dose 100-300mg/day with 600-3000mg Li^+/day; 6 weeks.
H.114.904/BE	Open, baseline-controlled trial in depressed epileptics; n=35; dose range 50-200mg/day; 4 weeks.
H.114.905/BE	Randomized, DB, PC trial in psychocutaneous disorders; n_f=37, n_p=33; fluvoxamine dose range 100-300mg/day; 4 weeks.
H.114.XXX/BE	Open, baseline-controlled trial in depression, OCD, & panic disorder; n=312; dose range 25-300mg/day; 3 months.
H.114.958/CH	Randomized, single-blind, PC, parallel group trial in fibromyalgia/fibrositis syndrome; n_f=4, n_p=4; dose 100mg/day; 4 weeks.
H.114.906/G	Randomized, DB, crossover comparison of the effect of fluvoxamine vs maprotiline on chronic pain; n_{cv}=16; fluvoxamine dose 100-150 mg/day; 6 weeks.
H.114.906/IT	Open, uncontrolled study of tolerability and efficacy in dysthymia; n=20; fluvoxamine dose 100-300mg/day; 6 months, optional up to 12 months.
H.114.907/IT	Open, uncontrolled study of tolerability and efficacy in dysthymia; n=10; fluvoxamine dose 100-300mg/day; 6 months, optional up to 12 months.
H.114.908/IT	Open, uncontrolled study of tolerability and efficacy in dysthymia; n=20; fluvoxamine dose 100-300mg/day; 6 months, optional up to 12 months.
H.114.909/IT	Open, uncontrolled study of tolerability and efficacy in anxious depression; n=15; fluvoxamine dose 100-300mg/day; 6 months, optional up to 12 months.
H.114.910/IT	Open, uncontrolled study of tolerability and efficacy in chronic and acute tension headache; n=40; fluvoxamine dose 100-200mg/day; 3 months.
H.114.900/NL	DB, partial crossover comparison trial with oxaprotiline in depression; n_x=70; fluvoxamine dose 100-300mg/day, oxaprotiline dose 100-300mg/day; 4 week treatment periods.

H.114.909/NL	Open, baseline-controlled trial in depression; n=20; dose 100-300mg/day; duration 8 weeks-10 months.
H.114.921/NL	Randomized, PC, crossover study in panic disorder; n=20; dose range 50-150mg/day; 4 week treatment periods.
H.114.934/NL	Open, baseline-controlled, pilot study in chronic PTSD; n=24; dose to 300mg/day; 12 weeks.
H.114.902/PO	Open, baseline-controlled study in patients with functional somatic complaints; n=80; dose range 100-300mg/day; 6 weeks.
H.114.907/SP	Open, uncontrolled study of the effects of acute and chronic fluvoxamine treatment on extracellular and platelet serotonin; depressed patients, n=11; fluvoxamine dose 100-150mg/day; 12 weeks.
H.114.914/SP	Open, uncontrolled study of tolerability and efficacy in depression; n=6; fluvoxamine dose 50-300mg/day; 12 weeks.
H.114.912/UK	Randomized, DB, parallel group comparison with mianserin in depressed patients with H/O M.I.; n_f=1, n_m=1; fluvoxamine dose range 100-300mg/day, mianserin dose range 60-180mg/day; 12 weeks.
H.114.917/UK	Randomized, DB, parallel group study comparing weight changes associated with fluvoxamine vs amitriptyline maintenance therapy in depression; n_{total}=31; dose ranges: fluvoxamine 100-150mg/day, amitriptyline 100-150mg/day; 6 months.
H.114.930/UK	See "Miscellaneous Clinical Pharmacology Studies"
H.114.901/WG	Single-blind, crossover study of the cardiac effects of single doses of fluvoxamine vs placebo in patients with minor cardiovascular disease; n=25; dose 150mg.
H.114.903/WG	Randomized, DB, parallel group comparison of the onset of antidepressant action of fluvoxamine vs maprotiline; depression, n_{total}=40; fluvoxamine dose 200mg/day, maprotiline dose 200mg/day; 3 weeks.
H.114.901/YU	DB, parallel group comparison of the safety & efficacy of fluvoxamine vs maprotiline in depression; n_{total}=115; fluvoxamine dose range 100-300mg/day, maprotiline dose range 100-300mg/day; 4 weeks.

APPENDIX 7.2.1

STUDY 5529: DEMOGRAPHIC CHARACTERISTICS							
Treatment Group	n	Age (years)		Sex [n(%)]		Race [n(%)]	
		Mean	Range	Male	Female	White	Non-White
Fluvoxamine	79	35.4		38 (48)	41 (52)	77 (98)	2 (2)
Placebo	80	35.8		39 (49)	41 (51)	75 (94)	6 (6)

STUDY 5529: BASELINE ILLNESS SEVERITY		
Efficacy Variable	Fluvoxamine (mean)	Placebo (mean)
Y-BOCS	23.3	22.8
NIMH-OC	8.9	8.9
CGI-Severity	4.5	4.5

STUDY 5529: NUMBER OF PATIENTS IN STUDY OVER TIME						
Treatment Group	Baseline	Week 2	Week 4	Week 6	Week 8	Week 10
Fluvoxamine	80	79	74	68	65	64
Placebo	80	80	80	78	78	76

STUDY 5529: MEAN DAILY DOSE BY WEEK										
	Week									
	1	2	3	4	5	6	7	8	9	10
Number of Patients	79	77	75	74	72	68	66	65	64	64
Mean Daily Dose Fluvoxamine (mg)	68	127	164	192	216	234	246	245	256	251

STUDY 5529: CONCOMITANT PSYCHOTROPIC MEDICATION USE		
Medication	Fluvoxamine (ITT=79)	Placebo (ITT=80)
	N	N
Lorazepam	8	3
Chloral Hydrate	5	5
Triazolam	3	0
Limbitrol	1	0
Methylphenidate	1	0

STUDY 5529 (OC DATASET): MEAN CHANGE FROM BASELINE IN Y-BOCS												
Treatment Group	Baseline		Week									
			2		4		6		8		10	
	n	X	n	Δ	n	Δ	n	Δ	n	Δ	n	Δ
Fluvoxamine	79	23.3	78	-0.8	69	-3.0	68	-4.6	67	-5.4	67	-5.8
Placebo	80	22.8	80	-1.2	79	-1.9	77	-1.7	77	-2.0	76	-1.8
p-value	0.51		0.44		0.11		0.0001		0.0001		0.0001	

STUDY 5529 (OC DATASET): MEAN CHANGE FROM BASELINE IN NIMH-OC												
Treatment Group	Baseline		Week									
			2		4		6		8		10	
	n	X	n	Δ	n	Δ	n	Δ	n	Δ	n	Δ
Fluvoxamine	79	8.9	78	-0.3	69	-0.9	68	-1.3	67	-1.6	67	-2.0
Placebo	80	8.9	80	-0.3	79	-0.4	77	-0.5	77	-0.7	76	-0.8
p-value	0.77		0.99		0.035		0.002		0.002		0.0001	

STUDY 5529 (LOCF DATASET): MEAN CHANGE FROM BASELINE TO WEEK 10				
Treatment Group	Y-BOCS		NIMH-OC	
	n	Δ	n	Δ
Fluvoxamine	79	-4.9	79	-1.7
Placebo	80	-1.7	80	-0.7
p-value	0.0002		0.0003	

STUDY 5529: MEAN VALUES OF CGI (Improvement Item)												
	Observed Cases Dataset										LOCF	
Treatment Group	Week										Week	
	2		4		6		8		10		10	
	n	X	n	X	n	X	n	X	n	X	n	X
Fluvoxamine	78	3.7	69	3.2	68	3.0	67	2.9	67	2.9	79	3.0
Placebo	80	3.8	79	3.7	77	3.6	77	3.5	75	3.5	80	3.5
p-value	0.70		0.0005		0.0001		0.0001		0.0002		0.003	

STUDY 5529: PERCENTAGE RESPONDERS BASED ON CGI (Improvement Item) SCORES												
	Observed Cases Dataset										LOCF	
Treatment Group	Week										Week	
	2		4		6		8		10		10	
	n	%	n	%	n	%	n	%	n	%	n	%
Fluvoxamine	78	6.4	69	15.9	68	27.9	67	38.8	67	43.3	79	38.0
Placebo	80	1.3	79	6.3	77	11.7	77	14.3	75	13.3	80	15.0
p-value	0.11		0.060		0.013		0.001		<0.001		0.001	

STUDY 5534: DEMOGRAPHIC CHARACTERISTICS							
Treatment Group	n	Age (years)		Sex [n(%)]		Race [n(%)]	
		Mean	Range	Male	Female	White	Non-White
Fluvoxamine	78	36.7		39 (50)	39 (50)	76 (97)	2 (3%)
Placebo	78	36.6		39 (50)	39 (50)	76 (97)	2 (3%)

STUDY 5534: BASELINE ILLNESS SEVERITY		
Efficacy Variable	Fluvoamine (mean)	Placebo (mean)
Y-BOCS	22.6	23.8
NIMH-OC	8.9	9.0
CGI-Severity	4.5	4.5

STUDY 5534: NUMBER OF PATIENTS IN STUDY OVER TIME						
Treatment Group	Baseline	Week 2	Week 4	Week 6	Week 8	Week 10
Fluvoxamine	80	78	71	66	64	59
Placebo	80	79	76	72	70	64

STUDY 5534: MEAN DAILY DOSE BY WEEK										
	Week									
	1	2	3	4	5	6	7	8	9	10
Number of Patients	78	76	71	71	69	66	64	64	61	59
Mean Daily Dose Fluvoxamine (mg)	69	124	164	198	215	222	228	230	241	245

STUDY 5534: CONCOMITANT PSYCHOTROPIC MEDICATION USE		
Medication	Fluvoxamine (ITT=78)	Placebo (ITT=78)
	N	N
Lorazepam	13	7
Chloral Hydrate	5	3
Diazepam	3	0
L-Tryptophan	1	0
Fluoxetine	0	1
Alprazolam	0	1
Triazolam	1	0
Imipramine	1	0
Cannabis	0	1
Clorazepate	0	1

STUDY 5534 (OC DATASET): MEAN CHANGE FROM BASELINE IN Y-BOCS												
Treatment Group	Baseline		Week									
			2		4		6		8		10	
	n	X	n	Δ	n	Δ	n	Δ	n	Δ	n	Δ
Fluvoxamine	78	22.6	69	-1.6	69	-3.1	63	-3.3	60	-4.6	53	-5.2
Placebo *	77	23.8	76	-1.4	72	-1.5	70	-1.4	69	-1.6	58	-1.7
p-value	0.24		0.77		0.061		0.033		0.003		0.006	

* Excludes one patient who had no baseline Y-BOCS score.

STUDY 5534 (OC DATASET): MEAN CHANGE FROM BASELINE IN NIMH-OC												
Treatment Group	Baseline		Week									
			2		4		6		8		10	
	n	X	n	Δ	n	Δ	n	Δ	n	Δ	n	Δ
Fluvoxamine	78	8.9	69	-0.4	69	-0.8	63	-0.8	60	-1.3	53	-1.7
Placebo	78	9.0	77	-0.2	73	-0.2	71	-0.2	70	-0.3	58	-0.5
p-value	0.66		0.34		0.021		0.053		0.007		0.005	

STUDY 5534 (LOCF DATASET): MEAN CHANGE FROM BASELINE TO WEEK 10				
Treatment Group	Y-BOCS		NIMH-OC	
	n	Δ	n	Δ
Fluvoxamine	78	-3.9	78	-1.3
Placebo	77 *	-1.7	78	-0.4
p-value	0.013		0.004	

* Excludes one patient who had no baseline Y-BOCS score.

STUDY 5534: MEAN VALUES OF CGI (Improvement Item)												
	Observed Cases Dataset										LOCF	
Treatment Group	Week										Week	
	2		4		6		8		10		10	
	n	X	n	X	n	X	n	X	n	X	n	X
Fluvoxamine	69	3.6	69	3.3	63	3.1	61	3.0	53	2.8	78	3.1
Placebo	77	3.7	73	3.8	71	3.7	70	3.6	58	3.6	78	3.6
p-value	0.34		0.003		0.0001		0.001		0.0002		0.0008	

APPENDIX 8.5.2.1.2a - 90th PERCENTILES FOR CHANGES FROM BASELINE IN SGOT & SGPT: STRATA I OCD POOL AND STRATA I DEPRESSION POOL *						
Liver Enzyme	Strata I Study Pool	Timepoint (week #)	FLUVOXAMINE		PLACEBO	
			N	90% Level (U/L)	N	90% Level (U/L)
SGOT	OCD	10	106	+16	128	+5
SGOT	Depression	2	494	+9	456	+10
SGOT	Depression	4	178	+11	189	+9
SGOT	Depression	6	431	+11	440	+10
SGPT	OCD	10	106	+37	128	+8
SGPT	Depression	2	476	+12	445	+12
SGPT	Depression	4	170	+18	181	+16
SGPT	Depression	6	426	+21	436	+12

* The value which equals or exceeds the change from baseline for 90% of the patients for each enzyme at each timepoint.

STUDY 5534: PERCENTAGE RESPONDERS BASED ON CGI (Improvement Item) SCORES

Treatment Group	Observed Cases Dataset										LOCF	
	Week										Week	
	2		4		6		8		10		10	
	n	%	n	%	n	%	n	%	n	%	n	%
Fluvoxamine	69	7.3	69	17.4	63	25.4	61	27.9	53	43.4	78	33.3
Placebo	77	5.2	73	6.9	71	7.0	70	11.4	58	8.6	78	9.0
p-value	0.74		0.053		0.004		0.017		<0.001		<0.001	

STUDIES 5529/5534 (COMBINED OC DATASET): MEAN CHANGE FROM BASELINE IN Y-BOCS OBSESSION SUBSCORE

Treatment Group	Baseline		Week									
			2		4		6		8		10	
	n	X	n	Δ	n	Δ	n	Δ	n	Δ	n	Δ
Fluvoxamine	157	11.3	147	-0.6	138	-1.7	131	-2.2	127	-2.7	120	-2.7
Placebo	158	11.7	157	-0.6	152	-0.8	148	-0.8	147	-0.9	134	-1.0
p-value	n.s.		n.s.		0.003		0.000		0.000		0.000	

STUDIES 5529/5534 (COMBINED OC DATASET): MEAN CHANGE FROM BASELINE IN Y-BOCS COMPULSION SUBSCORE

Treatment Group	Baseline		Week									
			2		4		6		8		10	
	n	X	n	Δ	n	Δ	n	Δ	n	Δ	n	Δ
Fluvoxamine	157	11.7	147	-0.7	138	-1.1	131	-1.8	127	-2.2	120	-2.5
Placebo	158	11.6	157	-0.7	152	-0.9	148	-0.9	147	-1.1	134	-0.8
p-value	n.s.		n.s.		n.s.		0.005		0.001		0.000	

STUDIES 5529/5534 (COMBINED LOCF DATASET): MEAN CHANGE FROM BASELINE TO WEEK 10				
Treatment Group	Y-BOCS OBSESSION SUBSCORE		Y-BOCS COMPULSION SUBSCORE	
	n	Δ	n	Δ
Fluvoxamine	157	-2.3	157	-2.2
Placebo	158	-0.8	158	-0.9
p-value	0.000		0.000	

APPENDIX 7.2.2 - OTHER TRIALS PERTINENT TO OCD EFFICACY EVALUATION

IND Number	Study Number	Study Design	Number of Patients	Fluvoxamine Dose Range (mg/day)	Study Duration	Outcome
	FR009	Randomized, double-blind, parallel group: fluvoxamine with exposure/ antiexposure vs. placebo with exposure.	$Fluv_c$= 16 $Fluv_{ae}$= 13 $Plac_c$= 15	Max.: 300	24 wks.	No consistent intergroup differences over time RE: rituals or depression. (Ratings of ritual duration/ discomfort.)
	MSD-17	Double-blind, crossover trial of fluvoxamine vs. placebo.	Fluv= 10 Plac= 10	300	8 weeks/ TX phase	13 fluv. patients improved vs. 3 placebo patients improved. (Multiple scales)
	-	Double-blind, fluvoxamine vs. placebo.	Fluv= 21 Plac= 21	50-300	6-8 wks.	9 fluvoxamine responders, 0 placebo responders (Y-BOCS)
	-	Double-blind, fluvoxamine vs. desipramine.	Fluv= 21 Desi= 19	100-300 (each drug)	8 weeks	11 fluvoxamine responders, 2 desipramine responders. (Y-BOCS)
	5529E	Open label, humanitarian extension.	Fluv= 114	100-300	1 year	No defined efficacy results; therapeutic response maintained. (NIMH-OC)

APPENDIX 7.2.2 - OTHER TRIALS PERTINENT TO OCD EFFICACY EVALUATION						
IND Number	Study Number	Study Design	Number of Patients	Fluvoxamine Dose Range (mg/day)	Study Duration	Outcome
	5534E	Open label, humanitarian extension.	Fluv= 71	100-300	1 year	No defined efficacy results; therapeutic response maintained. (NIMH-OC)
	5533	Open label, compassionate use protocol.	Fluv= 209	50-400	1 year	No reliable efficacy data.
	5540-O	Open label, compassionate use protocol.	Fluv= 124	100-300	Ongoing	No reliable efficacy data.
	-	Single-blind, uncontrolled trial in refractory pts.	Fluv= 10	50-300	4 weeks	6 responders. (Y-BOCS)
	-	Open label trial of adjunctive neuroleptic in fluvoxamine-refractory pts.	Fluv= 17	Mean dose= 291	Mean= 4.7 wks.	9 responders with the addition of neuroleptic. (Y-BOCS)
	-	Double-blind trial of fluv/lithium vs fluv/placebo in fluvoxamine-refractory pts.	Fluv/Li^+= 11 Fluv/plac= 9	200-300	2 weeks	2 fluv/Li^+ responders, 0 fluv/plac responders. (Y-BOCS)

APPENDIX 7.2.2 - OTHER TRIALS PERTINENT TO OCD EFFICACY EVALUATION						
IND Number	Study Number	Study Design	Number of Patients	Fluvoxamine Dose Range (mg/day)	Study Duration	Outcome
	-	Double-blind trial of fluv/lithium vs fluv/placebo in fluvoxamine-refractory pts.	Fluv/Li+= 5 Fluv/plac= 5	200-300	4 weeks	0 fluv/Li+ responders, 0 fluv/plac responders. (Y-BOCS)
	-	Double-blind trial of fluv/buspirone vs fluv/plac in fluvoxamine-refractory pts.	Fluv/ buspirone= 32 Fluv/plac= 32	200-300	14 weeks	Trial ongoing at NDA cut-off.
	-	Double-blind trial of fluv/haloperidol vs fluv/plac in fluvoxamine-refractory pts.	Fluv/hal= 32 Fluv/plac= 32	200-300	12 weeks	Trial ongoing at NDA cut-off.

APPENDIX 8.2.1 - DEATHS ON FLUVOXAMINE						
Protocol#	Patient#	Age	Sex	Dose(mg/day)	Days of TX	Cause of Death
STRATA II						
5017		63	M	150	5	Suicide
5046		51	M	30	1	Accidental Injury
5066		75	F	100	~120	Stroke
5066		61	M	75	~210	Heart Attack
5066		65	M	200	~1100	Hemorrhagic Pleurisy
5079		56	M	150	~60	Lung Cancer
5091		84	F	100	~8	Suicide (hanging)
5091		84	F	100	~8	Cardiac Failure
5091		61	F	150	~10	Suicide (drowning)
5533		29	M	350	~26	Suicide
5540		38	M	300	~900	Suicide (CO poisoning)
5045[1]		52	F	300	27, 60[2]	Suicide
5066[1]		70	M	150	~180, 7[2]	Heart Attack
5066[1]		71	F	75	2, Unk.[2]	Unknown
5066[1]		43	F	75	3, 180[2]	Heart Attack

[1]Post-study death (>3 days after last dose).

[2]Days post-study at time of death.

APPENDIX 8.2.1 - DEATHS ON FLUVOXAMINE						
Protocol#	Patient#	Age	Sex	Dose(mg/day)	Days of TX	Cause of Death
5067[1]		30	F	300	11, 45[2]	Pulmonary Embolism
5101[1]		66	F	50	~100, 165[2]	Suicide (drowning)
5533[1]		37	F	50	10, 75[2]	Sepsis
STRATA III						
BE.903		39	M	100	39	Cerebral Aneurysm Rupt.
FR.007		56	F	100	4	Suicide
FR.007		74	F	100	Unk.	Suicide (defenestration)
FR.012		84	F	100	16	Influenza
FR.015		60	F	200	86	Suicide (drowning)
FR.015		68	F	200	119	Heart Attack
FR.015		57	M	200	14	Suicide (hanging)
FR.015		42	F	300	117	Suicide
FR.019		66	F	100	28	Cardiac Arrest
FR.019		67	F	150	Unk.	Uterine Cancer
FR.024		78	M	100	3	Bronchopulmonary Infection
FR.024		34	M	150	23	Suicide
FR.024		78	F	300	Unk.	Unknown
FR.024		81	M	150	Unk.	Suicide (gunshot)
FR.024		82	F	100	70	Unknown

APPENDIX 8.2.1 - DEATHS ON FLUVOXAMINE						
Protocol#	Patient#	Age	Sex	Dose(mg/day)	Days of TX	Cause of Death
FR.024		52	F	300	19	Suicide
FR.024		77	F	100	32	Aneurysm Rupture
FR.024		62	F	100	16	Unknown
FR.024		45	M	100	Unk.	Suicide
FR.024		80	M	200	44	Gastrointestinal Cancer
FR.024		24	M	150	Unk.	Suicide
FR.024		32	F	150	Unk.	Unknown
FR.024		28	M	200	17	Suicide
FR.024		47	M	100	Unk.	Cardiac Arrest
FR.024		68	M	100	Unk.	Suicide (hanging)
NL.902		67	Unk	150	Unk.	Suicide
NL.902		63	F	100	83	Heart Attack
NL.902		92	M	50	3	Pneumonia
NL.909		?	F	300	49	Suicide
UK.904		58	M	50	8	Brain Tumor
UK.905		78	F	100	53	Bronchopneumonia
UK.905		75	M	50	18	Suicide (hit by train)
UK.908		18	M	100	11	Skull Fracture (accidental)
UK.921		47	F	150	14	Unknown

APPENDIX 8.2.1 - DEATHS ON FLUVOXAMINE

Protocol#	Patient#	Age	Sex	Dose(mg/day)	Days of TX	Cause of Death
WG.900		80	F	100	6	Breast Cancer
WG.900		52	F	150	31	Suicide
G.915		84	F	50	37	Unknown
PO.903		23	M	100	Unk.	Accidental Injury
SP.912		47	M	100	21	Suicide
SP.912		57	M	100	29	Suicide
SP.912		72	F	200	29	Unknown
SP.912		72	F	100	25	Stroke
SP.912		57	M	100	~50	Suicide
SP.912		76	F	100	12	Accidental Injury
SP.914		77	M	100	76	Pneumonia
SP.914		34	M	100	12	Sepsis (HIV-related)
EU.901[1]		Unk	F	100	3	Unknown
FR.003[1]		85	F	150	16, 4[2]	Stroke
FR.004[1]		75	M	200	169, >30[2]	Suicide
FR.024[1]		33	F	100	56, 16[2]	Lymphoma
FR.024[1]		60	F	300	Unk., Unk[2]	Suicide
FR.024[1]		64	F	200	43, Unk[2]	Unknown
FR.024[1]		84	F	100	8, 30[2]	Pulmonary Embolism

APPENDIX 8.2.1 - DEATHS ON FLUVOXAMINE						
Protocol#	Patient#	Age	Sex	Dose(mg/day)	Days of TX	Cause of Death
NL.902[1]		76	Unk	100	19, 15[2]	Glioblastoma
NL.902[1]		73	Unk	100	15, Unk[2]	CNS Mesothelioma
UK.903[1]		69	M	200	18, ~30[2]	Pancreatic Cancer
UK.907[1]		75	M	50	15, 5[2]	Bronchopneumonia
UK.907[1]		54	F	100	13, 12[2]	Suicide (poisoning)
STRATA IV						
		77	M	150	7	Heart Attack
		42	F	50	5	Suicide (hanging)
		50	F	Unk.	Unk.	Suicide (overdose)
		67	M	150	3	Suicide
		43	F	150	28	Suicide (hanging)
		54	M	150	7	Suicide (hanging)
		70	F	100	~730	Unknown
		Unk	F	Unk.	5	Suicide
		38	F	50	2	Heart Attack
		45	F	300	~35	Unknown
		74	F	Unk.	Unk.	Unknown
		35	F	Unk.	Unk.	Suicide (overdose)
		7	M	Unk.	Unk.	Suicide (overdose)

APPENDIX 8.2.1 - DEATHS ON FLUVOXAMINE						
Protocol#	Patient#	Age	Sex	Dose(mg/day)	Days of TX	Cause of Death
		61	M	100	4	Pancreatitis
		71	F	Unk.	Unk.	Suicide (overdose)
		40	F	Unk.	Unk.	Suicide (overdose)
		79	F	50	4	Cardiac Failure
		82	M	50	2	Rupt. Aortic Aneurysm
		33	F	Unk.	Unk.	Suicide (overdose)
		66	F	200	23	Unknown
		66	F	50	3	Heart Attack
		Unk	M	150	15	Sepsis
		80	M	100	9	Duod. Ulcer Hemorrhage
		53	F	100	~150	Stroke
		Unk	M	50	10	Heart Attack
		63	F	100	5	GI Hemorrhage
		78	M	150	46	Pancreatitis
		66	F	100	~35	Heart Attack
		80	F	50	4	Cardiac Failure
		81	F	50	5	Stroke
		Unk	M	100	Unk.	Suicide
		53	F	250	~180	Suicide (overdose)

APPENDIX 8.2.1 - DEATHS ON FLUVOXAMINE						
Protocol#	Patient#	Age	Sex	Dose(mg/day)	Days of TX	Cause of Death
		59	F	200	22	Aspiration Pneumonia
		38	M	300	~330	Sudden Death (thioridazine)
		36	M	50	Unk.	Suicide (overdose)
		49	F	Unk.	Unk.	Suicide (overdose)
		75	F	50	~90	Unknown
		80	M	100	3	Leuko/Thrombocytopenia
		Unk	Unk	Unk.	Unk.	Suicide (overdose)
		29	F	Unk.	Unk.	Suicide (overdose)
		Unk	M	100	20	Heart Attack
		59	M	100	~60	Suicide (drowning)
		26	F	100	4	Bronchopneumonia
		80	F	300	Unk.	Suicide
		88	F	100	12	Unknown
		30	F	Unk.	Unk.	Suicide (overdose)
		80	M	Unk.	Unk.	Suicide (overdose)
		74	F	Unk.	Unk.	Suicide (overdose)
		48	F	100	6	Suicide (overdose)
		62	M	50	Unk.	Accidental Drowning
		Unk	F	Unk.	Unk.	Suicide (overdose)

APPENDIX 8.2.1 - DEATHS ON FLUVOXAMINE						
Protocol#	Patient#	Age	Sex	Dose(mg/day)	Days of TX	Cause of Death
		35	M	100	<14	Sudden Death (epilepsy)
		62	M	50	126	Cardiac Arrest
		29	M	50	Unk.	Suicide (overdose)
		83	F	100	63	Unknown
		37	M	Unk.	259	Pulmonary Embolism
		77	F	Unk.	Unk.	Unknown
		77	F	50	<7	Heart Failure
		50	F	200	Unk.	Suicide (overdose)
		32	M	50	7	Suicide (hit by train)
		43	M	100	14	Suicide (defenestration)
		Unk	M	Unk.	Unk.	Unknown
		Unk	Unk	Unk.	14	Suicide (overdose)
		Unk	F	Unk	Unk	Suicide (defenestration)
		Unk	Unk	Unk	Unk	Unknown
		Unk	Unk	Unk.	Unk.	Unknown
		36	M	100	49	Sudden Death (phenothiazine)
STRATA V						
5056[1]		Unk	M	150	Unk, Unk[2]	Hepatic Carcinoma
5056		56	F	200	16	Sepsis

APPENDIX 8.2.1 - DEATHS ON FLUVOXAMINE						
Protocol#	Patient#	Age	Sex	Dose(mg/day)	Days of TX	Cause of Death
5072[1]		36	F	200	20, 8[2]	Cardiac Arrest

APPENDIX 8.2.2 DEATHS ON PLACEBO & OTHER ACTIVE DRUGS						
Protocol#	Patiert#	Age	Sex	Treatment	Days of TX	Cause of Death
STRATA I						
5510[3]		48	F	Imipramine	36, 11[4]	Suicide (overdose)
STRATA II						
5045[3]		42	F	Placebo	20, 60[4]	Suicide
5015[3]		60	F	Clomipramine	1, ~60[4]	Suicide (overdose)
STRATA III						
UK.910		67	F	Dothiepin	35	Suicide (drowning)
UK.914[3]		66	F	Dothiepin	16, 13[4]	Suicide (overdose)
UK.915		72	M	Mianserine	17	Heart Attack
UK.915		77	M	Mianserine	42, ~30[4]	Unknown
UK.915		68	M	Mianserine	52	Heart Attack
STRATA V						
5056[3]		58	F	Imipramine	>120	Choking
5056E		57	M	Imipramine	85	Suicide (hanging)

[3]Post-study death (> 3 days after last dose).

[4]Days post-study at the time of death.

[5]Patient continued imipramine therapy post-study until the time of death.

APPENDIX 8.4.1 - SERIOUS ADVERSE EVENTS NOT SELECTED FOR REVIEW *	
Abdominal Pain	Dyspepsia
Abortion	Dysphagia
Abscess	Ecchymosis
Accidental Injury	Emotional Lability
Agitation	Head Trauma
Amblyopia	Headache
Angina Pectoris (1)	Hernia
Anorexia	Hostility
Anxiety	**Hyperglycemia (2)**
Arteritis (1)	Hyperkinesia
Arthritis (1)	**Hyperuricemia (1)**
Asthenia	Hypesthesia
Asthma (4)	**Hypokalemia (2)**
Ataxia	Hysteria
Back Pain	Increased Salivation
Bronchiectasis (1)	Infection
Bronchitis (1)	Insomnia
Chest Pain	Malaise
Cholecystitis (5)	Manic Reaction
Cholelithiasis (2)	Masked Facies
Colitis (1)	Menstrual Disorder
Confusion	Nausea
Constipation	Neck Pain
Convulsion	Nervousness
Dehydration	**Neuritis (1)**
Depersonalization	Neurosis
Depression	Overdose
Diarrhea	Pain
Dizziness	Pallor
Drug Dependence	Palpitation

APPENDIX 8.4.1 - SERIOUS ADVERSE EVENTS NOT SELECTED FOR REVIEW *	
Paranoid Reaction	Suicide Attempt
Paresthesia	Sweating
Pathological Fracture (1)	**Syncope (17)**
Peptic Ulcer (3)	Testicular Torsion
Personality Disorder	Thinking Abnormal
Pneumonia (2)	Tremor
Pregnancy	Urinary Frequency
Psoriasis	**Urinary Incontinence (2)**
Psychosis	Urinary Tract Infection
Psychotic Depression	Urticaria
Salpingitis (1)	Varicose Veins
Sinusitis (1)	Vascular Anomaly
Somnolence	Vasodilatation
Speech Disorder	Vertigo
Suicidal Ideation	Vomiting
	Weight Loss

* Bolded events are those which could possibly represent significant, drug-related findings but which occurred in numbers not deemed to be unusual in this large database (N_{fluv}> 37,000); the number of observed cases in this database for each such event is provided in parentheses.

APPENDIX 8.5.1.1

Treatment-Emergent Adverse Experience Incidence in Pooled Placebo-Controlled Clinical Trials in OCD[1]

Body System	Preferred Term	Fluvoxamine (n=160)	Placebo (n=160)
Nervous	Insomnia	31.3%	14.4%
	Somnolence	28.1%	9.4%
	Nervousness	15.6%	6.2%
	Dry Mouth	11.9%	3.1%
	Anxiety	10.6%	8.1%
	Dizziness	9.4%	5.0%
	Thinking Abnormal[2]	8.8%	3.1%
	Tremor	8.1%	0.6%
	Depression	6.9%	4.4%
	Libido Decreased	5.6%	1.9%
	Myoclonus and/or Twitch	4.4%	1.9%
	Agitation	3.7%	0.0%
	Vasodilatation	3.7%	1.3%
	Abnormal Dreams	3.1%	1.9%
	Paresthesia	3.1%	4.4%
	Akathisia	1.3%	0.0%
	CNS Stimulation	1.3%	0.6%
	Confusion	1.3%	0.0%
	Hypertonia	1.3%	2.5%
Digestive System	Nausea	29.4%	6.9%
	Constipation	14.4%	8.8%
	Dyspepsia	13.8%	9.4%
	Diarrhea	11.9%	8.8%
	Anorexia	8.1%	3.1%
	Flatulence	4.4%	5.6%
	Thirst	3.7%	0.0%
	Vomiting	3.1%	2.5%
	Tooth Disorder[3]	2.5%	0.6%
	Increased Appetite	1.9%	1.3%
	Gingivitis	1.3%	0.0%
	Rectal Disorder[4]	1.3%	0.0%
Body as a Whole	Asthenia	28.1%	10.0%
	Headache	20.0%	23.8%
	Infection[5]	11.3%	9.4%
	Abdominal Pain	6.2%	8.1%
	Flu Syndrome	5.0%	3.7%
	Pain[6]	4.4%	2.5%
	Chest Pain	3.1%	1.9%
	Back Pain	2.5%	3.7%
	Fever	2.5%	2.5%
	Chills	1.9%	0.0%
	Accidental Injury	1.3%	1.3%

APPENDIX 8.5.1.1

Treatment-Emergent Adverse Experience Incidence in Pooled Placebo-Controlled Clinical Trials in OCD[1]

Body System	Preferred Term	Fluvoxamine (n=160)	Placebo (n=160)
Respiratory	Rhinitis	8.8%	3.1%
	Pharyngitis	6.2%	5.6%
	Dyspnea	3.1%	0.6%
	Yawn	1.9%	0.0%
Skin	Sweating	7.5%	1.9%
	Pruritis	2.5%	0.0%
	Rash	2.5%	3.1%
	Skin Disorder[7]	1.3%	0.0%
Special Senses	Taste Perversion	5.0%	0.0%
	Ear Pain[8]	1.9%	0.6%
	Amblyopia[9]	1.3%	0.6%
Musculoskeletal	Leg Cramps	1.9%	0.0%
	Myalgia	1.9%	2.5%
	Myasthenia	1.3%	0.6%
Metabolic/Nutritional	Weight Loss	3.7%	0.6%
Cardiovascular	Palpitation	1.9%	2.5%
Hematic	Ecchymosis	1.3%	0.0%
Urogenital	Abnormal Ejaculation[10,11]	17.9%	0.0%
	Anorgasmia (Males)[11]	7.7%	0.0%
	Urinary Frequency	5.0%	1.3%
	Impotence[11]	3.8%	1.3%
	Anorgasmia (Females)[11]	2.4%	0.0%
	Dysmenorrhea[11]	2.4%	8.6%
	Urinary Retention	1.9%	0.0%

1 Events reported by at least 1% of patients treated with fluvoxamine are included.
2 Mostly concentration difficulty.
3 Bruxism.
4 Hemmorhoids.
5 Mostly colds, rhinitis, and URI.
6 Mostly joint pain.
7 Skin surgery.
8 Earache.
9 Mostly blurred vision.
10 Mostly delayed ejaculation.
11 Incidence rates corrected for gender.

APPENDIX 8.5.1.2

Treatment-Emergent Adverse Experience Incidence in Pooled Short-Term Placebo-Controlled Clinical Trials in Depression[1]

Body System	Preferred Term	Fluvoxamine (n=732)	Placebo (n=618)
Digestive	Nausea	42.2%	16.0%
	Diarrhea	11.2%	6.3%
	Constipation	9.4%	7.1%
	Dyspepsia	9.0%	4.4%
	Anorexia	6.0%	2.3%
	Vomiting	5.2%	1.9%
	Flatulence	4.0%	2.3%
	Dysphagia	1.8%	0.8%
	Increased Appetite	1.0%	1.8%
Nervous System	Somnolence	20.8%	8.1%
	Insomnia	18.3%	8.3%
	Dry Mouth	14.6%	12.3%
	Nervousness	11.2%	4.7%
	Dizziness	10.8%	5.8%
	Tremor	4.6%	1.0%
	Anxiety	4.0%	2.1%
	Thinking Abnormal[2]	3.7%	2.3%
	Hypertonia	2.6%	0.8%
	Vasodilatation	2.3%	1.0%
	Paresthesia	1.8%	2.8%
	Agitation	1.6%	0.6%
	CNS Stimulation[3]	1.5%	0.5%
	Abnormal Dreams	1.4%	1.9%
	Libido Decreased	1.1%	0.2%
	Confusion	1.0%	1.6%
Body as a Whole	Headache	21.9%	18.9%
	Asthenia	10.5%	4.4%
	Infection[4]	6.0%	5.5%
	Abdominal Pain	4.0%	2.6%
	Pain	3.6%	4.0%
	Back Pain	2.3%	3.4%
	Flu Syndrome	2.2%	1.1%
	Chills	2.0%	1.8%
	Chest Pain	1.9%	2.9%
	Fever	1.4%	1.8%
Skin	Sweating	6.8%	3.2%
	Rash	2.0%	1.9%
	Pruritis	2.0%	3.1%
Respiratory	Rhinitis	2.6%	3.7%
	Dyspnea	1.6%	1.6%
	Yawn	1.5%	0.2%
	Pharyngitis	1.4%	1.1%

APPENDIX 8.5.1.2

Treatment-Emergent Adverse Experience Incidence in Pooled Short-Term Placebo-Controlled Clinical Trials in Depression[1]

Body System	Preferred Term	Fluvoxamine (n=732)	Placebo (n=618)
Special Senses	Amblyopia[5]	2.9%	1.9%
	Taste Perversion	2.2%	1.6%
	Tinnitus	1.2%	0.8%
Cardiovascular	Palpitation	2.9%	1.8%
	Migraine[6]	1.2%	0.3%
	Postural Hypotension	1.2%	1.5%
Musculoskeletal	Myalgia	1.1%	1.0%
Urogenital	Abnormal Ejaculation[7,8]	4.5%	0.8%
	Urinary Frequency	2.2%	1.9%
	Impotence[8]	1.9%	0.8%
	Anorgasmia (Males)[8]	1.9%	0.0%
	Dysmenorrhea[8]	1.7%	1.6%
	Urinary Retention	1.2%	0.5%
	Menstrual Disorder[8,9]	1.1%	0.5%
	Vaginitis[8]	1.1%	1.9%

1 Events reported by at least 1% of patients treated with fluvoxamine are included.
2 Mostly spacey, difficulty concentrating, and feeling drugged.
3 Mostly nightmares, bad dreams, and increased dreaming.
4 Mostly colds, rhinitis, and URI.
5 Mostly blurred vision.
6 Mostly migraine headaches.
7 Mostly delayed ejaculation and ejaculatory failure.
8 Incidence rates corrected for gender.
9 Mostly delayed menses.

APPENDIX 8.5.1.3 - ADAPTATION TO COMMON, DRUG-RELATED ADVERSE EXPERIENCES						
	N	Incidence (%) *				
	Week 1	Week 2	Week 3	Week 4	Week 5	Week 6
Abnormal Ejaculation	1	100%	100%	100%	100%	100%
Anorexia	36	67%	39%	17%	11%	6%
Anorgasmia (males)	1	100%	100%	100%	100%	100%
Asthenia	50	72%	50%	36%	28%	20%
Dry Mouth	67	73%	54%	48%	40%	37%
Dyspepsia	39	62%	21%	18%	13%	5%
Insomnia	74	62%	39%	30%	23%	20%
Libid. Decreased	1	0%	0%	0%	0%	0%
Nausea	53%	27%	18%	11%	7%	4%
Nervousness	56	45%	21%	18%	9%	7%
Rhinitis	8	75%	63%	63%	63%	50%
Somnolence	92	70%	43%	36%	30%	23%
Sweating	19	74%	53%	47%	26%	21%
Taste Perversion	11	73%	36%	36%	27%	18%
Thinking Abnormal	21	86%	33%	29%	24%	14%
Tremor	19	53%	37%	21%	21%	21%
Urinary Frequency	5	40%	0%	0%	0%	0%
Vomiting	13	31%	8%	0%	0%	0%

* The rate denominator equals N, the number of patients with the adverse event at Week 1.

APPENDIX 8.5.2.1.1
Median Change from Baseline to Last Visit in Serum Chemistry Values in Placebo-Controlled Studies: OCD Study Pool

Serum Chemistry Variables	FLUVOXAMINE		PLACEBO	
	Total Patients	Median Change	Total Patients	Median Change
Albumin (g/dl)	144	-0.10	147	-0.10
Alk. P'tase (U/L)	144	+7.00	147	0.00
BUN (mg/dl)	144	0.00	147	-1.00
Calcium (mg/dl)	144	-0.10	147	0.00
Chloride (mEq/L)	144	-1.00	147	0.00
Cholesterol (mg/dl)	144	-8.00	147	-10.00
Creatinine (mg/dl)	144	0.00	147	0.00
Globulin (g/dl)	144	0.00	147	0.00
Glucose (mg/dl)	144	-3.00	147	0.00
LDH (U/L)	144	+10.50	147	-2.00
Phosphorus (mg/dl)	144	-0.20	147	0.00
Potassium (mEq/L)	144	-0.10	147	0.00
SGOT (U/L)	144	+2.00	147	0.00
SGPT (U/L)	144	+3.00	147	0.00
Sodium (mEq/L)	144	0.00	147	0.00
T. Bilirubin (mg/dl)	144	0.00	147	0.00
Uric Acid (mg/dl)	144	+0.05	147	0.00

APPENDIX 8.5.2.1.2
Median Change from Baseline to Last Visit in Serum Chemistry Values in Placebo-Controlled Studies: Depression Study Pool

Serum Chemistry Variables	FLUVOXAMINE		PLACEBO		OTHER ACTIVE	
	Total Patients	Median Change	Total Patients	Median Change	Total Patients	Median Change
Albumin (g/dl)	350	0.00	351	-0.10	291	0.00
Alk. P'tase (U/L)	756	+1.00	679	-2.00	479	+4.00
BUN (mg/dl)	755	0.00	677	0.00	476	0.00
Calcium (mg/dl)	349	-0.10	352	-0.10	292	-0.10
Chloride (mEq/L)	349	0.00	351	0.00	291	-1.00
Cholesterol (mg/dl)	350	-9.00	351	-4.00	291	-2.00
Creatinine (mg/dl)	751	0.00	673	0.00	46	0.00
Globulin (g/dl)	348	-0.10	350	-0.10	289	0.00
Glucose (mg/dl)	349	+1.00	352	+1.00	292	-1.00
LDH (U/L)	752	+4.00	676	-1.00	474	0.00
Phosphorus (mg/dl)	349	-0.10	352	0.00	292	+0.10
Potassium (mEq/L)	349	0.00	351	0.00	291	0.00
SGOT (U/L)	756	0.00	678	0.00	476	+1.00
SGPT (U/L)	736	+1.00	665	0.00	455	+2.00
Sodium (mEq/L)	349	0.00	351	0.00	291	-1.00
T. Bilirubin (mg/dl)	757	0.00	676	0.00	476	0.00
Uric Acid (mg/dl)	755	+0.10	679	0.00	479	-0.10

APPENDIX 8.5.2.1.2a - 90th PERCENTILES FOR CHANGES FROM BASELINE IN SGOT & SGPT: STRATA I OCD POOL AND STRATA I DEPRESSION POOL *						
Liver Enzyme	Strata I Study Pool	Timepoint (week #)	FLUVOXAMINE		PLACEBO	
			N	90% Level (U/L)	N	90% Level (U/L)
SGOT	OCD	10	106	+16	128	+5
SGOT	Depression	2	494	+9	456	+10
SGOT	Depression	4	178	+11	189	+9
SGOT	Depression	6	431	+11	440	+10
SGPT	OCD	10	106	+37	128	+8
SGPT	Depression	2	476	+12	445	+12
SGPT	Depression	4	170	+18	181	+16
SGPT	Depression	6	426	+21	436	+12

* The value which equals or exceeds the change from baseline for 90% of the patients for each enzyme at each timepoint.

APPENDIX 8.5.2.1.3
Proportions of Patients Having Potentially Clinically Significant Blood Chemistry Values in Placebo-Controlled Studies: OCD Study Pool

Blood Chemistry Variables	FLUVOXAMINE			PLACEBO		
	Total Patients	Abnormal #	Abnormal %	Total Patients	Abnormal #	Abnormal %
Albumin-Low	144	0	0%	147	0	0%
Alk. P'tase-High	144	0	0%	147	0	0%
BUN-High	144	1	<1%	147	0	0%
Calcium-Low	144	0	0%	147	1	<1%
Calcium-High	144	0	0%	147	0	0%
Chloride-Low	144	0	0%	147	0	0%
Chloride-High	144	0	0%	147	0	0%
Cholesterol-High	144	0	0%	147	0	0%
Creatinine-High	144	0	0%	147	1	<1%
Globulin-Low	144	0	0%	147	0	0%
Glucose-High	144	4	3%	147	1	<1%
Glucose-Low	144	0	0%	147	0	0%
LDH-High	144	0	0%	147	0	0%
Phosphorus-Low	144	0	0%	147	0	0%
Potassium-Low	144	0	0%	147	0	0%
Potassium-High	144	1	<1%	147	1	<1%
SGOT-High	144	0	0%	147	0	0%
SGPT-High	144	1	<1%	147	0	0%
Sodium-Low	144	0	0%	147	0	0%
Sodium-High	144	0	0%	147	0	0%
Total Bilirubin-High	144	0	0%	147	1	<1%
Uric Acid-High	144	0	0%	147	0	0%

APPENDIX 8.5.2.1.4
Proportions of Patients Having Potentially Clinically Significant Blood Chemistry Values in Placebo Controlled Studies: Depression Study Pool

Blood Chemistry Variables	FLUVOXAMINE			PLACEBO			OTHER ACTIVE		
	Total Patients	Abnormal #	%	Total Patients	Abnormal #	%	Total Patients	Abnormal #	%
Albumin-Low	350	0	0	355	0	0%	292	0	0%
Alk. P'tase-High	774	1	<1%	487	0	0%	487	0	0%
BUN-High	774	3	<1%	696	2	<1%	485	4	<1%
Calcium-Low	349	1	<1%	355	1	<1%	292	1	<1%
Calcium-High	349	0	0%	355	0	0%	292	0	0%
Chloride-Low	349	1	<1%	355	0	0%	291	0	0%
Chloride-High	349	0	0%	355	0	0%	291	0	0%
Cholesterol-High	350	0	0%	355	0	0%	292	0	0%
Creatinine-High	770	1	<1%	693	0	0%	481	2	<1%
Globulin-Low	348	0	0%	354	0	0%	291	0	0%
Glucose-Low	349	1	<1%	355	0	0%	292	1	<1%
Glucose-High	349	11	3%	355	7	2%	292	7	2%
LDH-High	770	0	0%	696	0	0%	483	0	0%
Phosphorus-Low	349	1	<1%	355	0	0%	292	0	0%
Potassium-Low	349	0	0%	355	0	0%	291	0	0%
Potassium-High	349	0	0%	355	2	<1%	291	0	0%
SGOT-High	774	0	0%	695	2	<1%	486	5	1%
SGPT-High	762	6	<1%	682	5	<1%	465	14	3%
Sodium-Low	349	0	0%	355	0	0%	291	0	0%
Sodium-High	349	0	0%	355	0	0%	291	0	0%
Total Bilirubin-High	773	3	<1%	697	0	0%	485	0	0%
Uric Acid-High	772	9	1%	697	6	<1%	487	4	<1%

APPENDIX 8.5.2.2.1
Median Change from Baseline to Last Visit in Hematology Values in Placebo-Controlled Studies: OCD Study Pool

Hematology Variables	FLUVOXAMINE		PLACEBO	
	Total Patients	Median Change	Total Patients	Median Change
Hemoglobin (g/dl)	140	-0.20	144	-0.10
Hematocrit (%)	140	0.00	144	-0.45
RBC ($\times 10^6/mm^3$)	139	0.00	144	0.00
MCV (fl)	140	0.00	144	0.00
MCH (pg)	139	-0.10	144	-0.10
MCHC (%)	139	0.00	144	0.00
WBC ($\times 10^3/mm^3$)	140	0.00	144	-0.10
Neutrophils (%)	143	-1.00	147	-1.00
Lymphocytes (%)	143	+1.00	147	+1.00
Monocytes (%)	143	0.00	147	0.00
Eosinophils (%)	143	0.00	147	0.00
Basophils (%)	143	0.00	147	0.00
Platelets ($\times 10^3/mm^3$)	138	-5.00	142	-1.50

APPENDIX 8.5.2.2.2
Median Change from Baseline to Last Visit in Hematology Values in Placebo-Controlled Studies: Depression Study Pool

Hematology Variables	FLUVOXAMINE		PLACEBO		OTHER ACTIVE	
	Total Patients	Median Change	Total Patients	Median Change	Total Patients	Median Change
Hemoglobin (g/dl)	747	-0.10	667	-0.20	473	-0.10
Hematocrit (%)	747	-0.		-0.80	472	0.00
RBC (× 10^6/mm^3)	349	-0		-0.08	290	+0.02
MCV (fl)	349	0.		0.00	288	0.00
MCH (pg)	349	0.00		0.00	289	0.00
MCHC (%)	349	0.00	3.3	0.00	289	0.00
WBC (× 10^3/mm^3)	747	-0.10	666	0.20	473	-0.30
Neutrophils (%)	744	+0.60	660	0.00	463	0.00
Lymphocytes (%)	350	-1.00	354	+1.00	290	0.00
Monocytes (%)	351	0.00	354	0.00	290	0.00
Eosinophils (%)	743	0.00	659	0.00	460	0.00
Basophils (%)	350	0.00	352	0.00	290	0.00
Platelets (× 10^3/mm^3)	686	-6.00	620	-4.00	410	0.00

APPENDIX 8.5.2.2.3

Proportions of Patients Having Potentially Clinically Significant Hematology Values in Placebo-Controlled Studies: OCD Study Pool

Hematology Variables	FLUVOXAMINE			PLACEBO		
	Total Patients	Abnormal #	%	Total Patients	Abnormal #	%
Hemoglobin-Low	140	0	0%	146	0	0%
Hematocrit-Low	140	1	<1%	146	1	<1%
RBC-Low	139	0	0%	146	0	0%
MCV-Low	140	0	0%	146	0	0%
MCV-High	140	0	0%	146	0	0%
MCH-Low	139	1	<1%	146	0	0%
MCHC-Low	139	0	0%	146	0	0%
WBC-Low	140	2	1%	146	0	0%
WBC-High	140	0	0%	146	1	<1%
Neutrophils-Low	143	0	0%	147	0	0%
Lymphocytes-High	143	0	0%	147	0	0%
Monocytes-High	143	0	0%	147	0	0%
Eosinophils-High	143	0	0%	147	0	0%
Basophils-High	143	0	0%	147	0	0%
Platelet Ct-Low	138	0	0%	144	0	0%
Platelet Ct-High	138	0	0%	144	0	0%

APPENDIX 8.5.2.2.4

Proportions of Patients Having Potentially Clinically Significant Hematology Values in Placebo-Controlled Studies: Depression Study Pool

Hematology Variables	FLUVOXAMINE			PLACEBO			OTHER ACTIVE		
	Total Patients	Abnormal #	%	Total Patients	Abnormal #	%	Total Patients	Abnormal #	%
Hemoglobin-Low	771	1	<1%	687	0	0%	485	0	0%
Hematocrit-Low	771	3	<1%	687	6	<1%	485	4	<1%
RBC-Low	350	0	0%	355	0	0%	292	0	0%
MCV-Low	350	0	0%	355	0	0%	292	0	0%
MCV-High	350	0	0%	355	0	0%	292	0	0%
MCH-Low	350	0	0%	354	0	0%	292	0	0%
MCHC-Low	350	0	0%	354	0	0%	292	0	0%
WBC-Low	771	7	<1%	686	2	<1%	484	7	1%
WBC-High	771	0	0%	686	3	<1%	484	3	<1%
Neutrophils-Low	770	0	0%	684	0	0%	480	1	<1%
Lymphocytes-High	351	0	0%	356	1	<1%	292	0	0%
Monocytes-High	351	0	0%	356	0	0%	292	1	<1%
Eosinophils-High	769	1	<1%	683	1	<1%	477	4	<1%
Basophils-High	350	0	0%	355	0	0%	292	0	0%
Platelet Ct-Low	731	0	0%	652	1	<1%	434	0	0%
Platelet Ct-High	731	0	0%	652	0	0%	434	1	<1%

APPENDIX 8.5.2.3.1
Median Change from Baseline to Last Visit in Urinalysis Values in Placebo-Controlled Studies: OCD Study Pool

Urinalysis Variables (Dipstick)	FLUVOXAMINE		PLACEBO	
	Total Patients	Median Change	Total Patients	Median Change
pH	139	0.00	142	0.00
Protein	139	0.00	142	0.00
Ketones	138	0.00	142	0.00
Glucose	139	0.00	142	0.00
+Blood	139	0.00	142	0.00

APPENDIX 8.5.2.3.2
Median Change from Baseline to Last Visit in Urinalysis Values in Placebo-Controlled Studies: Depression Study Pool

Urinalysis Variables (Dipstick)	FLUVOXAMINE		PLACEBO		OTHER ACTIVE	
	Total Patients	Median Change	Total Patients	Median Change	Total Patients	Median Change
pH	347	0.00	346	0.00	290	0.00
Protein	734	0.00	655	0.00	464	0.00
Ketones	347	0.00	347	0.00	290	0.00
Glucose	735	0.00	655	0.00	465	0.00
+Blood	347	0.00	347	0.00	290	0.00

TABLE 8.5.2.3.3
Proportions of Patients Having Potentially Clinically Significant Urinalysis Values in Placebo-Controlled Studies: OCD Study Pool

	FLUVOXAMINE			PLACEBO		
Urinalysis Variables	Total Patients	Abnormal #	%	Total Patients	Abnormal #	%
pH-Low	141	0	0%	143	0	0%
pH-High	141	0	0%	143	0	0%
Protein	139	1	<1%	142	1	<1%
Ketone	141	0	0%	143	0	0%
Glucose	139	1	<1%	142	0	0%
+Blood	141	0	0%	143	0	0%

TABLE 8.5.2.3.4
Proportions of Patients Having Potentially Clinically Significant Urinalysis Values in Placebo-Controlled Studies: Depression Study Pool

	FLUVOXAMINE			PLACEBO			OTHER ACTIVE		
Urinalysis Variables	Total Patients	Abnormal #	%	Total Patients	Abnormal #	%	Total Patients	Abnormal #	%
pH-Low	348	1	<1%	352	1	<1%	291	0	0%
pH-High	348	1	<1%	352	0	0%	291	0	0%
Protein	734	4	<1%	655	3	<1%	464	2	<1%
Ketone	348	1	<1%	352	0	0%	291	0	0%
Glucose	735	5	<1%	655	5	<1%	465	1	<1%
+Blood	348	1	<1%	352	3	<1%	291	2	<1%

APPENDIX 8.5.3.1
Median Change from Baseline to Last Visit in Vital Sign Measurements in Placebo-Controlled Studies: OCD Study Pool

Vital Sign Variable	FLUVOXAMINE		PLACEBO	
	Total Patients	Median Change	Total Patients	Median Change
Systolic BP (mmHg) Sitting	154	0.00	159	0.00
Diastolic BP (mmHg) Sitting	154	0.00	158	0.00
Pulse (bpm) Sitting	153	0.00	159	0.00
Temperature (°F)	151	0.00	158	0.00
Weight (lb)	154	0.00	159	0.00

APPENDIX 8.5.3.2
Median Change from Baseline to Last Visit in Vital Sign Measurements in Placebo-Controlled Studies: Depression Study Pool

Vital Sign Variable	FLUVOXAMINE		PLACEBO		OTHER ACTIVE	
	Total Patients	Median Change	Total Patients	Median Change	Total Patients	Median Change
Systolic BP (mmHg) Supine	596	0.00	487	0.00	330	0.00
Systolic BP (mmHg) Sitting	268	0.00	264	0.00	202	0.00
Systolic BP (mmHg) Standing	591	0.00	485	0.00	327	-2.00
Diastolic BP (mmHg) Supine	596	0.00	487	0.00	330	+1.50
Diastolic BP (mmHg) Sitting	268	0.00	264	0.00	202	0.00
Diastolic BP (mmHg) Standing	591	0.00	485	0.00	327	0.00
Pulse (bpm) Supine	454	0.00	340	0.00	254	+5.50
Pulse (bpm) Sitting	409	0.00	411	0.00	278	+8.00
Pulse (bpm) Standing	448	0.00	336	0.00	250	+6.00
Temperature (°F)	806	0.00	691	0.00	480	0.00
Weight (lb)	861	-0.50	751	0.00	529	-0.99

APPENDIX 8.5.3.3
PROPORTIONS OF PATIENTS HAVING POTENTIALLY CLINICALLY SIGNIFICANT CHANGES IN VITAL SIGN VARIABLES IN PLACEBO-CONTROLLED STUDIES: OCD STUDY POOL

Vital Signs Variables	FLUVOXAMINE			PLACEBO		
	Total Patients	Abnormal #	%	Total Patients	Abnormal #	%
Systolic BP (mmHg) Sitting- Low	154	3	2%	159	5	3%
Systolic BP (mmHg) Sitting- High	154	0	0%	159	0	0%
Diastolic BP (mmHg) Sitting- Low	154	5	3%	159	3	2%
Diastolic BP (mmHg) Sitting- High	154	0	0%	159	0	0%
Pulse (bpm) Sitting- Low	154	0	0%	159	0	0%
Pulse (bpm) Sitting- High	154	1	<1%	159	0	0%
Temperature (°F)- Low	152	0	0%	159	0	0%
Temperature (°F)- High	152	0	0%	159	0	0%
Weight Increased	154	6	4%	159	4	3%
Weight Decreased	154	4	3%	159	4	3%

APPENDIX 8.5.3.4
PROPORTIONS OF PATIENTS HAVING POTENTIALLY
CLINICALLY SIGNIFICANT CHANGES IN VITAL SIGN VARIABLES
IN PLACEBO-CONTROLLED STUDIES: DEPRESSION STUDY POOL

Vital Signs Variables	FLUVOXAMINE			PLACEBO			OTHER ACTIVE		
	Total Patients	Abnormal #	%	Total Patients	Abnormal #	%	Total Patients	Abnormal #	%
Systolic BP (mmHg) Supine- Low	601	11	2%	492	14	3%	334	13	4%
Systolic BP (mmHg) Supine- High	601	1	<1%	492	2	<1%	334	3	<1%
Systolic BP (mmHg) Sitting- Low	270	8	3%	268	9	3%	205	2	1%
Systolic BP (mmHg) Sitting- High	270	1	<1%	268	1	<1%	205	0	0%
Systolic BP (mmHg) Standing- Low	600	20	3%	491	13	3%	334	32	10%
Systolic BP (mmHg) Standing- High	600	2	<1%	491	1	<1%	334	1	<1%
Diastolic BP (mmHg) Supine- Low	601	14	2%	492	7	1%	334	2	<1%
Diastolic BP (mmHg) Supine- High	601	3	<1%	492	6	1%	334	8	2%
Diastolic BP (mmHg) Sitting- Low	270	3	1%	268	3	1%	205	3	2%
Diastolic BP (mmHg) Sitting- High	270	2	<1%	268	1	<1%	205	3	2%

APPENDIX 8.5.3.4
PROPORTIONS OF PATIENTS HAVING POTENTIALLY
CLINICALLY SIGNIFICANT CHANGES IN VITAL SIGN VARIABLES
IN PLACEBO-CONTROLLED STUDIES: DEPRESSION STUDY POOL

Vital Signs Variables	FLUVOXAMINE			PLACEBO			OTHER ACTIVE		
	Total Patients	Abnormal #	%	Total Patients	Abnormal #	%	Total Patients	Abnormal #	%
Diastolic BP (mmHg) Standing- Low	600	13	2%	491	5	1%	334	10	3%
Diastolic BP (mmHg) Standing- High	600	6	1%	491	7	1%	334	4	1%
Pulse (bpm) Supine- Low	456	3	<1%	345	2	<1%	258	0	0%
Pulse (bpm) Supine- High	456	2	<1%	345	0	0%	258	12	5%
Pulse (bpm) Sitting- Low	414	2	<1%	415	2	<1%	281	0	0%
Pulse (bpm) Sitting- High	414	2	<1%	415	3	<1%	281	9	3%
Pulse (bpm) Standing- Low	454	0	0%	343	0	0%	258	0	0%
Pulse (bpm) Standing- High	454	12	3%	343	9	3%	258	33	13%
Temperature (°F)- Low	817	0	0%	704	0	0%	492	0	0%
Temperature (°F)- High	817	1	<1%	704	0	0%	492	2	<1%
Weight Increased	866	9	1%	756	6	<1%	531	11	2%
Weight Decreased	866	7	<1%	756	4	<1%	531	7	1%

APPENDIX 8.5.3.5 - RATES (%) OF DROPOUT ASSOCIATED WITH SPECIFIC VITAL SIGN ABNORMALITIES: COMBINED STRATA I/STRATA II POPULATION			
	FLUVOXAMINE (N=2737)	PLACEBO (N=1055)	ACTIVE-CONTROL (N=979)
Fever	0.2%	0%	0.2%
Hypertension	0.2%	0%	0.2%
Tachycardia	0.3%	0%	0.7%
Bradycardia	<0.1%	0%	0%
Weight Gain	0.2%	0%	0.3%
Weight Loss	0.1%	<0.1%	0%

APPENDIX 8.5.4.1 - STRATA I OCD STUDIES: CLINICALLY SIGNIFICANT, TREATMENT-EMERGENT ECG FINDINGS AMONG PATIENTS WITH DETERIORATED ECG'S *			
ECG Characteristic		FLUVOXAMINE (28 patients) # Deteriorated ECG's	PLACEBO (20 patients) # Deteriorated ECG's
Heart Rate	Total	3	5
Increased		1	4
Decreased		2	1
Rhythm	Total	2	1
Sinus Arrhythmia		0	1
Premature Atrial Contractions		1	0
Paired PVC's		1	0
Conduction	Total	0	1
First Degree AV Block		0	1
Axis	Total	2	1
Vertical QRS Axis		1	0
Right Axis Deviation		0	1
Counterclockwise Rotation		1	0
P Wave Morphology	Total	3	0
Non-Specific P Wave Change		3	0

APPENDIX 8.5.4.1 - STRATA I OCD STUDIES: CLINICALLY SIGNIFICANT, TREATMENT-EMERGENT ECG FINDINGS AMONG PATIENTS WITH DETERIORATED ECG'S *		
ECG Characteristic	FLUVOXAMINE (28 patients) # Deteriorated ECG's	PLACEBO (20 patients) # Deteriorated ECG's
QRS Total	14	8
Right Bundle Branch Block	1	0
Intraventicular Conduction Delay	1	0
Left Ventricular Hypertrophy	0	2
Significant Q Wave (>0.04 sec)	1	1
R Wave Amplitude Increased	1	0
R Wave Amplitude Decreased	3	0
Prolonged QT$_c$	3	1
Poor R Wave Progression	5	3
Myocardial Infarction, Old Inferior	1	1
ST-T Total	12	11
Non-Specific ST-T Changes	6	6
ST Segment Depression	2	3
ST Segment Elevation	1	1

APPENDIX 8.5.4.1 - STRATA I OCD STUDIES: CLINICALLY SIGNIFICANT, TREATMENT-EMERGENT ECG FINDINGS AMONG PATIENTS WITH DETERIORATED ECG'S *		
ECG Characteristic	FLUVOXAMINE (28 patients) # Deteriorated ECG's	PLACEBO (20 patients) # Deteriorated ECG's
T Wave Flat	1	2
T Wave Inversion	2	1
T Wave Peaked	3	1
Other Total	1	0
Persistent Precordial S Waves	1	0

* Treatment group totals are the number of patients per group with a deteriorated ECG. This table excludes one fluvoxamine patient with an unreadable ECG tracing.

APPENDIX 8.5.6.2 - STRATA I DEPRESSION STUDIES: CLINICALLY SIGNIFICANT, TREATMENT-EMERGENT ECG FINDINGS AMONG PATIENTS WITH DETERIORATED ECG'S *

ECG Characteristic	FLUVOXAMINE (148 patients with 256 deteriorated ECG's)		PLACEBO (126 patients with 221 deteriorated ECG's)		ACTIVE-CONTROL (186 patients with 395 deteriorated ECG's)	
	# Deteriorated ECG's	%	# Deteriorated ECG's	%	# Deteriorated ECG's	%
Heart Rate						
Increased	13	5.1%	9	4.1%	29	7.3%
Decreased	1	0.4%	1	0.5%	0	0.0%
Rhythm						
Sinus Arrhythmia	1	0.4%	3	1.4%	3	0.8%
Sinus Bradycardia	13	5.1%	6	2.7%	1	0.3%
Sinus Tachycardia	11	4.3%	19	8.6%	40	10.1%

APPENDIX 8.5.4.2 - STRATA I DEPRESSION STUDIES: CLINICALLY SIGNIFICANT, TREATMENT-EMERGENT ECG FINDINGS AMONG PATIENTS WITH DETERIORATED ECG'S *

ECG Characteristic	FLUVOXAMINE (148 patients with 256 deteriorated ECG's)		PLACEBO (139 patients with 221 deteriorated ECG's)		ACTIVE-CONTROL (186 patients with 395 deteriorated ECG's)	
	# Deteriorated ECG's	%	# Deteriorated ECG's	%	# Deteriorated ECG's	%
Premature Atrial Contractions	12	4.7%	9	4.1%	7	1.8%
Supraventricular Tachycardia	0	0.0%	0	0.0%	1	0.3%
Wandering Atrial Pacemaker	1	0.1%	3	1.4%	0	0.0%
Nodal Premature Complexes	0	0.0%	1	0.5%	0	0.0%
Nodal Tachycardia	4	1.6%	3	1.4%	0	0.0%
Premature Ventricular Contractions	3	1.2%	9	4.1%	7	1.8%
Sick Sinus Syndrome	0	0.0%	1	0.5%	0	0.0%
Conduction						
First Degree AV Block	4	1.6%	11	5.0%	15	3.8%
Short PR Interval	10	3.9%	3	1.4%	1	0.3%
Wolff-Parkinson-White Syndrome	1	0.4%	0	0.0%	0	0.0%
Axis						
Horizontal QRS Axis	3	1.2%	2	0.9%	1	0.3%
Vertical QRS Axis	1	0.4%	1	0.5%	2	0.5%

APPENDIX 8.5.4.2 - STRATA I DEPRESSION STUDIES: CLINICALLY SIGNIFICANT, TREATMENT-EMERGENT ECG FINDINGS AMONG PATIENTS WITH DETERIORATED ECG'S *

ECG Characteristic	FLUVOXAMINE (148 patients with 256 deteriorated ECG's)		PLACEBO (129 patients with 221 deteriorated ECG's)		ACTIVE-CONTROL (186 patients with 395 deteriorated ECG's)	
	# Deteriorated ECG's	%	# Deteriorated ECG's	%	# Deteriorated ECG's	%
Left Axis Deviation	4	1.6%	3	1.4%	8	2.0%
Right Axis Deviation	0	0.0%	1	0.5%	5	1.3%
Clockwise Rotation	16	6.3%	12	5.4%	14	3.5%
Counterclockwise Rotation		2.7%	5	2.3%	4	1.0%
P Wave Morphology						
Left Atrial Hypertrophy	3	1.2%	3	1.4%	5	1.3%
Right Atrial Hypertrophy	1	0.4%	1	0.5%	4	1.0%
Non-Specific P Wave Change	10	3.9%	6	2.7%	8	2.0%
QRS						
Right Bundle Branch Block	4	1.6%	2	0.9%	5	1.3%
Left Bundle Branch Block	0	0.0%	0	0.0%	1	0.3%
Left Anterior Hemiblock	0	0.0%	0	0.0%	4	1.0%
Left Posterior Hemiblock	0	0.0%	0	0.0%	1	0.3%
Intraventicular Conduction Delay	4	1.6%	1	0.5%	27	6.8%

APPENDIX 8.5.4.2 - STRATA I DEPRESSION STUDIES: CLINICALLY SIGNIFICANT, TREATMENT-EMERGENT ECG FINDINGS AMONG PATIENTS WITH DETERIORATED ECG'S *

ECG Characteristic	FLUVOXAMINE (148 patients with 256 deteriorated ECG's)		PLACEBO (129 patients with 221 deteriorated ECG's)		ACTIVE-CONTROL (186 patients with 395 deteriorated ECG's)	
	# Deteriorated ECG's	%	# Deteriorated ECG's	%	# Deteriorated ECG's	%
Left Ventricular Hypertrophy	3	1.2%	[illegible]	2.3%	5	1.3%
Right Ventricular Hypertrophy	3	1.2%	2	0.9%	2	0.5%
Significant Q Wave (>0.04 sec)	0	0.0%	1	0.5%	1	0.3%
R Wave Amplitude Increased	0	0.0%	0	0.0%	2	0.3%
R Wave Amplitude Decreased	5	2.0%	10	4.5%	4	1.0%
Prolonged QT_c	21	8.2%	19	8.6%	54	13.7%
Poor R Wave Progression	22	8.6%	12	5.4%	17	4.6%
Myocardial Infarction, Old Ant.	3	1.2%	0	0.0%	4	1.0%
Myocardial Infarction, Old Inf.	0	0.0%	1	0.5%	0	0.0%
ST-T						
Non-Specific ST-T Changes	26	10.2%	21	9.5%	44	11.1%
ST Segment Depression	11	4.3%	10	4.5%	18	4.6%
ST Segment Elevation	1	0.4%	1	0.5%	1	0.3%
T Wave Flat	16	6.3%	5	2.3%	17	4.3%

APPENDIX 8.5.4.2 - STRATA I DEPRESSION STUDIES: CLINICALLY SIGNIFICANT, TREATMENT-EMERGENT ECG FINDINGS AMONG PATIENTS WITH DETERIORATED ECG'S *

ECG Characteristic	FLUVOXAMINE (148 patients with 256 deteriorated ECG's)		PLACEBO (129 patients with 221 deteriorated ECG's)		ACTIVE-CONTROL (186 patients with 395 deteriorated ECG's)	
	# Deteriorated ECG's	%	# Deteriorated ECG's	%	# Deteriorated ECG's	%
T Wave Inversion	6	2.3%	6	2.7%	11	2.8%
T Wave Peaked	4	1.6%	8	3.6%	3	0.8%
Myocardial Ischemia	2	0.8%	1	0.5%	6	1.5%
Subendocardial Ischemia	0	0.0%	2	0.9%	1	0.3%
Myocardial Infarction, Acute Ant.	1	0.4%	0	0.0%	0	0.0%
Other						
Persistent Precordial S Waves	5	2.0%	2	0.9%	12	3.0%

* Treatment group totals are the number of patients per group with a deteriorated ECG. Percentages equal [(number of deteriorated ECG's with that finding)/(total number of deteriorated ECG's in that treatment group)] × 100%.

APPENDIX 8.5.8.1 - FLUVOXAMINE OVERDOSE DEATHS					
Subject	Age	Sex	Fluvoxamine Taken (mg)	Associated Drugs	Comments
	50	F	2500-5000	Clozapine Etilefrine(250-500mg) Promethazine(750-2500mg) Propranolol(2-4g) L-trytophan	90 fluvoxamine tablets not disintegrated in stomach. Death may have been due to other drugs.
	35	F	Unknown	Astemizole Prochlorperazine	Plasma fluvoxamine level = 0.18 mg/100 ml. Other drugs may have been taken.
	27	M	Unknown	Aceprometazine Bromazepam Clorazepate Meprobamate	No toxicological or pathological data.
	40	M	6100	Clonazepam(56mg) Diclofenac(2575mg) Flurazepam(840mg) Paracetamol Pizctifene(28g) Primidone(5250mg) Promethazine(6300mg)	Plasma fluvoxamine level= 1.5 mg/100ml. Died 30 hrs. after O.D. Acetaminophen levels suggested severe intoxication.
	71	F	2600	Thioridazine	No toxicological or pathological data.
	33	F	Unknown	Chlorpheniramine Phenelzine Temazepam Thioridazine	Fluvoxamine not detectable in plasma.
	53	F	Unknown	Insulin Other antidepressants	Death after 2 weeks due to sequelae of hypoglycemia.
	36	M	3000	Propoxyphene(4500mg) Nitrazepam(150mg)	Body discovered ~3 weeks after overdose.

APPENDIX 8.5.8.1 - FLUVOXAMINE OVERDOSE DEATHS					
Subject	Age	Sex	Fluvoxamine Taken (mg)	Associated Drugs	Comments
	49	F	Unknown	Amitriptyline	Plasma fluvoxamine level = 0.055 mg/100ml. Very high amitriptyline/ nortriptyline levels (>10X ther.)
	29	F	Unknown	Clomipramine	Plasma fluvoxamine level = 0.05 mg/100ml. Very high levels of clomipramine and its main metabolite.
	Unk	Unk	Unknown	Alcohol Dothiepine	Plasma fluvoxamine level = 1.17 mg/100ml. Very high level of dothiepine reported.
	30	F	3000	Trimipramine Hydroxyzine Alprazolam Flunitrazepam Alcohol	Plasma fluvoxamine levels in therapeutic range.
	80	M	Unknown	Flunitrazepam	Died after 3 day coma. No toxicological data.
	74	F	6000	Lorazepam(30-40mg)	Body found 2 days after O.D.
	55	F	>5 g	IV diazepam 5 mg after O.D. ? temazepam	Plasma fluvoxamine level = 0.3 mg/100ml. Coroner recorded cause of death as fluvoxamine O.D.
	Unk	F	7.5 g	Carbamazepine 20 g Doxylamine 1 g Diphenhydramine 500 mg	Cause of death reported to be high level of carbamazepine.
	29	M	1.4 g	Dextropropoxyphene Paracetamol Alcohol	Likely cause of death was dextroproxyphene O.D. with alcohol.

APPENDIX 8.5.8.1 - FLUVOXAMINE OVERDOSE DEATHS					
Subject	Age	Sex	Fluvoxamine Taken (mg)	Associated Drugs	Comments
	Unk	F	Unknown	Meprobamate Ethoheptazine Aspirin Alcohol	Plasma fluvoxamine level = 0.038 mg/100ml (in therapeutic range). Plasma meprobamate level = 140 mg/l (serious toxicity >40mg/l). Death certified as D/T meprobamate O.D.
	Unk	F	Unknown	None detected.	Plasma fluvoxamine level = 0.35 mg/100ml (5X therapeutic level).

APPENDIX 8.5.8.2 - OVERDOSE SYMPTOMS ATTRIBUTABLE TO FLUVOXAMINE INGESTION (PPC STUDY)		
Symptom	Number of Cases	Fluvoxamine Consumed (mg)
Drowsiness	15	150-9000
Shallow Coma	1	1500
Hyperreflexia	4	1000-1500
Tremor	2	150, 1500
Hypertonia	1	1500
Seizures	5	1000-5000
Mydriasis	3	750-1500
Dry Mouth	2	1500
Urine Retention	3	1500
Bradycardia	5	150-1000
Sinus Tachycardia	4	1500
Hypotension	1	2500
PVC's	3	1500
A-V Conduction Disturbance	3	800-6500
Repolarization Changes	2	750, 2500
Nausea, Vomiting	6	1500-9000
Abdominal Pain	4	150-1500
Hypoglycemia	1	1500
Hypokalemia	12	400-6500
↑ Transaminases	5	550-9000
Cholestasis	1	Unknown

APPENDIX 8.5.8.3 - SYMPTOMS OF FLUVOXAMINE OVERDOSE (DUPHAR STUDY)	
Symptoms	Amount of Fluvoxamine (mg)
Anorexia, insomnia, dizziness, myoclonus, ↑LFT's.	450
Bradycardia, ↑ prothrombin time (2 yo child).	600
Mydriasis, intraventricular block.	750
Drowsiness.	900
Asthenia, drowsiness.	1000
Vomiting, drowsiness.	1000
Drowsiness.	1000-1500
Coma, hypothermia, bradycardia.	1100
Vomiting.	1500
Hypotension, tachycardia.	1500
Drowsiness.	1500
Drowsiness, abdominal pain.	2000
Drowsiness, mydriasis.	2000
Nausea, vomiting, asthenia, insomnia, tremor, myoclonus, tachycardia.	2000
Tremor, dizziness.	3000
Unsteadiness, dizziness, diplopia, hypotension.	3500
Vomiting, diarrhea.	4800
Nausea, abdominal pain, diarrhea.	4800
Vomiting, diarrhea.	Unknown.
Drowsiness.	Unknown.

APPENDIX 8.7.1
Summary of Selected Serious Adverse Events Occurring in Fluvoxamine-Treated Patients and Considered Unlikely to be Drug-Related

Study/Patient Number	Age (yrs)	Sex	Dose (mg/d)	Duration (days)	Adverse Event
CARDIOVASCULAR EVENTS					
FR.003/5601	59	F	150	16	Mesenteric Occlusion.
CANCERS/NEOPLASM					
5540_D	50	F	250	450	Benign tumor.
EU.901	70	M	200	<18	Esophageal Carcinoma.
UK.918	56	M	100	14	Colonic Carcinoma.
FR.019/	63	F	100	40	Pancreatic Carcinoma.
UK.905	70	M	50	9	Pancreatic Carcinoma.
FR.024,	59	F	100	30	Cerebral Neoplasm.
FR.024	38	M	100	4	Cerebral Tumor.
NL.904/	54	F	100	7	Cerebral Glioma.
EU.901	69	M	100	6	Lung Cancer.
FR.010	64	M	200	35	Breast Cancer.
UK.908	61	F	100	26	Breast Neoplasm.
FR.024	80	M	100	7	Prostatic Carcinoma.
SP.913	40	F	250	92	Ovarian Cancer.
UK.926	55	F	150	23	Hepatic Carcinoma.
G.915	59	F	100	50	Neoplasm.

APPENDIX 8.7.1
Summary of Selected Serious Adverse Events Occurring in Fluvoxamine-Treated Patients and Considered Unlikely to be Drug-Related

Study/Patient Number	Age (yrs)	Sex	Dose (mg/d)	Duration (days)	Adverse Event
SP.914	65	F	150	98	Leukemia.
AU.901	50	F	200	15	Brain neoplasm.
SP.914	56	M	300	5	Lung Cancer.
GASTPOINTESTINAL EVENTS					
FR.024	55	M	100	?	Peritonitis.
FR.024	?	F	100	21	Pancreatitis.
OPHTHALMOLOGICAL					
5540_0	49	F	?	830	Cataract.
5531E,	71	M	300	160	Retinal Detachment.
UK.904	59	F	100	300	Macular Degeneration.
CNS					
5017,	59	F	150	23	Coma, Paralysis.
5067,	63	F	100	13	Hemiplegia.
5066	79	M	75	37	Cerebrovascular Accident.
UK.904	57	M	50	7	Cerebrovascular Accident.
UK.905	75	M	100	12	Cerebrovascular Accident.
FR.024	60	F	100	?	Paraplegia.
FR.024	23	F	200	21	Delirium.
SP.912	54	F	200	51	Coma.

APPENDIX 8.7.1
Summary of Selected Serious Adverse Events Occurring in Fluvoxamine-Treated Patients and Considered Unlikely to be Drug-Related

Study/Patient Number	Age (yrs)	Sex	Dose (mg/d)	Duration (days)	Adverse Event
UK.926	40	F	100	1	Dementia.
MISCELLANEOUS					
UK.921/	73	F	50	17	Hypothyroidism.

APPENDIX 8.7.2
Summary of Serious Adverse Events Occurring in Placebo and Active-Control Patients and Considered Unlikely to be Drug-Related

Study/Patient Number	Age (yrs)	Sex	Dose (mg/d)	Duration (days)	Adverse Event
ACTIVE-CONTROL					
CARDIOVASCULAR EVENTS					
5056	60	F	(IMI) 50	3	Pericarditis.
CANCERS					
5508E	51	F	(IMI) 250	-250	Uterine cancer.
5526E	59	F	(DESI) 100	78	Basal cell cancer.
MISCELLANEOUS					
5527	62	M	(DESI) 300	34	Osteomyelitis.
5056	37	F	(IMI) 100	7	Seizure, hyperthermia.
5072	64	F	(MAP) 100	22	Hyperparathyroidism.

Review and Evaluation of Clinical Data
NDA # 20,243

Sponsor:	Solvay Pharmaceuticals
Drug:	Luvox (Fluvoxamine)
Material Submitted:	Consult from HFD-344 (DSI)
Correspondence Date:	May 22, 1992
Date Received:	May 28, 1992

I. Background

DSI conducted an inspection of a bioequivalency study submitted to NDA 20,243 which was performed by Pharmaco Dynamics Research, a contract research organization in Austin, TX, on behalf of the sponsor. Solvay had provided written agreement (Attachment 1) to provide Pharmaco Dynamics with "sufficient clinical trial samples to meet the study requirements and FDA sample retention requirements to permit the FDA to perform five times all of the release tests required in the application." It was discovered during the inspection that Solvay did not forward retention samples to the CRO until nine months after study completion and, furthermore, that Solvay apparently subsequently requested that the retention agreement letter be removed from the file at Pharmaco Dynamics (Attachment 2). HFD-120, which is reviewing NDA 20,243, was consulted for recommendations.

II. Summary

A meeting was convened on July 8, 1992, and included attendees from HFD-120 and HFD-426 (Biopharmaceutics) as well as Dr. Viswanathan (see Attachment 3 for meeting minutes). The interim rule referred to by Dr. Ludden is provided as Attachment 4. It was concluded that the completed study would not be nullified as a result of this inspection since lack of industry compliance with the interim rule is not uncommon due to its relatively recent publication; holding this sponsor to the provisions in this rule was not justified and repeating the study would unnecessarily expose more volunteers.

III. Conclusions and Recommendations

It was recommended that DSI consult with General Counsel regarding Solvay's attempt to have their retention agreement document removed from the file to better assess the degree to which this behavior deviates from legal standards.

Gregory M. Dubitsky, M.D.
August 26, 1992

Attachments (4)

cc: HFD-344/CViswanathan
NDA 20,243
HFD-120
HFD-120/GDubitsky
TLaughren
PDavid
KHiggins

8-27-92

I agree that no further action on the part of HFD-120 is required.

James P. Laughren, MD
GL, PDP

Review and Evaluation of Clinical Data
NDA # 20,243

Sponsor:	Solvay Pharmaceuticals
Drug:	Fluvoxamine Maleate (LUVOX)
Indication:	OCD
Material Submitted:	Proposed format for Strata III update.
Correspondence Date:	September 4, 1992
Date Received:	September 8, 1992

I. Background

The sponsor has collected clinical data from 24 European marketing studies, which were completed between 1/1/91 and 6/30/92 and thus were not included in the original NDA submission, which had a cut-off date of 12/31/90. These studies included 11,461 subjects. This submission outlines a proposed format for submitting this data as an update to the NDA.

II. Summary

All Case Report Forms, which will be the sole source of information, will undergo a medical review by a Contract Research Organization. Patient Safety Summary Forms will be prepared and indicate, for each patient, completer vs. terminator status, the presence of any serious adverse events (serious as defined by 21 CFR 312.32(a)), and, in the case of premature termination, the reason for termination. This data will then be entered into the sponsor's database. Narrative summaries will be prepared for all deaths, serious adverse experiences, and premature terminations due to adverse events.

The sponsor proposes to submit these NSR's and, for deaths and serious adverse events, full CRF's. Other data will be tabulated and submitted as follows:

Scope of investigations

- Overview of studies by indication, dose range, duration, and numbers of subjects exposed by treatment group.

- General description of each study to include start/stop dates, planned dose range, planned duration, and number exposed to fluvoxamine.
- Overview of active controls.

Deaths

- Line listings of all deaths to include age, sex, weight, duration of therapy, dose up to time of event, event related to death, and "On Drug" status.
- Narrative description of death incidence rates for both new exposures and the cumulative Strata III database.

Serious adverse events

- Line listings of all serious adverse events to include age, sex, weight, serious event, and "On Drug" status; these listings will be organized by both study and preferred term.
- Tables of serious adverse event incidence rates for both new exposures and the cumulative Strata III database.

Premature terminations

- Enumeration of discontinuations by indication, study type, and reason for termination.
- Enumeration of discontinuations by each study and reasons for termination.

Non-serious events leading to termination

- Line listings of all adverse events leading to termination to include age, sex, weight, duration of therapy, dose up to time of termination, and adverse event leading to dropout; these listings will be organized by both study and preferred term.
- Table of incidence rates for adverse events leading to dropout for the new exposures.
- Narrative description of incidence rates of adverse events leading to dropout for both new exposures and the cumulative Strata III database.

III. Recommendations

The above proposal was dicussed with Dr. Laughren on 9/15/92 and the following modifications are recommended:

Scope of investigations

- Cumulative tables for demographic overview, duration of exposure, modal daily dose, and duration/ modal dose should be prepared and submitted. These would be similar to Tables 2.1, 3.1, 4.1, and 5.1, respectively, in the Strata III section of the original NDA and summate the new exposure data with the original Strata III data.

Serious adverse events

o A narrative section to discuss incidence rates of serious adverse events for new exposures and cumulative experience should be submitted.

o Dose and duration data should be included in the line listings of serious adverse events.

o A column should be added to the line listings of serious adverse events to indicate which events led to premature termination.

Premature terminations

o Tables enumerating premature discontinuations by reason for termination should depict the cumulative Strata III database as well as the new exposures (similar to Table 6.1).

Non-serious events leading to termination

o A table of the incidence rates for adverse events leading to premature termination for the cumulative Strata III database should be provided in addition to the table for new exposures.

It is expected that any further changes to the proposal will be minor in nature and be requested as needed during the review process.

Gregory M. Dubitsky, M.D.
September 15, 1992

cc: NDA 20,243
HFD-120
HFD-120/GDubitsky
TLaughren
PDavid

9-15-92

ADDENDUM TO:

Review and Evaluation of Clinical Data
NDA #20,243

Sponsor:	Solvay Pharmaceuticals
Drug:	Fluvoxamine Maleate
Indication:	Obsessive Compulsive Disorder
Material Submitted:	1) Safety Update 2) Literature Search 3) Foreign Regulatory Update
Correspondence Date:	November 23, 1993
Date Received:	November 26, 1994

I. Background

NDA 20,243 was submitted on December 24, 1991, for the use of fluvoxamine maleate in the treatment of Obsessive Compulsive Disorder (OCD). The cutoff date for safety data in the original submission was December 31, 1990. Subsequently, the foreign post-marketing clinical trial database as well as the foreign post-marketing surveillance safety databases were updated to July 1, 1992. The primary clinical review of the aforementioned data was completed on October 22, 1993.

The present submission consists of: 1) a report of all serious adverse events[1] identified after the above cutoff dates and up to October 1, 1993[2], 2) an updated report on worldwide literature pertaining to fluvoxamine for the period December 1990 to October 1993, and 3) an update on the foreign regulatory status and foreign labeling for fluvoxamine.

II. Safety Update: Serious Adverse Events

A. Sources of Clinical Data

Serious adverse event data was categorized by source as defined below.

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[1]As defined in 21 CFR 314.80.

[2]Except for Strata III data, which was updated to July 31, 1993.

Strata I: thirteen North American, controlled studies in depression and OCD. Since these studies were completed prior to and reported in the original NDA submission, there was no information to update.

Strata II: seventy North American uncontrolled and European controlled and uncontrolled studies. Only updated information from two studies is reported, 5536 (completed since the original submission) and 5540 (an ongoing study). Other studies were completed before and reported in the original submission.

Strata III: 92 worldwide post-marketing studies. Only adverse events from Strata III studies completed since the Strata III update cutoff date (July 1, 1992) are reported in this submission.

Additional Strata III: the sponsor identified 29 additional serious adverse events from Strata III studies reported in either the original NDA submission or the Strata III update which were inadvertantly not reported previously. These events comprise this category.

Strata IV: spontaneous reports of serious adverse events to the sponsor during the period July 1, 1992 to October 1, 1993 are included in this category. It is estimated that million patients worldwide were treated with fluvoxamine during this interval.

Strata V: a residual category reserved for studies which produced incomplete or unverifiable data, trials not initiated by the cutoff date for inclusion in the original NDA database, or individual patient data which was incomplete or inadvertantly ommitted from the original database. Reported are 12 serious adverse events reported from studies which were completed since submission of the original NDA.

Pivotal Depression Studies: 6 U.S. trials in depression which form the basis for efficacy demonstration in NDA 20,350 (114.01.01 through 114.01.06). Also included are serious adverse events from the European depression study 5105. All these studies were completed since the original NDA submission.

U.S Investigational Studies: ongoing investigational studies in the U.S., to include studies in panic disorder, pediatric/adolescent OCD, and 2 Phase 4 studies.

European Investigational Studies: investigational studies conducted in Europe which have been completed but for which safety data has not been fully analyzed.

Ongoing European Investigational Studies: European studies not yet completed.

B. Safety Findings

There were 35 deaths from all clinical data sources. These deaths are summarized by source in **Appendix 1.** The causes of death are summarized below. By far, the most common cause of death was suicide. Of nine suicides by overdose, none appeared to involve the ingestion of fluvoxamine alone; 4 of these involved no ingestion of fluvoxamine.

Suicide	18
Cardiac	4
Infection	2
Accidental Injury	2
Carcinoma	1
GI Hemorrhage	1
Metabolic (DKA)	1
Neurological (NMS)	1
Congenital	1
Unknown	4

Adverse experience reports (1639's) or clinical summaries (Solvay's clinical summary page, roughly equivalent to FDA 1639) for all deaths were reviewed. No death was felt to be reasonably attributable to fluvoxamine. Two events which were felt to be unusual in nature occurred among the Strata IV death cases:

> A male with large vessel transposition and patent ductus arteriosis was born to a female who had been treated with fluvoxamine 50 mg/day and clorazepate 30 mg/day during pregnancy. Surgery was performed 10 days after birth and the infant died during the procedure. While fluvoxamine may have played a role in the congenital anomaly, this case is confounded by the use of clorazepate as well as the background incidence of such anomalies. (FLUV1930193)
>
> A female died with the cause of death listed as neuroleptic malignant syndrome (NMS). She had been treated with fluvoxamine 300 mg/day for an unknown duration of time as well as L-tryptophan (dose and dates of administration unknown). Clinical data was insufficient to further evaluate this case; there is no description of the event nor evidence that the patient was receiving fluvoxamine at the time this event developed. (Note that the proposed labeling states that the combination of fluvoxamine and tryptophan should be used with caution since tryptophan may enhance the serotonergic effects of fluvoxamine.) (FLUV1930211)

A total of 366 <u>non-fatal</u> serious adverse events were reported from these sources. A detailed line listing of these events was reviewed to identify those occurrences which were felt to possibly

represent clinically significant, drug-related adverse events[3]. Seventy-seven such events were selected; the clinical summary data for these 77 events was then examined to further evaluate clinical significance and relationship to fluvoxamine. Clinical summaries for all patients with events coded as "Reaction Unevaluable" were reviewed. Following this examination, only eleven of these cases were felt to be clinically important and possibly related to fluvoxamine treatment. These patients will be briefly discussed below.

Four cases of liver dysfunction were located. These cases are summarized in **Table 1**. The first case is from Strata IV and the remainder are from European investigational studies. None of these cases were known to be associated with permanent liver damage or liver failure.

Table 1 - Cases of Liver Dysfunction

Patient#	Age	Sex	Dose (mg/day)	Duration (days)	Comments
	41	M	200	87	↑LFT's to 20xULN with jaundice; resolved 3 days after D/C of fluv.
	25	F	300	59	↑LFT's to 30xULN; fluv D/C'd., outcome unknown.
	29	F	300	11	↑LFT's to 4xULN, resolved 5 days after D/C of fluv.
	Unk	M	100	327	↑LFT's with jaundice, improved 12 days after D/C.

Five serious adverse events may have been the result of an interaction between fluvoxamine and a concurrent medication. The first four cases are from the post-marketing surveillance database; the fifth occurred during an ongoing European investigational study. These cases are summarized in **Table 2**. Clinical cases suggesting drug-drug interactions between fluvoxamine, on the one

[3]An assessment of drug-relatedness was based on the judgement of the reviewer and included the following considerations: timing of the event relative to fluvoxamine exposure, likelihood of alternative etiologies, approximate incidence in the general population, and results of dechallenge/rechallenge.

hand, and propranolol, metoprolol, and a hepatically metabolized oral anticoagulant (fluorindione), on the other hand, have been previously discussed in the primary clinical review of this NDA. Elevated anticonvulsant levels when carbamazepine is administered to steady-state fluvoxamine support the possibility of P450IID6 competitive inhibition by fluvoxamine. Levomepromazine, a phenothiazine, is associated with a lowered seizure threshold; it is possible that fluvoxamine may further lower this threshold when these two drugs are used together.

Table 2 - Cases of Possible Drug-Drug Interactions

Patient#	Age	Sex	Dose (mg/day)	Duration (days)	Comments
	Unk	F	100	30	Pt. stable on **propranolol** prior to fluvoxamine, experienced bradycardia (40bpm) after fluv added.
	40	M	300	35	Pt. on fluvoxamine, **carbamazepine** added; rapidly developed ↑↑CBZ level.
	78	M	50	14	Pt. stable on **acenocoumarol** (a hepatically metabolized anticoagulant), GI bleed + ↑PT after fluv added.
	26	F	21/5	50	Fluvoxamine + **levomepromazine** assoc. with tonic-clonic seizures; positive rechall.; levomepromazine D/C'd, Fluv cont'd. without further seizures.
	49	M	Unk	Unk	Ciculatory collapse (shock) assoc. with fluv + **metoprolol** TX.

The remaining two cases felt to be possibly related to fluvoxamine treatment are described below.

A 68 year old female with a pre-existing incomplete left bundle branch block experienced bradycardia (42 bpm) after treatment with fluvoxamine 100 mg/day for 9 days; this persisted despite treatment with isoproterenol. Fluvoxamine and isoproterenol were discontinued with resolution of the adverse event. (FL143 - Strata III) Only one case of significant bradycardia possibly related to fluvoxamine was found in the post-marketing surveillance database of the primary review.

A 30 year old female was treated for depression with fluvoxamine 150 mg/day for 4 months when she experienced joint pain and swelling, purpura and gastrointestinal bleeding. This was diagnosed as Henoch-Schoenlein purpura (nonthrombocytopenic purpura). Lorazepam was taken concomitantly, with dosage and dates of administration unknown. (FLUV1930155 - Strata IV) Cases of Henoch-Schoenlein purpura are atypical in adults. All cases have been attributed to an allergic or hypersensitivity reaction, with drugs, including sedatives, among possible etiologic agents.[4] Thus, lorazepam may be a confounding factor in this case. No similar cases were identified in the primary review database.

III. World Literature Update

The sponsor conducted a systematic review of the worldwide literature pertaining to the safety of fluvoxamine using the following search strategies:

1) The sponsor's literature database[5] for the period 1990 to October 1, 1993 was searched using key words and a scan of titles and abstracts.

2) A fluvoxamine bibliography prepared by the Medical and Drug Information Center of Solvay Pharmaceuticals/Upjohn was also searched.

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[4]Demis DJ. Clinical Dermatology. Philadelphia: JB Lippincott Company; 1991: Chapter 7-26.

[5]Literature is collected for this database by scanning online databases every 2 months (Medline, Embase, BIOSIS, Scisearch, Chemical Abstracts, and RINGDOC), scanning about 100 biomedical journals in the Solvay library, and, once or twice a year, scanning new books and more exotic databases.

3) Articles identified by the Solvay Drug Safety Unit which had been submitted to IND as safety reports were added to the bibliography.

A listing of the titles and sources of 219 articles that were identified by the above search procedures was submitted and reviewed. Also, full copies of 7 articles were provided which describe cases of 5 different adverse events, which were deemed by the sponsor to be unexpected based on proposed labeling. Three of these events have been addressed in the primary review: acute dystonia, hyponatremia due to SIADH, and toxic epidermal necrolysis. The other 2 events were questionably related to fluvoxamine treatment: a report of polydipsia in 3 females and a frontal lobe syndrome with a subsequent negative rechallenge. In summary, none of these events were felt to be previously unreported, important, and likely related to fluvoxamine.

All articles, except those in a foreign language, were reviewed by Bradley Jeffries, M.D., M.S., Senior Medical Scientist at Solvay. Dr. Jeffries has provided his warrant that his review revealed no finding that would adversely affect conclusions about the safety of fluvoxamine. Thirty-three articles in a foreign language were reviewed by European affiliates of Solvay, Wolfgang Wagner, M.D., Ph.D., and Lode Dewulf, M.D., Ph.D. Dr. Jeffries examined the medical reviews by Drs. Wagner and Dewulf and certified that this examination, likewise, revealed no new safety concerns.

IV. Foreign Regulatory Update/Labeling

Statements regarding foreign regulatory status of fluvoxamine as well as current master text for fluvoxamine film-coated tablets representative of foreign labeling, the Canadian monograph, and U.K. labeling are included in this submission. This information was examined for evidence of safety concerns regarding the use of fluvoxamine which were not addressed in the primary review of this NDA.

Fluvoxamine has not been withdrawn from any market. It is marketed in 37 foreign countries, to include South Africa where it was introduced in January 1994. Additionally, fluvoxamine was recently approved for the treatment of OCD in Canada (8/93) and Switzerland (10/93).

A comparison of the Canadian monograph, U.K. labeling, and master text for foreign labeling with the conclusions derived from the primary review revealed only one discrepancy: the former documents consistently indicate a time to reach steady-state (T_{ss}) as 10 to 14 days, whereas pharmacokinetic data in this NDA suggest a T_{ss} of 4 to 6 days. This issue should be further addressed by the Biopharmaceutics reviewer.

V. Conclusions and Recommendations

In summary, a review of the aforementioned data (serious adverse event update, world literature, and foreign labeling) revealed only one case each of three serious adverse events which may be related to fluvoxamine treatment and which were not observed in the primary review of this NDA:

1) an abnormally high carbamazepine level when carbamazepine was added to steady-state fluvoxamine therapy, suggesting P450IID6 innibition by fluvoxamine.

2) tonic-clonic seizures associated with the concomitant use of a phenothiazine (levomepromazine) and fluvoxamine, suggesting a further lowering of the seizure threshold when fluvoxamine is added to phenothiazine therapy.

3) Henoch-Schoenlein purpura, possibly confounded by concurrent lorazepam use.

Consideration should be given to a brief mention of these events in the appropriate sections of labeling (i.e. Seizures, Drug Interactions, and Other Post-Marketing Events, respectively).

Overall, the submitted data supports the previous conclusion that fluvoxamine appears to be reasonably safe under the conditions of use recommended in labeling.

Gregory M. Dubitsky, M.D.
February 22, 1994

2.24.94

This safety update does not reveal any important new safety concerns that need interfere with our plans to proceed with an approvable action.

T. Laughren, MD

cc: NDA#20,243
HFD-120
HFD-120/GDubitsky
TLaughren
PDavid

APPENDIX 1
Summary of Deaths Occurring in Fluvoxamine-Treated Patients

Patient Number	Age (yrs)	Sex	Dose (mg/d)	Duration (days)	Cause of Death and Comments
STRATA III					
	36	M	100	76	Suicide (Gun Shot Wound)
ADDITIONAL STRATA III					
	68	F	100	14	Diabetic Ketoacidosis (pre-existing diabetes mellitus)
	44	M	Unk	Unk	Suicide (method unknown)
STRATA IV					
	48	M	Unk	Unk	Suicide (Multi-drug OD, Fluvoxamine unlikely ingested)
	62	M	Unk	Unk	Suicide (Multi-drug OD)
	85	M	100	15	Cardiac Failure (H/O COPD)
	Unk	M	Unk	Unk	Suicide (TCA + BZ OD)
	62	M	Unk	Unk	Suicide (Analgesic OD)
	57	F	150	112	Unknown cause
	55	F	150	Unk	Suicide (Multi-drug OD)
	44	M	Unk	Unk	Suicide (method unknown)
	Unk	Unk	Unk	Unk	Unknown cause (not OD)
	59	M	100	16	Pneumonia
	70	F	200	Unk	Myocardial infarction
	22	F	Unk	Unk	Suicide (probable BZ + EtOH OD)
	46	F	Unk	Unk	Suicide (Multi-drug OD)
	71	F	50	86	Unknown (died 4 days after fluvoxamine discontinued.)
	Unk	M	50	225	Infant with congenital large vessel transposition and patent ductus, mother treated with fluvoxamine and clorazepate during pregnancy.

APPENDIX 1
Summary of Deaths Occurring in Fluvoxamine-Treated Patients

Patient Number	Age (yrs)	Sex	Dose (mg/d)	Duration (days)	Cause of Death and Comments
	Unk	F	300	Unk	Neuroleptic Malignant Syndrome, details unavailable.
	22	M	Unk	Unk	Unknown
PIVOTAL DEPRESSION STUDIES					
FL735	68	M	50	15	Accidental injury (motor vehicle accident)
EUROPEAN INVESTIGATIONAL STUDIES (INCOMPLETELY ANALYZED)					
	54	M	50	31	Esophageal varices hemorrhage (H/O alcoholism)
	64	M	Unk	Unk	Carcinoma (died following radiation and chemotherapy)
	35	M	Unk	168	Myocardial infarction
	Unk	M	Unk	Unk	Suicide (hanging)
ONGOING EUROPEAN INVESTIGATIONAL STUDIES					
	36	M	100	152	Suicide (phlebotomy)
	56	F	100	160	Suicide (multi-drug OD)
	69	M	150	61	Sepsis (following mesenteric infarction and surgery)
	Unk	F	125	370	Suicide (barbiturate OD)
	74	F	Unk	Unk	Accidental injury (fell down stairs)
	19	M	100	14	Suicide (intentional motor vehicle accident)
	69	M	50	42	Suicide (hanging)
	73	F	300	79	Cardiac failure (died 6 days after fluvoxamine discontinued)
	54	M	250	Unk	Suicide (hanging)
	73	F	50	2	Suicide (method unknown)

ADDENDUM TO:

Review and Evaluation of Clinical Data
NDA #20,243

Sponsor:	Solvay Pharmaceuticals
Drug:	Fluvoxamine Maleate
Indication:	Obsessive Compulsive Disorder
Material Submitted:	1) Labeling Proposal 2) Safety Update 3) Literature Search 4) Foreign Regulatory Update 5) Evaluation of Long-Term Efficacy. 6) Pediatric OCD Information
Correspondence Date:	September 9, 1994
Date Received:	September 12, 1994

I. Background

NDA 20,243 was submitted on December 24, 1991, for the use of fluvoxamine maleate in the treatment of Obsessive Compulsive Disorder (OCD). This NDA was discussed at a meeting of the Psychopharmacologic Drugs Advisory Committee on October 18, 1993, and fluvoxamine was recommended for approval in the treatment of OCD. The clinical review was completed on October 22, 1993.

An update submitted on November 23, 1993, consisted of: 1) a report of all serious adverse events identified after the cutoff dates in the original NDA, 2) an updated report on worldwide literature pertaining to fluvoxamine for the period December 1990 to October 1993, and 3) an update on the foreign regulatory status and foreign labeling for fluvoxamine. Data at that time supported the previous conclusion that fluvoxamine appeared to be reasonably safe under the recommended conditions of use.

An approvable letter was forwarded from the agency on August 30, 1994. This submission responds to requests in that letter, which are prerequisites to final approval.

II. Labeling

The sponsor has provided a counter-proposal to the labeling proposed by the agency in the approvable letter. Significant changes in the clinical sections of labeling which are advocated by

Solvay are described below and are referenced to Attachment II, Labeling Modification (pages 35-70) in this submission.

1) EFFICACY DATA PRESENTATION (pages 39-40; see also Attachment IIb) In lieu of presenting NIMH-OC Scale data to depict the proportions of patients with given levels of improvement, the sponsor requests that CGI improvement score data be used. Their request is based on the following considerations: a) physicians are more familiar with the CGI compared to the NIMH-OC Scale; b) the CGI is "more clinically relevant;" c) in the pivotal trials, the sponsor claims that the CGI was a more sensitive indicator of treatment response; and d) Prozac labeling uses the CGI for this purpose and its use with LUVOX would permit direct comparison between these two anti-OCD drugs.

While there is some validity to the above statements, the following counterpoints should also be considered: a) it is not clear that the CGI improvement score, as used by investigators in these studies, actually measured improvement in OCD symptomatology, based on a review of the original protocol and the form used in these trials (if this is not the case, the CGI may be less clinically relevant); b) the basis for the claim that the CGI was a "more sensitive indicator of treatment response" is unclear (the NIMH-OC Scale, which has a larger number of gradations for rating symtomatology, would seem to be more sensitive); c) there is a divergence between the efficacy results using these two scales, the CGI presenting LUVOX therapy in a more favorable light than the NIMH-OC Scale; and d) direct comparison of LUVOX with Prozac is not warranted since comparisons would be across development programs and not on the basis of a head-to-head comparison study.

2) CONTRAINDICATIONS (pages 41, 43, and 50; see also Attachment V) The sponsor objects to the contraindicated use of LUVOX with terfenadine or astemizole. They contend that this concern warrants a PRECAUTION. Their stance is that clinically significant LUVOX inhibition of P450IIIA4 is, to date, a theoretical concern and these combinations should not, according to 21CFR 201.57(d), be contraindicated in labeling.

Evidence is adduced (see Attachment V of this submission) that, while fluvoxamine clearly inhibits P450IIIA4 metabolism of alprazolam, the degree of inhibition is much less than ketoconazole inhibition of alprazolam metabolism (Table 1, Attachment V). A study is currently underway by David Greenblatt, M.D. (Tufts University) to examine the Ki's associated with inhibition of terfenadine metabolism by various SSRI's, including fluvoxamine, and SSRI metabolites. Based on mathematical modeling, Dr. Greenblatt has hypothesized that terfenadine clearance must be decreased by 13- to 59-fold in order to produce levels of parent terfenadine sufficient to measurably prolong the QTc; in contrast, alprazolam clearance is only halved when administered with fluvoxamine. Actual terfenadine levels during coadministration

with ketoconazole were close to those predicted by this model and these levels were associated with QTc prolongation. While fluvoxamine data from his study of terfenadine metabolism is not yet available, preliminary data with other SSRI's (Table 2, Attachment V) suggests that in vitro inhibition of terfenadine clearance will be considerably less than that produced by ketoconazole.

The sponsor has also examined the records of patients in Strata I OCD core and extension studies and Strata I depression studies who had been treated with either terfenadine or astemizole during a clinical trial. No patient received astemizole but 15 received fluvoxamine with terfenadine. Only one clinically important event occurred among these patients:

> A 58 year old female, with pre-study hypercholesterolemia and non-specific T-wave changes and a 3 year history of intermittant chest pain, began treatment under blinded conditions with fluvoxamine for depression. After nine days of treatment, she experienced the sudden onset of substernal chest pain radiating to her left arm. She presented at the emergency room and a diagnosis of acute myocardial infarction was made; there were no laboratory values provided. Subsequent evaluation revealed an occluded left coronary artery and a 50% occlusion of the right coronary artery. She was successfully treated with angioplasty. It was concluded by the sponsor that this event was likely to be the product of an evolving atherosclerotic process. (Patient /Study 5526/Strata I).

Also, the Drug Safety Unit of Solvay conducted a search of its database (foreign post-marketing and clinical trial reports) for any serious adverse events which might represent an interaction between fluvoxamine and either terfenadine or astemizole. No such cases were found.

However, there are two reports of serious adverse events associated with the use of terfenadine or astemizole with <u>fluoxetine</u>:

> A 41 year male with no previous cardiac disease experienced an irregular heart beat, shortness of breath, and orthostasis while receiving fluoxetine 20 mg/day and terfenadine 60mg bid. Other medications included ibuprofen, misoprostol, and ranitidine. Cardiac evaluation was remarkable for a systolic ejection murmur and ECG revealed a normal sinus rhythm. The symptoms resolved after discontinuation of terfenadine. A few days after discontinuation of terfenadine, a Holter monitor revealed intermittant sinus tachycardia, with rates to 147 bpm, and no significant ectopic beats. It was speculated by

the author that fluoxetine inhibited the metabolism of terfenadine, leading to the reported cardiac symptoms.[1]

A 41 year old female died, apparently while taking fluoxetine and astemizole in combination. Autopsy revealed no apparent cause of death. She had a past history of breast cancer. No other details are available but one cannot rule out the possibility that a drug-induced arrhythmia was responsible for death.[2]

In sum, there is no clinical evidence thus far of a significant fluvoxamine/terfenadine or fluvoxamine/astemizole interaction, in vivo. Data from an in vitro study of fluvoxamine and terfenadine should be available shortly. It has been hypothesized that the degree of inhibited terfenadine metabolism seen with fluvoxamine will be small compared to that seen with ketoconazole and thus will likely be insufficient to produce levels of terfenadine associated with serious cardiovascular events.

However, the extrapolation of in vitro data to in vivo situations is tenuous and, perhaps, an in vivo study should be done, after in vitro testing, to evaluate the potential for this interaction. Should the agency insist that this contraindication stand, the issue of amending the labeling of the other marketed SSRI's will need to be addressed since it appears that they also inhibit P450IIIA4 to a degree roughly comparable to that observed with fluvoxamine in in vitro studies.

3) "BENZODIAZEPINES" AND "PROPRANOLOL AND OTHER BETA-BLOCKERS" (pages 42, 44, 48, and 50-51) The sponsor states that discussions of interactions of LUVOX with these two classes of drugs should be moved from WARNINGS to the PRECAUTIONS section since these drugs have a wide margin of safety and since there is no evidence of an associated serious hazard with such combined use (Ref: 21CFR 201.57(e)).

In counterpoint, elevated alprazolam levels have been associated with increased decrements in memory and psychomotor performance, which may have quite serious consequences under some circumstances, e.g. driving an automobile. Likewise, bradycardia and hypotension, associated with concurrent fluvoxamine and beta-blocker use, may be quite hazardous, e.g. serious falls or impaired consciousness.

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[1] Swims MP. Potential terfenadine-fluoxetine interaction [letter]. The Annals of Pharmacotherapy 1993; 27: 1404-1405.

[2] MedWatch report to the Prozac NDA, submitted 2/10/94 (Mfr. Report # US94013052A).

4) INTERACTION WITH TRICYCLIC ANTIDEPRESSANTS (page 47; see also Attachment IId)
The sponsor suggests deletion of reference to clinical data which indicates that fluvoxamine may inhibit the P450IID6 metabolism of TCA's.

While they are correct in saying that fluvoxamine appears to be a relatively weak inhibitor of IID6 in vitro and that a more potent effect may be inhibition of P450IA2, which is responsible for N-demethylation of TCA's, there are nonetheless two case reports of clinically significant elevations of desipramine levels in patients receiving desipramine therapy in conjunction with fluvoxamine: one patient experienced a seizure associated with a desipramine level of 285 ng/ml (pre-fluvoxamine level was 159 ng/ml) and the second patient experienced tremor, dizziness, and confusion associated with a desipramine level of 194 ng/ml (pre-fluvoxamine level was 126 ng/ml).[3] Since desipramine is metabolized by IID6-mediated hydroxylation, these cases strongly suggest that fluvoxamine does have the potential to inhibit this enzyme to a clinically significant degree.

5) PHARMACOKINETIC EFFECTS OF OTHER DRUGS ON FLUVOXAMINE (page 47)
The sponsor would like to delete the statement that none of the interaction study data suggested an effect of other drugs on the pharmacokinetics of fluvoxamine, although potent inhibitors of IID6 and IIIA4 have not been studied. They explain that these possible interactions may not be accurate since the isoenzymes involved in fluvoxamine metabolism have not yet been fully investigated and, in any event, fluvoxamine has a wide margin of safety and such interactions would pose little risk.

They are correct in that it is not known as a fact, at this time, whether IID6 or IIIA4 are involved in fluvoxamine metabolism. Thus, mention of these specific enzymes should, perhaps, be omitted. However, as a corollary to this lack of data, the clinical consequences of using a drug which inhibits fluvoxamine metabolism have not been systematically studied. The phrase "None of the drugs studied for drug interactions significantly affected the pharmacokinetics of fluvoxamine" should remain and consideration should be given to indicating, in addition, that the isoenzymes responsible for fluvoxamine metabolism have not yet been identified.

6) CLOZAPINE INTERACTION (page 49) The sponsor has added information regarding elevated clozapine levels when fluvoxamine is taken with this drug, based on a literature report. This report was reviewed by the undersigned on September 1, 1994, and a

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[3] See Case 1 and Case 4 in: Spina E, et al. Interaction Between Fluvoxamine and Imipramine/Desipramine in Four Patients. Therapeutic Drug Monitoring 1992; 14(3): 194-196.

recommendation to add this information to labeling was made at that time.

7) REVISED ADR TABLE (1% TABLE) (pages 55-59) As recommended in the approvable letter, the sponsor has revised the ADR table by combining the table for the two pivotal OCD studies with the table for the six short-term depression studies.

This is acceptable although other features of this table deserve comment: a) the number of patients experiencing each event is provided: this is unnecessary since the total N's are given and percentages are listed for each event; b) many vague terms persist in this table (e.g. thinking abnormal, tooth disorder, and pain): clarification of these events with footnotes should be considered; c) Footnote 2, which lists infrequent events in this study pool, is not needed since the "Other Events" table will include these studies and, thus, these events.

8) "OTHER EVENTS" TABLE (pages 63-66) The study pool for this table now encompasses ALL Strata I and Strata II studies (previously, only those studies that used spontaneous reporting to collect adverse event data were included). Also, for events not deemed potentially serious, those reported for only one patient are omitted.

This is acceptable. However, there are a few recommendations for further minor changes in this table: a) under Body as a Whole, "lab test abnormal" is too non-specific to be helpful and should be listed as the specific abnormalities; b) under Cardiovascular System, "cerebralvascular disorder" is probably better known as cerebrovascular disorder; c) under Endocrine System, "hypothyroidism" was replaced with "goiter," which is less specific: this change should be reversed.

III. Safety Update: Serious Adverse Events

A. Sources of Clinical Data

Discussed in this section are all serious[4] adverse events reported to the sponsor between October 2, 1993 and August 31, 1994. Each case is supported by a MedWatch Form 3500A. Sources of this data are defined as follows:

Strata I: thirteen North American, controlled studies in depression and OCD. Since these studies were completed prior to and reported in the original NDA submission, there is no information to update.

Strata II: North American uncontrolled and European controlled and uncontrolled studies.

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[4] As defined in 21 CFR 314.80.

Strata III: worldwide post-marketing studies.

Strata IV: spontaneous reports of serious adverse events to the sponsor.

Strata V: U.S. or European completed clinical studies reported subsequent to the previous update.

Pivotal Depression Studies: 6 U.S. trials in depression which form the basis for efficacy demonstration in Since these studies were completed prior to and reported in the previous NDA safety update, there is no new information.

U.S Investigational Studies: ongoing investigational studies in the U.S. under IND .

European Postmarketing and Japanese Investigational Studies: ongoing studies not conducted under an IND.

Miscellaneous Study/Literature: European investigator initiated studies not sponsored by Solvay but published in the literature.

B. Safety Findings

There were 12 deaths reported from all clinical data sources. MedWatch 3500A's for all deaths were reviewed and are summarized in **Appendix 1**. The causes of death are as follows:

Suicide	10
Cardiac	1
Asthma Attack	1

By far, the most common cause of death was suicide. Half (5) of these suicides occurred in patients with documented depression; one patient suffered schizophrenia, one obsessive compulsive disorder, and the remaining three had unknown diagnoses. The sponsor submitted a suicidality meta-analysis on January 15, 1993, which systematically explored for an association between fluvoxamine treatment and suicidality emergence or worsening: there was no evidence to support such an association. Four suicides were by physical means,[5] four by overdose, and two by unknown methods. None of the four overdose deaths appeared to involve the ingestion of fluvoxamine alone.

The cardiac death occurred in a 30 year old male with psychotic depression who had received fluvoxamine for eight days (100 mg/day for 4 days, then 200 mg/day for 4 days), in addition to lithium, at

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[5] Hanging, strangulation, carbon monoxide poisoning, and drowning.

an unknown dose. He experienced anxiety, dizziness, and nausea during the first four days of treatment. On or about day 3, chlorpromazine, trilafon, and orphenadine were add . On the eighth day of fluvoxamine treatment, he was pale, xious, and hyperventilating; cardiac arrest occurred and he expired. It is difficult to make an assessment of the contribution of fluvoxamine to death, particularly given the multiplicity of other medications used at the time of death and past association of sudden death with neuroleptic use. Data in this case does not support the occurrence of severe EPS, as would be seen in neuroleptic malignant syndrome. Previous review of the vast fluvoxamine database did not reveal a pattern of similar deaths. There are only two reports of death designated "sudden death" occurring in fluvoxamine treated patients, both from the original foreign postmarketing safety database (N≈ 4.5 million patients): one occurred in a 38 year old male[6] receiving concomitant thioridiazine, to which the death was attributed, and the other in a 35 year old male[7] with epilepsy, with which sudden death has been associated. In conclusion, it is felt to be unlikely that fluvoxamine contributed to this death in a significant way.

The other non-suicide death occurred in a female who died during an asthma attack. Concomitant medication was hydroxyzine. No other clinical information is provided. Given the paucity of clinical information available in this case, it is again difficult to fully assess the role of fluvoxamine in this death. However, since no pattern of similar serious adverse events has been associated with fluvoxamine to date, it is hard to implicate fluvoxamine as an etiologic agent.

In summary, none of these deaths were felt to be reasonably attributable to fluvoxamine.

A total of 148 <u>non-fatal</u> serious adverse events were reported from these sources. All submitted 3500A's were reviewed by the undersigned to identify clinically significant adverse events which had not been previously observed in association with fluvoxamine and which are possibly attributable to fluvoxamine exposure. A total of two such cases were located and are described below, referenced to the Manufacturer's report number and page number in volume #2 of this submission.

#FLUV1940058 (page 160-161) A 45 year old depressed male inpatient began treatment with fluvoxamine 50 mg/day and amitriptyline. Due to lack of improvement, fluvoxamine was increased to 300 mg/day and levomepromazine and supiride, both antipsychotics, were added. One week later, he experienced a severe akinesia and fever. A

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[6] FL0575.

[7] FL2241.

pulmona: tion, felt to be secondary to akinesia, was subseq nosed. The antipsychotics were discontinued, but akine: ed. When fluvoxamine was discontinued, the extra syndrome improved dramatically within 48 hours, tota. ing in 6 days.

A question revolving around this case is whether this patient actually experienced neuroleptic malignant syndrome based on the findings of akinesia and fever. While this data would not fulfill formal criteria for NMS and the fever may have been due to an evolving pneumonia, it must be borne in mind that complete information about this event (e.g. blood pressure and pulse) is not known.

A second question is whether fluvoxamine played an important role in this event, since antipsychotic use in itself may explain such findings. The answer is unclear: while discontinuation of fluvoxamine, and not the antipsychotics, was temporally related to resolution of the symptoms, it is known that EPS does not subside immediately after neuroleptic discontinuation and resolution may be delayed for several days.

"Extrapyramidal syndrome" is included in the "Other Events" table of labeling. However, given the severity of akinesia in this case, association with fever and possibly pneumonia, and the possibility that fluvoxamine may have played a significant role in this event, it is suggested that the following be added to the Non-US Postmarketing Reports section of labeling: "akinesia and fever associated with the concurrent use of LUVOX and antipsychotic medication."

#FLUV1940069 (page 168) A 56 year old male with a six year history of hypertension was treated with fluvoxamine 100 mg/day for approximately two months when acute renal failure, of uncertain etiology, was diagnosed. He underwent hemodialysis, received methylprednisolone, and work-up revealed only cryoglobulinemia, which may be seen in a number of diverse vasculitic syndromes. Concurrent medication was atenolol, which had be started about 5 years prior to this event.

No similar events have been previously noted within the fluvoxamine safety database. But acute renal failure has been associated with some drugs and, while a role for fluvoxamine in the etiology of this event is felt to be remote based on past experience, it cannot be entirely ruled out. It is recommended that the event "acute renal failure" also be added to the Non-US Postmarketing Reports section of labeling.

Reports of the following drug-drug interaction were just recently reviewed.

#FLUV1940098 (pages 178-179) A 66 year old female who received two courses of fluvoxamine treatment during chronic clozapine therapy experienced significant clozapine serum level elevations with combined therapy versus clozapine alone. A literature report of elevated clozapine levels after the addition of fluvoxamine was reviewed by the undersigned on September 1, 1994, this interaction was recommended for notation in labeling and the sponsor appears to concur with this recommendation (see page 49, volume #1 of this submission). Thus, this case will not be further discussed here.

IV. World Literature Update

The sponsor searched the literature to identify any significant safety findings. The primary source of literature data for this search was the Solvay Duphar Pharmaceuticals' Literature Information Service (OPLIS), covering the period October 2, 1993 through September 6, 1994. The OPLIS database comprises literature from Medline, Embase, BIOSIS, Scisearch, Chemical Abstracts, and Derwent Drug File. Additionally, Solvay Duphar scans about 100 biomedical journals in its library for the most recent literature.

Based on the above search, 70 publications and/or abstracts were identified for review; these are listed in the bibliography in Attachment IVb (pages 293-302, volume #2). The sponsor also submitted copies of five published articles from the above mentioned bibliography which they considered to be particularly relevant. These are briefly summarized below:

1) A case report of aplastic anemia in an individual treated with both fluvoxamine and remoxipride; this adverse event is most likely attributable to the latter medication.

2) A letter discussing the postmortem distribution of fluvoxamine following an overdose.

3) and 4) A study and a report of two cases of fluvoxamine inhibition of clozapine metabolism; this interaction is included in currently proposed labeling.

5) A report of five cases of fluvoxamine inhibition of methadone metabolism; this interaction is also included in currently proposed labeling.

Bradley Jeffries, M.D., M.S., Senior Medical Scientist for Solvay Pharmaceuticals, has provided written certification (Attachment IVa) that he has reviewed those articles in the English language and has discovered no finding that would adversely affect conclusions about the safety of fluvoxamine, with the exception of the potential interaction between clozapine and fluvoxamine. Foreign articles are being reviewed by individuals qualified by European affiliates of Solvay; all new or significant clinical findings will be forwarded in a subsequent submission.

V. Foreign Regulatory Update

Since the previous update, fluvoxamine has been registered for the treatment of depression in three additional countries: Bahrain, Lebanon, and Slovakia. Otherwise, there is no new significant information to report regarding the worldwide registration status of fluvoxamine, according to the sponsor.

VI. Long-Term Efficacy Data

A deficiency in the development program for fluvoxamine in the treatment of OCD was the lack of adequate relapse prevention data, which would assist the clinician in treatment planning following response to acute treatment. The sponsor does commit to conducting an adequate and well-controlled relapse prevention trial. They plan to work closely with the agency in developing an appropriate protocol.

VII. Pediatric OCD Information

Another important deficiency in the sponsor's development program was the absence of safety and efficacy data in children and adolescents, given that OCD frequently has an onset in childhood or adolescence. The sponsor reports that study RH.114.02.01, "Fluvoxamine in the Treatment of Obsessive Compulsive Disorder: A Multi-Center, Placebo-Controlled Study in Outpatient Children and Adolescents," is almost completed. They plan to submit the study report, when available, as part of a labeling supplement.

VIII. Conclusions and Recommendations

There are some outstanding labeling issues which need to be resolved before final approval, the most important of which are:

1) Efficacy data presentation using the CGI-improvement scores.

2) Contraindications with terfenadine and astemizole.

These and other labeling concerns are discussed above. The sponsor has requested a meeting with the agency to discuss labeling.

To summarize the safety findings, a review of the aforementioned safety data (serious adverse event update and world literature) revealed only two adverse events which were not observed in previous safety databases and are not adequately reflected in the currently proposed labeling:

1) Acute renal failure.

2) Severe akinesia with fever when fluvoxamine was used with two neuroleptic drugs.

While both events were quite serious, the role of fluvoxamine in these events is unclear. Thus, until further evidence of a causal relationship to fluvoxamine emerges, it is suggested that both events be added to Non-US Postmarketing Reports.

Overall, the submitted data supports the previous conclusion that fluvoxamine appears to be reasonably safe under the conditions of use recommended in proposed labeling.

There are no new significant foreign regulatory developments since the prior update.

The sponsor does commit to conducting an adequate and well-controlled relapse prevention study.

The sponsor has agreed that the study report from RH.114.02.01 (fluvoxamine in the treatment of childhood and adolescent OCD) will be submitted as a labeling supplement when available.

Gregory M. Dubitsky, M.D.
September 26, 1994

cc: NDA#20,243
HFD-120
HFD-120/GDubitsky
TLaughren
PDavid

11-9-94
I agree that all the critical, substantive issues for this NDA have been sufficiently resolved to justify proceeding with an approval action (see my 11-9-94 memo for detailed comments).
T. Laughren

APPENDIX 1
Summary of Deaths Occurring in Fluvoxamine-Treated Patients

Patient Number	Age (yrs)	Sex	Dose (mg/d)	Duration (days)	Cause of Death and Comments
STRATA IV (EUROPEAN POSTMARKETING SURVEILLANCE REPORTS)					
FLUV1930230	30	M	200	5	Cause of death undetermined. TX at the time of death consisted of fluvoxamine, lithium, orphenadrine, and two dopamine receptor antagonists.
FLUV1930267	Unk	F	Unk	Unk	Suicide (overdose of multiple, unidentified drugs).
FLUV1940006	32	M	50	8	Suicide (method unknown).
FLUV1940074	28	F	Unk	Unk	Suicide (strangulation, with evidence of a possible fluvoxamine overdose and alcohol ingestion).
FLUV1940100	Unk	F	Unk	Unk	Asthma attack. Concomitant medication: hydroxyzine. No other clinical information.
FLUV1940103	52	Unk	Unk	Unk	Presumptive suicide by overdose (fluvoxamine + thioridazine) based on post-mortem blood samples.
FLUV1940115	31	M	150	31	Suicide (carbon monoxide poisoning).
FLUV1940116	26	F	Unk	1	Suicide (overdose of fluvoxamine + amoxapine followed by coma, convulsion, and malignant hyperthermia, then hypothermia, disseminated intravascular coagulation, rhabdomyolysis, shock, renal insufficiency, and death).
ONGOING EUROPEAN & JAPANESE INVESTIGATIONAL STUDIES					
FLUV1940118	28	M	50	47	Suicide (method unknown).
FLUV1940119	37	M	150	25	Suicide (drowning).
FLUV1940179	36	M	Unk	10	Suicide (hanging).
FLUV1940185	29	F	Unk	Unk	Suicide (overdose with fluvoxamine + alcohol).

Review and Evaluation of Clinical Data
NDA 20,243

Sponsor:	Solvay Pharmaceuticals
Drug:	LUVOX (Fluvoxamine Maleate)
Material Submitted:	Literature Report of Drug Interaction: Fluvoxamine/Clozapine
Source:	Hiemke C, et al. Elevated Levels of Clozapine in Serum After Addition of Fluvoxamine [letter]. J Clin Psychopharmacol 1994; 14(4): 279-281.

The aforementioned letter (see attachment) describes three cases from Germany of significantly elevated levels of clozapine when clozapine and fluvoxamine were coadministered.

The best documented case occurred in a 36 year old female with chronic paranoid schizophrenia who had been treated with clozapine 400 mg/day, haloperidol 0.5 mg/day, and lorazepam 0.5 mg/day. Due to extrapyramidal side effects and the onset of depressive symptoms, haloperidol was discontinued and fluvoxamine was begun at a dose of 100 mg/day (Day 0). Serum levels at this time were: clozapine 267 ng/ml, N-desmethylclozapine 206 ng/ml, and clozapine N-oxide 199 ng/ml. Subsequently, lorazepam was discontinued and levels on Day 4 were: clozapine 2166 ng/ml (an eight-fold elevation), N-desmethylclozapine 615 ng/ml, and clozapine N-oxide 70 ng/ml. The Day 8 parent drug level was even higher (3151 ng/ml). There was an associated decrease in metabolite:parent ratio for the two metabolites at Days 4 and 8, suggesting dereased metabolism of the parent compound. Neither metabolite has substantial activity. Clozapine was withheld on Day 7 for two days and was restarted at a lower dose of 50 mg/day; the fluvoxamine dose was also decreased to 50 mg/day. The clozapine level on Day 14 was reduced substantially but still higher than pre-fluvoxamine levels; the metabolite:parent ratio was increased.

Two other cases are briefly described in which the combination of fluvoxamine and clozapine was associated with markedly high clozapine levels (1678, 2689, and 2911 ng/ml). Although clozapine monotherapy levels were not available, the observed levels are considerably higher than those usually seen with clozapine treatment alone.

No notable clinical symptoms were reported in these patients.

The authors suggest that inhibition of the N-demethylating enzyme may be implicated in these findings, as appears to be the case with elevated TCA levels when fluvoxamine is coadministered.

Since the risks of some significant adverse events associated with clozapine therapy, such as seizures and orthostatic hypotension, appear to be dose-related, and thus probably concentration-related, it is felt that this apparent pharmacokinetic interaction warrants mention in the **Drug Interactions** section of labeling for LUVOX. Under the subsection CNS Active Drugs, it is recommended that the following be added:

Clozapine - Significantly increased clozapine levels have been reported when fluvoxamine was coadministered with clozapine. Since clozapine related seizures and orthrostatic hypotension appear to be dose related, the risk of these adverse events may be higher when fluvoxamine is taken with clozapine.

Gregory M. Dubitsky, M.D.
September 1, 1994

9-7-94

cc: NDA 20,243
HFD-120
HFD-120/GDubitsky
TLaughren
PDavid

Attachment: one report (3 pages).

Exclusivity Summ.
Ped. pts

EXCLUSIVITY SUMMARY FOR NDA # 20-293 SUPPL #_____

Trade Name Luvox Generic Name Fluvoxamine Maleate

Applicant Name Solvay Pharmaceuticals HFD # 120

Approval Date If Known _____

PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, but only for certain supplements. Complete PARTS II and III of this Exclusivity Summary only if you answer "yes" to one or more of the following question about the submission.

a) Is it an original NDA?

YES /✓/ NO /___/

b) Is it an effectiveness supplement?

YES /___/ NO /✓/

If yes, what type? (SE1, SE2, etc.) _____

c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "no.")

YES /✓/ NO /___/

If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

_____

_____

If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

_____

_____

d) Did the applicant request exclusivity?

YES /___/ NO /✓/

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

_____

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. Has a product with the same active ingredient(s), dosage form, strength, route of administration, and dosing schedule, previously been approved by FDA for the same use?

YES /___/ NO /✓/

If yes, NDA #_____. Drug Name _____.

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

3. Is this drug product or indication a DESI upgrade?

YES /___/ NO /✓/

IF THE ANSWER TO QUESTION 3 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (even if a study was required for the upgrade).

PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES

(Answer either #1 or #2 as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES /___/ NO /✓/

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA# _____ _____

NDA# _____ _____

NDA# _____ _____

2. Combination product. N/A

If the product contains more than one active moiety(as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES /___/ NO /___/

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA# _____ _____

NDA# _____ _____

NDA# _____ _____

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8. IF "YES" GO TO PART III.

PART III THREE-YEAR EXCLUSIVITY FOR NDA'S AND SUPPLEMENTS

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2 was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

YES /___/ NO /___/

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

(a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES /___/ NO /___/

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval AND GO DIRECTLY TO SIGNATURE BLOCK ON PAGE 8:

_____

_____

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES /___/ NO /___/

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion?

YES /___/ NO /___/

If yes, explain: _____

_____

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES /___/ NO /___/

If yes, explain: _____

_____

(c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

_____

_____

Studies comparing two products with the same ingredient(s) are considered to be bioavailability studies for the purpose of this section.

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1 YES /___/ NO /___/

Investigation #2 YES /___/ NO /___/

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

_____ _____

_____ _____

b) For each investigation identified as "essential to the approval", does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1 YES /___/ NO /___/

Investigation #2 YES /___/ NO /___/

If you have answered "yes" for one or more investigation, identify the NDA in which a similar investigation was relied on:

_____ _____

_____ _____

c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

_____ _____

_____ _____

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1	
IND # _____ YES /___/	NO /___/ Explain: _____
	_____
Investigation #2	
IND # _____ YES /___/	NO /___/ Explain: _____
	_____

(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

Investigation #1	
YES /___/ Explain _____	NO /___/ Explain _____
_____	_____
_____	_____
Investigation #2	
YES /___/ Explain _____	NO /___/ Explain _____
_____	_____
_____	_____

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES /___/ NO /___/

If yes, explain: _____

_____

Signature
Title: Regulatory Management Officer

3-1-94
Date

Signature of Office/
Division Director

3/7/94
Date

cc: Original NDA Division File HFD-85/ HA/OVAC

DRUG STUDIES IN PEDIATRIC PATIENTS
(To be completed for all NME's recommended for approval)

NDA # 20-293 Trade (generic) names Luvox (Fluvoxamine Maleate)

Check any of the following that apply and explain, as necessary, on the next page:

___ 1. A proposed claim in the draft labeling is directed toward a specific pediatric illness. The application contains adequate and well-controlled studies in pediatric patients to support that claim.

___ 2. The draft labeling includes pediatric dosing information that is not based on adequate and well-controlled studies in children. The application contains a request under 21 CFR 210.58 or 314.126(c) for waiver of the requirement at 21 CFR 201.57(f) for A&WC studies in children.

___ a. The application contains data showing that the course of the disease and the effects of the drug are sufficiently similar in adults and children to permit extrapolation of the data from adults to children. The waiver request should be granted and a statement to that effect is included in the action letter.

___ b. The information included in the application does not adequately support the waiver request. The request should not be granted and a statement to that effect is included in the action letter. (Complete #3 or #4 below as appropriate.)

✓ 3. Pediatric studies (e.g., dose-finding, pharmacokinetic, adverse reaction, adequate and well-controlled for safety and efficacy) should be done after approval. The drug product has some potential for use in children, but there is no reason to expect early widespread pediatric use (because, for example, alternative drugs are available or the condition is uncommon in children).

✓ a. The applicant has committed to doing such studies as will be required.

___ (1) Studies are ongoing.
___ (2) Protocols have been submitted and approved.
___ (3) Protocols have been submitted and are under review.
___ (4) If no protocol has been submitted, on the next page explain the status of discussions.

___ b. If the sponsor is not willing to do pediatric studies, attach copies of FDA's written request that such studies be done and of the sponsor's written response to that request.

___ 4. Pediatric studies do not need to be encouraged because the drug product has little potential for use in children.

Page 2 -- Drug Studies in Pediatric Patients

____ 5. If none of the above apply, explain.

Explain, as necessary, the foregoing items: _____

Signature of Preparer

3-2-94
Date

cc: Orig NDA
HFD- /Div File
NDA Action Package

Pharm

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. June 22, 1994

FROM: Glenna G. Fitzgerald, Ph.D. GGF 6/24/94

TO: NDA 20-234, Luvox (fluvoxamine), Solvay

The finding of 0, 0, 0, 3/40 pancreatic adenocarcinomas in the lifetime carcinogenicity study in control, low, middle and high dose male rats receiving Luvox in the diet was considered to be equivocal by the Executive Committee of the CDER Carcinogenicity Assessment Committee. Unanimous agreement could not be reached on whether or not the finding should be in the labeling. The report of the study did not specify whether these tumors were found in acinar cells or islet cells, or even if they all occurred in the same cell type. Also, there appeared to be a discrepancy between the number of tumors reported in the hard copy (2) and on the diskette supplied to the Division of Biometrics (3). The committee was in agreement that the findings did not warrant repeat testing.

I phoned Virginia Ackerman, Regulatory Liaison at Solvay, to inform her that we were not planning at this time to include the finding in the labeling, but that our approvable letter would include a request for clarification of the numbers of malignant tumors and the cell types in which they occurred.

The sponsor has reviewed the pathology of the slides which were involved and provided the information in the attached pages. There were two pancreatic adenocarcinomas in high dose males, one exocrine and one in islet cells. With different cell types involved, and one adenocarcinoma per cell type, this finding would fall within the range of historical data. I conclude that the findings are not related to drug administration and should not be included in the labeling.

ATTACHMENT

cc:
NDA File
IND 11,925
HFD-120
HFD-120/TLaughren
/GFitzgerald
/PDavid
/BRosloff
N:\Fitzgerald\NDA20234

Re-evaluation of pancreata to confirm the cell type of origin (Report, H114.462)

Date 14 June 1994

Pathologist: Drs. R.J.M.M. Thoolen, SOLVAY DUPHAR B.V., WEESP, The Netherlands

Consulting pathologist: Dr. R.A. Woutersen, TNO ZEIST, The Netherlands
Expert in pancreatic carcinogenesis in azaserine-treated rats and BOP-treated hamsters.

We have reviewed the pathology of the slides mentioned in the table (Page 2) with regard to the neoplastic changes, and confirmed, changed or added the cell type of origin of the lesions, or the nomenclature of the lesions as indicated by Prof dr. P Wenswoon, except for animal no 141 (slide no. 20021) where no tumour was present. We used the criteria for classifying the exocrine pancreatic lesions as developed by the National Toxicology Program in the United States.

References

1) Longnecker, D.S. (1984) Lesions induced in rodent pancreas by azaserine and other pancreatic carcinogens. Environ. Health Perspect., 56, 245-251

2) Longnecker, D.S. (1986) Experimental models of exocrine pancreatic tumors. In: Go, V.L.W. Ed., The Exocrine Pancreas: Biology, Pathobiology, and Diseases. New York, Raven Press, pp. 443-458

3) Woutersen, R.A., Garderen-Hoetmer van, A., Lamare, C.B.H.W. & Scherer, E. (1991) Early indicators of exocrine pancreas carcinogenesis produced by non-genotoxic agents. Mutation Research, 248, 291-302

PANCREATIC TUMORS IN MALE RATS OF LUVOX CARCINOGENICITY STUDY					
GROUP	SOLITARY TUMORS	MALIGNANT TUMORS	MICROSCOPIC OBSERVATIONS	INDIVIDUAL DATA	ELECTRONIC DATABASE
Control	2 A.A.C.N. 1 adenoma (islet cell)	none	2 A.A.C.N. 1 adenoma (islet cell)	#10 - A.A.C.N. #11 - adenoma (islet cell) #32 - A.A.C.N.	#10 - A.A.C.N. #11 - adenoma (islet cell) #32 - A.A.C.N.
Low Dose	1 adenoma (islet cell)	none	1 adenoma (islet cell)	#72 - adenoma (islet cell)	#72 - adenoma (islet cell)
Mid Dose	1 adenoma (islet cell)	none	1 adenoma (islet cell)	#95 - adenoma (islet cell)	#95 - adenoma (islet cell)
High Dose	1 A.A.C.N. 1 adenoma (islet cell)	2 adenocarcinomas (one islet cell, one exocrine)	1 A.A.C.N. 1 adenoma (islet cell) 2 adenocarcinomas (one islet cell, one exocrine)	#134 - adenocarcinoma (exocrine) #139 - adenocarcinoma (islet cell) #140 - A.A.C.N. #169 - adenoma (islet cell)	#134 - adenocarcinoma (exocrine) #139 - adenocarcinoma (islet cell) #140 - A.A.C.N. #169 - adenoma (islet cell)

A.A.C.N.: Atypical acinar cell nodule (D < 3 mm)

REFERENCE:

Longnecker D.S (1984). Lesions induced in rodent pancreas by azaserine and other pancreatic carcinogens. Environ. Health Perspect., 66, 245-251.

Re-evaluation of pancreata to confirm the cell type of origin (Report. H114,462) *(CONTINUED)*

Slides of Pancreata tumours in Wistar (Cpb:WU) rats. (Report. H114,462)

Males

ANIMAL NO.	SLIDE NO.	MODE OF DEATH	TUMOR
10	17779	Terminal Kill	A.A.C.N.
11	17798	Terminal Kill	Adenoma (islet cell)
32	19197	Terminal Kill	A.A.C.N.
72	18881/188838	Decedent	Adenoma (islet cell)
95	19242/192488	Decedent	Adenoma (islet cell)
134	19888/198908	Decedent	Adenocarcinoma *(exocrine)*
139	19983	Decedent	Adenocarcinoma *(islet cell)*
140	20002	Terminal Kill	A.A.C.N.
141	20021	Decedent	Normal pancreas, no tumor
147	200135	Decedent	Perioitoma (metastasis)
169	20563/20661	Terminal Kill	Adenoma *(islet cell)*

142

A.A.C.N. Atypical acinar cell nodule Ø < 3 mm (ref. Longnecker, D.S (1984) Lesions induced in rodent pancreas by azaserine and other pancreatic carcinogens. Environ. Health Perspect., 56, 245-251)

Drs. R.J.M.M. THOOLEN
PATHOLOGIST
DEPARTMENT OF TOXICOLOGY
PHARMACEUTICAL DIVISION
SOLVAY DUPHAR B.V.

Dr. R.A. WOUTERSEN
HEAD DEPARTMENT OF PATHOLOGY
PATHOLOGIST
DIVISION TOXICOLOGY
TNO NUTRITION AND FOOD RESEARCH INSTITUTE

Barry N. Rosloff, Ph.D.
3/10/92

Pharmacologist Review of NDA 20-234
Original Summary

Sponsor: Solvay Pharmaceuticals
901 Sawyer Road
Marietta, GA 30062

Drug: fluvoxamine maleate

Category: treatment of obsessive-compulsive disorder (OCD)

Related IND/NDA:

1) IND

2)

Summary and Evaluation:

Commercial NDA for the use of fluvoxamine as an antidepressant was previously reviewed by me and considered approvable; my reviews of that application (reviews of 11/30/84, 5/29/85, and 9/3/86), as well as a statistical review (7/18/85), are attached. No new animal toxicity or ADME/PK studies were submitted with the present application. Numerous new pharmacodynamic studies (primarily published articles) were submitted. Findings with potential relevance to the human use of this drug include the following:

1) In vitro brain receptor binding profile indicates little or weak binding to a variety of receptor types. Potent binding to (and antagonism at) some of these receptors (e.g. muscarinic, histaminergic, alpha adrenergic) is thought to be associated with several side effects of classical tricyclic antidepressants, e.g. anticholinergic effects (dry mouth, blurred vision, etc), sedation, and orthostatic hypotension . Fluvoxamine resembles some of the more recent antidepressants such as fluoxetine and sertraline in this regard.

2) Two studies of potential drug dependency-producing effects were performed by in monkeys: (1) Doses of 45→90 mg/kg p.o. b.i.d. were given for two 28 day periods; a benzodiazepine receptor antagonist was given and withdrawal signs looked for. (Diazepam used as a positive control). (2) Monkeys were tested for self-administration of fluvoxamine (HD= 4 mg/kg intragastric). Overall it was concluded that fluvoxamine had no significant effects, although it is noted that in the second study 1 of 4 monkeys transiently self-administered the drug.

3) Fluvoxamine at 12.5-25 mg/kg i.p. elevated plasma prolactin in rats; tolerance to this effect developed with repeat dosing.

4) In interaction studies with lithium, fluvoxamine did not potentiate lithium toxicity in mice. In rabbits, lithium (at 100 mg/kg i.v., giving plasma levels of about 1.3-1.6 mmol/l during the study) appeared to potentiate the hyperthermia seen after fluvoxamine (0.3 mg/kg i.v.) + 5-HTP; the effect was not statistically significant although the author seemed to believe it was biologically significant.

Barry N. Rosloff, Ph.D.
3/10/92

RECOMMENDATIONS:

This NDA is approvable, although final action should not be taken until the carcinogenicity studies have been presented to the Carcinogenicity Assessment Committee (CAC). Recommendations concerning the proposed labelling will be made subsequent to the CAC review.

Barry Rosloff

Barry N. Rosloff, Ph.D.

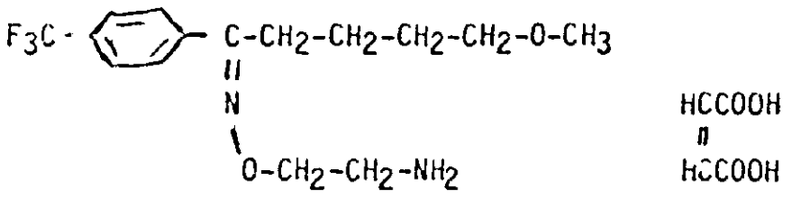
cc:NDA 20-234
HFD-120
HFD-120/GFitzgerald/BRosloff
/PDavid
rd/llt/3/11/92
F:\ROSLOFF\NDA20234

Barry N. Rosloff, Ph.D.
November 30, 1984

Pharmacologist Review of NDA
Original Summary

SPONSOR:

DRUG: fluvoxamine maleate



CHEMICAL NAME: 5-methoxy-4'-(trifluoromethyl) valerophenone (E)-O-(2-aminoethyl) oxime maleate (1:1)

CODE NAME: DU 23000

CATEGORY: Antidepressant

RELATED IND/NDA:

1. IND
2. IND

TABLE OF CONTENTS:

LABS WHERE STUDIES PERFORMED:

A. The following were performed by

1. Acute toxicity
2. 2 week studies in mouse and hamster
3. 2 of the four 4-week studies in mouse
4. 6 month toxicity in rats
5. 18 month toxicity in rats
6. Lifetime carcinogenicity study in rats
7. 7 month toxicity in dog
8. 1 year toxicity in dog
9. Ames Test
10. Most of the ADME/pharmacokinetic studies

B. The following were performed by

1. 2 of the four 4-week studies in mouse
2. 21 week toxicity in mouse

C. The following was performed by

Lifetime carcinogenicity study in hamsters

D. The following were performed by

1. 4 week toxicity in hamster
2. 13 week toxicity in hamster
3. All reproduction studies
4. Mutagenesis study (human lymphocytes)

Tables

The following tables summarize the experiments carried out and the most important results obtained in animal pharmacology.

An explanation of the format of the tabular presentation and of the abbreviations used is given below:

Title - Titles are the same as used in the main report on pharmacology: Claassen, 1981, no. 56648/10/81, report: Claassen, 1977b, no. 56648/13/77 and report: Claassen, 1981b, no 56648/8/77.

Reference - If not indicated otherwise, reference is made by mentioning the relevant chapter of report 56648/10/81.

Species/sex - M = mice; D = dogs; R = rats; Rb = rabbits; C = cats; Cv = guinea pigs; m = male; f = female

Weight - Weight range of animals used.

Dose* - The quantity of fluvoxamine administered, expressed in mg/kg. To obtain ED_{50} values log dose ranges were used e.g. 2.15, 4.6; 10; 21; 46 mg/kg orally with increments of 2.15.

pI_{50} : negative log of molar concentration causing 50% inhibition

Route*	- i.v. = intravenous i.p. = intraperitoneal i.m. = intramuscular
Number of animals	- When not otherwise indicated, this number refers to the total number of animals used in the experiment.
Treatment period*	- Gives the time in minutes, hours or days over which the drug was administered.
Type of experiment	- Describes the effects which the experiment was designed to demonstrate.
Results	- Only the most important findings are noted. For comparison purposes the results obtained with reference compounds are also noted.

Coded reference drugs:

H 75/12 = 4-methyl-α-ethyl-meta-tyramine

H 77/77 = 4, α-dimethyl-meta-tyramine

Ro-4-1284 = benzoquinolizine (reserpine-like drug)

Ro-4-4602 = benserazide (DOPA-decarboxylase inhibitor)

* N.B. In vitro and isolated organ test conditions are described with different nomenclature.

Other abbreviations used in these tables can be found in the complete list of abbreviations at the beginning of this section.

ANIMAL PHARMACOLOGY

table 1

POTENTIATION OF SEROTONIN EFFECTS
ACUTE EXPERIMENTS

Title	Ref	Spec. /sex	Weight	Dose mg/kg	Route	Number animals	Treatment period	Type of experiment	Results
Inhibition of serotonin uptake by blood platelets	3.2.1	Cv m and f	500-600 g	-	-	-	-	In vitro uptake of ^{14}C-serotonin by blood platelets from platelet rich-plasma.	pI 50 ± s.e.m. Fluvoxamine 6.4 ± 0.2 Chlorimipramine 7.6 ± 0.26
Inhibition of serotonin uptake by brain synaptosomes	3.2.2	R m	160-180 g	-	-	-	-	In vitro uptake of ^{3}H-serotonin by synaptosomes from rat brain.	Ki x 10^{6}M Fluvoxamine 0.084 Imipramine 0.23 pI_{50} ± s.e.m Fluvoxamine 6.5 ± 0.2 Chlorimipramine 6.1 ± 0.08 Fluoxetine 5.9 ± 0.12 Zimelidine 5.1
Inhibition of serotonin uptake by brain synaptosomes after in vivo administration	3.2.3	R m	230-280 g	25	i.p.	36	30-60-90 min	In vitro uptake of ^{3}H-serotonin by synaptosomes from rat brain after pre-treatment for different periods.	Uptake p mol/g tissue/5 min Control 6.10 ± 0.14 (s.e.m.) Fluvoxamine 1.07 ± 0.07 Imipramine 3.26 ± 0.60 measured 60 min. pre-treatment. other periods: same order of inhibition
				10	i.p.	2-12	60 min		Fluvoxamine 90% Chlorimipramine 27%
				20	oral	2-12	60 min		Uptake inhibition (% of control) Fluvoxamine 50% Chlorimipramine 28%
Inhibition of serotonin release by H75/12 and H77/77	3.2.4	R m	160-180 g	2 x 25	i.m.	72	270 min	H75/12 and H77/77 release serotonin and noradrenaline. Inhibition of this releasing action is measured by assaying 5-HT and NA levels.	Protective effect of fluvoxamine is 68% and 60% for both releasers of 5-HT. Imipramine: 31 (H75/12); DMI: 12% (H77/77). 5-HT levels are unaffected by fluvoxamine and decreased by imipramine and DMI.
Antagonism of serotonin depletion by p-chloroamphetamine	3.2.5	R m	180-200 g	range	oral	30	4 hrs	p-chloroamphetamine depletes serotonin. Inhibition of this depletion is measured by assaying 5-HT levels.	ED_{50} (mg/kg) Fluvoxamine ~ 10 Chlorimipramine > 20 Zimelidine ~ 4
Effect on serotonin turnover rate, measured by probenacid method	3.2.6	R m	160-180 g	25	i.m.	54	4 hrs	Accumulation of 5-HIAA is measured after 200 mg/kg i.p. probenecid Accumulation rate correlates with turnover rate.	Turnover rate (nmol/g/hr) Control 1.01 Fluvoxamine 0.84 Imipramine 0.94
		R m	150-200 g	40-50 70	oral	19	135 min		All doses inhibit 5-HIAA accumulation rate from 50-95%

ANIMAL PHARMACOLOGY table 1 (cont.) POTENTIATION OF SEROTONIN EFFECTS ACUTE EXPERIMENTS

Title	Ref	Spec /sex	Weight	Dose mg/kg	Route	Number animals	Treatment period	Type of experiment	Results
Effect on serotonin levels in the raphe area	3.2.7	R m	170-190 g	25	i.p.	28	4 hrs	The content of 5-HT and 5-HIAA in the raphe areas in rat brain was measured after pre-treatment with reserpine + nialamide (R + N)	Raphe content (µg/g tissue) ± s.e.m. 5-HT 5-HIAA Control R + N 2.1 ± 0.16 1.2 ± 0.22 Fluvoxamine 3.1 ± 0.30 1.1 ± 0.11 Chlorimipramine 2.5 ± 0.27 1.5 ± 0.05
Potentiation of 5-hydroxytryptophan effects	3.2.8	M m	16-19 g	log range	oral	5/test dose	1 and 6 hrs	Scoring of behavioural symptoms after combination of drug with 5-HTP, 150 mg/kg i.p.	ED_{50} orally, mg/kg ± s.e.m. 1 hr 6 hrs Fluvoxamine 37 ± 4 141 ± 21 Chlorimipramine 83 ± 5.5 ~ 240
Potentiation of 5-hydroxytryptophan induced head-twitch	3.2.9	M m	16-19 g	log range	oral	5/test dose	1 hrs	Scoring of head-twitch after combination of drug with 5-HTP 62.5 mg/kg s.c.	Fluvoxamine gave a dose-dependent increase at doses of 21-100 mg/kg
Potentiation of paroxyline effects in mice	3.2.10	M m	16-19 g	log range	oral	5/test dose	30-60-90-120 min	Scoring of behavioural symptoms after combination of drug with pargyline, 100 mg/kg i.p.	ED_{50} orally, mg/kg ± s.e.m. Fluvoxamine 33 ± 4 after 2 hrs Chlorimipramine 160 ± 31 after 2 hrs strongest effect was noted after 2 hrs.
Effect on hyperactivity induced by MAO-inhibitor and tryptophan	3.2.11	R m	180-230 g	10	i.p.	8	30 min	Measuring motor activity after combination of drug with tranylcypromine (10 mg/kg i.p.) and l-tryptophan (250 mg/kg i.p.)	Fluvoxamine gave a clear potentiation of the induced hyperactivity at the dose tested. Chlorimipramine was less active at the same dose.
Potentiation of 5-hydroxytryptophan hyperthermia	3.2.12	Rb m	2.5 kg	0.3	i.v	15	30 min	Measuring of rectal temperature after combination of drug with 5-HTP, 50 mg/kg i.v.	Fluvoxamine produced a strong hyperthermia after combination with 5-HTP (3 of 5 animals died of hyperthermia) Chlorimipramine produced less hyperthermia and 1 of 5 animals died
Antagonism of the reserpine-induced lowering of the pentamethylene tetrazole convulsive threshold	3.2.13	M m	16-19 g	10-20-40	oral	10/test dose	1 hr before reserpine	Convulsive threshold of pentamethylene tetrazole can be measured by establishing the dose necessary to cause convulsions. This threshold is lowered by pre-treatment with reserpine 5 mg/kg s.c. over 2 hrs. This decrease can be antagonized by pre-treatment with drugs	Fluvoxamine (orally) at doses of 10-20-40 mg/kg significantly antagonized the reserpine effect. Chlorimipramine was active at 20 mg/kg
Effect on serum prolactin content	3.2.14	R m	200-220 g	25	oral	5	60 min	Serum prolactin content was measured by anti-body - radioimmuno assay	Fluvoxamine did not significantly affect serum prolactin levels

ANIMAL PHARMACOLOGY

table 2

POTENTIATION OF NORADRENALINE EFFECTS
ACUTE EXPERIMENTS

Title	Ref.	Spec /sex	Weight	Dose mg/kg	Route	Number animals	Treatment period	Type of experiment	Results
Effect on noradrenaline and dopamine uptake by brain synaptosomes	3.3.1	R m	160-180 g	-	-	-	-	In vitro uptake of ^{3}H-noradrenaline and ^{3}H-dopamine by synaptosomes from rat brain cerebral hemispheres. In vitro uptake of ^{3}H-noradrenaline and ^{3}H-dopamine by synaptosomes from rat hypothalamus	Fluvoxamine was almost as active as desimipramine in inhibiting NA and DA uptake pI_{50} ± s.e.m. NA DA Fluvoxamine 4.4 4.3 Desimipramine 7.0 ± 0.09 4 4 ± 0.23
Effect on noradrenaline and dopamine uptake by brain synaptosomes after in vivo administration	3.3.2	R m	250-280 g	25	i.p.	20	30-60-90 min	In vitro uptake of ^{3}H-noradrenaline and ^{3}H-dopamine by synaptosomes from rat brain after pre-treatment during several periods	^{3}H-NA uptake pmol/g tissue/5 min after 60 min pre-treatment Control 3.70 ± 0.16 (mean ± s.e.m.) Fluvoxamine 3.56 ± 0.12 Imipramine 3.26 ± 0.18 significant At 90 min fluvoxamine also caused a minimal, significant inhibition. ^{3}H-DA uptake p mol/g tissue/5 min after 60 min. pre-treatment Control 16.3 ± 0.47 Fluvoxamine 17.1 ± 0.38 Imipramine 17.6 ± 0.60 At 90 min. fluvoxamine caused a significant inhibition: 13.9 ± 0.61
Effect on noradrenaline release by H75/12 and H77/77 .	3.3.3	R m	160-180 g	2 x 25	i.m.	75	270 min	H75/12 and H77/77 release serotonin and noradrenaline. Inhibition of this releasing action is measured by assaying 5-HT and NA levels	Fluvoxamine did not protect against the NA depleting action of either agent. Desimipramine caused a 68% protection. NA levels were not affected by fluvoxamine or desimipramine. (dose: 2 x 25 i.m.)
Potentiation of noradrenaline effects on vas deferens in vitro	3.3.4	R m	160-180 g	-	-	-	-	The minimal and optimal dose for the potentiation of small noradrenaline contractions were determined for the isolated vas deferens	min.dose opt dose mg/ml Fluvoxamine 200 700 Imipramine 7 70
Antagonism of tetrabenazine ptosis	3.3.5	M m	16-19 g	log. range	i.p. oral	5/test dose/ treatm. period	45 min 6 hrs	Antagonism towards tetrabenazine induced ptosis can be regarded as a measure of the potentiation of noradrenaline	ED_{50} mg/kg ± s.e.m. i.p. oral oral 45 min 45 min 6 hrs Fluv. 35 107 ± 25 ≥ 464 Chlor. 8 12 ± 2.7 20
Antagonism of tetrabenazine ptosis in rats	3.3.6	R m	160-180 g	log. range	oral	5/test dose	135 min	See above	ED_{50} mg/kg ± s.e.m. Fluvoxamine ≥215 Chlorimipramine 19 ± 2.4

ANIMAL PHARMACOLOGY

table 2 (cont.)

POTENTIATION OF NORADRENALINE EFFECTS
ACUTE EXPERIMENTS

Title	Ref.	Spec /sex	Weight	Dose mg/kg	Route	Number animals	Treatment period	Type of experiment	Results
Observation of compulsive hyperactivity	3 3.7	R m	250-300 g	log range	oral	5/test dose	135 min	After combination of tricyclic anti-depressants and tetrabenazine, in the test above hyperactivity is seen	Eb_{50} on basis of the number of rats per dose group showing hyperactivity: mg/kg ± s.e.m. Fluvoxamine >215 Chlorimipramine > 46 Desimipramine 8.3
Ro-4-1284 hyperactivity test in rat	3 3.8	R m	250-300 g	12-40-120	oral	2/test dose/ treatment period	30-45-90-180 min	Desimipramine can antagonise Ro-4-1284 induced sedation as measured in activity cages and restores the normal hyperactivity	Fluvoxamine did not produce any hyperactivity. Imipramine and desimipramine were active
Reversal of hypothermia in reserpinised mice	3 3 9	M m	18-23 g	3.0-3.2 10-32	oral	5/test dose/ treatment period	1-2-3-4½ hrs	Reserpine (2 mg/kg s.c.) pre-treatment induces strong hypothermia, which can be antagonized by anti-depressants of the tricyclic type	Fluvoxamine produced a significant hypothermia reversal only at dose levels of 10 and 32 mg/kg Imipramine and amitriptyline were active at 1 mg/kg orally

ANIMAL PHARMACOLOGY

table 3

OTHER INFLUENCES ON AMINERGIC PROCESSES
ACUTE EXPERIMENTS

Title	Ref	Spec /sex	Weight	Dose mg/kg	Route	Number animals	Treatment period	Type of experiment	Results
Receptor binding	3.4.1	R m	200-300 g	-	-	-	-	Measurement of the affinity for various aminergic brain receptors	Fluvoxamine had a weak or very weak affinity towards adrenergic, dopaminergic and serotonergic receptors. Chlorimipramine had a clear affinity towards σ_1-receptors.
Effect on monoamine oxidase (MAO) in vitro	3.4.2	-	-	-	-	-	-	Mitochondria of liver or brains were used as enzyme source. Substrates: kynuramine and serotonin	Fluvoxamine in concentrations of 10^{-3} and 10^{-4} mol did not affect MAO-activity
Tryptamine potentiation test	3.4.3	M m	18-27 g	10-46-100-460	oral	5/test dose	1 and 22 hrs	Tryptamine (250 mg/kg s.c.) is lethal after MAO-inhibition	Fluvoxamine and tricyclic antidepressants did not potentiate tryptamine toxicity
Antiserotonin effect in vitro	3.4.3	CV m	-	-	-	-	-	Antagonism of 5-HT-induced spasm of isolated ileum	Fluvoxamine had no anti-serotonergic activity
Effect upon serotonin induced edema	3.4.3	R m	180-200 g	0.8-4-20-100	oral	6/test dose	30 and 90 min	Local injection of serotonin (5 µg) into the plantar surface of the hindfeet produces edema. Serotonin antagonists prevent edema formation	Fluvoxamine did not influence the development of edema
Antihistamine effect in vitro	3.4.4	CV m	-	-	-	-	-	Antagonism of histamine-induced spasm of isolated ileum	Fluvoxamine did not show antihistaminic activity

ANIMAL PHARMACOLOGY

table 4

MISCELLANEOUS ANTIDEPRESSANT EFFECTS
ACUTE EXPERIMENTS

Title	Ref	Spec /sex	Weight	Dose mg/kg	Route	Number animals	Treatment period	Type of experiment	Results
Effect on distress vocalizations	3.5.1	CV m and f		10	s.c.	25	30 min	Isolation from the mothe induces distress vocalization in 2 days old litters	Fluvoxamine decreased distress vocalization in the dose tested Also morphine markedly diminished this effect at a dose of 1 mg/kg. DMI (5 mg/kg) was ineffective
Potentiation of the motor activity of dl-amphetamine	3.5.2	M m	18-24 g	46-100-215	oral	4 x 5/ test dose	75-90 min	dl-amphetamine induces hyperactivity (3.2 mg/kg i.p.) Potentiation is sometimes considered as an antidepressant screen	Fluvoxamine did not significantly increase the locomotor stimulant effect of amphetamine
Potentiation of the anorexogenic effect of dl-amphetamine	3.5.3	R m	160-180 g	log range	oral	3/test dose/ treatm. period	2-4-6 hrs	dl-amphetamine (4 mg/kg s.c.) has strong anorexogenic properties Potentiation is sometimes considered as an antidepressant screen	Approximate ED_{50} 4 hrs mg/kg oral Fluvoxamine 15.5 Chlorimipramine 7.5 Desimipramine 1.8
Potentiation of yohimbine toxicity	3.5.4	M m	18-24 g	log range	oral	8/test dose	1 hr before yohimbine	Potentiation of the lethality of a sublethal dose of yohimbine (50 mg/kg s.c.) is a property of imipramine like compounds	ED_{50} (50% mortality) mg/kg oral Fluvoxamine ~20 Imipramine 0.8

ANIMAL PHARMACOLOGY table 5 INFLUENCES ON AMINERGIC PROCESSES CHRONIC EXPERIMENTS

Title	Ref.	Spec /sex	Weight	Dose mg/kg	Route	Number animals	Treatment period	Type of experiment	Results
Effect on the contents of biogenic amines	3.6.1	R m	190-210 g	100/ daily 5 20. 100 daily	oral oral	5/test dose 5/test dose	7 days 5 weeks	Content of NA, DA and 5-HT is measured after chronic treatment of the drug	Fluvoxamine did not produce a significant change in contents of biogenic amines Also after a 5 weeks treatment no change was found
Effect on serotonin and noradrenaline turnover rate measured by probenecid and α-MT method	3.6.2	R m	200-250 g	10/daily	i.p.	20	3 weeks	Accumulation of 5-HIAA after administration of probenecid and the decrease in contents of catecholamines after α-MT are measurements for 5-HT resp. NA turnover rate	Fluvoxamine did not influence on the turnover rate of NA and 5-HT after chronic treatment
Effect on 5-HT content in blood platelets	3.6.3	R m	150-200 g	25/daily	oral	20	8 days	Measuring content of 5-HT in blood platelets	Chronic fluvoxamine treatment resulted in a significant decrease of the platelet 5-HT content
Effect on β-adrenergic serotonergic and dopaminergic receptor populations	3.6.4	R m	200-250 g	10/daily	i.p.	4	14 or 28 days	Measuring the affinity and number of receptors after chronic treatment	Fluvoxamine did not affect the number of β-receptors in the frontal cortex or the limbic forebrain. Fluvoxamine increased the number of DA-receptors in the striatum after a treatment period of 28 days. Fluvoxamine had no effect on 5-HT receptors in the frontal cortex
Effect on 5-HTP induced head-twitch	3.6.5	M m	20-24 g	10/daily	oral	10/dose	14 days	Scoring head-twitch after combination of drug with 5-HTP	Chronic treatment with fluvoxamine decreased to some extend the potentiating properties of fluvoxamine
Potentiation of 5-hydroxytryptophan effects	3.6.5	M m	16-19 g	log. range	oral	5/test dose	10 days 20 mg/kg per day	Scoring of behavioural symptoms after combination of drug with 5-HTP, 150 mg/kg i.p.	ED_{50} oral of fluvoxamine: 32 mg/kg measured at day 10

ANIMAL PHARMACOLOGY table 6 PARASYMPATHOLYTIC ACTIVITY

title	Ref.	Spec /sex	Weight	Dose mg/kg	Route	Number animals	Treatment period	Type of experiment	Results
Binding to the muscarinic receptor	4.2	R m	200-250 g	-	-			Measurement of the affinity for the muscarinic receptor	IC_{50} (nM) Fluvoxamine 90,000 Chlorimipramine 160 Amitriptyline 68
Spasmolytic activity against carbachol in isolated guinea pig ileum	4.3	Cv m or f	450-600 g	-	-	-	-	Spasmolytic activity in vitro against contractions by 1 µg carbachol was compared with papaverine	Spasmolytic activity (x papaverine) Fluvoxamine 1.5 Chlorimipramine 15 Amitriptyline 160 Atropine 1250
Effect on pupil diameter in mice	4.4	M m	22-29 g	46-100-215 dose range	oral i.p.	5/test dose 5/test dose	1-2 hrs 30 min	Pupil size was determined under a stereo microscope with a graduated scale	ED_{200} (increase of pupil size to 200% of control) mg/kg 1 hr Fluvoxamine >215 Chlorimipramine ~215 Amitriptyline 46 ED_{200} (mg/kg) Fluvoxamine 86 + methysergide (20 mg/kg i.p.) 55 L-5-HTP 320 + methysergide (20 mg/kg i.p.) 800
Blocking effect on oxotremorine induced analgesia	4.5	M m	18-24 g	log range	oral	5/test dose	45 min	Oxotremorine (0.1 mg/kg s.c.) induced analgesia can be antagonized by atropine. Analgesia is measured by inhibition of the pain response after placing a buildog clip on the tail root	ED_{50} mg/kg oral Fluvoxamine >215 Chlorimipramine >215 Atropine 5.1
Antagonism of pilocarpine induced effects in mice	4.6	M m	28-31 g	100-215	oral	5/test dose	35 min	Autonomic and behavioural symptoms induced by pilocarpine (80 mg/kg i.v.) are due to peripheral and CNS cholinergic actions	Fluvoxamine (100 and 215 mg/kg) did not show anticholinergic effects, atropine was clearly effective from 2.5 mg/kg
Effect on intestinal motility	4.7	M m	22-26 g	log range	oral	10/test dose	60 min	Propulsion of charcoal suspension is a measure of intestinal motility. Inhibition of this motility is shown by anticholinergic compounds e.g. atropine	ED_{50} oral mg/kg Fluvoxamine >215 Chlorimipramine 195 Atropine 2.8

ANIMAL PHARMACOLOGY table 7 CENTRAL NERVOUS SYSTEM ACTITIVIES

title	Ref	Spec /sex	Weight	Dose mg/kg	Route	Number animals	Treatment period	Type of experiment	Results
Effect on locomotor activity	5.1	R m	18-24 g	46-100-215	oral	4x5/test dose	60-90 min	Locomotor activity was measured in photocell activity cages	Fluvoxamin did not influence motor activity significantly. amitriptyline produced markedly lowered activity
Effect on exploratory behaviour	5.2	M m	140-195 g	12.5-50-200	oral	8/test dose	60 min	Ambulation, rearing and defecation were measured in an open field situation	Fluvoxamine did not affect behaviour in the open field. Imipramine (same dose levels) reduced ambulation and rearing
Effect on motor coordination	5.3	M m	18-23 g	log range	oral	10/test dose	60 min	Rotarod: mice were selected to maintain position on a rotating rod. Compounds were studied for causing motor incoordination	ED_{50} mg/kg oral Fluvoxamine >215 Chlorimipramine >250 Amitriptyline 75
Effect on food consumption	5.4	R m	160-180 g	10-32-100	oral	3/test dose/ treatm period	165-285 405 min	Food consumption of rats with reversed light/dark cycle was measured	Fluvoxamine did not influence food consumption
Effect on exploratory and feeding behaviour	5.5	R m	350-375 g	5-10	i.p	12/dose	30 min	Measuring exploration and feeding behaviour by an ethological method	Fluvoxamine had no effect on exploration and feeding behaviour Quipazine at 5 and 10 mg/kg i.p. decreased feeding
Effect on social behaviour	5.6 5.7	M m R m	16-19 g 350-375 g	25-50 5-10	oral i.p	13/dose 12/dose	60 min 30 min	Measuring social behaviour between male animal by ethological methods	Fluvoxamine decreased aggressive behaviour components and increased defensive posture in mice Fluvoxamine decreased introductory social and aggressive behaviour elements, and decreased sexual behaviour elements in rats
Effect on sexual behaviour	5.8	R m	375-450 g	5-10	i.p	9	30 min	Scoring ejaculation frequency and latency of the male placed together with a receptive female	Fluvoxamine did not influence ejaculation frequency and latency
Effect on sleep in the rat	5.9	R m	200-250 g	10-25-50	i.p.	12-6/ test dose	6¼-7¾ hrs	EEG was continuously recorded and analysed at 3 stages: awake, slow wave sleep and rem sleep	Fluvoxamine (25 and 50 mg/kg i.p.) lowered REM sleep time
Effect on E.E.G	5.10	R m	240-260 g	2-4	i.p.	9	30-60-90 min	Measuring E.E.G.	Fluvoxamine had a marked dose dependent effect upon the hippocampal leads. Upon the other brain areas measured, the effect of fluvoxamine on E.E.G. was less pronounced

ANIMAL PHARMACOLOGY — table 7 (cont.) — CENTRAL NERVOUS SYSTEM ACTIVITIES

Title	Ref	Spec /sex	Weight	Dose mg/kg	Route	Number animals	Treatment period	Type of experiment	Results
Effect on behaviour of solitary cats	5.11	C m	4-6 kg	10	i.p.	15	30 min	Measuring behaviour by an ethological method	Fluvoxamine induced a somewhat activated behaviour d-LSD (50 and 100 µg/kg) induced limb-flicking and abortive grooming (hallucinatory-like behaviour)
Effect on rectal temperature in mice	5.12	M m	18-22 g	46-100-215	oral	10/test dose	1-2-4-6 hrs	Rectal temperature was measured in singly placed mice	Fluvoxamine did not affect body temperature, tricyclic antidepressants produced hypothermia
Reversal of hypoactivity in reserpinised rats	5.13	R m	140-195 g	100-215	oral	4/test dose/ treatm. period	15-30-45-60 min	Reversal of reserpine (5 mg/kg s.c., 18 hrs pre-treatment) hypoactivity was measured in activity cages	Fluvoxamine and imipramine failed to reverse the hypoactivity induced by reserpine. dl-Amphetamine was active at an oral dose of 2 mg/kg
Potentiating effect on hexobarbital narcosis	5.14	M m	18-24 g	log range	oral	10/test dose	60 min	Potentiation of hexobarbital (30 mg/kg i.v.) narcosis is measured	$ED_{\times\times}$ mg/kg oral Fluvoxamine >215 Chlorimipramine >215 Amitriptyline 42
Anticonvulsive activity against	5.15								
Supra-maximal electroshock		M f	18-24 g	log range	oral	5/test dose	60 min	Anticonvulsive effects are measured by suppression of tonic extensor phase after corneal electroshock	$ED_{\times\times}$ mg/kg oral Fluvoxamine >215 Chlorimipramine >215 Amitriptyline 46
Supra-maximal dose pentamethylene-tetrazole		M f	18-24 g	log range	oral	5/test dose	60 min	Suppression of tonic extensor phase after pentamethylene-tetrazole 50 mg/kg i.v.	Fluvoxamine >215 Chlorimipramine >215 Amitriptyline 37
Minimal dose of pentamethylene-tetrazole		M f	18-24 g	log range	oral	5/test dose	60 min	Suppression of clonic convulsion 25 min after pentamethylene-tetrazole, 80 mg/kg s.c.	Fluvoxamine and tested tricyclic antidepressants except amitriptyline were not active
Anti-aggressive activity	5.16								
Effect on isolation induced aggression		M m	~ 30 g	log range	oral	5/test dose	60 min	Mice were isolated for 4 weeks. Fighting occurs when a non-isolated mouse is placed in the cage. Inhibitory activity of compounds is measured	ED_{50} mg/kg oral Fluvoxamine 76 Chlorimipramine 72 Amitriptyline 30

ANIMAL PHARMACOLOGY table 7 (cont.) CENTRAL NERVOUS SYSTEM ACTIVITIES

Title	Ref	Spec 'sex	Weight	Dose mg/kg	Route	Number animals	Treatment period	Type of experiment	Results
Effect on footshock induced aggression	5.16	M m	18-24 g	log range	oral	5 pairs/ test dose	60 min	Fighting occurs when mice are placed on an electrified grid floor. Inhibitory activity and paralytic activity are measured	ED_{50} mg/kg oral: footshock / paralysis Fluvoxamine >215 / >215 Chlorimipramine 147 / 176 Amitriptyline 27 / 50
Prolongation of alcohol narcosis	5.17	M m	18-24 g	10-30-90	oral	10/test dose	60 min	Potentiation of ethanol (3.2 g/kg i.p.) induced narcosis was studied	Fluvoxamine did not produce a marked potentiation
Effect on suppressed ongoing behaviour	5.18	M f	18-26 g	10-32-100	oral	4/test dose	60 min	Electric footshock suppresses exploratory behaviour; number of accepted shocks is a measure of ambulation	No effect on the number of accepted shocks was seen with fluvoxamine

ANIMAL PHARMACOLOGY table 8 EFFECTS ON CIRCULATION AND RESPIRATION

Title	Ref	Spec /sex	Weight	Dose mg/kg	Route	Number animals	Treatment period	Type of experiment	Results
Effect on blood pressure	6.1	C m and f	2.5-3.0 kg	1-3-10	i.v	6	3-4 hrs	Normotensive anaesthetized cats were used and systolic, diastolic and mean blood pressure recorded. Standard doses of several drugs were given and the influence of fluvoxamine determined	Fluvoxamine produced a marked fall in blood pressure. This was shown in later experiments to be due to the speed of injection. Carotid occlusive reflex was depressed. Tyramine pressor response was not affected
Effects on blood pressure in renal hypertensive rats after acute administration	6.2	R m	160-180 g	25	oral	6	15-30 60-90 hrs	Renal hypertensive rats were prepared by placing a silver clip on the left renal artery. Blood pressure was recorded by the tail cuff method	Fluvoxamine did not produce any change in systolic blood pressure
Effects on blood pressure in renal hypertensive rats after chronic administration		R m	160-180 g	5-25	oral	5/test dose	4 days 1 dose/ day	See above	See above
Effects on the electrocardiogram	6.3	D m and f	8-13 kg	3-10-25	i.v.	6-5-3 per dose	5-15-30-60 min	Bipolar ECG leads I, II and III and also unipolar aVR, aVL and aVF leads were recorded from anaesthetized dogs	Fluvoxamine (10 mg/kg i.v.) produced an increase in QT interval. ECG-parameters were within usual limits. Two of the three dogs, treated with 25 mg/kg i.v. fluvoxamine died later. (With amitriptyline (1 mg/kg i.v.) dogs died during the experiment
Effect on coronary circulation	6.4	Rb m and f	800 g	-	-	-	-	Isolated hearts were perfused using Langendorff method	Fluvoxamine possessed somewhat less activity than the standard drug papaverine
Effect on the myocardial contractility of guinea pig atria in vitro	6.5	Cv m and f	450-600 g	Conc. 10^{-5}, 10^{-4} Mol	-	-	-	Inotropic effects were determined on electrically driven left atria from which isometric contraction force was measured	Fluvoxamine affects contraction force markedly less than tricyclic antidepressants

ANIMAL PHARMACOLOGY table 8 (cont.) EFFECTS ON CIRCULATION AND RESPIRATION

title	Ref	Spec /sex	Weight	Dose mg/kg	Route	Number animals	Treatment period	Type of experiment	Results
[illegible] blocking effect	6.6	C m and f	2.5-3.0 kg	3-10 mg	i.v.	-	-	In anaesthetized cats the superior cervical ganglion and its pre- and postganglionic nerves were dissected free for electrical stimulation. Contraction of the nictitating membrane was recorded	Fluvoxamine did not produce a reduction of nictitating membrane contractions
Adrenergic neurone blocking activity	6.6	Rb m M m	2 kg 22-28 g	- 100 500	- s.c. oral	- 5 test dose	- ½-1-2-4 hrs	The isolated mesenteric nerve-intestine preparation of Finkleman was used Produced ptosis was measured	Both fluvoxamine and bretylium inhibited the effect of nerve stimulation Fluvoxamine did not produce ptosis at the doses tested. Also bretylium in a non toxic dose did not induce a marked ptosis
Inhibition of ADP induced platelet aggregation	6.7	-	-	-	-	-	-	Platelet rich plasma from pig blood was used. ADP induced aggregation was measured with an aggregometer	IC_{50} mg/kg Fluvoxamine 3.7 ± 0.43 (s.e.m.) Chlorimipramine 3.6
Effect on respiration in conscious rabbits	6.8	Rb m and f	2-3 kg	3-10	i.v.	4 dose	10 min	Respiration was measured by passing expired air through a low resistance wet gas meter	Fluvoxamine produced an increase in total respiration volume at dosage levels 3 and 10 mg/kg. Imipramine 5 mg/kg i.v. showed no effects. 10 mg/kg i.v. imipramine was lethal
Cardiac effects in conscious rabbits	*	Rb m and f	2.2-3.3 kg	up to 90 (cumulative)	i.v. infusion rate 0.70 mg/kg/min	6-9	60-90 min; till death	Measurement of cumulative lethal dose, heart rate; left ventricle pressure and LV dP/dt (contractility); ECG and rectal temp.	Fluvoxamine: cumul. lethal dose 60 mg/kg (range 42-90); bradycardia at lower (35), tachycardia at higher (toxic) doses; ECG abnormalities at near toxic doses; little changes in LV dP/dt; hyperthermia just before death.

* article W. Wouters/W. Delman

ANIMAL PHARMACOLOGY table 9 OTHER EFFECTS

Title	Ref.	Spec /sex	Weight	Dose mg/kg	Route	Number animals	Treatment period	Type of experiment	Results	
Analgesic activity: Randall and Selitto test	7.1	R m	90-130 g	log range	oral	8/test dose	2-3-5 hrs	Pain threshold was measured after injection of yeast suspension in the paw	Fluvoxamine	$ED_{x,x}$ mg/kg oral >215
Writhing test		M m	20-24 g	log range	oral	10/test dose	80 min	Writhing was induced by i.p. injection of 0.25 ml of 0.5% solution of acetic acid	Fluvoxamine	200
Bianchi test		M f	18-24 g	log range	oral	5/test dose	60 min	Pain threshold was measured after placing a bulldog clip on the tail root	Fluvoxamine	>215
Affinity for opiate receptor		R m	200-300 g	-	-	-	-	Measurement of the affinity for the opiate receptor (^{3}H-dihydromorphine binding)	Fluvoxamine Morphine	IC_{50} (nM) 63.000 16
Anti-inflammatory activity	7.2	R m	160-200 g	50	oral	6/test dose	4 hrs	Carrageenin induced edema formation was used as an index of anti-inflammatory activity	Fluvoxamine Butazolidine	Inhibition of edema (%) 50 mg/kg 7 25 mg/kg 54
Local anaesthetic activity	7.3									
Surface anaesthetic activity		M m	18-24 g	log range	local appl.	10/test dose	-	Inhibition by solutions of compounds of corneal reflex	Fluvoxamine Imipramine	ED_{50} (% w/v) 1.0 0.8
Conduction anaesthetic activity		M m	18-24 g	log range	s.c.	5/test dose	15 min	Inhibition of nerve conduction was measured by establishing pain response after placing a clip on the root of the tail	Fluvoxamine Imipramine	1.37 0.44
Spasmolytic activity against $BaCl_2$ in isolated guinea pig ileum	7.4	Cv m or f	450-600 g	-	-	-	-	Spasmolytic activity in vitro against contractions induced by a submaximal dose $BaCl_2$ was compared with papaverine	Fluvoxamine	Spasmolytic activity (1.7 x papaverine)
Effect on phenolred transport out of the stomach	7.5	R m	150-180 g	40-200	oral	5/test dose	150 min	Stomach emptying was measured by assaying the remaining phenolred	Fluvoxamine markedly inhibited stomach emptying at a dose of 200 mg/kg. A dose of 40 mg/kg seemed to increase transport	
Effect on acid secretion by the stomach of the rat	7.6	R m	200 g	1-3-10	i.p.	12/test dose	3 hrs	Acid secretion was measured by titrating with 0.1 N NaOH	Fluvoxamine did not affect acid secretion. Desimipramine (1 mg/kg i.p.) clearly diminished acid secretion	

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ANIMAL PHARMACOLOGY

table 9 (cont.)

OTHER EFFECTS

[illegible]	Ref	Spec /sex	Weight	Dose mg/kg	Route	Number Animals	Treatment period	Type of experiment	Results
[illegible] activity	7.7	R m	180-230 g	100-200	oral	5/test dose	4 hrs	Stomachs were removed and observed for ulceration	Fluvoxamine did not cause gastric irritation. Tricyclic antidepressants produced ulcers
[illegible] edema induction	7.8	R m	160-180 g	conc 0.3-1-3%	-	5/test dose	1-2-4-6-24 hrs	Solutions were injected into the plantar surface of the hindpaw and dorsal-plantar distance measured	Fluvoxamine produced a marked and longlasting local edema
Effect on liver triglyceride content	7.9	R m	190-210 g	5-100	oral	5/test dose	daily during 7 days	16 hrs after the last administration, livers were isolated and analysed for triglyceride content	Fluvoxamine did not affect triglyceride content. Tricyclic antidepressants gave a significant increase at a dose of 50 mg/kg
Effect on water and electrolyte excretion	7.10	R m	250 g	50	oral	6/test dose	2½ and 5 hrs	Starved rats were loaded with 25 ml/kg saline; volume, Na^+, K^+ and Cl^- content were measured	Fluvoxamine produced (in a number of experiments) an anti-saluretic effect. Tricyclic anti-depressants produce a diuretic response
Effect on detoxification:	7.11								
Prolongation of hexobarbital narcosis		M m	18-24 g	log range	oral	10/test dose	60 min	Hexobarbital (100 mg/kg i.p.) induced narcosis was used	ED_{200} mg/kg oral Fluvoxamine 35 Chlorimipramine >90 Amitriptyline 12
Inhibition of p-hydroxylation and N-demethylation by rat liver microsomes in-vitro		R m	200-250 g	-	-	-	-	N-demethylation: p-chlor-N-methylaniline was used as substrate; p-hydroxylation: aniline was used as substrate	Fluvoxamine shows an inhibiting effect on N-demethylation and p-hydroxylation. Imipramine and desimipramine have a comparable activity
Inhibition of p-hydroxylation and N-demethylation in-vivo		R m	190-210 g	100	oral	5/test dose	daily during 7-days	Detoxification enzymes activity in liver homogenates; measured analogous to in-vitro exp. (see above)	Fluvoxamine did not significantly affect N-demethylation in-vivo; p-hydroxylation experiments gave inconclusive results.

(0540)

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table 10

PHARMACOLOGICAL INTERACTION STUDIES WITH FLUVOXAMINE

Title	Ref. 56648/13/77	Spec /sex	Weight	Dose mg/kg	Route	Number animals	Treatment period	Type of experiment	Results
Effect of combination drugs upon neurotoxicity and toxicity of fluvoxamine	2.1	M m	17-25 g	log range	oral	5/test dose	2 hrs	Drugs were administered orally 30 min. before fluvoxamine. Mice were observed for autonomic and behavioural changes	Tranylcypromine (10 mg/kg) gave a strong increase in serotonin behavioural effects. Chlordiazepoxide (25 mg/kg), nitrazepam (2 mg/kg), butobarbital (15 mg/kg), chlorpromazine (5 mg/kg) and amphetamine (10 mg/kg) pre-treatment induced little or no changes in neurotoxicity symptoms of fluvoxamine
Effect of fluvoxamine upon neurotoxicity and toxicity of combination drugs	2.2	M m	17-25 g	100	oral	5/test dose	150 min	Fluvoxamine was administered orally before the test compound. Mice were then observed for autonomic and behavioural changes	LD_{50} values of chlordiazepoxide, nitrazepam and butobarbital were not influenced by fluvoxamine. Chlorpromazine and tranylcypromine showed a decreased LD_{50} and amphetamine an increased LD_{50}. Increase in a few neurotoxicity symptoms was seen after administration of chlordiazepoxide, nitrazepam, butobarbital and chlorpromazine. Amphetamine neurotoxicity symptoms decreased
Heart-rate and and blood pressure in pentobarbital anaesthetized cats	2.3	C m and f	2-3 kg	1-3-5	i.v.	2-3 per comb. drug	3-4 hrs	Combination drugs were administered orally before assessing influence of fluvoxamine on cardiovascular parameters	Nitrazepam (2 mg/kg) induced variable changes in blood pressure after fluvoxamine injections. Only moderate changes in blood pressure after fluvoxamine were observed after pre-treatment with chlordiazepoxide (10 mg/kg), butobarbital (10 mg/kg) and chlorpromazine (2 mg/kg). Only slight effects on heart-rate were noted
Effect on hypotensive action of α-methyl-dopa		C m and f	2.3-2.4 kg	1-3-5	i.v.	3	3-4 hrs	α-methyl-dopa was injected before fluvoxamine effects on cardiovascular parameters were determined	Pre-treatment with α-methyl-dopa (50 mg/kg i.v.) after Ro-4-4602 (3 mg/kg i.v.) did not influence fluvoxamine effects on blood pressure and heart rate

(111)

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ANIMAL PHARMACOLOGY

table 10 (cont.)

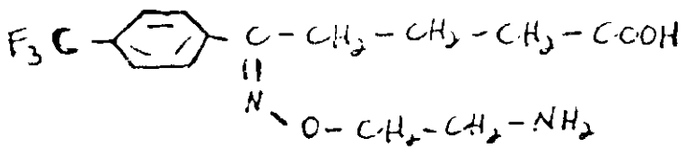
PHARMACOLOGICAL INTERACTION STUDIES WITH FLUVOXAMINE

Title	Ref 56648/ 13:77	Spec /sex	Weight	Dose mg/kg	Route	Number animals	Treatment period	Type of experiment	Results
Potentiating effect on hexobarbital narcosis and anti-convulsive activity	2 4	M m and f	18-24 g	100	oral	5/test dose/ comb. drug	90 min	Fluvoxamine was administered 30 min before combination drugs. Effects on hexobarbital induced narcosis (30 mg/kg i.v.) was established. A supra-maximal dose of pentamethylene tetrazole was given (50 mg/kg i.v.)	Fluvoxamine increased the effectiveness of combination drugs in both tests. This effect of fluvoxamine was most pronounced in combination with butobarbital and chlordiazepoxide. Chlorpromazine efficacy was not affected by fluvoxamine
Amphetamine toxicity	2 5	M m	22-28 g	100	oral	8/dose of amphetamine	60 min	LD_{50} of amphetamine (i.p.) was determined in mice either kept in groups of 8 in a small cage or individually	Fluvoxamine lowered the LD_{50} of amphetamine in isolated mice. In group mice no significant difference could be established
Sympathetic blocking activity	2 6	C m and f	3-4 kg	3-10	i v	2	15 min	Nictitating membrane contractions were measured and blocking effect of guanethidine (5 mg established	ine did not affect the action of guanethidine. esimipramine decreased the effect of guanethidine

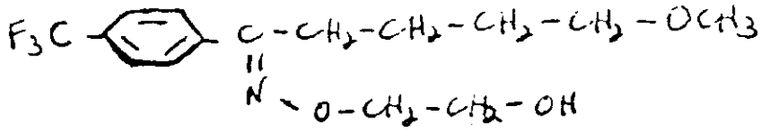
Pharmacodynamic Studies Not Included in Preceeding Tables:

1) Studies on two metabolites of fluvoxamine

A) Metabolite "B"



B) Metabolite "GI"



It was started that 9 metabolites have been identified in human urine, representing 85% of total metabolites. Metabolite "B" is the main metabolite in human urine (35% of all metabolites); the % of metabolite "GI" was not given. The following results were obtained:

	antagonism of tetrabenazine ptosis (mice)	potentiation of 5-HTP effects (mice)	inhibition of amine uptake by rat brain synaptosomes	
	ED_{50}-value (mg/kg ± s.e.m.) orally		pI_{50}-value	
			^{3}H-NA	^{3}H-5-HT
DU 24537 (=B)	> 215 (3)	> 215 (2)	< 4 (1)	5.0 (3)
DU 28972 (=GI)	> 215 (2)	> 215 (2)	< 4 (1)	< 4 (2)
Fluvoxamine	99 ± 24 (10)	39 ± 2.1 (16)	4.5 ± 0.11 (3)	6.6 ± 0.11 (11)

between brackets: number of ED_{50} (pI_{50})-determinations.

It can be seen that metabolite "B" blocked 5-HT uptake in vitro, but less potently than the parent compound. The metabolites were inactive in the other tests.

2) Cardiac Effects in Conscious Rabbits:
(listed in table; presented here in greater detail)

Fluvoxamine (F), amitriptyline (AMI), and mianserin (M) were given i.v. at 0.70 (F and M) or 0.35 (AMI) mg/kg/min. The median lethal doses were 60, 14 and 56 for F, AMI, and M, resp. Both F and M produced bradycardia followed, at higher doses, by tachycardia; AMI produced the reverse (tachycardia followed by bradycardia). F caused increases in PR and QRS intervals (maximum 19 and 29%, respectively, at a mean dose of 35 mg/kg). M was approximately equipotent in this regard; the effects of AMI could not be evaluated due to the occurence of severe arrhythmias and deaths at relatively low doses. Gross EKG changes were seen as follows:

Antidepressant-induced, gross ECG abnormalities, expressed as median doses with ranges of their first appearance.

	QRS changes[2]	n[1]	arrhythmias[3]	n[1]	fibrillation/ flutter	n[1]
Amitriptyline	4.0 (1.3-8.0)	6/6	4.2 (1.8-5.3)	3/6	6.3 (4.2-8.4)	2/6
Mianserin	24.5 (21.0-49.0)	3/6	40.3 (21.0-59.5)	2/6	61.6 (42.0-81.2)	2/6
Fluvoxamine	54.3 (31.5-70.0)	8/9	39.2	1/9	-	0/9

1) n denotes number of animals in group showing the phenomenon.

2) Gross changes in QRS complexes consisted of extremely broadened, peaked complexes and inversed complexes.

3) All disturbances from the normal sinus rhythum as dropped beats and single or coupled extrasystoles were scored as rhythm disturbances.

It can be seen that F appeared to be the least cardiotoxic of the 3 drugs. The changes seen with AMI occurred at less than 1/2 of the median lethal dose, and the changes seen with F occurred at near lethal doses. The changes with M also occurred at near lethal doses except for QRS changes which occurred at about 1/2 the median lethal dose.

Cardiac contractility (LV dp/dt max.) was also measured. At 1/2 lethal dose, F produced a decrease of 24%. (No effect with M; AMI not evaluated). At lethal doses, F produced a nonsignificant decrease of 14% and AMI caused a 53% decrease; M had no effect.

Body temperature (measured just before death) was increased by F only (2.2°C above control).

3) Pro-convulsive effects:

EEG changes and seizure occurence were measured in rats receiving F or 1 of 9 other antidepressants at 0.25-0.50 mg/kg/min. i.v. (cumulative doses of 50-60 mg/kg. F and clovoxamine were considered to be the least epileptogenic, and AMI the most.

4) Isolated (estrus) rat uterus:

F did not cause contractions up to 3×10^{-5} M. F caused a non-competitive inhibition of oxytocin-induced contractions at 8×10^{-6} M +; F was 3.9 x as active as papaverine.

5) Endocrine effects:
(Published Study: Cella et.al., Br. J. Clin. Pharmac. 15; 357S-363S, 1983)

F at 12.5 or 25 mg/kg i.v., and 25 mg/kg i.p. (lower doses not tested), elevated plasma prolactin in male rats 2-4 x control. (This is in contrast to data reported by the sponsor which showed no effect at 25 mg/kg p.o. Also, in a human study [Kletzky et.al., Curr. Ther. Res. 33: 394, 1983], F at 50 mg p.o. given to males did not alter either basal prolactin levels or the rise in prolactin induced by TRH or insulin-induced hypoglycemia). F was also shown to potentiate the 5-HTP-induced increase in plasma prolactin. Subacute treatment with F blocked the ability of an acute dose of F to raise plasma prolactin. IT was also reported in this paper that F, similarily to 5-HTP, caused a reduction in B-endorphin-like immunoreactivity in the anterior pituitary, and an increase in B-endorphin and B-lipotropin in plasma (male rats, 25 mg/kg i.p.). F given to female rats at 25 mg/kg i.p. for 14 days did not alter either the number of estrus episodes or plasma LH levels.

ADME; PHARMACOKINETICS

A) Plasma Levels

1) Rat:

After p.o. dosing at 40 mg/kg, peak levels were seen at 1 hour. Levels appeared to decline biphasically in M but monophasically in F; however, only a single T 1/2 value was calculated for both sexes (= 1.2 and 1.8 hour in M and F, respectively). After 40 mg/kg/day p.o. given for 10 days, results were similar although plasma levels were slightly lower than those seen after acute dosing; T 1/2 was 1.3 hour for both sexes. For both acute and 10 days' dosing, plasma AUC was greater in F than M (2 and 3 x, respectively). The reason for this difference is not clear since peak levels and T 1/2 were similar between sexes; the difference seems to result from a sharper decline in levels seen in M between 1 and 3 hours post-dosing. In a dietary study (approximately 200 - 400 mg/kg/day for 9 days), T 1/2 after removal of diet was 3.6 and 3.3 hours in M and F resp. Again, AUC was greater (2 x) in F and M; "0 hr." levels (i.e. just after removal of diet) were 10 x greater in F. Plasma level studies on rats using labelled in F were minimal and no information on the above parameters could be obtained.

2) Hamster:

Hamsters recieved 40 mg/kg F p.o. both acutely and for 10 days. Plasma were several fold lower than those in rat after the same dose; levels was generally below the detection limit (0.5 ng/ml) by 7 hour post-dose and thus AUC and T 1/2 could not be calculated.

3) Dog:

Dogs received single p.o. doses of 1, 10, or 25 mg/kg F. At LD, peak levels were seen at 2 - 4 hr.; after the higher doses, much broader peaks were seen, in the 2 - 8 hr. range. Due to these broad peaks, T 1/2 could not be calculated, rough estimates were given as 3 hr. at LD and 10 - 15 hr. at MD and HD. There were no apparant sex differences in T 1/2 or AUC. Peak levels and AUC increased much greater than proportionally to dose between 1 and 10 mg/kg; between 10 and 25 mg/kg (and 63 mg/kg in another study) AUC (but not peak level) increased greater than proportionally to dose but to a smaller degree than the increase seen between 1 and 10 mg/kg. A large (3 x) inter-subject variability in AUC was seen. In another study, a single dose of 1 mg/kg was given p.o., i.v., or i.m. The AUC values after i.v. and i.m. were similar; AUC after p.o. was 60% of that after i.v. indicating a bioavailability of 60%.

In studies with labelled (C^{14}) F, peak levels after 0.25 mg/kg p.o. were reached at 2 - 4 hr.; T 1/2 was roughly 10 - 15 hr. At higher doses (5 and 60 mg/kg p.o.), much broader peaks were seen, generally at 1 - 24 hr. with much intersubject variability within this range. Levels after 60 mg/kg were several fold lower than proportional to dose when compared with 0.25 and 5 mg/kg doses, despite in fact that the rate of decline of label at 60 mg/kg was that at the lower doses. Levels after 5 - 6 months treatment at 5 and 60 mg/kg/day were similar ot those seen after acute dosing.

B) Distribution

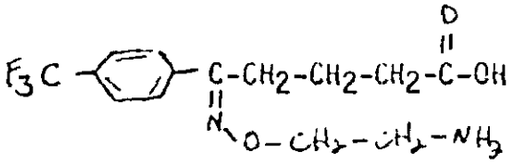
1) Rat:

C^{14} - labelled F was given (2.5 mg/kg) p.o. or i.v. to female rats. After p.o. dosing, peak tissue levels were generally reached by the first time point measured (1 hr.). Highest levels of label were seen in liver, kidney, and lung; levels remained greater than those in plasma in liver and kidney up to the final time point measured (96 hr) and in lung to 6 - 24 hr. Levels in other tissues were similar to or less than those in plasma. After i.v. dosing, levels in all tissues studied were greater than those in plasma until 1 hr. post-dose; at 3 hrs. (final time point measured) levels were greater than those in plasma in lungs, adrenals, liver, kidneys, spleen, and ovary. An autoradiographic study was done comparing pregnant (day 10 of gestation) and non-pregnant rats (dose = 10 mg/kg p.o.); distribution of label was similar between the 2 groups and levels of label in the embryos were less than those of blood up to the final time point measured (24 hr. post-dose).

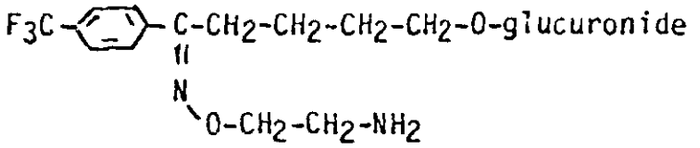
2) Hamster:

An autoradiographic study was done in male hamsters who had received daily doses of 9, 35, 138, or 432 mg/kg/day p.o. for 30 days. (Dose of labelled F = 10 mg/kg p.o.). Label was found mainly in liver, kidney, and G.I. tract; no label was found in brain or spinal cord. Results were similar across dosage groups (including control animals, indicating that 30 day's treatment did not alter distribution).

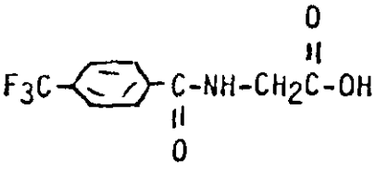
F was extensively metabolized after oral dosing in the species studied (rat, mouse, hamster, rabbit, dog). Except in dog, little or no unchanged F was excreted in urine after oral dosing with labelled F at the highest does used (40 mg/kg in rat, hamster, and mouse; 10 mg/kg in rabbits). In dogs, little or no unchanged F was found in urine after 0.25 mg/kg p.o.; however, after higher doses (5 - 60 mg/kg p.o.), approx. 10 - 40% of the urinary label was due to unchanged F. (After 6 months' dosing at 60 mg/kg in dogs, unchanged F in urine was 3 - 8% of label compared with 30 - 40% after acute dosing, suggesting an induction of metabolism.) The principal metabolic step was O-demethylation to form an alcohol derivative. This was followed by oxidation of the alcohol to form the following acid derivative:



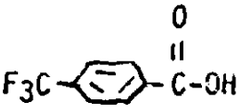
In all the above species except mouse, this was the principal metabolite excreted in urine. In mouse, the alcohol was preferably glucuronidated to form the following principal metabolite:



Several other minor metabolites were also identified in the urine of these species, indicating pathways involving ester formation at the ether terminus (mouse, hamster), N - acetylation (rat, mouse, hamster), oxidative deamination of the amine side chain to an acid derivative (dog, rat, hamster), and elimination of the amine side chain with subsequent glucuronidation of the resulting N-oxime (dog). A small amount of the following was found in urine of dog, rat, and hamster;



this was thought to represent an acetylated product of



thus indicating a small degree of nearly total biotransformation of F. (Mouse and rabbit were not studied as completely as the other species; thus some of these minor pathways may also occur in these species.)

In man, studies of urinary metabolites demonstrated that many of the metabolic pathways are the same as those occurring in animals. The principal urinary metabolite (resulting from O-demethylation and subsequent oxidation) was the same acid metabolite that was principal in rat, hamster, rabbit, and dog. Products of side chain oxidative deamination, side chain elimination, and N-acetylation were also found. No unchanged F was detected (dose = 100 mg p.o.).

D) Excretion

1. Rat, hamster, mouse, rabbit

Labelled F was given to rats and hamsters at 40 mg/kg p.o. (acutely or after 7 days of cold F at 40 mg/kg/day), and to mice and rabbits at single p.o. doses of 2 and 0.4 mg/kg, respectively. Excretion, as % of administered label, was as follows:

	Urine	Feces
rat	40-60	30-40
hamster	50-80	15-30
mouse	30-50	45-50
rabbit	80	15

Urinary excretion was mostly completed by 24 hr. post-dose. Results were similar after acute and 7 days' treatment (done in rat and hamster). In another study in rats, using a lower dose of labelled F (2.5 mg/kg) given p.o. and i.v., the following results were obtained (% of administered label excreted):

	Urine	Feces
p.o.	74	22
i.v.	70	23

Both urinary and fecal excretion were mostly completed by 24 hr. post-dose. There were no clear sex differences after p.o. dosing,; after i.v. dosing urinary excretion was slightly less in males than in females. The similarity in excretory pattern after p.o. and i.v. dosing suggests complete absorption after p.o. dosing. Approximately 40% of the dose was excreted in bile after either p.o. or i.v. dosing; a study on enterohepatic circulation indicated that most of this is reabsorbed.

2. Dog:

Several studies were performed with oral dosing with C^{14}-labelled F, covering a dosage range of 0.25 - 60 mg/kg. At doses up to 10 mg/kg, approximately 25 - 50% of the administered label was excreted in urine; at the higher doses urinary excretion was somewhat less (20 - 30%). (In addition, the rate of urinary excretion was slower at the higher doses; for example in one study 91 and 60% of the dose was excreted by 48 hr. at 5 and 60 mg/kg, resp.) Fecal excretion ranged from 40 - 60% of the dose; the decreased urinary excretion at the higher doses did not appear to be accompanied by an increased fecal excretion. Subacute treatment (5 - 6 months at 5 and 60 mg/kg; 7 days at 10 mg/kg) did nor appear to modify excretion patterns. After a dose of 0.10 mg/kg labelled F given i.v., the excretory pattern was similar to that seen after 0.25 mg/kg p.o.; this suggest complete G.I. absorption of the label (provided that biliary excretion, which was not studied in dogs, is similar for the p.o. and i.v. routes).

ACUTE TOXICITY

A) LD 50

Species	Strain	Weight	Sex	Route	14 DAY* LD 50 in mg/kg (with 95% CL)
Rat	SPF Wistar	160-200 g	M	p.o.	2000 (1370-2910)
	SPF Wistar	160-200 g	F	p.o.	1470 (862-2500)
			M	i.v.	43 (30-63)
			F	i.v.	68 (46-100)
Mouse	Swiss	17-21 g	M	p.o.	1100 (550-2200)
	Swiss	17-21 g	F	p.o.	1330 (737-2410)
Dog	Beagle	7-13 kg	M	p.o.	see below
	Beagle	7-13 kg	F	p.o.	

* 5 DAY LD 50 for i.v. dosing

B) Toxic Signs

1) Rat, p.o.:

Dose range = 100-4640 mg/kg. Highest nonlethal dose = 464 and 1000 in F and M, respectively. No signs at 100. Mydriasis, slowed reflexes, and increased muscle tone at 215+. Death occurred within 90 minutes of dosing and was associated with convulsions and respiratory depression; autopsy showed erosion and hemorrhage of stomach and duodenum.

2) Rat, i.v.:

Dosage range = 4.6-100 mg/kg. Highest nonlethal dose = 46 and 22 mg/kg in F and M, respectively. Signs included cyanosis (4.6 mg/kg +), mydriasis (10 mg/kg +), apathy, decreased activity, abnormal body posture and gait, decreased righting reflex, decreased body tone, respiratory difficulties, piloerection, and exophthalmos (22 mg/kg +), and increased startle response, straub tail, and aggressiveness (46 mg/kg +). Deaths occurred within 5 min. post-dose. Hemoglobinuria was seen at 10 mg/kg+, indicating a hemolytic effect. Local irritation at injection site was seen at 10 mg/kg (10 mg/ml) + , with necrosis at 22 mg/kg (22 mg/ml) +.

3) Mouse, p.o.:

Dosage range = 46-4640 mg/kg. Highest nonlethal dose = 215 mg/kg. No signs up to 100 mg/kg. Mydriasis and exaggerated startle response seen at 215 +. Lacrimation, salivation, increased muscle tone and restlessness seen at 1000 +. Deaths occurred 30 min. post-dosing, associated with convulsions.

4) Dog p.o.:

A total of 10 dogs were used covering a dosage range of 15-464 mg/kg; the actual dose was likely reduced by emesis which occurred at 25 mg/kg +. There were no deaths, although the single dog given 464 mg/kg had convulsions which were treated with i.v. pentbarbitone. Other signs included increased sleep (15 mg/kg), marked mydriasis, frowning and cutaneous vasodilatation (15 mg/kg +), and ataxia, increased limb tone, and rhythmic side-to-side head movement (215 mg/kg +). The above head movement persisted for up to 6 days post-dosing at 215 mg/kg.

SUBACUTE TOXICITY STUDIES

Numerous subacute studies were performed, primarily with the aim of establishing doses for longer term studies and/or of investigating the effects of fluvoxamine in serum and liver lipids. The following studies were performed (daily oral doses in mg/kg):

Species	Strain	Dose	Duration (weeks)	Dietary (D) or Gavage (G)
Mouse	ICI	100, 200	2	G
Mouse	ICI	200, 300, 400	4	D
Mouse	ICI	400, 600, 800, 1600	4	D
Mouse	ICI	10, 80, 640	21	D
Mouse	ICI	75, 150, 300, 600	4	D
Mouse	CDI	75, 150, 300, 600	4	D
Rat	Wistar	10, 40, 160→200	52	D
Hamster	Bio 15-16	100, 200	2	G
Hamster	Bio 15-16	9, 36, 142, 432	4	D
Hamster	Bio 15-16	240	13	D

Principal findings may be summarized as follows:

1) Mice:

Weight gain was generally decreased at 640 mg/kg +. SGOT and SGPT (21 wk. study only) were elevated at 80 mg/kg + in M and at 640 mg/kg in F. Serum lipids (cholesterol, phospholipids, TG, and total lipids, assayed in 21 wk. study) were decreased at 640 mg/kg (also, cholesterol decreased in M at 80 mg/kg); this was a large effect (means 1/5-1/2 C). Liver lipids (assayed in 21 wk. study) were increased at 80 and 640 but not at 10 mg/kg; mean values up to 3x control. (In a 2 wk. comparison study with imipramine and amitriptyline, F was less potent than these drugs in producing decreased serum lipids and increased liver lipids, although F was less generally toxic to the mice at the doses used). Several studies found increased liver weights, generally at higher doses; the lowest dose at which this was seen was 80 mg/kg after 10 wk. treatment (M only). Several studies noted increased fatty vacuolation of hepatocytes. This effect was both dose and time related; e.g., in a 4 week study it was seen at 600 but not at 75 mg/kg; in the 21 wk. study it was seen at 10, 80, and 640 mg/kg. (Imipramine and amitriptyline caused vacuoles similar to those caused by F in a 2 wk. comparison study). Other liver effects in the 21 wk. study included a D-R increase in pleomorphic cell inflammation (all doses; in most cases incidence was even higher after 8 wks. withdrawal) and hemorrhage into hepatocytes (increased in all F groups, after withdrawal period only). In addition, although most of the types of fatty vacuolation decreased in incidence after the withdrawal period in the 21 wk. study, the incidence of "large fatty vacuolation of panacinar hepatocytes," which was not increased at termination, was increased after the withdrawal period in all groups but LD M (100% incidence at HD). A finding of enlargement of centrilobular hepatocytes was reported in a 4 wk study at 300-600 mg/kg. Kidney was routinely examined only in two 4 wk. studies at 75, 150, 300, and 600 mg/kg; no clear drug effects were noted.

2) Rat:

The study performed was a spinoff of the carcinogenicity study (Doses: 10, 40, and 160→200 mg/kg.) Four/sex/group were sacrificed at 1 year. H and E and Massons trichrome staining of selected organs showed no clear drug effects except for an increase in fat vacuoles in liver in HD M (4/4 incidence, none in other groups). EM exam, done in mesenteric lymph node of 1 control M and 1 HD M, showed a 6x higher number of cytoplasmic lamellar inclusions in the treated rat.

3) Hamsters:

Weight gain was reduced at doses of 100 mg/kg and higher. Blood lipids were decreased at all doses in the 4 week study (1/3-1/2 control values, except smaller effect on phospholipid). (After 4 wks. off drug, these effects were reduced or absent.) In the 13 wk. study, however, only slight effects, in M only, were seen, and there was no effect on total lipids. (In the 2 wk. study, F at 200 but not 100 mg/kg caused slight decreases in blood lipids; imipramine and amitriptyline did not cause decreases at the doses used [25-100 mg/kg]). Regarding liver lipids, slight increases were seen in all studies, generally at the higher doses (max. generally 30% above C), with the exception of decreased cholesterol in the 4 wk. study at all doses except HD F. (In the 2 wk. study, imipramine and amitriptyline were tested at 25-100 mg/kg and did not increase liver lipids.) The following drug-related histopathological effects were seen: (1) liver-cloudy swelling seen at both doses (100 and 200 mg/kg) in the 2 wk. study (also produced by imipramine and amitriptyline at 25-100 mg/kg), no effect in the 4 wk. study (9-432 mg/kg), and increased severity of fat droplets in hepatocytes at the only dose used (240 mg/kg) in the 13 wk. study. (2) Kidney-In the 4 wk. study, there was an increased incidence of various findings at HD (432 mg/kg), including dilated and/or basophilic tubules (with some containing amphophilic homogenous material and/or cell debris) and foci of mineralization in cortex and/or medulla and/or papilla. (In addition to increased incidence at HD, these lesions were also more widespread, i.e. often involving both cortex and medulla, and usually affecting both kidneys.) After the 30 day recovery period, the incidence of these changes was not clearly increased; however, their severity was greater in HD compared to controls. (The severity at HD was less than that seen at HD at termination, however). In the 13 wk. study it was concluded that there were no drug effects on kidney; however the incidence of foci of mineralization was 12/30 in the treated group (240 mg/kg) vs. 5/44 in controls. Kidney weight was slightly increased in this study; there were no drug effects on blood urea or creatinine.

6 MONTH TOXICITY IN RATS

A) Dosage:

15 M + 15 F at 0, 5, 20, and 80 → 100 → 150 mg/kg/day, by gavage. (Dosage increases at HD took place at weeks 10 and 21, respectively.) An additional 10/sex/group were treated; half of these were sacrificed after 6 weeks and half after 12 weeks for hematology and blood chemistry.

Strain: Wistar SPF

B) Results:

1) Observed Signs:

No drug effects.

2) Mortality:

It was stated that 6 rats died due to intratracheal aspiration of test material; group distribution was not given. (From the individual bodyweight tables, it appears that five of the deaths were in HD F and 1 in MD M).

3) Bodyweight Gain:

Very slightly increased in all groups but LD F; not D-R. (Despite earlier increase, HD M had returned to control weight by termination.)

4) Food Consumption:

Slight increases in all groups but LD F (not D-R); also, slight decreases in HD M seen in last few weeks of study.

5) Water Consumption:

Increased in HD M. Very slight increases also seen in LD and MD M. Increased in HD F first month only.

6) Hematology:

(Done in 5/sex, in C and HD weeks 7 and 13 and all groups wk. 26.)

No clear drug effects (RBC, Hb, Hct, WBC, differential, PTT)

7) Blood Chemistry:

(Done in 5/sex in C and HD, weeks 7, 13, and 26. [Cholesterol, total bilirubin, SGOT, and SGPT were also done in LD and MD week 26. Na, K, and Cl were done in 5/sex in C and HD at weeks 2 and 4 only.])

No clear drug effects (Na, K, Cl, Ca, total protein, cholesterol, glucose, urea, uric acid, creatinine, AP, SGOT, SGPT, total bilirubin).

6 MONTH TOXICITY IN RATS (continued)

8) Urinalysis:

(Volume, pH, SG. Na, K, and Cl done in 5/sex/group days 3. 7, 16, and 28. SG and pH done in 5/sex in C and HD weeks 7 and 13 and in all groups week 26)

a) Volume:

Increased in HD M, days 3 and 7 only (2-3 x control); smaller increases in LD and MD M also seen on days 3 and 7.

b) Na, K, Cl:

Increased in HD M and HD F, days 3 and 7. Mean values approximately 2x controls. (Smaller increases often seen at LD and MD on days 3 and 7.) Na also increased in HD F on day 28.

c) SG:

Slightly increased in MD and HD F on day 28 and week 26.

d) pH:

Slight increase in HD M (0.5 - 1.0 units) through day 28 only.

e) Sediment Exam - not done.

9) Organ Weights:

a) Slight decrease in absolute and relative thymus weight in HD F

b) 1 HD M had extremely large pituitary weight; it is not clear if pathology was done on this animal or what the results were.

10) Gross Pathology:

No results given.

11) Microscopic Pathology:

(Done in 10/sex at C and HD; liver and kidney examined in 10/sex in all groups)

No summary tables were presented. Individual results were given, but for liver and kidney (and lung in a few rats) only. It was concluded that there were no drug effects. However, from the individual results, the incidence of fat in hepatocytes (generally minimal) was increased in all groups:

M: 3/10, 7/10, 6/10, 8/10 in C, LD, MD, HD, respectively
F: 1/10, 4/10, 5/10, 8/10 in C, LD, MD, HD, respectively

One HD M has unilateral hydronephrosis, which was not considered drug-related.

18 MONTH TOXICITY IN RATS

A) Dosage:

20 M and 20 F at 0, 10, 40, or 150 → 200 → 240 mg/kg/day, in diet. (Dosage increases at HD were at weeks 40 and 47, respectively.)

Strain: Wistar SPF

B) Results:

1) Observed signs:

No drug effects

2) Mortality:

No drug effects (# of deaths = 3, 3, 1, and 4 in C, LD, MD, HD, respectively.)

3) Weight Gain:

M - Decreased at HD during first few weeks, and after 1 year. Final weight at HD 90% of C.

F - Decreased at HD after 1 year. Final weight at HD 85% of C. Smaller decreases at LD and MD. (Final weight - 95% of C, but NS.)

4) Food Consumption:

Decreased at HD most weeks (approximately 10 and 15% below C in M and F, respectively.)

5) Water Consumption:

Decreased at HD most weeks (approximately 20 and 35% below C in M and F, respectively.) Smaller decreases occasionally seen at LD and MD.

6) Hematology:

(Done in 4-5/sex/group at weeks 13, 26, 52, 78)

a) RBC, PCV, Hb:

Very slight increases in HD M all weeks but week 78.

b) Other parameters measured: MCV, MCH, MCHC, WBC, differential, platelets, ESR, PTT.

18 MONTH TOXICITY IN RATS (continued)

7) Blood Chemistry:

(Done in 4 - 5/sex/group at weeks 13, 26, 52, 78)

a) Cholesterol:

Decreased in HD M all weeks (but not progressive with time), and in LD and MD M week 13 only (Mean at HD 20-40% below c)

b) Other parameters measured: total protein, glucose, urea, creatinine, bilirubin, SAP, SGPT, SGOT, Na, K, total lipids, sterol ester, triglycerides, free sterols, FFA, monoglycerides, phospholipids.

8) Urinalysis:

(Done in 3 - 5/sex/group weeks 13, 26, 52, 78)

a) SG slightly increased in HD M, week 26 +.

b) Other parameters measured: pH, volume, protein, glucose, bilirubin, ketone, hemoglobin, sediment exam.

9) Organ Weights:

a) Liver:

Absolute weight increased in HD M (10%) but NS; relative weight increased 20%. No effect in F.

b) Lung:

Absolute and relative weight increased in HD F; relative weight only increased in HD M. (Relative weight 17 and 30% above C in HD M and F, respectively.)

c) Ovaries:

Absolute and relative weight increased at HD (relative weight 35% above c.)

d) Kidney:

Relative weight slightly increased in HD M and F but no significant effect on absolute weight.

10) Gross Pathology:

No drug effects.

18 MONTH TOXICITY IN RATS (continued)

1) Microscopic Pathology:

(Stains: H and E; Massons Trichrome in liver and kidney; ORO in liver and PAS in liver and kidney in C and HD only)

a) Liver:

Increased incidence of vacuolation of cytoplasm in MD and HD M: 3/20, 2/20, 11/20, and 16/20 in C, LD, MD, HD, respectively. (No effect in F: 17/20, 10/20, 13/20, 14/20). The severity of this change was greatest in HD M. It was stated that the vacuolation "mostly" represented an increased fat deposition.

The incidence of chronic inflammation of the parenchyma was also increaed in MD and HD M: (6/20, 8/20, 15/20 and 13/20 in C, LD, MD, HD, respectively), although the pathologist considered this to be a spontaneous, non drug-related lesion.

b) Kidney:

1) Chronic inflammation - increased in all M groups (1/20, 4/20, 6/20, 10/20 in C, LD, MD, HD, respectively.)

2) Basophilic staining tubules - increased in MD and HD M and HD F:

M: 3/20, 4/20, 10/20, 8/20 in C, LD, MD, HD
F: 5/20, 6/20, 2/20, 16/20 in C, LD, MD, HD

3) Distended tubules/tubules containing eosinophilic material increased in MD and HD M (3/20, 4/20, 8/20, 6/20 in C, LD, MD, HD, respectively.) (However, the incidence was lower in HD F: 8/20, 7/20, 7/20, 4/20 in C, LD, MD, HD, resp.)

4) The above changes were considered "minor" by the pathologist. There was no drug effect on the incidence of progressive glomerulonephrosis.

c) Lung:

1) Increased incidence of rats with groups of distended macrophages at HD:

M: 4/20, 2/20, 2/20, 10/20 in C, LD, MD, HD
F: 4/20, 0/20, 1/20, 11/20 in C, LD, MD, HD

The severity was also greater at HD compared to other groups.

2) The incidence of perivascular accumulations of lymphocytes was increased in all M groups, but not D-R, and in MD and HD F; the pathologist considered this as not drug related.

M: 8/20, 14/20, 15/20, 12/20 in C, LD, MD, HD
F: 5/20, 5/20, 10/20, 11/20 in C, LD, MD, HD

LIFETIME CARCINOGENICITY STUDY IN RATS

A) Dosage:

40 M + 40 F at 0, 10, 40, or 160 → 200 → 240 mg/kg/day, in diet. (Dosage increase at HD occurred weeks 40 and 53, respectively). Treatment terminated when survival reached 40% (weeks 123-124 and 129-130 in M and F, respectively).

Strain: Wistar SPF

B) Results:

1) Observed Signs:

Alopecia decreased at HD, said to be due to decreased activity.

2) Mortality:

Mortality was slightly decreased in HD M, although this was apparently not statistically significant. (By week 100 there were 9 deaths in CM and 1 at HD M. By week 120 there were 20 deaths in CM and 14 at HD M.) There were no effects in F.

3) Bodyweight:

Slight decreased gain in HD M, HD F, and MD F. (Weights near end of study were 5-10%, 10-15%, and 5% below C, respectively).

4) Food Consumption:

Decreased in HD M and HD F (5% and 10-15% below C, respectively), and to a smaller extent at LD and MD.

5) Water Intake:

M - dose-related decrease in all groups (30% below C at HD)

F - decreased at HD (30% below C); sporadic, slight decreases also at LD and MD

6) Ophthalmoscopic Exam:

(Done at various times in C and HD, and in all survivors 1 week before termination).

Text states no drug effects; no results were presented.

7) Hematology:
(Done in 10/sex/group at termination)

The only parameters measured were RBC, Hct, platelets, and total WBC. No drug effects.

LIFETIME CARCINOGENICITY STUDY IN RATS (continued)

8) Blood Chemistry:
(Done in same animals as in hematology)

a) Cholesterol - decreased in all HD F rats (mean 40% below C)

b) Urea - slight decrease in MD and HD F; no very low values (all but 1 within concurrent control range)

c) Na - slight decrease in HD F; no very low values (within concurrent control range).

d) Other parameter measured: potassium

9) Urinalysis:

Not performed

10) Organ Weights:

No drug effects

11) Gross Pathology:

Atrophied body fat/emaciation increased in all drug groups but not clearly D-R, likely associated with bodyweight and food/water consumption effects noted above. No other drug related effects. Text says no effects on palpable masses (incidence or time to first detection), although results were not tabulated.

12) Microscopic Pathology:
(Stain: H and E, plus unspecified fat stain for liver and kidney).

a) Neoplastic lesions:

1) No drug effects on total number of neoplasms. Numbers of rats with neoplasms are as follows (denominator = 40/sex/group):

Benign:	M - 23, 29, 20, 24 (in C, LD, MD, HD, resp.)
	F - 31, 31, 26, 29
Malignant:	M - 7, 2, 6, 9
	F - 14, 5, 10, 7

There were no group differences when these results were broken down into rats which died vs. those which survived to termination, suggesting no drug effects on tumor onset.

LIFETIME CARCINOGENICITY STUDY IN RATS

Microscopic Pathology

Neoplastic lesions (continued)

2) There was an equivocal increase in incidence of adenoma of the parafollicular cells of thyroid at HD:

M - 3/40, 4/40, 6/40, 7/40 in C, LD, MD, HD, resp.
F - 2/40, 4/40, 3/40, 7/40

Total: - 5/80, 8/80, 9/80, 14/80

(These findings were not statistically significant in a Fisher Exact Test, performed by the firm, apparently in each sex separately).

Most of these tumors were seen at termination; thus there is no evidence for earlier onset in drug groups. The incidence of parafollicular hyperplasia was not clearly increased.

b) Non-neoplastic lesions:
(Denominators = 40/sex/group)

1) Liver:

a) Clusters of vacuolated liver cells increased at HD and equivocally at lower doses:

M - 1, 6, 0, 8 in C, LD, MD, HD, respectively
F - 0, 7, 5, 21

Total: - 1, 13, 5, 29

b) Centrilobular dengeration increased in all M groups:

4, 10, 14, 22 in C, LD, MD, HD, respectively

2) Stomach:

Dilated fundic glands increased in HD M (at termination only): 17/25 vs. 3/19 in C.

3) Lung:

Incidence of foci of desquamating pneumonia increased at HD:

M - 4, 7, 6, 17 in C, LD, MD, HD, respectively
F - 5, 1, 7, 15

Total: - 9, 8, 13, 32

However, there were no drug-induced increases in foci of interstitial pneumonia or in other types of pneumonia.

LIFETIME CARCINOGENICITY STUDY IN SYRIAN HAMSTERS

A) Dosage:

105 M + 105 F at 0, and 60 M + 60 F at 9, 36, or 135 → 180 → 240 mg/kg/day in diet. (Dosage increases at HD occurred on days 98 and 133, resp.).

15/sex in control, and 10/sex/drug group were sacrificed at 1 year. Treatment was terminated when mortality reached 70-30% (week 85 and 112 in F and M, respectively)

Strain: BIO F-D "Alexander"

B) Results:

1) Observed Signs:

No drug effects.

2) Mortality:

No drug effects on overall mortality. Overall mortality rate was similar amoung groups except for a slight decrease in MD F. The temporal pattern of mortality showed some group differences, however (see attached table); there were fewer deaths in MD and HD M compared to controls during most of the treatment period although mortality in these groups caught up to controls by termination; there were also slightly fewer deaths in MD F (compared to controls) throughout the treatment period.

3) Bodyweight:

Slight weight gain was seen in HD F during weeks 38-62, during which time control weights did not change.

4) Food Consumption:

Slight increase in HD F week 33 +.

5) Water Consumption:

Very slight decrease in HD M week 81 +.

6) Ophthalmoscopic Exam:

(Done in all C and HD at 12 months, and in all surviving animals at 18 months)

Incidence of cataracts increased in HD F at 18 months: 3/52, 2/31, 1/31, 6/29 in C, LD, MD, HD, respectively. Incidence also increased in HD M at 18 months, but not statistically significant (6/80, 3/44, 2/47, 5/49 in C, LD, MD, HD, respectively). Combined incidence (M + F) = 9/132, 5/75, 3/78, and 11/78 in C, LD, MD, HD, respectively.

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Table 1 Rate of Mortality

Time Period (weeks)	Cumulative Mortality in Percent*			
	HD	MD	LD	CON
		-Male Hamsters-		
0-38	0	0	0	1.0
39-51	2.0	0	2.0	3.3
52-64	2.0	0	4.0	4.4
65-77	2.0	6.0	12.0	10.0
78-90	8.0	12.0	18.0	20.0
91-103	36.0	26.0	36.0	48.9
104-111	66.0	65.0	67.0	70.0
		-Female Hamsters-		
0-38	0	0	0	2.0
39-51	4.0	0	2.0	2.2
52-64	10.0	0	6.0	8.9
65-77	36.0	30.0	32.0	34.4
78-82	66.0	58.0	64.0	67.8

* Excludes animals killed at 12 months.

LIFETIME CARCINOGENICITY STUDY IN SYRIAN HAMSTERS (continued)

7) Hematology:

(Done on 15/sex in C, and 10/sex/drug group, at 1 year, and in all survivors at termination).

a) Hb:

Slight D-R decreases in all M groups at 1 year; also seen at termination but of smaller magnitude and not D-R.

b) MCHC:

Slight decreases in MD and HD M at 1 yr. but not at termination.

c) Other parameters measured: RBC, Hct, MCV, MCH, WBC, differential.

8) Serum Lipids:

(Done in same animals as Hematology, above. Total lipids, cholesterol, triglycerides, phospholipids).

No clear drug effects. (Some group differences were seen, but generally not D-R, and effects at termination often opposite from those at 1 year. Different assay methods were used at 1 year vs. termination.)

9) Organ Weights:

a) Liver and Kidney - slight increase in absolute and relative weights in MD M and HD M (and, except for relative kidney weight, in HD F) at 1 year but not at termination.

b) Testes - increased absolute and relative weight in HD at termination (relative weight 45% above C).

c) Spleen - slight decrease in absolute and relative weight in HD F at 1 year and termination (relative weight 29% and 19% below C at 1 year and termination, respectively).

10) Gross Pathology:

No summary tables were given; sponsor concludes no drug-related pathology.

LIFETIME CARCINOGENICITY STUDY IN SYRIAN HAMSTERS (continued)

11) Microscopic Pathology:

(Stains used not given. Results in animals sacrificed at 1 year given in a separate table; results in animals dying after 1 year and sacrificed at termination were lumped together.)

a) Results in animals sacrificed at 1 year: No drug effects.

b) Results in animals dying after 1 year and sacrificed at termination.

1) Neoplastic Findings:

a) There was a equivocal increase in the incidence of adrenal adenoma in MD and HD F (3/86, 2/45, 4/47, 5/48 in C, LD, MD, HD, resp.) This was statistically significant according to a test which takes mortality rates into account (Peto method). However, the incidence of adrenal carcinoma was not increased in HD F (although the incidence was higher than control in LD and MD F): 2/86, 6/45, 3/47, 1/48 on C, LD, MD, HD, resp. (An additional carcinoma was seen in 1 of 10 HD F at the 1 year sacrifice). Neither the incidence of adrenal adenoma nor carcinoma was increased in males. (Adenoma: 12/86, 11/49, 4/50, 7/49; carcinoma: 11/86, 8/49, 8/50, 6/49, in C, LD, MD, HD, resp.). The incidence of adrenal hyperplasia was not increased in F, and tended to be slightly decreased in treated M groups.

b) Peto analyses (i.e. statistical analyses of tumor incidence which takes mortality rate into account) were performed on several of the more commonly occurring tumors and on remaining benign tumors lumped together and on remaining malignant tumors lumped together; aside from the adrenal adenomas (see above), no drug-related effects were found.

2) Non-neoplastic Findings:

There were no drug-related increases. The incidence of amyloidosis (in liver, kidney, spleen, and adrenal) was decreased in HD F (5/48 vs. 44/86 in controls.)

7 MONTH TOXICITY IN DOGS

A) Dosage:

3 M + 3 F at 0, 5, 15, and 45→60 mg/kg/day, 7 days/week, in capsules. Dose increase at HD occurred week 8. Dose at HD was increased to 80 mg/kg week 14 but returned to 60 mg/kg week 16. An additional 2/sex were treated at either 0 or 15→80→60 mg/kg/day to serve as recovery animals, although only the males were eventually used for this purpose. (Duration of the recovery period was not stated.)

Strain: Beagle

B) Results:

1) Observed Signs:

The doses in this study were initially to be 10, 30, and 90 mg/kg/day. However, these doses were discontinued after 3 days due to marked deterioration in general condition at HD. At 90 mg/kg: emesis, ataxia, restlessness, frowning, whimpering, coughing, mydriasis, anorexia. At 30 mg/kg: frowning, whimpering, coughing, mydriasis. At 10 mg/kg: mydriasis. Dosing was discontinued for 4 days after which the dogs "appeared to recover," and doses of 5, 15, and 45 mg/kg were begun. HD was well tolerated; for the first 1-2 wks. frowning, coughing and rhythmic side-to-side head movements were seen. These signs were not seen when HD raised to 60 mg/kg, but 80 mg/kg caused ataxia, anorexia, and (in 1 dog) convulsions. The syndrome disappeared after dose reduction to 60 mg/kg, although the dog which convulsed at 80 mg/kg was aggressive and was noted to have a short convulsive episode. Other signs in this study were mydriasis (lasting up to 24 hr; regressed over 6 days after discontinuation of 30 wks. dosing) at all doses, and emesis at 15 mg/kg +.

2) Mortality:

a) 1 HD F sacrificed in extremis week 10 (60 mg/kg). This dog developed respiratory difficulties and over a period of 48 hrs. became moribund with labored respiration. Extensive broncho-pneumonia seen at autopsy.

b) 1 HD F found dead week 14 (80 mg/kg). There had been clinical signs of general illness of 1 day's duration after dosage increase to 80 mg/kg. At autopsy, stomach and intentine were filled with blood, "probably due to a diffuse, gastric bleeding." There was some blood in the lungs probably due to the aspiration of vomited blood.

3) Bodyweight:

Anorexia and weight loss seen at 80 mg/kg. One dog had reduced weight gain at 60 mg/kg.

7 MONTH TOXICITY IN DOGS (continued)

4) Food Consumption:

Slight decrease at 60 and marked decrease at 80 mg/kg.

5) Water Consumption:
(Measured 1st at 12 weeks only)

No drug effect.

6) Ophthalmoscopic Exam:
(Done pre-study, and weeks 6, 12, and 26 in C and HD)

No drug effects. (No individual results given)

7) EKG:
(Done immediately pre-dosing and 90 minute post-dosing on day 1 and week 1 (all animals) and weeks 6, 12, and 26 (C and HD only).

a) PR Interval:

Slight decreases (10-20%) seen at HD, week 6 +. (Not measured in LD or MD after week 1).

b) No drug effect on heart rate, QRS, QT, QTc, or visual exam of tracings.

8) Hematology:
(Dose pre-study and weeks 6, 12, 26)

No drug effects. (RBC, Hb, Hct, WBC, differential, ESR, PT, and [week 26 only] reticulocytes).

9) Blood Chemistry:
(Done pre-study and weeks 6, 12, 26)

a) Numerous abnormalities seen in the HD F sacrificed week 10, including elevated cholesterol, urea, creatinine, AP, SGPT, SGOT, and LDH, and decreased glucose and total protein. (The HD F which dies had normal values except for slightly elevated Cl and slightly decresed Na).

b) AP was increased in 2 HD M week 26 (2 x control values); one of these also had SGOT and cholesterol values 2x control.

c) Other parameters measured: Ca, uric acid, and total bilirubin. Na, K, and Cl were measured weeks 6 and 12 only.

10) Urinalysis:
(Done weeks 6, 12, 26; some parameters also pre-study)

a) SG - very slight decrease in HD M.

b) Other parameters measured: pH, protein, glucose, bilirubin, ketones, blood, sediment exam.

7 MONTH TOXICITY IN DOGS (continued)

11) Organ Weights:

Relative liver weight increased at HD (25-30% above C), although absolute weight only 10% above C. No effect in recovery dogs (2 control M vs 2 HD M only).

12) Gross Pathology:

No drug effects among dogs sacrificed at termination. (See above for findings in dogs which died.)

13) Microscopic Pathology:
(Stains: H and E, plus PAS in liver and kidney and ORO in liver.)

a) Foamy Macrophages:

Seen in all HD dogs except 1. Also seen in 1 of the 2 HD recovery dogs. Not seen in any other group. Organs affected: lymph nodes, Peyer's patches of intestine, and white pulp of spleen. The foamy macrophages appeared to contain lipid.

b) Kidney Findings:

1) Chronic interstitial nephritis was diagnosed in 1 HD M and 1 HD F. In the M, PAS sections showed moderate "sclerosis of the basement membranes of tubules and the capsular epithelium of glomeruli." In the F, occasional small aggregations of chronic inflammatory cells were seen in the interstitial tissue; these were frequently associated with slightly dilated tubules, thickening of tubular basement membranes, and a minimal increase in interstitial fibrosis.

2) Aggrgations of chronic inflammatory cells seen in cortex of 1 LD M, 1 MD M, and 1 HD recovery M. In the latter, "the associated tubules show moderate thickening of basement membranes."

3) The pathologist states that the above changes "are frequently encountered in the dog and were considered to be without significance." However, it should be noted that there was also an apparent increase in kidney lesions in the 1 year dog study.

c) Findings in the Dogs that Died:

1) HD F scarificed wk 10 - severe confluent bronchopneumonia; minimal fat in periportal hepatocytes.

2) HD F that died wk. 14 - hemorrhage in lung and intestine; autolysis of several organs.

A) Dosage:

Control:	4 M + 5 F
10 mg/kg:	3 M + 3 F
25 mg/kg:	3 M + 3 F
30 → 45 → 62.5 mg/kg:	4 M + 5 F

Dogs were dosed by capsule, 7 days/week. Dosage increases at HD and were at weeks 3 and 4, resp. Three/sex/group were sacrificed at 1 year. One control F and 1 HD F were sacrificed after a 6 week recovery period. One control F, 1 HD F, 1 control M, and 1 HD M were sacrificed after a 13 week recovery period. An additional control M and HD M were treated for 26 weeks only and then sacrificed.

Strain: Beagle

B) Results:

1) Observed Signs:

a) Anorexia - HD (Diet supplementation used). One HD M was withdrawn from treatment for 2 weeks due to poor condition, and received 1% of glucose i.v. for 3 days. Another HD M in poor condition also received i.v. glucose.

b) Diarrhea - slightly increased in MD and HD M.

c) Emesis - slightly increased at HD

d) Mydriasis - all groups (see below under Ophthalmoscopic Exam)

2) Mortality:

None

3) Bodyweight:

Decreased gain at HD. (HD gained about 50% as much as controls). Weight gain was also slightly decreased in LD and MD F, but generally NS.

4) Food Consumption:

The only statistically significant effects were decreases in MD M and HD M weeks 1-16 (65-83% of C). However, food consumption in all drug groups was lower than controls at almost all weeks (generally 80-95% of C, with greatest effect in HD M but otherwise not clearly D-R).

5) Water Consumption:

Decreased al all groups but LD M, first 4 weeks only (70-80% of C).

1 YEAR TOXICITY IN DOGS (continued)

6) Ophthalmoscopic Exam:

(Done pre-study, and weeks 13, 25, and 52 in C and HD. Pupil diameter estimated in all animals in weeks 6 and 42, pre-dosing and at various time post-dosing).

No abnormalities seen. (No results were given). Mydriasis was seen in all groups. This was generally slight to moderate although occasionally marked in MD and HD M. Mydriasis was occasionally seen pre-dosing, i.e. 24 hour after the previous day's dose.

7) EKG:

(Done pre-study, and pre-dosing and 90 min. post-dosing on day 1 [C and HD only] and weeks 13, 26, and 53).

No significant drug effects on h.r., visual inspection of EKG, or PR, QRS, QT, and QTc intervals.

8) Hematology:

(Pre-study, and weeks 13, 26, and 53)

a) RBC, Hct, and Hb were slightly (10%) decreased in HD M weeks 26 and 53.

b) Other parameters measured: MCV, MCH, MCHC, platelets, PT, WBC, differential, ESR.

9) Blood Chemistry:

(Pre-study, and weeks 13, 26, 53)

a) Alkaline Phosphatase:

Increased in HD at all times except week 13 in M. Mean values were less than 2 x control mean. All dogs showed some elevation although there were no very large individual values. (Max. 2 x control mean). The increase was not progressive with time.

b) Urea:

2/4 HD M had slight elevations week 53 (< 2 x control mean). (Mean creatinine was also elevated very slightly [13%, $p < .05$] elevated in this group but there were no greatly elevated individual values).

c) Other Parameters Measured:

Total protein, cholesterol, glucose, total bilirubin, SGOT, SGPT, Na, K, total lipids, triglycerides, sterols, sterol ester, FFA, monoglycerides, phospholipids.

1 YEAR TOXICITY IN DOGS (continued)

10) Urinalysis:

(Pre-study, and weeks 16, 26, 53)

a) Urine Volume:

Sporadic increases in most groups at most times. Max. 2 x control mean. Not dose- or time-related.

b) SG:

Slight decreases at HD (all times), MD (week 26 only), and LD M (week 53 only). Not dose- and time-related.

c) Protein:

Proteinuria (at least 300 mg/100 ml) was seen in the following dogs:

1) 1 LD M - all times

2) 1 HD M - week 16 only. (Urine also contained moderate glucose and "countless" epithelial cells. BUN elevated week 53 but not weeks 13 and 26.)

3) 1 HD F - weeks 26 and 53 (countless epithelial cells also present). (BUN elevated week 53, but not above highest concurrent control value.)

4) 1 HD F - week 53

11) Organ Weights:

a) Liver - increased absolute and relative weight at HD (relative weight 33 and 66% above C in M and F, resp.)

b) Kidney - increased relative weight in all M groups (not D-R) and in HD F. (Absolute weight also increased except in HD M). Mean increase in relative weight was approxiamtely 20 and 35% in M and HD F, resp.)

c) Lung - increased absolute and relative weight in HD M and MD and HD F. (Relative weight 30 and 25% above C in M and F, resp.).

d) Spleen - increased absolute and relative weight in HD M. (Relative weight 82% above C).

e) Recovery Animals:

Conclusions are limited due to small N (3 controls and 3 HD). Relative liver and lung weights appeared to be increased in 2 HD, relative kidney weight increased in 1 HD, relative spleen weight incrreased in 1 HD.

1 YEAR TOXICITY IN DOGS (continued)

12) Gross Pathology:

No drug effects.

13) Microscopic Pathology:

(Stains: H & E routine. Masson's trichrome in kidney. In C & HD only: PAS in liver and kidney, ORO in liver. In the 2 dogs sacrificed week 26, lymphoreticular organs were examined histochemically to determine nature of foam cell lipids.)

a) Kidney:

Numerous changes were seen only (or more frequently or of greater severity) at HD. These included dystrophic mineralization, distended tubules, basophilic staining tubules, tubules showing vacuolation of cells of the epithelium, fibrosis, glomeruli showing distension of Bowman's capsule, presence of eosinophilic material in Bowmans capsule, and shrinkage of glomerular tuft. Some of these were also seen in recovery dogs. The text states that distension of Bowman's capsule and shrinkage of the glomerular tuft (seen in 6/6 HD and 0/6 C sacrificed at 1 year, and among recovery dogs in 2/3 HD and 1/3 C) is consistent with glomerular atrophy, which "is known to occur at a low level in untreated dogs of this age." Several of the lesions noted above were also seen in 1 LD M. In addition, this dog also had mesangial cell proliferation, and was diagnosed as having "proliferative glomerulonephritis," which was stated to occur spontaneously in dogs.

It should be noted that in many cases the dogs with kidney lesions had shown lab test abnormalities (elevated BUN and proteinuria). Elevated kidney weights were also seen.

b) Foam Cells:

Foam cells were seen in several organs, primarily at HD, but also in 1 MD. Organs affected included spleen, G.I. tract (Peyer's patches), and lymph nodes. (Lung apparently not affected). Foam cells were not seen in recovery dogs. (Histochemical exam of foam cells in dog sacrificed at 26 weeks showed the major lipid present was lecithin; many foam cells also contained FFA.)

c) Lung:

Chronic interstitial inflammation slightly greater in severity at HD; not considered drug-related.

SEGMENT I REPRODUCTION IN RATS

A) Dosage:

12 M + 24 F at 0, 5, 20, or 80 mg/kg/day, by gavage, from 63 and 14 days premating (in M and F, resp.), through day 20 of gestation (10 F/group) or day 21 PP (remaining F). Mating ratio= 1 M: 2 F

Strain: SPF-CD from Charles River, UK

B) Results:

1) Observed Signs:

No drug effects

2) Mortality:

No drug effects

3) Bodyweight Change:

a) Males - Slight D-R decrease in gain al all doses (Final weight at HD 94% of control)

b) Females - No drug effects

4) Mating Performance and Pregnancy Rate:

No drug effects. (At HD, 23/24 F mated and 22/23 mated F were pregnant. In other groups, all 24 F mated and were pregnant.)

5) Duration of Gestation:

No drug effect

6) Litter Data for F Sacrificed Day 20 of Gestation:

No drug effects on CL, implantations, resorptions, viable young, or pre- and post-implantation loss. Mean fetal weight was slightly decreased at MD and HD but not statistically significant.

7) Litter Data for F Allowed to Deliver:

a) Litter Size at Birth - Slight decreases in total litter size and viable pups in all groups but not D-R. (Mean values 10-15% below C; statistically significant at LD only). No drug effect on dead fetuses.

b) Pup Survival Through Day 21 PP - Slight decreases seen at MD and HD, but not statistically significant.

c) Mean Pup Weight - Slight increase (10%) at HD at birth and day 4 PP, but no drug effect on days 12 and 21 PP. At LD and MD, pup weight was slightly greater than controls but not statistically significant.

d) Major Malformations (gross exam): None observed.

SEGMENT II REPRODUCTION STUDY IN RATS

A) Dosage:

20 F at 0, 5, 20, or 80 mg/kg/day, by gavage, days 6-15 of gestation.

Dams were sacrificed day 20 of gestation. All pups examined externally, 1/3 given visceral exam (Wilson method), and the remaining 2/3 given skeletal exam (Alizarin staining).

Strain: SPF - CFY from Charles River, France

B) Results:

1) Observed Signs:

No drug effect

2) Mortality:

None

3) Bodyweight Change:

No drug effect

4) Pregnancy rate, viable young, resorptions, pre- and post-implantation loss, fetal weight:

No drug effects

5) Fetal Exam:

a) Major Malformations:

(# examined: 182, 202, 175, 170 in C, LD, MD, HD, resp.; from 19, 18, 16, and 17 litters, resp.).
No drug effects. (One fetus each in C and HD had malformation).

b) Minor Anomalies:

1) Visceral:

(# examined: 52, 73, 59, 55 in C, LD, MD, HD)
No drug effects (# with anomalies = 2, 0, 1, 4 in C, LD, MD, HD)

2) Skeletal:

(# examined: 129, 129, 116, 114 in C, LD, MD, HD)
No drug effects (# with anomalies = 4, 2, 0, 7 in C, LD, MD, HD).

c) Skeletal Variants:

No drug effects. (The incidence of variant sternebrae appeared to be decreased at HD).

SEGMENT 1: REPRODUCTION STUDY IN RABBITS (1st OF 2 STUDIES)

A) Dosage:

13 F at 0, 5, 10, or 20 mg/kg/day (given in 2 divided daily doses), by gavage, days 6-18 of gestation. (Doses were based on a preliminary study in non-pregnant F, in which anorexia and transient weight loss were seen at daily doses of 20 and 80 mg/kg; no effects were seen at daily single doses of 5 or 10, or at daily divided doses of 20 mg/kg).

Dams were sacrificed day 29 of gestation. Fetuses were examined externally and internally followed by clearing and staining for skeletal exam.

Strain: New Zealand White

B) Results:

1) Observed Signs:

Transient anorexia in occasional dams at all doses.

2) Mortality:

One death in each drug group; not considered drug related.

3) Weight Change:

No drug effects.

4) Abortions, resorptions, viable young, pre- and post-implantation loss:

No drug effects.

5) Fetal Exam:

a) Number Examined:

93, 82, 99, and 97 in C, LD, MD, HD, resp.
(from 12, 10, 12, 12 litters, resp.)

b) Major Malformations:

1 at MD and 2 at HD; these were all different and have occurred in previous studies; not considered drug related.

c) Minor Anomalies:

1) Gross Autopsy:

1, 2, 7, and 4 fetus had anomalies in C, LD, MD, HD, resp. Most were reduced or bilobed gall bladder. Said to be within historical control range; not considered drug-related.

Fetal Exam

c) Minor Anomalies (continued):

2) Skeletal Exam:

4, 12, 10, 11 fetuses had anomalies in C, LD, MD, HD, resp. The most common anomalies were bipartite or asymmetric sternebrae, and 1 or 2 sutural bones. Many of the affected fetuses in the drug groups, esp. at HD, had multiple anomalies, including hemicentric thoracic centrum with agenesis of corresponding rib, ankylosed vertrebral arches, dysmorphosis of the cervical region (agenesis of first right vertebral arch and cephalad displacement of the second, bipartite and assymetrical second centrum, additional right hemcienter and vertebral arch, extra rib, etc..), extra sternebrae, fused sternebrae, branched ribs, reduced ribs, agenesis of ribs, etc.. (These were seen in various combinations in different fetuses). The increased incidence of skeletal anomalies was not considered drug related by the sponsor since the incidences were not dose related and were within the historical range (although historical data for the individual anomalies were not presented).

d) Skeletal Variants:

No drug effects.

SEGMENT II REPRODUCTION STUDY IN RABBITS (2nd OF 2 STUDIES)

A) Dosage:

15-18 F at 0, 5, 10, 20, or 40 mg/kg/day (given in 2 divided daily doses), by gavage, days 6-18 of gestation. (Doses were based on a preliminary study in non pregnant F, in which 80 mg/kg/day [divided] caused cold ears, anorexia, and transient weight loss; 20 and 40 mg/kg [divided] caused a slight increase in cold ears and a slight, transient decrease in weight gain followed by a rate of weight gain similar to controls.)

Dams were sacrificed day 29 of gestation. Fetuses were examined externally and dissected for visceral exam. Head were sliced through the line of the frontoparietal suture and the brain examined for visible abnormalities prior to clearing and staining of the carcasses for skeletal exam (modified Dawson technique).

Strain: New Zealand White

B) Results:

1) Observed Signs:

Mydriasis seen at 4/15 HD dams

2) Mortality:

2 deaths at MD and 3 at HD; none at C, LD or M-HD. Deaths not considered drug-related.

3) Weight Change:

Very slight, transient decreased gain at HD.

4) Abortions, resorptions, viable young, pre- and post-implantation loss

No drug effects.

5) Fetal Weight:

Very slight decrease in all groups. The effects at LD and M-HD were likely secondary to slightly increased litter size (litter weights were slightly increased in these groups). The largest decrease in mean fetal weight was at HD (8% below C), but this was not statistically significant.

SEGMENT II REPRODUCTION STUDY IN RABBITS (2nd OF 2 STUDIES) (continued)

6) Fetal Exam:

a) Number Examined:

92, 113, 98, 95, and 85 in C, LD, MD, M-HD, and HD, resp. (from 12, 11, 13, 11, and 11 litters, resp.).

b) Major Malformations:

No drug effects. (Seen in 3 LD and 1 HD; none on other groups).

c) Minor Anomalies:

1) Gross Autopsy:

No drug effects (2, 4, 3, 8, and 3 fetuses had anomalies in C, LD, MD, M-HD, and HD, resp.)

2) Skeletal Exam:

No drug effect (16, 24, 10, 17, and 14 fetuses had anomalies in C, LD, MD, M-HD, and HD, resp.) No effect on number of fetuses with multiple anomalies.)

d) Skeletal Variants:

No drug effects.

SEGMENT III REPRODUCTION IN RATS (1st OF 2 STUDIES)

A) Dosage:

20 F at 0, 5, 20, or 80 mg/kg/day, by gavage, from day 15 of gestation through day 21 PP.

Strain: SPF - CFY from Anglia Laboratory Animals, Alconbury, Huntingdon

B) Results:

1) Observed Signs:

No drug effects

2) Mortality:

None

3) Bodyweight Change:

Slight, non D-R increased gain during postpartum period only.

4) Duration of Gestation:

No drug effects

5) Litter Size at Birth:

Slight decrease in total and viable pups, and slight increase in dead pups, at HD. (Mean total litter size 11% below C; fetal loss was 7.1% vs. 1.8% in control)

6) Pup Survival Through Day 21 PP:

D-R decrease at all doses. This effects occurred mainly during days 4-12 PP at LD and MD, and from birth through day 12 PP at HD. At day 21 PP, cumulation pup loss was 4.3, 17.2, 17.4, and 24.6% in C, LD, MD, and HD, resp.

7) Mean Pup Weight:

Very slightly increased in all groups through day 21 PP, not D-R; likely secondary to decreased litter size.

8) Pup Malformations: (gross external and internal exam)

No drug effects.

SEGMENT III REPRODUCTION IN RATS (2nd OF 2 STUDIES)

A) Dosage:

50 F at 0 or 160 mg/kg/day, by gavage, from day 15 of gestation through day 21 PP. Approximately half of the litters of each group were cross-fostered to dams of the other group on day 1 PP.

Strain: SPF - CFY from Anglia Laboratory Animals, Alconbury, Huntingdon, England.

B) Results:

1) Observed Signs:

No drug effects (aside from dystocia and delayed parturition; see below)

2) Mortality:

3 treated dams died; 2 were attributable to dystocia

3) Bodyweight Change:

No drug effects

4) Gestation Period:

Three treated dams showed dystocia and a further 2 showed delayed parturition. Of the dams showing dystocia, 2 died and the other subsequently showed total litter loss. There were no drug effects on duration of gestation period.

5) Litter Size at Birth:

Treated group had decreased number of viable pups (16% below C) and increased dead pups (fetal loss = 11.4% vs. 0.9% in C.)

6) Pup Survival Through Day 21 PP:

All 48 pregnant control dams reared their own or a fostered litter to day 21 PP; in contrast 15 of the 46 treated dams failed to rear any young. Of these failures, 11 were due to total litter loss occurring before day 4 PP, 2 were due to death and dystocia, 1 was due to dystocia, and 1 total litter loss occurred between days 8 and 12 PP. Of the total litter losses occurring in treated dams after cross - fostering, only a slightly (and not statistically significantly) greater proportion occurred in non-fostered litters (8/23) vs. fostered litters (4/20).

Excluding the above litters, pup survival during the first 4 days PP was lower in litters reared by treated dams (whether cross-fostered or not) than in litters reared by control dams; % loss was about 2 x than in control dams during this time but apparently not statistically significant.

7) Mean Pup Weight:

At birth, mean pup weight was very slightly (5%, statistically significant) increased in the treated group. At 12 and 21 days PP, mean pup weights among treated dams rearing treated pups were lower (10-15%) than weights among treated dams rearing control pups, or among control dams rearing either treated or control pups.

8) Pup Malformations: (gross exam)

No drug effects.

MUTAGENICITY TESTS

A) Ames Test:

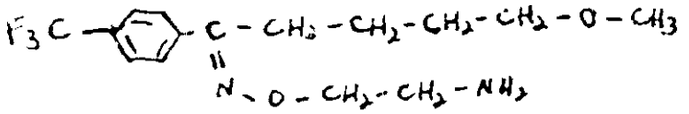
Five Salmonella typhimurium strains (TA 1535, 1537, 1538, 98, and 100) were used, with and without metabolic activation. Two separate studies were performed. Fluvoxamine was not mutagenic up to 200 ug per plate; higher concentrations ug per plate) was bacteriotoxic and could thus not be evaluated. Positive controls gave the expected results.

B) Analysis of Metaphase Chromosomes From Human Lymphocytes Cultured in vitro

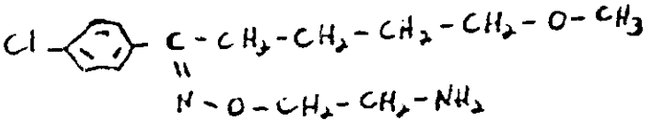
Concentrations of fluvoxamine used: ug/ml (HD caused approximately 50% reduction in mitotic index.) Assays were run both with and without a metabolic activating system. Without metabolic activation, fluvoxamine caused an approx. 3 x increase in number of aberrant cells and number of aberrations, although this was neither dose-related nor statistically significant. The primary aberration increased was "acentric fragments." The positive control produced substantially greater effects, approximately 15 x controls. After metabolic activation, there were no increases in aberrations due to fluvoxamine. (The text states that there was an increase in the number of "complex aberrant chromosome figures"; this apparently refers to single cases of an interchange and a dicentric seen at the lowest concentration). It should be noted that in the metabolic activation assays, the test drug was incubated with the lymphocytes for 2 hours; whereas in the nonactivated assays the incubation time was 26 hours.

A) PHARMACODYNAMICS:

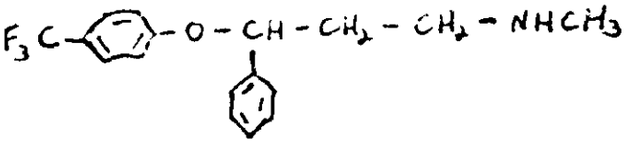
Fluvoxamine (F) is structurally dissimilar to marketed antidepressants. It is a structural analog of the putative antidepressant clovaxamine (IND There is also some structural similarity to the putative antidepressant fluoxetine (NDA 18-936); both F and fluoxetine may be categorized as "5-HT-specific" compounds (see below).



FLUVOXAMINE



CLOVOXAMINE



FLUOXETINE

The pharmacological profile of F is similar in several respects to that of classical tricyclic antidepressants. The uptake of serotonin into platelets and brain synaptosomes in vitro was blocked by F at concentrations comparable to those of reference antidepressants. Likewise, F was active in several in vivo tests reflective of serotonin uptake blockade (block of uptake into brain synaptosomes in vitro after in vivo dosing, decrease in 5-HT turnover, antagonism of the 5-HT-depleting effects of compounds which must be actively taken up into serotonergic neurons to act, potentiation of various effects of 5-HTP, etc.); in these tests, performed in rat, mouse, and guinea pig, F was generally active in the 10-50 mg/kg range (p.o , i.p., i.m.) and was usually slightly more potent than the reference antidepressants. On the other hand, at concentrations and doses which showed blockade of 5-HT uptake, little or no indication of blockade of NE uptake was seen in the following: blockade of NE uptake into brain synaptosomes in vitro (or in vitro after in vivo dosing), antagonism of the NE-depleting effects of compounds which must be taken up into noradrenergic neurons to act, potentiation of NE effect on vas deferens in vitro, blockade of guanethidine effect, and reversal of effects of reserpine-like drugs. Thus, the sponsor categorizes F as a "serotonin-specific" drug, similar to newer putative antidepressants such as fluoxetine and zimelidine. However, although there are some indications that this is true, it does not appear that such specifity was conclusively proven in that in several of the in vivo test for NE uptake blockade, "nonspecific" drugs (e.g. imipramine and amitriptyline) were often also inactive, and other "serotonin specific" drugs were not tested. Also, whereas in one study F was mush less potent than DMI in blocking NE uptake into rat brain synaptosomes, in another study the 2 drugs were nearly equipotent. F, in common with other antidepressants, showed weak activity in blocking DA uptake into neurons.

Several pharmacodynamic studies were performed after subacute dosing with F; such studies have been performed with other antidepressants since subacute dosing is required in man before therapeutic effect is manifest and it is thus thought that effects seen with subacute (but not acute) dosing may be more relevant to the mechanism of action of these drugs. However, subacute dosing with F showed no changes in most of the parameters studied (brain and heart levels of NE, 5-HT, and DA, 5-HT and NE turnover in brain, and B-adrenergic, serotonergic, and dopaminergic receptor density in brain). In one study, subacute dosing caused a smaller potentiation of 5-HTP-induced head twitch in mice than did acute dosing, but such a difference was not seen in another, similar study. Nine days' dosing (25 mg/kg p.o. per day) caused a 50% decrease in platelet serotonin content in rats; likewise, in a human study a similar decrease was seen at 150 mg/day p.o. given for 4 weeks. Such a decrease is an expected consequence of 5-HT uptake blockade since platelets do not synthesize 5-HT and are dependent on uptake for their 5-HT content.

Little or no MAO inhibiting activity was seen, although in most tests a positive control was not used.

Several tests were done to assess the anticholinergic effects of F, since such effects are responsible for several of the side effects of marketed antidepressants. F was generally significantly less potent than the reference tricyclics used. (Tests: antagonism of carbachol effect on guinea pig ileum in vitro, pupil diameter in mice, intestinal motility in mice, antagonism of pilocarpine and oxotremorine effects in mice, and antagonism of blood pressure response to acetylcholine in anesthetized cats). F was also much less potent than reference tricyclics in inhibiting the binding of a muscarinic ligand to rat brain. In a human study, F at 100 mg p.o. did not alter salivary flow whereas amitriptyline and doxepin at 50-75 mg deceased flow by about 30%.

F appeared to be less potent that reference tricyclics as an antagonist of 5-HT and histamine, although the data were extremely limited. In anesthetized cats, F (1, 3, or 10 mg/kg i.v.) caused a dose-related decrease of the carotid occlusion reflex; the b.p. responses to epinephrine or isoproterenol were not affected, and the b.p. response to NE was slightly potentiated at the highest dose; otherwise, the ability of F to block α or β adrenergic receptors was not studied. In the isolated uterus of estrus rat, F at 8×10^{-6} M + blocked the response to oxytocin noncompetitively. Receptor binding studies in rat brain failed to show potent binding to α_1, α_2, β, 5-HT_2, DA, or morphine receptors; however, except in the case of morphine receptors, positive controls were not used.

In most studies, F produced no gross CNS stimulant or depressant effects in rodents at relatively high oral doses (up to 200 mg/kg); reference trycyclics often caused CNS depression at the higher doses. In one study in rats, 5-10 mg/kg i.p. produced no effect on exploratory or feeding behavior, but in another study the same doses caused several signs of behavioral depression (e.g. increased inactivity, decreased social behavior); these effects tended to reverse after 14 days' daily treatment.

In a published study (Cella et.al., Br. J. Clin. Pharmac. 15: 3575, 1983), F at 25 mg/kg i.p. caused behavioral sedation lasting in 1 hour. In cats, 10 mg/kg i.p. caused behavioral activation. A dose-related decrease in REM sleep was seen in rats at 10-50 mg/kg i.p.; chlorimipramine was somewhat more potent in this regard. In mouse, rectal temperature was not affected at 215 mg/kg p.o.; reference tricyclics caused decreases at this and lower doses. On the other hand, in rabbits, lethal i.v. doses of F caused a 2.2°C rise in temperature whereas lethal doses of amitriptyline and mianserin did not have an effect. In a study of epileptogenic potential (measured by EEG changes and seizure occurrence) in rats, F and clovoxamine were considered to be least active out of 9 antidepressants tested; amitriptyline was most active (dosage range studied = 0.25-0.5 mg/kg/min. i.v., to a cumulative dose of 50-60 mg/kg). F was shown to have local anesthetic properties; on mouse cornea it was 3 x less potent than cocaine; the potentcy of reference tricyclics was in between that of F and cocaine.

In cardiovascular studies, F was shown to cause a large, transient decrease in b.p. in anesthetized cats when 1-10 mg/kg was given i.v. as a bolus or over 20 seconds; this was not seen with a 2 minute infusion. These doses (as bolus) also caused a dose-related decrease in the carotid occlusion reflex. No blood pressure effects was seen in renal hypertensive rats at 25 mg/kg p.o. In anesthetized dogs, 3-25 mg/kg caused a slight non dose-related decrease in h.r. A slight dose-related increase in QT interval was seen which was said to be likely due to the decreased h.r.; these were no effects on PR, QRS, or ST intervals. (It was stated that at thses doses amitriptyline caused AV block and other EKG changes and, at 25 mg/kg, death due to severe arrhythmias, although this data was not shown and it is not clear if this was part of the study done with F.) In a study in conscious rabbits, F (0.70 mg/kg/min i.v.) was compared with mianserin (0.70 mg/kg/min) and amitriptyline (0.35 mg/kg/min). The adverse effects of these drugs on EKG appeared to be qualitatively similar, but amitriptyline was much more potent. (Amitriptyline was also much more potent in causing lethality. The sponsor argues that the adverse EKG effects of amitriptyline occurred at less than 1/2 lethal doses, whereas those of the other drugs occurred at near lethal doses, suggesting a greater safety margin for the latter. However, it was stated that half of the amitriptyline treated rabbits died "at a low dose with severe cardiac disturbances," suggesting a lack of separation of doses producing adverse EKG effects and those producing death in animals. It was also not specified what the cause of death was in any of the drug groups, i.e. either cardiotoxic effects or other effects such as convulsions, which were seen in all groups. If deaths were in fact due to cardiotoxic effects, then lethality cannot be used as an independent measure of drug toxicity to which to compare doses causing adverse EKG effects, and the most that could be said from this study is that amitriptyline was more potent than Fand mianserin in causing both EKG changes and lethality.) In this study amitriptyline also caused a pronounced decrease in cardiac contractility at lethal doses; F at lethal doses caused a slight, equivocal decrease. In a study of myocardial contractility of guinea pig atria in vitro, F decreased contractility at 10^{-4} but not 10^{-5} M; reference tricyclics were more potent.

F was shown to have a toxic interactive effect with the MAO inhibitor tranylcypromine in mice: lethality was increased, and a number of neurotoxic signs (said to be attributable to increased central 5-HT) were produced. In a pharmacological study at lower doses in mice, F potentiated "5-HT-like" neurobehavioral effects of the MAOI pargyline with an oral ED_{50} of 20 mg/kg; chlorimipramine was much less potent and other reference tricyclics were inactive. In rats, F at 10 mg/kg i.p. potentiated the hyperactivity in rats produced by tranylcypromine + tryptophan; chlorimipramine and fluoxetine was less potent and DMI caused decreased activity. Various effects of 5-HTP were potentiated by F in mice and rats. F at 100 mg/kg p.o. (lower doses not tested) potentiated the anticonvulsant and hexobarbital-potentiating effects of chlordiazepoxide and butabarbital in mice; on the other hand, F did not increase the lethality of these drugs. F potentiated the anorexigenic effect of amphetamine in mice with an oral ED_{50} of 15.5 mg/kg (reference tricyclics had similar potency) but did not potentiate amphetamine-induced hyperactivity at 215 mg/kg. In one study, F at 100 mg/kg p.o. (lower doses not tested) slighty increased the lethality of amphetamine in mice; but in another study F at the same dose had the opposite effect. F at 100 mg/kg p.o. (lower doses not tested) enhanced the lethality of chlorpromazine in mice; the neurotoxic effects of the latter were not markedly altered. F at 10 mg/kg i.v. did not affect the sympathetic blocking effect of guanethidine in anesthetized cats; DMI antagonized guanethidine at 1 mg/kg i.v.

Some pharmacological tests were done on 2 metabolites of F: "B" and "GI" (see Pharmacodynamics section for structures; metabolite B was said to be the principal metabolite in human urine). Neither metabolite antagonized tetrabenazine ptosis or potentiated 5-HTP effects in mice at the highest dose tested (215 mg/kg p.o.). Neither metabolite inhibited NE uptake into rat brain synaptosomes in vitro; metabolite B (but not GI) inhibited 5-HT uptake but with a potency of 10-100 x less than that of the parent compound.

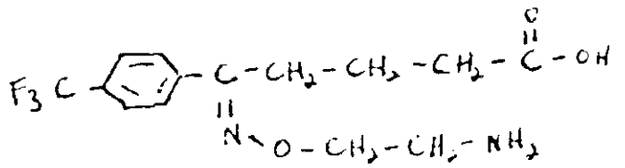
B) ADME, PHARMACOKINETICS:

After oral dosing with unlabelled F (40 mg/kg) in rats, peak plasma levels were reached within 1 hour. Plasma levels appeared to decline biphasically in males but monophasically in females; however, only single T 1/2 values were calculated for both sexes (1-2 hr.). Females had plasma levels 2-3 x greater than those in males which could not be explained by a difference in half-lives. Pharmacokinetic parameters in rats after dosing with labelled F could not be determined from the limited data presented. In hamsters receiving the same oral dose of unlabelled F as rats, plasma levels were several fold lower than those of rats, and were generally below the detection limit by 7 hour post-dose. In dogs receiving unlabelled F orally, peak times were quite broad, often lasting several hours. Plasma levels in dogs increased greater than proportionally to dose over the dose range studied (1-63 mg/kg). Half-lives, which could only be roughly estimated, appeared to be dose related (approx. 3 hr. at 1 mg/kg and 10-15 hrs. at 10 and 25 mg/kg). There were no apparent sex differences in plasma levels or T 1/2 in dogs. By comparing plasma AUC after p.o. and i.v. dosing (1 mg/kg), a bioavailability of 60% was estimated in dogs. In studies with C^{14}-labelled F in dogs, plasma T 1/2 after 0.25 mg/kg was roughly 10-15 hours. In contrast to the results with unlabelled F, plasma levels of label after 60 mg/kg were several fold lower than expected compared to levels after 0.25 or 5 mg/kg, despite the fact that the T 1/2 of plasma label was not greater than that after the lower doses; no adequate explanation for this was given. In human studies, plasma T 1/2 of F after oral doses of 25-100 mg unlabelled F averaged 14-15 hours with a range of 8-28 hours. Plasma AUC was roughly proportional to dose at doses of 25, 50, and 100 mg p.o. In patients receiving daily doses of 100-300 mg p.o. for 4 weeks, steady-state plasma levels were greater than proportional to dose, although a large intersubject variation was seen.

Tissue distribution of label was studied in female rats receiving 2.5 mg/kg C^{14}-F p.o. or i.v. After p.o. dosing, greatest levels were seen in liver, kidney, and lung; other tissues (including embryos in pregnant rats) had levels lower than those in plasma. Protein binding studies were not done in animals; in man, binding to plasma proteins was 77% over a concentration range of ug/ml. (From the data provided, binding appeared to fall off slightly at the higher end of this range. Steady state plasma levels in patients receiving F at 100-300 mg/day ranged from 0.015-1.75 ug/ml, with means at 200-300 mg/day of approx. 0.2-0.6 ug/ml; thus, the protein binding study did not cover the lower end of expected "therapeutic" concentrations.)

F was extensively metabolized in animals. Little or no inchanged F was excreted in urine in rat, hamster, mouse, or rabbit at the doses used (40 mg/kg p.o. in rat, hamster, and mouse; 10 mg/mg p.o. in rabbit). In dog, little or no unchanged F was found in urine after 0.25 mg/kg p.o.; however, after higher doses (5-60 mg/kg) approx. 10-40% of the urinary label was due to unchanged F; this is in agreement with the greater-than-expected plasma levels and greater T 1/2 for F seen at higher doses (above) and indicates a possible saturation of metabolic pathways. In man, little or no unchanged F was excreted in urine after a p.o. dose of 100 mg. The primary metabolic step in all species was o-demethylation to form an alcohol derivative.

This was followed by oxidation of the alcohol to form the following acid derivative:



Except for mouse, this compound was the principal metabolite excreted in urine in all species studied, including man. (In mouse, the alcohol was preferentially glucuronidated rather than oxidized). Several other minor pathways and resultant metabolites were also demonstrated. As mentioned above, the principal urinary metabolite shown above was 10-100 x less potent than the parent compound in blocking 5-HT uptake into rat brain synaptosomes in vitro, and were inactive in antagonizing tetrabenzaine ptosis or potentiating 5-HTP effects in mice.

Urinary excretion was a significant route of elimination in all species studied. After oral dosing with C^{14}-F, the % of administered label excreted in urine varied among species, from a low of about 25-50% in mouse and dog to a high of about 80% in rabbit. (In a human study, urinary excretion of label after a low dose [1-5 mg p.o.] of C^{14}-F was 87-105%). However, interspecies comparisons are uncertain since different doses were given and there were some indications that the % of dose excreted in urine is a function of dose, e.g. % excretion of label was decreased in dogs at doses above 10 mg/kg p.o. Most of the label not excreted in urine was excreted in feces. Studies in rats shows a significant biliary excretion and extensive enterohepatic circulation. In dogs and rats, the excretory patterns were similar after p.o. and i.v. dosing, suggesting complete G.I. absorption of the administered label.

Studies of the effects of subacute treatment on ADME/pharmacokinetic parameters in animals were limited. In dogs, 5-6 month's treatment did not modify plasma levels or excretory pattern of total label after administration of C^{14}-F; however, at the higher doses the % of urinary label represented by unchanged F decreased, indicating a possible induction of metabolism. An analagous study was not performed in other species, although in rat it was shown that 10 day's treatment caused a slight decrease in plasma levels of F (but without change in T 1/2) seen after administration of a single dose of unlabelled F. On the other hand, a study in humans showed that after 4 weeks' treatment at 100 mg/day, trough plasma levels of F were 2 x greater than expected based on single dose pharmacokinetic data. (This study showed that 4 weeks' treatment at 100 mg/day caused a 40% decrease in the clearance of a single 50 mg dose without a significant change in its T 1/2). However, in this study there was no change over time in the amount of F excreted in urine (mean = 4% of dose).

In a pharmacological study in mice, F given acutely prolonged hexobarbital narcosis time (ED 200% = 35 mg/kg p.o.); since F did not potentiate a subthreshhold dose of hexobarbital it was concluded that F inhibited hexobarbital metabolism. (Hexobarbital levels were not measured).

ACUTE TOXICITY:

Oral LD_{50} values were 2000, 1470, 1100, and 1330 mg/kg in M rats, F rats, M mice, and F mice, resp. The greater lethality in F vs. M rats corresponds to the greater plasma levels seen in F after oral dosing (see above); although by the i.v. route fluvoxamine was slightly more lethal in male rats (LD_{50} = 43 and 68 mg/kg in M and F, resp.) Toxic signs after p.o. dosing included the following: rats - mydriasis, slowed reflexes, and increased muscle tone; death associated with convulsions ans respiratory depression; mice - mydriasis, exaggerated startle response, increased muscle tone, restlessness, lacrimation, and salivation; death associated with convulsions. In a study in a small number of dogs, oral doses of 15-464 mg/kg were given. No deaths occurred although the single dog given 464 mg/kg had convulsions which were treated with i.v. phenobarbitone. The drug was generally not well tolerated in dogs, with signs including emesis, marked mydriasis, cutaneous vasodilation, ataxia, increased limb tone, and rhythmic side-to-side head movements. (The latter lasted up to 6 days post-dosing).

In an in vitro study it was shown that F was substantially adsorbed onto medicinal charcoal in artificial gastric juice at 37°C, suggesting possible efficacy of charcoal in the early treatment of drug overdose.

D) SUBACUTE/CHRONIC TOXICITY:

The following studies were performed: (daily p.o. dose in mg/kg):

	Duration	Strain	Dose	Dietary or Gavage
Mouse:				
	2 weeks	ICI	100, 200	G
	4 weeks	ICI	200, 300, 400	D
	4 weeks	ICI	400, 600, 800, 1600	D
	4 weeks	ICI	75, 150, 300, 600	D
	4 weeks	CD-1	75, 150, 300, 600	D
	21 weeks	ICI	10, 80, 640	D
Rat:				
	6 month	WISTAR	5, 20, 80 → 100 → 150	G
	18 month	WISTAR	10, 40, 160 → 200 → 240	D
	Lifetime (2 + years)	WISTAR	10, 40, 160 → 200 → 240	D
Hamster:				
	2 weeks	BIO 15-16	100, 200	G
	4 weeks	BIO 15-16	9, 36, 142, 432	D
	13 weeks	BIO 15-16	240	D
	Lifetime (85-112 wks)	BIO F_1D "ALEXANDER"	9, 36, 135 → 180 → 240	D
Dog:				
	7 month	BEAGLE	5, 15, 45 → 60	Capsule
	1 year	BEAGLE	10, 25, 30 → 45 → 62.5	Capsule

The principal results of these studies are summarized as follows:

1) Mouse

(These studies were done primarily with the aim of establishing doses for longer term studies and/or of investigating the effects of F on serum and liver lipids; histopathology was not extensive).

body weight gain was generally decreased at 640 mg/kg +. Serum lipids (assayed in 21 week study) were greatly decreased at 640 mg/kg but (except for cholesterol in M at 80 mg/kg) not at the lower doses (10 and 80 mg/kg). Liver lipids (assayed in 21 week study) were increased at 80 and 640 but not at 10 mg/kg. (In a 2 week study, imipramine [IMI] and amitriptyline [AMI] were also shown to decrease serum lipids and to increase liver lipids; F was less potent in these effects but was also generally less toxic than IMI and AMI at the doses used). SGOT and SGPT (assayed in 21 wk study) were elevated at 80 mg/kg + in M and at 640 mg/kg in F. Increased liver weight was seen in several of the studies at the higher doses. Several studies showed increased fatty vacuolation of hepatocytes; this effect was both dose- and time-related; it was seen at all doses in the 21 week study and apparently persisted through an 8 week recovery period. (In a 2 week comparison study, IMI and AMI also caused hepatocytic vacuoles). Several other histopathologic effects were seen in liver, including pleomorphic cell inflammation (all doses in 21 week study; incidence even greater after recovery period), hemorrhage into hepatocytes (seen in all females groups in 21 week study after recovery period only), and enlargement of centrilobular hepatocytes (4 week study at 300-600 mg/kg).

2) Rat

In the lifetime study, a decrease in alopecia was seen at HD which was attributed to decreased activity, otherwise no behavioral signs were seen in the rat studies. There was no increase in mortality in any study; mortality was slightly decreased in HD M in the lifetime study but this was not statistically significant. Slight decreases in weight gain and food consumption were seen, generally at the higher doses (above 150 mg/kg). Ophthalmoscopic exam (done in lifetine study study only) showed no drug effects. Blood cholesterol was decreased in HD M in the 18 month study and in HD F in the lifetime study; however, total lipids and other lipids classes were measured in the 18 month study and no drug effects were seen. In the 6 month study, a large increase in urine volume in HD M (and to a smaller extent in LD and MD M) and a large increase in urine Na, K, and Cl in HD M and F (and to smaller extent in LD and MD) were noted during the first week; an increased water consumption was also noted during this time. (In the 18 month study there was no effect in urine volume; urine electrolytes were not measured. Urinalysis was not performed in the lifetime study). Urine specific gravity was slightly increased in MD and HD F in the 6 month study and HD M in the 18 month study. The most prominent histopathological finding was increased vacuolation and/or fat in liver, which was seen at all doses (5 mg/kg +) in the 6 month study, at MD and HD M (40 mg/kg +) in the 18 month study, and at HD (160 240 mg/kg) and equivocally at LD and MD (10 mg/kg +) in the lifetime study. Other effects in liver included chronic inflammation of the parenchyma in MD and HD M (40 mg/kg +) in the 18 month study, and centrilobular degeneration in all M groups (10 mg/kg +) in the lifetime study. There were no changes in lab tests indicative of alter liver structure or function in these studies. Various kidney changes were increased in the 18 month study: chronic inflammation (all M groups), basophilic staining tubules (MD and HD M and HD F), and distended tubules or tubules containing eosinophilic material (MD and HD M).

These changes were considered minor; there was no drug effect on the incidence of progressive glomerulonephrosis. There were no lab changes indicative of altered renal function, nor were there any drug-related kidney changes seen in the 6 month or lifetime studies. In lung, there was an increased incidence of distended macrophages at HD in the 18 month study; in this study there was also a slight and non-dose-related increased incidence of perivascular accumulations of lymphocytes in all groups but LD F. In the lifetime study the incidence of foci of desquamating pneumonia was increaed at HD; however there was no increase in other types of pneumonia in this study. The incidence of dilated fundic glands of the stomach was increased in HD M in the lifetime study. Two rats (1 control and 1 HD) in the lifetime study were sacrficed at 1 year and mesenteric lymph node was examined by EM; the treated rat had a 6 x greater number of cytoplasmic lamellar inclusions.

In the lifetime (i.e. carcinogenesis) study there were no drug effects on palpable masses (either incidence or time to first detection) or on total benign or malignant tumors. (Incidence values were apparently not corrected for rat survival. It was stated that there were no statistically significant group differences in survival. The slight increase in survival in HD M, noted above, was apparently not statistically significant; at any rate, not taking the increased survival in HD M into account would work "against" the drug in that it overestimates the true tumor incidence in this group relative to controls). There was an equivocal increase in the incidence of adenoma of the parafollicular cells of the thyroid in both sexes at HD: (total M + F): 5/80, 8/80, 9/80, and 14/80 in C, LD, MD, and HD, resp. (This results was not statistically significant by the Fisher Exact Test, which was performed by the firm, apparently in each sex separately.) Most of the tumors were seen at the terminal sacrifice, thus there is no evidence for earlier onset in the drug groups. The incidence of parafollicular cell hyperplasia was not clearly increased. The incidence of thyroid adenocarcinoma was low but was equivocally increased in HD M; there was a discrepancy regarding the incidences with one table showing 1, 0, 1, and 3 tumors, and another table showing 0, 0, 0, and 3 tumors, in C, LD, MD, and HD M resp. (Based on this discrepancy and several other discrepancies and ambiguities noted in this study as listed in my memo of June 14, 1984, [copy attached] a request for clarification and an audit of the study was made to the sponsor [phone memo, by CSO Mr. Barash, of June 15, 1984]. On July 10, 1984 the sponsor replied that it was being worked on but that a response would be unlikely before October, 1984. A response has not been received as of the present date [November 30, 1984]. In addition, we have requested [phone memo, by CSO Mr. Barash, of July 3, 1984] that the sponsor submit individual animal data which would allow our Biometrics Division to perform a statistical analysis of the thyroid tumors which takes survival into account; this information also has not yet been received). Of the 3 adenocarcinomas seen in HD M, 1 was specifically stated to be of parafollicular cells; the other 2 were said to be "adenocarcinoma of the thyroid".

3) Hamster

No behavioral signs or increased mortality was seen in any of the studies. (In the lifetime study, some drug groups had a slightly decreased mortality rate). Weight gain was reduced at 100 mg/kg+ in the subacute studies only; in the lifetime study a slight increase in weight gain and food consumption was seen in HD F (240 mg/kg). Ophthalmoscopic exam (done in lifetime study) showed an increased incidence of cataracts in HD F (3/52, 2/31, 1/31, and 6/29 in C, LD, MD, and HD, resp.) The incidence of cataracts was also increased in HD M but this was said to be not statistically significant (6/80, 3/44, 2/47, 5/49). Results on serum lipids were inconsistent, some studies showed a decrease and some no effect. Liver lipids showed slight increases, generally at the higher doses. In a 2 week comparison study, IMI and AMI at 25-100 mg/kg did not increase liver lipids; F caused increases at 200 but not 100 mg/kg; F was less generally toxic than IMI and AMI at these doses. Slight increases in liver and kidney weights in MD and HD M, and slight increases in liver weight in HD F, were seen at 1 year but not at termination in the lifetime study. Kidney weight was slightly increased at the only dose used (240) in the 13 week study. Histopathological findings were seen in liver and kidney in the subacute studies, but not in the lifetime study. These findings included: (1) liver - cloudy swelling (also produced by IMI and AMI) at both doses (100 and 200 mg/kg) in the 2 week study, and increased severity of fat droplets at the only dose used (240) in the 13 week study. (No effect in the 4 week study, doses = 9-432 mg/kg). (2) kidney - various findings at HD (432 mg/kg) in the 4 week study, including dialted and/or basophilic tubules (with some containing amphiphilic homogenous material and/or cell debris) and foci of mineralization; after a 30 day recovery period the incidence of these findings was not clearly increased although severity was greater at HD than in controls. Lab tests for kidney function were not done in this study. In the 13 week study there was an increased incidence of foci of mineralization at the only dose used (240 mg/kg); there were no drug effects on blood urea or creatinine.

The hamster was chosen (rather than mouse) for the carcinogenesis (lifetime) study based on studies showing that the urinary metabolite pattern in hamsters was more similar to that of man (see above). In this study there was an equivocal increase in the incidence of adrenal adenoma in MD and HD F (3/86, 2/45, 4/47, and 5/48 in C, LD, MD, and HD, resp); this was statistically significant according to a test which took mortality rates into account. There was no evidence of an earlier onset in the drug groups. The incidence of adrenal carcinoma was not increased in HD F, although the incidence in LD and MD F was greater than in controls: 2/86, 6/45, 3/47, 1/48 in C, LD, MD, and HD F, resp.) (An additional carcinoma was seen in 1 HD F at the 1 year sacrifice). Neither the incidence of adrenal adenoma nor carcinoma was increased in males (adenoma: 12/86, 11/49, 4/50, 7/49; carcinoma: 11/86, 8/49, 8/50, 6/49 in C, LD, MD, and HD, resp.) The incidence of adrenal hyperplasia was not increased in F, and tended to be slightly decreased in treated M groups. A statistical analysis of tumor incidences taking mortality rates into account was performed on several of the more commonly occurring tumors and on remaining benign tumors lumped together and on remaining malignant tumors lumped together; aside from the increase in adrenal adenomas (above), no drug-related effects were found.

There was no summary incidence table presented for gross pathology findings; this has been requested from the sponsor. (Phone memo of June 15, 1984). (The sponsor concluded there were no drug-related effects.)

4) Dogs

F was [illegible]erated at 60 mg/kg and above; toxic signs at these doses [illegible]norexia, emesis, poor general condition, diarrhea, ataxia, whimpering, and coughing. One dog had convulsions and one dog died a 80 mg/kg, and one was sacrificed in extremis at 60 mg/kg. Signs at 25-30 mg/kg included emesis, diarrhea, whimpering, and coughing. Mydriasis was seen at all doses (5 mg/kg+) and lasted up to the next daily dose (i.e. 24 hours). Decreased weight gain was seen at 60 mg/kg, and weight loss occurred at 80 mg/kg. Food consumption was decreased at 60 mg/kg+ and to a smaller extent at 10-25 mg/kg. Ophthalmoscopic exams showed no drug effects (aside from the mydriasis). EKG exam showed slight decreases in PR interval at HD (45 → 60 mg/kg) in the 7 month study, but no effects were seen in the 1 year study (HD = 62.5 mg/kg). SAP was increased at HD in both studies. Blood urea was slightly increased in 2/4 HD M in the 1 year study. Urine SG was slightly decreased in HD M in the 7 month study and in HD M and F in the 1 year study; in the latter study sproadic decreases were also seen at LD and MD. Other urinalysis findings in the 1 year study included increased urine volume at all doses (water consumption was decreased in this study, but during the first 4 weeks only) and proteinuria in 1 LD M, 1 HD M, and 2 HD F (2 of these dogs also had the presence of "countless" epithelial cells). Organ weight changes included increased liver weight at HD (both studies), increased kidney weight in all M groups and HD F (1 year study), increased lung weight in HD M and in MD and HD F (1 year study), and increased spleen weight in HD M (1 year study). The principal histopathological findings were: (1) kidney - several changes present or increased in both studies, primarily at HD, including chronic interstitial nephritis, thickening of basement membrane, dystrophic mineralization, distended tubules, basophilic staining tubules, tubules showing vacuolation of cells of the epithelium, fibrosis, glomerular atrophy (distension of Bowman's capsule and shrinkage of glomerular tuft), and presence of eosinophilic material in Bowman's capsule. Some of the these changes were still present after recovery periods. A few dogs at LD and MD also showed some of these changes. In many cases, dogs with renal lesions had shown lab test abnormalities (increased BUN and proteinuria). (2) "Foam cells" or "foamy macrophages" were present in HD in both studies in several organs, including spleen, GI tract (Peyer's patches), and lymph nodes; lungs were apparently not affected. The foam cells were said to contain lipid. They were not seen in recovery dogs in the 1 year study; in the 7 month study they were seen in 1 of the 2 HD recovery dogs.

E) REPRODUCTION:

The following reproduction studies were performed (daily p.o. dose in mg/kg):

1) Segment I - rat (5, 20, 80) (both sexes treated)

2) Segment II - rat (5, 20, 80)

3) Segment II - rabbit
   a) (5, 10, 20)
   b) (5, 10, 20, 40)

4) Segment III - rat
   a) (5, 20, 80)
   b) (160) (with cross-fostering)

In the segment I study no adverse effects on mating or fertility were seen. The doses used caused no observable signs in the parents of either sex or on bodyweight of F; there was a very slight non-dose-related decrease in weight gain at all doses in M. In the segment II study in rats there were no adverse drug effects on major malformations, minor anomalies, or skeletal variants. The doses used produced no observable signs or bodyweight effects in the dams; there was also no indication of an embryotoxic or fetotoxic effect (i.e. no effect on post-implantation loss or fetal weight). Two segment II studies were performed in rabbits. (The doses used were based on preliminary studies showing anorexia and transient weight loss at doses higher than those chosen for the main studies.) In the first study there were no drug effects on major malformations or minor visceral anomalies. However, there appeared to be a greater incidence of a variety of minor skeletal anomalies at all doses; in addition, many of the affected fetuses in the drug groups, especially at HD, had multiple skeletal anomalies. The incidence of skeletal anomalies were said to be within the historical control range, although historical data for the individual anomalies seen were not presented. A second study in rabbits was performed using a HD (40 mg/kg) which was 2x that used in the first study, in which no drug effects on major malformations, minor anomalies or skeletal variants were seen. Two segment III studies were done in rats. In the first study an increased pup mortality at birth was seen at HD (80 mg/kg), and a dose-related decrease in pup survival through day 21 PP was seen at all doses. (Mean pup weight was slightly increased; this was probably a consequence of reduced litter size). The doses used produced no observable signs in the dams; a slight non-dose-related increase in weight gain was seen during the postpartum period which was likely not a true drug effect. A second segment III study was performed which used a single dose (160 mg/kg) which was 2 x higher than the HD of the initial study; this study also used cross-fostering. The results suggested that the decreased pup survival was likely secondary to maternal toxicity, i.e. pups delivered by treated dams and reared by control dams did not have decreased survival, whereas survival was decreased among pups delivered by either control or treated dams and reared by treated dams. (However, it should be noted that, aside from dystocia or delayed parturition in a few dams at 160 mg/kg, neither of the 2 segment III studies showed any overt toxicity in the dams as judged by observed signs and bodyweight change. It was also seen, at 160 mg/kg, that the weights of pups delivered by treated dams and reared by treated dams were lower than the weights in the other groups [including pups delivered by control dams and reared by treated dams], suggesting a drug influence in the pups occurring prior to the time of cross-fostering [which wad done on day 1 PP]).

F) MUTAGENICITY:

F was negative in the Ames Test. (Highest concentration used = 200 ug per plate; higher concentrations were bacteriotoxic). In an *in vitro* test in cultured human lymphocytes, F produced an equivocal increase in chromosomal aberrations when the assay was run without prior metabolic activation; no effect was seen after metabolic activation. (The concentrations used in this study, ug/ml, were substantially greater than steady-state plasma levels in patients receiving 100-300 mg per day [mean values approximately 0.2 - 0.6 ug/ml; range ug/ml]).

EVALUATION:

The pharmacological and toxicological profile of fluvoxamine (F) has been adequately characterized in animals. F has a pharmacological profile similar to that of "5-HT-specific" antidepressants such as fluoxetine and zimelidine, although the data demonstrating this specificity (vis a vis NE) were not conclusive. F did not cause general CNS depression or stimulation at relatively high acute oral doses, whereas classical tricyclic antidepressants generally produce CNS depression when given acutely. (Some studies showed that parenteral doses of F did cause some behavioral depression). F demonstrated local anesthetic activity, although it was slightly less potent than reference tricyclics. F was generally significantly less potent than reference tricyclics in tests of anticholinergic activity; such activity is responsible for several of the side effects of marketed antidepressants. A major clinical problem with classical tricyclics is the production of cardiac conduction changes and arrhythmias and depression of myocardial contractility; in a study in conscious rabbits F was less potent than amitriptyline in producing these effects.

F was shown to potentiate the lethality and neurobehavioral effects of MAO inhibitors, and was more potent in these effects than reference antidepressants when compared. Toxic interactions between MAO inhibitors and other antidepressants in man are well known (although their significance has been somewhat downplayed in recent years), and their concomitant use is generally contraindicated. Various effects of 5-HTP were also potentiated by F.

F caused a large decrease in platelet 5-HT content in both animals and man. The function of 5-HT in platelets is obscure. Platelets depleted of 5-HT by reserpine function normally and bleeding time is unchanged (reference cited in Goodman and Gilman, 6th edition, p. 637). Fluoxetine which is also a "5-HT-specific" antidepressant, also decreases platelet 5-HT, and a protocol has recently been submitted for a study of the effects of fluoxetine on platelet function in humans (IND 12,274, submission of October 19, 1984).

F is extensively metabolized. The principal urinary metabolite, which was the same in man and all animal species tested (except mouse), showed little or no activity in the small number of antidepressant screening tests performed.

The acute oral toxicity of F in rats and mice was relatively low, with LD 50 values in the 1000-2000 mg/kg range. (Acute i.v. LD 50 was much lower, 40-70 mg/kg in rat). Lethal oral doses were associated with convulsions. Dogs tolerated the drug less well; in a small acute oral study 464 mg/kg caused convulsions; in subacute studies 60-80 mg/kg/day caused convulsions and death. An in vitro study suggested the possible efficacy of charcoal in the early treatment of drug overdose.

Subacute and chronic oral toxicity studies suggested that the liver and kidney were the main target organs of toxicity. In liver, increased fatty vacuolation and a variety of other degenerative/inflammatory/reactive changes were seen in mice, rats, and hamsters (but not in dogs); in some studies these occurred at the lowest doses used (5 mg/kg). SGOT and SGPT were elevated in mice but not in rats. No necrosis was seen. Changes of this kind are often seen with drugs that are extensively metabolized by the liver, and their toxicological significance at therapeutic doses in man are unclear; at any rate it would be prudent to monitor liver function in man. Kidney changes were less consistent; they were seen in the 18 month (but not 6 month or lifetime) rat study, in the 4 and 13 week (but not the lifetime) hamster study, and in both dog studies. A wide variety of lesions were seen, including chronic inflammation, distended tubules, basophilic staining tubules, glomerular atrophy, and mineralization. In dogs, the lesions were associated with elevated BUN and proteinuria. These lesions generally occurred at the higher doses and may likely represent a response of the kidney to the handling of a large amount of drug metabolites.

There were some indications that F can produce phospholipidosis, e.g. foamy macrophages were seen in several organs in dog, cytoplasmic lamellar inclusions (detected by EM) were seen in lymph nodes in rats, and increased liver lipid content was seen in mice and hamsters. These effects occurred primarily at the higher doses. Phospholipidosis is produced by numerous drugs including several antidepressants; but its human significance is unknown. No adverse effects attributable to phospholipidosis have been produced in man by other antidepressants, although there are a few examples of other drugs where such effects may occur (e.g. chloroquine - retinal/corneal changes; 4,4'-diethylaminoethoxyhexestrol - hepatosplenomegaly/liver cirrhosis).

In the lifetime hamster study, the incidence of cataracts was significantly increased in HD F: 3/52, 2/31, 1/31, and 6/29 in control, LD, MD, and HD, resp. The incidence was also increased in HD M but this was said to be not statistically significant (6/80, 3/44, 2/47, and 5/49 in C, LD, MD, HD, resp.) The combined (M + F) incidence was 7%, 7%, 4%, and 14% in C, LD, MD, HD, resp. A similar effect was not seen in rats or dogs. Although this appears to be a high-dose, species-specific effect, it would seem wise to monitor for this in man to establish its non-occurrence at therapeutic doses.

Lifetime carcinogenesis studies were performed in rats and hamsters. There were no clear indications of carcinogenicity, although there were 2 equivocal effects:

1) Thyroid parafollicular cell adenomas in the rat study.

The incidence of this tumor was greater than controls in HD of both sexes. The combined (M + F) incidence was 5/80 (6%), 8/80 (10%), 9/80 (11%), and 14/40 (18%) in C, LD, MD, and HD, resp. (This finding was said to be not statistically significant by the Fisher Exact Test, which was apparently performed in each sex separately. Carcinomas were not combined with the adenomas in the statistical evaluation although this should be done since it is often difficult to distinguish between benign and malignant thyroid tumors on morphological grounds. The number of thyroid carcinomas was greatest in HD M, although the actual numbers were not clear as has been discussed above, and a clarification has been requested from the sponsor. [One table showed 1, 0, 1, 3, and another showed 0, 0, 0, 3 in C, LD, MD, and HD, resp.]. It is also not clear of the carcinomas seen were parafollicular or follicular; of the 3 seen in HD M, 1 was specified as parafollicular but the other 2 were not specified. A knowledge of the cell type involved is necessary for judging the propriety of combining tumors for statistical and interpretive purposes). Published historical control incidences for parafollicular tumors are generally in the 3-10% range, although an incidence as high as 27% was seen in a study in Fischer 344 rats (Tarone et.al., JNCI 56: 1175, 1981), and one paper reported incidences of 20-30% in several strains, including 19% in Wistar rats (Lindsey, et.al., Arch. Pathology 86: 353+, 1968). Thyroid incidence appears to depend heavily in the number of sections examined. (Thompson and Hart, Ann. N. Y. Acad. Sci. 108/3: 332+, 1963). It would be useful to have historical control data for Wistar rats in studies performed by the same lab that performed the present study in order to help assess the significance of the present findings; this should be requested from the sponsor.

It should be noted that the functional analog (i.e. "5-HT-specific" antidepressant) zimelidine caused an apparent increase in thyroid parafollicular adenomas in HD M in a carcinogenicity study in Sprague-Dawley rats (IND The incidence in HD M was 38% vs. 5% in control males. (The incidence in HD F was 28% vs. 17% in control F, but this was not statistically significant.) However, the mortality rate in this study was significantly reduced at HD; a statistical analysis of tumors taking this into account was not performed. The incidence of parafollicular carcinoma or hyperplasia was not increased by zimelidine; in addition zimelidine did not increase thyroid tumors in a mouse carcinogenesis study. The "5-HT-specific" antidepressant fluoxetine did not increase parafollicular tumors in carcinogenicity studies in Fischer 344 rats or B6 C3 F1 mice. (NDA 18-936). Also, the close structural analog clovoxamine did not produce in increase in parafollicular tumors in a carcinogenicity study in Wistar rats (IND submission of 3/30/84).

Evidence against a true drug effect in the present study includes: (1) the incidence of parafollicular hyperplasia was not increased, (2) most of the tumors were seen at termination; thus there is no evidence for an earlier onset in the drug groups, (3) the incidence of thyroid follicular tumors was not increased, and (4) thyroid tumors were not increased in hamsters. (As discussed above, there were several discrepancies noted in the tables of this study, and the sponsor has been requested to re-audit it. Depending in the results submitted, a revised evaluation of this study may be necessary.)

2) Adrenal adenomas in the hamster study.

The incidence of this tumor was greater than controls in MD and HD F: 3/86 (3%), 2/45 (4%), 4/47 (9%) and 5/48 (10%) in C, LD, MD, and HD, resp. This was statistically significant according to a test performed by the sponsor which took mortality rates into account. Evidence against this being a true drug effect is as follows: (1) The incidence if adrenal carcinoma was not increased in HD F (although the incidence in LD and MD F was greater than in controls, (2) the incidence of adrenal hyperplasia was not increased in females and in fact tended to be slightly decreased in males, (3) neither the incidence of adrenal adenoma nor carcinoma was increased in males, (4) there was no evidence for earlier onset of adrenal adenomas in the drug groups, (5) an increase in adrenal tumors was not seen in rats, and (6) the close structural analog clovoxamine did not produce an increase in adrenal tumors in the same strain of hamsters (IND , submission of October 25, 1984). Adrenal tumors in this strain are common and occur with widely varying incidences depending on substrain (Homburger and Russfield, Cancer Res. 30: 305, 1970). The incidence of adrenal adenomas in the above-mentioned clovoxamine study, which apparently used the same substrain as in the present study, was 4% in females (and 13% in males), with a range of 2-6% in the individual female groups. The incidence of MD and HD F in the present study was slightly above this range. The sponsor should be requested to provide additional historical control data, preferably from the same lab that performed the present study, to help in the evaluation of the present results.

Reproduction studies in animals provided no evidence of adverse effects on fertility or of teratogenic effects of F. However, it is not clear how the HD of 80 mg/kg was chosen for the rat segment I and II studies. This dose produced no observed signs or bodyweight effects in the dams and no indications of a general embryotoxic or fetotoxic effect (although some toxic effect on the dams may be inferred from the decreased postpartum pup survival seen at this and lower doses in the segment III study.) The sponsor should be requested to justify the doses used (although it should be noted that the HD used is at least 10 x the human therapeutic dose.)

RECOMMENDATIONS:

1) This NDA is approvable, contignent on the satisfactory resolution of the issues raised in my memo of June 14, 1984 (copy attached) concerning discrepancies and lack of certain information in the rat and hamster carcinogenicity studies. (This memo was read to the sponsor by CSO Mr. Barash on June 15, 1984. On July 10, 1984 the sponsor replied that it was being worked on but that a response would be unlikely before October, 1984. A response has not been received as of the present date [11-30-84]).

2) The sponsor should be requested to submit historical control data for the incidences of thyroid parafollocular tumors in Wistar rats, and of adrenal adenomas in Syrian hamsters, perferably from the same labs where the fluvoxamine carcinogenicity studies were performed, in order to help in the evaluation of the findings with fluvoxamine. In addition, the sponsor should be requested to specify the cell type involved in the thyroid adenocarcinomas found in the rat study (since this is necessary for determining whether these tumors should be combined with the parafollicular adenomas for statistical and interpretive purposes). (It should also be noted that we have requested [phone memo of 7/3/84 by CSO Mr. Barash] that the sponsor submit individual animal data which will allow our Biometrics Division to perform a statistical analysis of the thyroid tumors which takes survival into account; such an analysis will aid in determining the significance of the present rat findings.)

3) The sponsor should be requested to justify the selection of a high dose of 80 mg/kg in the segment I and II rat reproduction studies, since this dose produced no obvious manifestations of maternal, embryonic, or fetal toxicity.

4) The following are for consideration by the clinical reviewer:

   a) Liver and kidney appeared to be the primary target organs for toxicity in animals. Although the changes seen were generally not severe and most likely represent adaptive/reactive responses to the metabolism and excretion of drug, liver and kidney function should be paid attention to in man.

   b) Fluvoxamine caused an apparent increase in the incidence of cataracts at the high-dose (135→240 mg/kg) in a lifetime study in hamsters. Although this appears to be a high dose, species-specific (i.e., not seen in rats or dogs) effect, it would be prudent to assess its possible occurrence in man.

   c) Fluvoxamine potentiated the lethality and neurobehavioral effects of MAO inhibitors in animals, and was more potent in these effects than reference antidepressants when compared. Various effects of 5-HTP were also potentiated by fluvoxamine.

Barry N. Rosloff

Barry N. Rosloff, Ph.D.

NDA 19-189
HFN-120
HFN-120/ROSLOFF/CONTRERA/LAUGHREN
2-10-85
HFN-102/GLOCKLIN
Doc. 0054f

Department of Health and Human Services
Public Health Service
Food and Drug Administration

Memorandum

Date : June 14, 1984

To : NDA Division File

From : Barry Rosloff, Ph.D.
Reviewing Pharmacologist

Subject: NDA - information to be requested from sponsor

As part of my ongoing review of this NDA, I have the following questions and requests which should be transmitted to the sponsor:

1. Concerning the lifetime carcinogenicity study in hamsters:

   a. Please submit a summary table showing the group incidences of gross pathology findings, including masses.

   b. What stain (or stains) was used for the histopathological exam?

2. Concerning the 2 1/2 year carcinogenicity study in rats:

   a. It is stated in the "Materials and Methods" section that ophthalmoscopic exams were to be performed in the control and high dose groups during weeks 7, 13, 26, 78, and 104, and in all animals at termination. However, in the "Results" section it is stated that exams were performed in the control and high dose groups at weeks 7, 13, 27, and 52. Please explain this discrepancy, and submit the results for the individual rats examined.

   b. A spot check of the histopathology results shows several discrepancies, for example:

      1. Table B shows 2 low dose males had malignant tumors, whereas Table 13 shows 5 malignant tumors in this group.

      2. The individual rat data (Appendix II) shows that rat #39 (control male) had a cystadenoma of the bile duct epithelium, but Table 13 shows no cystadenomas listed for control males.

      3. Table 13 shows the number of thyroid adenocarcinomas as 1, 0, 1, and 3 in control, low, medium, and high dose males, respectively. However, the table in Appendix I lists these numbers as 0, 0, 0, and 3, respectively.

4. In Appendix I, some of the values for calcified cartilage in the trachea and/or bronchus are greater than the number of rats which were examined.

Please explain these discrepancies. In addition, please carefully audit this study to eliminate other contradictions in the results and to assure that the tabulated results accurately reflect the individual animal data.

c. In Appendix I, the number of animals said to have had histopathological exams was 40/sex/group for all tissues. Is this correct; i.e. were no tissues unevaluable due to autolysis, sample loss, or other reasons?

d. It was stated that the concentration of the compound in the diet decreased with time, by about 5% after storage at 20-30°C for 30 weeks. It was also stated that "for week 92 onwards the food in the hoppers was replenished twice weekly, the food for the latter part of the week being stored at +4°C [sic] before distribution." It is not clear from these statements when this stability problem was first detected, and how well it was corrected. Please submit data on the stability of the compound during the study as well as results on the homogeneity of mixing. Please submit estimates of the actual doses ingested by the rats during the study.

3. Concerning the 18 month rat toxicity study:

Please submit information on the stability of the compound during the study, the homogeneity of mixing, and an estimation of the actual doses ingested.

Barry N. Rosloff

Barry N. Rosloff, Ph.D.
Reviewing Pharmacologist

Barry N. Rosloff
May 29, 1985

PHARMACOLOGIST REVIEW OF NDA
Submissions of 11-26-84 and 4-10-85

Vol 2.1

SPONSOR:

DRUG:

CATEGORY: antidepressant

PREVIOUS PHARMACOLOGIST REVIEW: Original Summary of November 30, 1984

PURPOSE OF SUBMISSIONS:

1. Submission of 4-10-85 - responses to our questions concerning preclinical toxicity studies as previously communicated to the sponsor by phone. (See phone memo of 6-15-84 and 7-3-84. A copy of my memo of 6-14-84, on which the phone memo of 6-15-84 is based, is attached.)

2. Submission of 11-26-84 - 13 week oral toxicity study in rats using a fluvoxamine "adduct" ("impurity/degradation product.")

SUMMARY:

A) Answers to questions asked in our phone memo of 6-15-84. (Questions are listed in my memo of 6-14-84, attached).

1) A summary table of the gross pathology findings in the hamster carcinogenicity study was submitted. There are no drug-related findings (as was indicated in the text of the original report).

2) The stain used for histopathological exam in the hamster carcinogenicity study was H and E.

3) In the rat carcinogenicity study, ophthalmoscopic exams were performed in weeks 7, 13, 27, and 52 in C and HD, and in all groups at termination. The schedule listed in the "Methods" section was said to be in error. Individual animal findings were presented; no drug effect is apparent.

4) Several discrepancies were noted in a spot check of the pathology results of the rat carcinogenicity study:

a) 5 malignant tumors in LD M were indicated in Table 13, but only 2 tumors were indicated in Tables B and 1a. Sponsor states that Tables B and 1a were incorrect; revised tales were submitted.

b) Table 13 shows no cystadenomas for control M, whereas individual rat pathology sheets showed rat #39, a control M, having a cystadenoma. Sponsor states that Table 13 (and also Table 1C) was in error; corrected tables were submitted.

c) Table 13 showed the number of thyroid adenocarcinomas as 1, 0, 1, and 3 in C, LD, MD, and HD M, resp; but the Table in appendix I listed these numbers as 0, 0, 0, and 3, resp. Sponsor states that Table 13 (also 1b and 1d) was incorrect; corrected tables are submitted.

d) In the table in appendix I, some of the values for calcified cartilage in the trachea and/or bronchus were greater than the number of rats which were said to be examined. Sponsor states that this was due to a few rats being misclassified regarding whether death was intercurrent or occurred at terminal sacrifice. (The table was broken down into these 2 groups). Corrected table was submitted.

e) In appendix I, it was implied that all animals (40/sex/group) had histopathological exam in all tissues. We questioned whether this was true, i.e. were there no unevaluable tissues due to autolysis or other reasons? The sponsor has submitted a table of missing tissues. An average of less than 1 tissue was lost per animal. For most organs, only 0-3 tissues per group were missing.

4) In view of the above discrepancies (discovered upon spot-checking), we requested the firm re-audit the study. The sponsor states that the histopathology part of the study has been checked, and some discrepancies were found in the histopathology tables (Table 2, and Appendix I). Corrected tables are submitted. Changes appear to be minor. The most significant change involves an apparent re-classification of liver lesions. It appears that many of the cases of centrilobular degeneration in MD and HD M were reclassified as "vacuolation." The conclusions remain similar: "centrilobular degeneration" was increased in all M groups (but to a lesser degree at HD than in the original report), and vacuolation was increased in all groups (but to a greater degree in MD and HD M than in the original report).

5) The sponsor's original discussion of compound stability in the rat carcinogenicity study was unclear. The sponsor replies that a method for analyzing fluvoxamine in diet was not available until week 79 of study. It was then discovered that fluvoxamine (at 20°C) diminished at the rate of 2.7% per day. (Fresh diets given every 7 days). At 4°C the loss was 1.5% per day; thus, starting week 92, diets were stored at 4°C and replenished 2x/week. It was estimated that the daily average intake of fluvoxamine was about 10% lower than the intended doses throughout the study:

	Intended (mg/kg/day)	Actual
LD	10	9
MD	40	36
HD	160	146
	200	180
	240	214

Results presented on the homogeneity of mixing were acceptable.

6) Data on compound stability and homogeneity of mixing were requested for the 18 month rat toxicity study. It was stated that such data were not available. Based on an estimated 10% loss as determined in the rat carcinogenicity study, the actual daily dose were estimated to be the same as in that study (see above); the same nominal doses were used.

B) Response to request for information as stated in our phone memo of 7-3-84.

The sponsor has submitted the data on thyroid parafollicular adenomas from the rat carcinogenicity study as requested by the Division of Biometrics, to whom it will be forwarded.

C) Rat toxicity study with fluvoxamine "adduct".

16 M + 16 F Wistar rats were given either fluvoxamine (F) at 10 mg/kg/day, F with 10% "fluvoxamine adduct" (9 mg/kg F + 1 mg/kg adduct), or vehicle, by gavage, for 13 weeks. The "adduct" was said to be an "impurity/degradation product" which increases during storage; its structure was not given. There were no clearly drug-related effects on the usual toxicologic parameters, including lab tests and histopathology.

EVALUATION:

1) A spot check of the histopathology data in the rat carcinogenicity study, showing several minor discrepancies, led us to request a re-audit of the data by the sponsor to assure its accuracy. Revised tables were submitted; changes were minor and do not alter the conclusions made in my original review of 11-30-84. The total number of neoplasms found was as follows (denominator approximately 80/sex/group).

		C	LD	MD	HD
Benign	M	23	28	22	24
	F	31	34	30	30
Malignant	M	7	5	6	9
	F	15	5	14	8

These numbers are slightly different than those in the original report, but no drug effect is indicated.

The numbers of thyroid parafollicular adenomas are not different from those in the original report; however, it is now indicated that thyroid samples were missing from a few animals: 1 thyroid in 5 LD, 4 MD, and 3 HD, and both thyroids in 1 MD. It is not stated how many of the animals with 1 thyroid missing had adenomas found in the other thyroid; assuming this number to be 0 (i.e., "worst case" analysis), then the incidence values for parafollicular adenomas was 6, 11, 12, and 18% in C, LD, MD, and HD, resp. This is only slightly higher than the incidences originally calculated using a denominator of 80/group (6, 10, 11, 18%, resp.) and does not change the conclusions reached in my original review of 11-30-84. Likewise, the original conclusion that parafollicular hyperplasia was not increased still holds using the new values (and a "worst case" analysis regarding missing tissues as above): 9, 11, 8, and 13% incidence in C, LD, MD, and HD, resp.

An additional change in the histopathology data was a reclassification of some cases of hepatic centrilobular degeneration to vacuolation; in general the same groups were affected. (In the original table, the incidence of vacuolation was increased at LD but the incidence in MD M was 0, leading me to conclude that this effect at doses below HD was equivocal; however, the new table indicates a clear effect at LD and MD, although smaller than that at HD).

The numbers of missing tissues (i.e. due to autolysis, etc.), was given in a table. The numbers were small and ramdomly distributed among groups; this information does not change the conclusions reached in my original review of 11-30-84.

2) Compound stability and homogeneity of mixing data were presented for the rat carcinogenicity study. The sponsor estimates that for both this and the 18 month rat toxicity study, the actual doses ingested were about 10% less than intended. This does not affect the validity of these studies.

3) The sponsor be clarified discrepancies in the schedule for ophthalmoscopic exams in the rat carcinogenicity study, and has submitted individual results. This aspect of the study was important since the lifetime hamster study showed an apparent increase in cataracts at HD. There did not appear to be a drug effect in the rat study.

4) A 13 week oral toxicity study performed comparing fluvoxamine with fluvoxamine + an "adduct". The structure of this adduct was not given; it was said to be an "impurity/degradation product." There were no effects on the usual toxicological parameters. The dose of fluvoxamine used (10 mg/kg) is quite low for rats. The dose of the "adduct" (1 mg/kg given with 9 mg/kg fluvoxamine) was said to be approximately 7x the human intake on a mg/kg/day basis "under the most adverse conditions" (of storage).

RECOMMENDATIONS:

The submission of 4-10-85 clears up several discrepancies and ambiguities regarding some of the chronic animal studies. The new information does not change the conclusions reached in my original review of 11-30-84. The information on rat thyroid parafollicular adenomas requested by Biometrics should be sent to that division for their review.

Barry N. Rosloff

Barry N. Rosloff, Ph.D.

NDA 19-189
HFN-120
HFN-102/Glocklin
HFN-120/BRosloff
JContrera/5-31-85
TLaughren
Doc. 0107f p.1-7

Barry N. Rosloff, Ph.D.
September 3, 1986

PHARMACOLOGIST REVIEW OF NDA
SUBMISSION OF AUGUST 20, 1986

Sponsor:

Drug: fluvoxamine

Category: antidepressant

Previous Pharmacologist Reviews:

November 30, 1984 (Original Summary) and May 29, 1985.

Contents of Submission:

1. Response to questions asked in our letter of September 25, 1985 (based on recommendations made in my review of November 30, 1984).

2. 2-week p.o. rangefinding study in rats comparing fluvoxamine with an analog.

Summary:

1. Response to questions asked in our letter of September 25, 1985.

a) We requested historical control data for the incidences of thyroid parafollicular tumors in Wistar rats, and of adrenal adenomas in Syrian hamsters, preferably from the same labs where the fluvoxamine studies were done, in view of the equivocal increases in these tumors in the fluvoxamine studies.

1) Thyroid parafollicular tumors in Wistar rats:
It was stated that the fluvoxamine study has been the only carcinogenicity study with Wistar rats done in the Duphar labs, where the fluvoxamine study was performed. Control values were presented for Wistar rats from the lab's supplier (C.I.V.O., Zeist, The Netherlands), and are shown on the following page. The historical values of approximately 5-10% are in agreement with values commonly reported in the literature, although higher values (20% or more, including 19% in Wistar rats) have also been reported as noted in my review of November 30, 1984. Thus, while the HD fluvoxamine group had a greater incidence (18-20%) than most reported historical control groups, including those presented in the present submission, it was within the range of previously reported values.

Enclosure 1

Thyroid parafolicular tumors in CPB:WU Wistar rats

		Males control		fluvoxamine			
		A	B	C	L	M	H
duration (weeks)		105	135	124	124	124	124
n		276	55	40	40	40	40
Parafollicular cell adenoma	n	13	4	3	4	6	7
Parafollicular cell carcinoma	n	0	1	0	0	0	1
Total parafollicular tumors	(%)	5	9	8	10	15	20

		Females control		fluvoxamine			
		A	B	C	L	M	H
duration (weeks)		105	144	130	130	130	130
n		290	57	40	40	40	40
Parafollicular cell adenoma	n	12	7	2	4	3	7
Parafollicular cell carcinoma	n	0	0	0	0	0	0
Total parafollicular tumors	(%)	4	.	5	10	8	18

The control values A and B were obtained from the same strain of rats as used in the fluvoxamine study, however not from the same laboratory but from CIVO. Control B was a life-span study, that was terminated when 75% mortality was reached.

C = control

L = low dose

M = mid-dose

H = high dose

2) Adrenal adenomas in Bio Fl D Alexander hamsters:

Data are presented (shown on following page) from another carcinogenicity study performed "at the same time" as the fluvoxamine study by Bio Research labs. (It was said that other control data from this lab "are not available".) Both studies were said to be "life-span" studies, but the actual duration and mortality rates which would allow for a more valid comparison between the 2 studies were not given. From this table the % incidence of adrenal adenomas in the control groups were as follows:

	M	F
Fluvoxamine Study	14%	3%
"Other Drug" Study	12%	6%

The incidence of adrenal adenomas in MD and HD F in the fluvoxamine study was 9 and 10%, resp. Although this was statistically significantly different from the concurrent control (see my review of November 30, 1984), a decrease of 1 or 2 animals with tumors in among MD and HD F would give an incidence value of 6%, the same as that seen in the control F group in the "other drug" study.

b) b) We requested specification of the cell type involved in the thyroid adenocarcinomas seen in the rat carcinogenicity study. This was deemed important since there was an apparent increase in parafollicular adenomas at HD, and since it is difficult to distinguish between benign and malignant thyroid tumors on morphological grounds, the incidence of adenomas and carcinomas should be combined for statistical and interpretative purposes. However, as shown on the following page, only one of the carcinomas was parafollicular ("C-cell"), and thus impacts little upon the original interpretation.

c) c) We questioned why a high dose of only 80 mg/kg was used in the segment I and II reproduction studies in rats, since this dose produced no obvious manifestations of maternal, embryonic, or fetal toxicity. It was stated that this dose was based on a 14 day rangefinding study in rats (non-pregnant) using doses of 20-781 mg/kg. (See below). In this study various pathological changes in liver were seen (see below) at a threshhold of about 50 mg/kg.

Enclosure 2

Adrenal tumors in Bio F1 D Alexander hamsters

n = number of animals

		Males							
		fluvoxamine				other drug			
		H	M	L	C	H	M	L	C
	n	49	50	49	86	48	49	50	89
Adenoma	n	7	4	11	12	5	7	7	11
Carcinoma	n	6	8	8	11	3	4	5	13
Adenoma or carcinoma	n	12	12	18	23	7	11	12	22
	(%)	24	24	37	27	15	22	24	25

		Females							
		fluvoxamine				other drug			
		H	M	L	C	H	M	L	C
	n	48	47	45	86	48	47	47	90
Adenoma	n	5	4	2	3	1	2	2	5
Carcinoma	n	1	3	6	2	3	4	2	4
Adenoma or carcinoma	n	6	7	8	5	4	6	4	9
	(%)	13	15	18	6	8	13	9	10

The fluvoxamine and the other drug study were both life-span studies, that were performed with the same strain of hamsters at the same time in the same laboratory.

C = control
L = low dose
M = mid-dose
H = high dose

Enclosure 3

Fluvoxamine long-term rat study.

FLUVOXAMINE MALEATE - Thyroids from 2 1/2 year rat study (report 56645/4/81)

There were 5 rats with thyroid carcinomata:

Week	Animal No	Treatment	Diagnosis
Terminal	1 male	Control (T)	Solid (trabecular) carcinoma, epithelial in origin.
119	139 male	High (K)	Adenocarcinoma, epithelial in origin.
121	147 male	High (K)	c-cell adenocarcinoma.
115	148 male	High (D)	Polymorphofollicular carcinoma, epithelial in origin.
119	287 female	Middle (K)	Cystadenocarcinoma, epithelial in origin.

In addition there were 4 animals with adenomata (other than c-cell or parafollicular)

Week	Animal No	Treatment	Diagnosis
123	59 male	Low (K)	Cystadenoma
Terminal	105 male	Middle (T)	Adenoma
Terminal	160 male	High (T)	Adenoma
88	288 female	Middle (D)	Adenoma

D = Found dead K = Killed in extremis T = Terminal sacrifice

Finally there were the parafollicular adenomata which were the subject of a question from the FDA dated 3 July 1984.

The following fourteen pages give frequencies of: - rats with the various thyroid tumours, rats alive at the beginning of the week, all deaths during the week, sacrifices during the week and autopsies during the week.

2. 2-week p.o. rangefinding study in rats.

This study was not apparently previously submitted. Fluvoxamine was compared with an analog; the structure of the analog was not given and will not be discussed here. Doses were (5/sex) 20, 50, 125, 312, and 781 mg/kg/day by gavage; 10/sex were used as controls. Overt signs of intoxication were seen at HD only (limbs extended, impaired or absent righting reflex, many animals sacrificed in moribund condition). Weight gain and food consumption were very slightly decreased at 312 mg/kg during the first week only. Liver weights were increased at 312 mg/kg. Histopathology (see following page) showed dose-related liver changes (fatty metamorphosis, liver cell degeneration, necrosis) starting at 50 mg/kg. Other changes in kidney (tubular nephrosis), stomach, and spleen were confined to the high dose of 781 mg/kg.

Table: 4

Du 23000 Histopathology No. of animals affected/group

Organ/pathosis	Dose mg/kg Sex/No.of animals	Control 10♂	Control 10 ♀	20 5♂	20 5 ♀	50 5♂	50 5 ♀	125 5♂	125 5 ♀	312 5♂	312 5 ♀	781 5♂	781 5 ♀
	Death												1
Kidney: Tubular nephrosis	slight											2	
	moderate												3
Liver : focal necrosis (centrilobular)	marked											1	2
Scattered liver cell necrosis	slight							3	2	2	2	3	1
	marked												2
Liver cell degeneration	slight	2	1	2	3	1	2	3	2	1	5		
	Moderate					3		2	3	4			
	marked											5	4
fatty metamorphosis	slight	3	4	1	1	1	2	4		2			
	mild	7	5	3	3	2	2		1	2		1	
	moderate		1	1	1	2	1		3	1	3	3	2
	marked								1		2	1	2
Stomach:(cardiac part) epithelial erosions & hyperplasia.												3	2
Frank ulcers												3	2
Spleen: Splenitis with accumulations of foam cells and phagocytosis of cellular debris												5	4

Evaluation:

1) Thyroid parafollicular tumors in rats

Historical control values in Wistar rats from the sponsor's supplier were given and conformed with the values (3-10%) most commonly reported in the literature. Although the incidence in the HD fluvoxamine group (18%) was above this range, incidence values may vary from lab to lab and values of over 20% have been reported (see my review of November 30, 1984). A statistical evaluation (dated July 18, 1985) by Dr. Friedberg of BIOMETRICS (HFN-715) concluded there were "no-dose-dependent relationships in either sex attributable to fluvoxamine" regarding thyroid parafollicular adenomas. Also, as discussed my review of November 30, 1984, the ancillary data on the carcinogenic potential of fluvoxamine is not supportive of fluvoxamine being a carcinogen in thyroid. In addition, at the time of that review the cell type of the few thyroid carcinomas which were seen had not been specified; it is now stated that only one (in a HD M) was parafollicular, and thus combining this with the parafollicular adenomas does not change the conclusion originally made; i.e., that fluvoxamine is unlikely to be carcinogenic in rat thyroid.

2) Adrenal adenomas in hamsters

Control data were presented from a study on another drug performed by the same lab and at the same time as the fluvoxamine study. A value of 6% in control females was obtained; although the study duration and mortality were not stated this value is similar to the 3% reported for control females in the fluvoxamine study. The incidence in MD and HD F in the fluvoxamine study was 9-10%; however only 1 or 2 fewer animals with tumor in these groups would lower the incidence to the 6% cited above. For this reason, and for the lack of ancillary data suggestive of a carcinogenic potential of fluvoxamine in adrenal (see my review of November 30, 1984), it appears unlikely that fluvoxamine is carcinogenic in hamster adrenal.

3) Doses in segment I and II reproduction studies in rats.

It was stated that the uses of a high dose of only 80 mg/kg (which produced no overt signs of toxicity in dams, embryos, or fetuses) was based on a rangefinding study in which doses of 50 mg/kg and above produced pathological changes in liver. This is a rather unusual criterion for high dosage selection (particularly since some of these changes may merely reflect increased hepatic drug metabolism) which is usually based on some overt signs of dam toxicity. However, it should be noted that in subacute chronic toxicity studies with fluvoxamine (my review of November 30, 1984), no overt signs of toxicity were produced at the highest doses used (240 mg/kg), and weight gain and food consumption were only slightly decreased at doses above 150 mg/kg. Although ideally the doses in the reproduction studies should have been pushed to these higher levels, they may be considered adequate in that the high dose of 80 mg/kg is approximately 15 times the human therapeutic dose.

4) 2-week toxicity study in rats

This study used doses higher than previously reported in rats. In previous rat studies, the highest doses (240 mg/kg) had produced no toxic signs or deaths; these were seen here at the highest dose of 781 mg/kg. In addition, although the liver had previously been identified as a target organ of toxicity (my review of November 30, 1984), with various changes (fatty vacuolation and other degenerative/inflammatory/reactive changes) seen at doses as low as 5 mg/kg, necrosis, seen here at 125 mg/kg and above, has not been previously reported. These findings further reinforce the need for careful evaluation of the effects of fluvoxamine on liver function in man. Renal tubular nephrosis was also seen here, but only at the highest dose of 781 mg/kg; renal changes were seen in previous animal studies as discussed in my review of November 30, 1984. The foam cell accumulation in spleen at 781 mg/kg is likely related to the drug-induced phospholipidosis known to be produced by fluvoxamine and related drugs.

Recommendations:

Prior outstanding issues regarding this NDA (see my review of November 30, 1984) have been resolved, and thus this NDA is approvable. Recommendations regarding labelling may be made at the appropriate time.

Barry N. Rosloff

Barry N. Rosloff, Ph.D.

cc:
NDA ORIG.
HFN-120
HFN-120/Contrera:9/8/86
HFN-120/BNRosloff:9/3/86
DT:jgj:9/9/86:FT:9/25/86
DOC. 1131d


stat

Statistical Review and Evaluation

Date:

JUL 18 1985

NDA #:

Applicant:

Name of Drug: Fluvoxamine maleate

Documents Reviewed: Volume 1.93 of 238 dated October, 1980 and amendment dated April 12, 1985.

Background

The purpose of this study was to evaluate the oncogenicity of fluvoxamine maleate as a dietary admixture to Wistar rats for two and one half years. Dr. Barry N. Rosloff, Ph.D., (HFN-120), is the pharmacologist. He asked us to perform a statistical analysis on the incidence of adenomas of the parafollicular cells of the thyroid gland.

Design

Groups of 40 male and 40 female SPF Wistar rats were treated with 0, 10, 40 and 160-240 mg/kg/day fluvoxamine in the diet (the high dose level was initially 160 mg/kg/day, but this was increased to 200 mg/kg/day after 40 weeks and to 240 mg/kg/day after 53 weeks). The study was initially designed to last for 104 weeks, but the survival rate was good and the study was extended to 124 weeks for the males and 130 for females. All animals were observed daily for signs of ill-health or toxicity and these results were recorded weekly.

Sponsor's Analysis and Results

Fisher's exact test was used to evaluate the histological data. The incidence of the neoplastic lesions did not show any treatment or dose-dependent relationship when the incidence of the lesions was greater than 5% per group.

Reviewer's Analysis and Results

At terminal sacrifice, there were 48, 43, 38 and 63 percent survival in the control, low, middle, and high dose males, respectively. The corresponding percentages in the females were 45, 60, 38 and 53.

Adenomas of the parafollicular cells of the thyroid gland were statistically analyzed according to the paper of Peto, et. al. (IARC Monographs, Supplement 2, 1980, WHO), with the following results:

NDA

Sex	Z for Positive Dose-Response	P for Positive Dose-Response
Male	0.854	0.197
Female	1.518	0.064

In no case, was there a statistically significant positive dose-response at p=0.05. Therefore, we concur with the sponsor in that adenomas of the parafollicular cells of the thyroid gland are not dose-dependent with respect to fluvoxamine maleate.

Summary and Conclusions

This study was designed with only 40 male and 40 female rats per dose group, which was 10 rats per sex less than recommended. Otherwise, this study was properly designed to evaluate the lifetime carcinogenic potential of fluvoxamine maleate in rats. We were requested to statistically evaluate only the adenomas of the parafollicular cells of the thyroid gland. In this case, we found no dose-dependent relationships in either sex attributable to fluvoxamine maleate.

Mordecai Friedberg
Mathematical Statistician

Concur: William R Fairweather for Suresh C. Rastogi, Ph.D.

WR7 7/16/85
William R. Fairweather, Ph.D.

cc: Orig. Orig. NDA 19-189
HFN-120
HFN-120/Dr. Rosloff
HFN-710/Chron
HFN-715/Dr. Fairweather
HFN-715/Dr. Rastogi
HFN-715/Mr. Friedberg
HFN-715/DRU-2.1.1 NDA 19-189 FLUVOXAMINE MALEATE
HFN-715/MFriedberg/pls/07/05/85/34594/#1516p

Statistical Review and Evaluation

NDA #: 20-843/1S

NOV 9 1993

Applicant: Solvay Pharmaceuticals

Name of Drug: Luvox (fluvoxamine)

Documents Reviewed: Vol 1.49 (archival)

Medical Input: Gregory Dubitsky, M.D., HFD-120

Dr. Dubitsky's medical review contains the results which demonstrate that fluvoxamine is active in comparison to placebo in patients with Obsessive-Compulsive Disorder. Each of two adequate and well-controlled ten-week multicenter trials (5529 and 5534) randomized 80 patients per group (placebo and titrated active: 100-300 mg/day) for a total of 160 patients on active treatment between the two trials. Combining the two trials, 75.6% of the fluvoxamine patients and 86.9% of the placebo patients completed the trials. Standard analyses using both Observed Cases and Last Observation Carried Forward imputation produced statistically significant treatment differences on the Y-BOCS, NIMH Global, and Clinician Global Severity scales. This reviewer concurs with the conclusions from these analyses.
This document supplements the general efficacy results by presenting further descriptive analyses in an attempt to illustrate several ways of examining the change in clinical condition of those patients who took fluvoxamine.

The results presented are based upon the 120 active drug and the 134 placebo observed cases at week 10. However, denominators include patients who dropped out for any reason, thus preserving the intent to treat interpretation of the statistics.

The appendices at the end of this document present supplementary graphical illustrations of the trials' results for 10-week completers:

Pages 1a, 1b and 1c are plots of clinical outcome versus baseline for Y-BOCS, NIMH and CGI severity, respectively. Note the general improvement of both groups from baseline.

Pages 2a, 2b and 2c are bar graphs depicting the distributions of patients falling into interval categories of response based upon outcome score. Note the general shift of the fluvoxamine's group toward lower scores on each of the three scales.

Pages 3a, 3b and 3c depict empirical distribution curves for both groups. Note that the percentage of patients who score less than any particular score (on the horizontal axis) is greater in the

fluvoxamine group.

Pages 4a, 4b and 4c depict confidence intervals for the treatment effects among all 8 centers for the three major endpoints. The one outlier, center 5534_3, resulted mainly from two extremely good placebo responses.

The remainder of this document examines possible effects of baseline covariates on patients' responses.

Univariate Baseline Y-BOCS and Baseline HAM-D(17-items)

The maximum, median and minimum baseline Y-BOCS scores (Y) of all randomized patients were 38, 23, and 6, respectively. The corresponding percentiles for HAM-D baseline were 19, 9, and 0.

When active drug patients are divided between the upper and lower quartiles of their respective baseline distributions, there is no evidence that patients with more severe OCD alone or more depression alone achieve a greater change from baseline at week 10:

		Change From Baseline	
Subgroup	# patients	YBOCS	NIMH
Y-BOCS>=27	32	6.7	1.5
Y-BOCS<=20	39	4.6	1.9
HAM-D>=13	32	4.8	1.7
HAM-D<=5	32	5.6	1.7

Bivariate Baseline YBOCS and HAM-D(17-items)

The upper and lower quartiles of each of the two scales' distributions were then used to form the 4 bivariate subgroups. The following table displays the mean Y-BOCS and NIMH change from baseline at 10 weeks for each subgroup. Using **percent** change from baseline yielded similar results:

		Change From Baseline	
Subgroup	# patients	Mean Y-BOCS	Mean NIMH
H>=13, Y>=27	10	5.0	0.7
H<=5, Y<=20	19	4.2	1.8

There were not enough observations in the middle categories to assess depression-OCD baseline interaction. That is, whether the degree of response (measured by change from baseline on either scale) among the most depressed patients varies with baseline OCD and, conversely, whether the degree of response among the most severe OCD patients varies with the degree of depression. There is no evidence of differential response between the groups shown above, i.e. between the most depressed and most O-C patients and the least depressed and least O-C patients.

NIMH Categories

The following table uses the integer-valued ranges for clinical categories in order to cross classify frequency of outcome **among fluvoxamine patients** with baseline OCD severity (see attached NIMH scale). The denominators for percentages are all patients randomized to the baseline category and **bold** numbers indicate frequency of improvement:

Fluvoxamine Outcome at 10 weeks

Baseline	"Normal"	"Sub-clin"	"Clin"	"Sev"	"Very Sev"
"Sub-clin"	0	1	0	0	0
"Clin"	6(6%)	**34**(32%)	34	4	0
"Sev"	**1**(2%)	**9**(18%)	**14**(28%)	14	0
"Very Sev"	0	0	**1**(33%)	**1**(33%)	1

Using the NIMH Scale, there is a tendency for patients with worse OCD at baseline to exhibit a greater probability of some improvement (2% + 18% + 28%=**48%** vs 6% + 32%=**38%** **categorical** improvement comparing the two most prevalent baseline categories).

The following table displays frequency of change among placebo patients:

Placebo Outcome at 10 Weeks

Baseline	"Normal"	"Sub-clin"	"Clin"	"Sev"	"Very Sev"
"Clin"	**1**(1%)	**18**(17%)	60	6	0
"Sev"	0	**2**(4%)	**17**(30%)	29	1

Note that there is a similar tendency for more severe patients to have a higher probability of some improvement in NIMH category than among less severe patients. This means that some of the "baseline" effect found among the fluvoxamine patients is due to phenomena such as regression to the mean and possibly the "Hawthorne" effect from participating in the trial. Overall, 22% (35/160) of the randomized placebo patients experienced an improved NIMH category, whereas the corresponding figure was 41% (66/160) for the fluvoxamine patients. Thus, approximately 20% (absolute) more patients could be expected to improve at least one NIMH category on drug than otherwise, assuming that discontinuation of the drug in general use mirrors behavior found in the trials.

Clinical change can also be characterized by forming the frequency distribution of completers who fall into categories defining percent change from baseline using the Y-BOCS Scale depicted below.

% Change in Y-BOCS	# patients	
	Fluvoxamine	**Placebo**
<=0	29(24%)	52(39%)
0-.25	34(28%)	57(42%)
.25-.50	39(33%)	19(14%)
.50-.75	15(12%)	5(4%)
.75-1.0	3(3%)	1(1%)
Total	120	134

Greater percentages of fluvoxamine patients have greater (positive) changes from baseline than do placebo patients. Also, there is a tendency for more placebo patients to worsen during the trial.

Conclusions

1) Fluvoxamine's efficacy for OCD has been demonstrated in two independent adequate trials.

2) Various ways of examining the clinical data reveal consistent results.

3) Ultimately, approximately 20% more patients improve from baseline while on fluvoxamine as compared to placebo.

4) There does not appear to be any baseline factor which can reliably predict differential benefit among OCD patients.

David Hoberman, Ph.D.
Mathematical Statistician

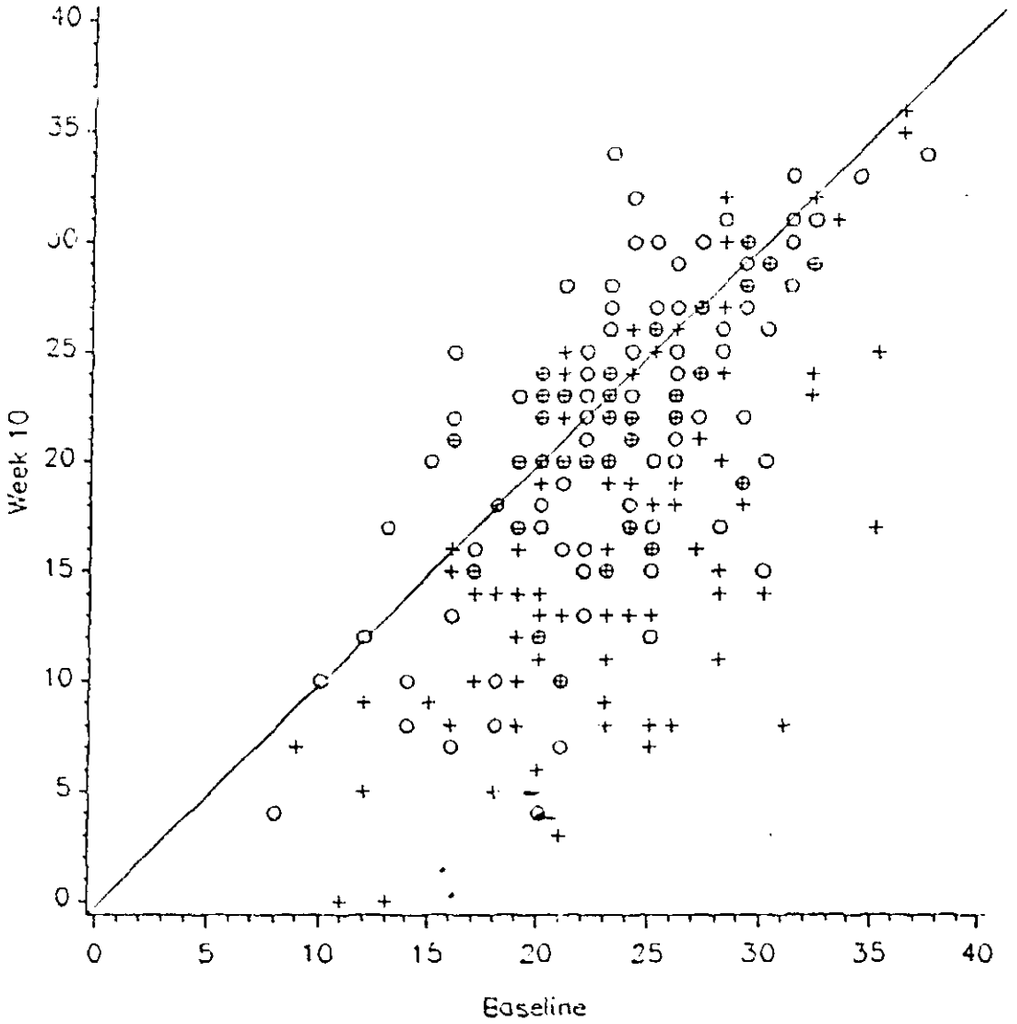
Concur: Dr. Nevius 11-9-93

Dr. Dubey 11-9-93

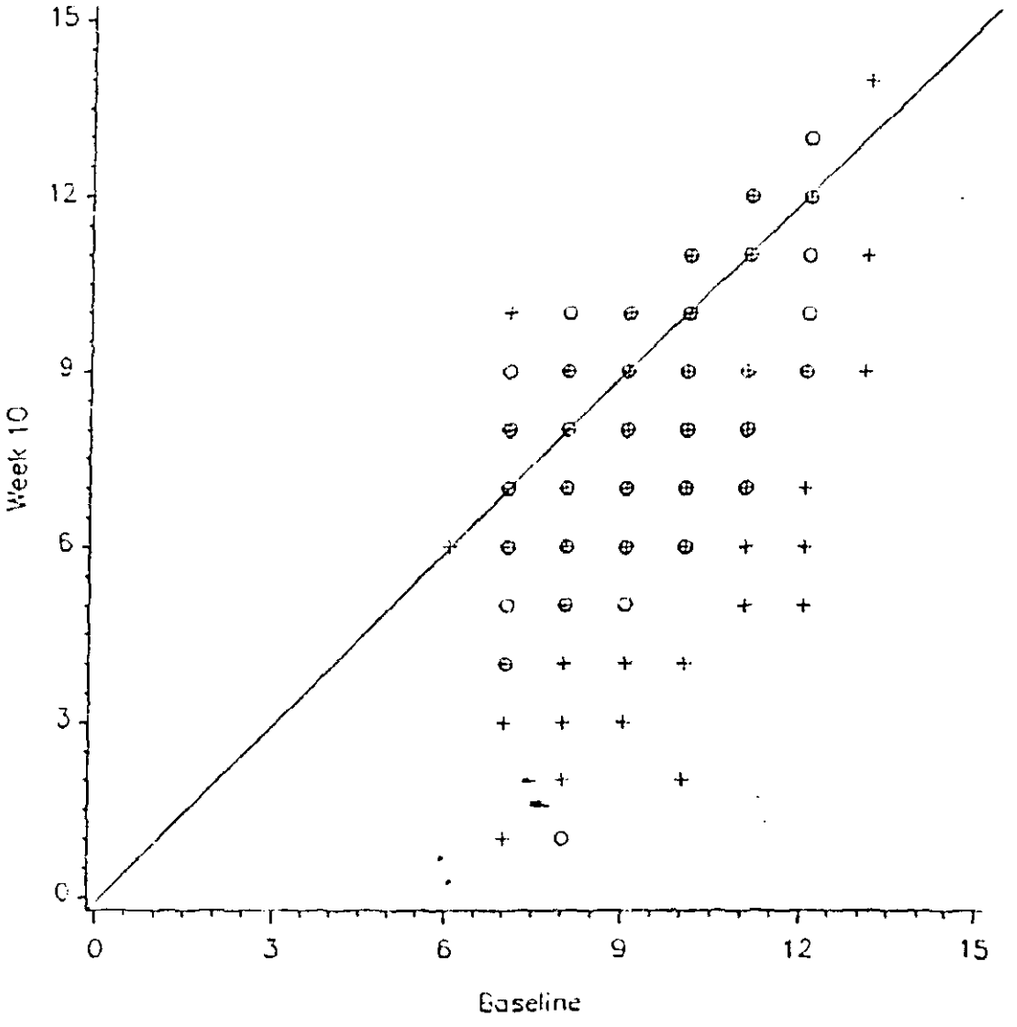
cc:
Orig NDA # 20-243
HFD-120
HFD-120/Dr. Leber
HFD-120/Dr. Dubitsky
HFD-120/Dr. Laughren
HFD-244/Dr. Lisook
HFD-713/Group 2 file
HFD-713/Dr. Hoberman
HFD-713/Dr. Dubey [file 1.3.2 NDA]
chron

This review consists of 5 pages of text and 12 figures.

Y–BOCS Total Score at Week 10
by Y–BOCS Total Score at Baseline
for Week 10 Completers
Studies H.114.5529 and H.114.5534 Combined

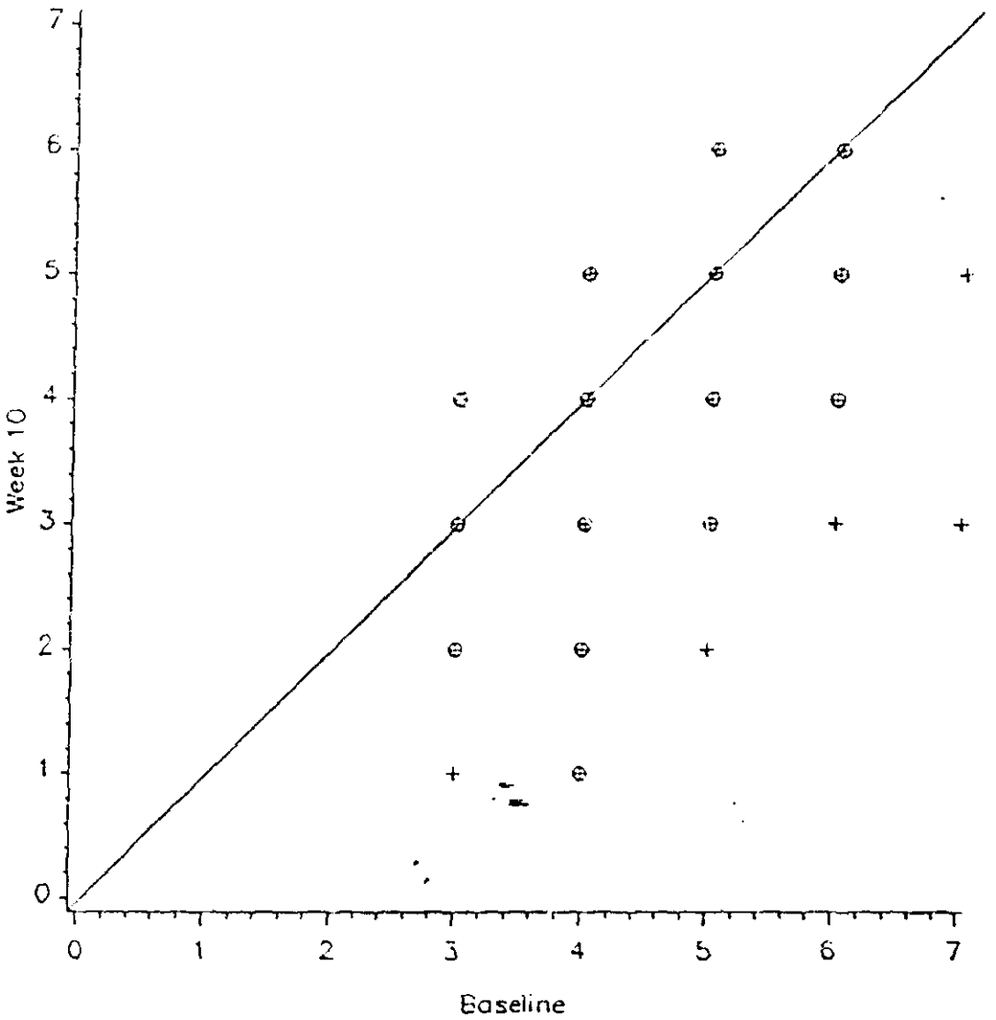


NIMH_OC Score at Week 10
by NIMH_OC Score at Baseline
for Week 10 Completers
Studies H.114.5529 and H.114.5534 Combined



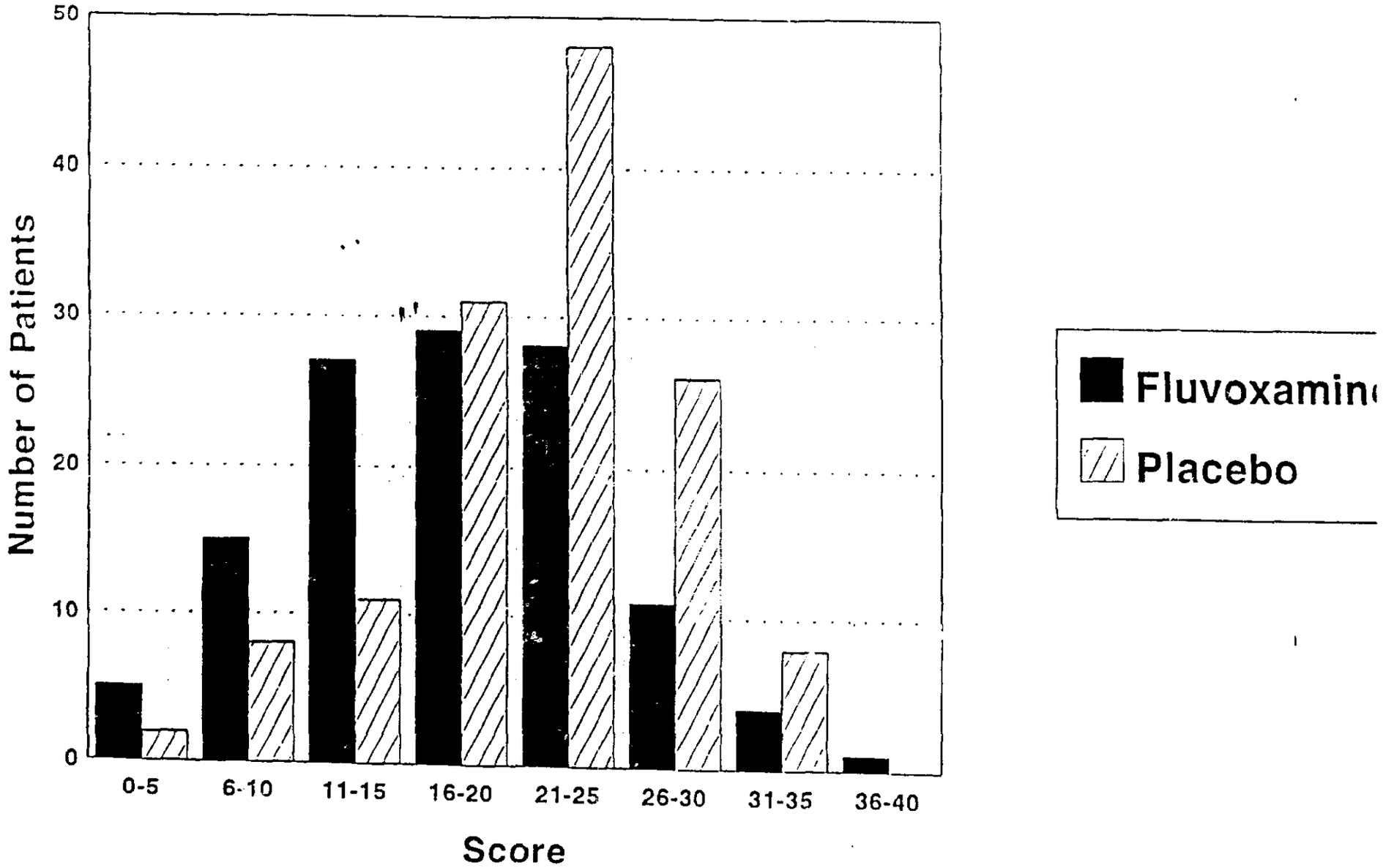
+ + + Fluvoxamine
o o o Placebo

CGI–Severity of Illness Item at Week 10 by CGI–Severity of Illness Item at Baseline for Week 10 Completers Studies H.114.5529 and H.114.5534 Combined

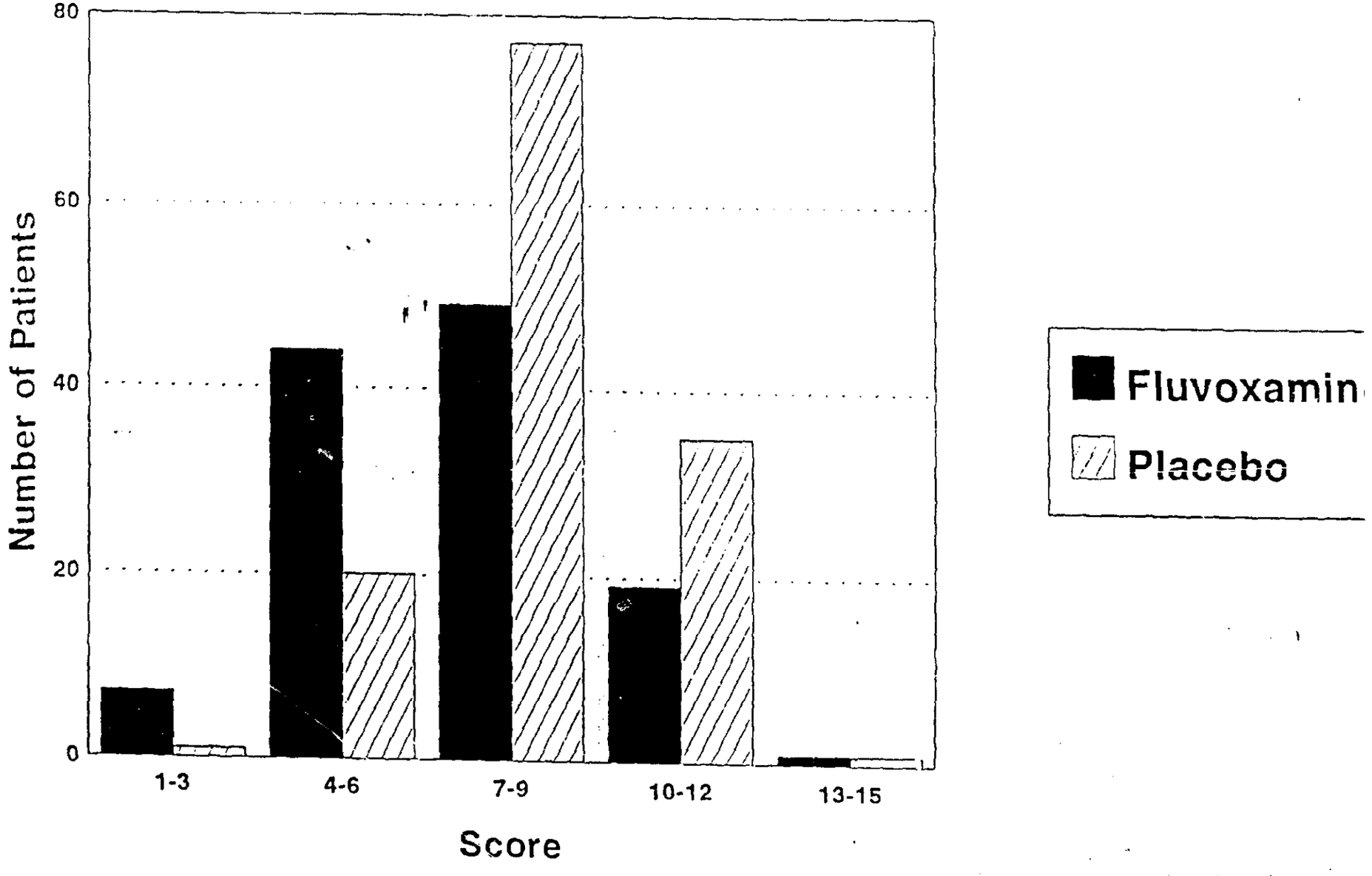


+ + + Fluvoxamine
o o o Placebo

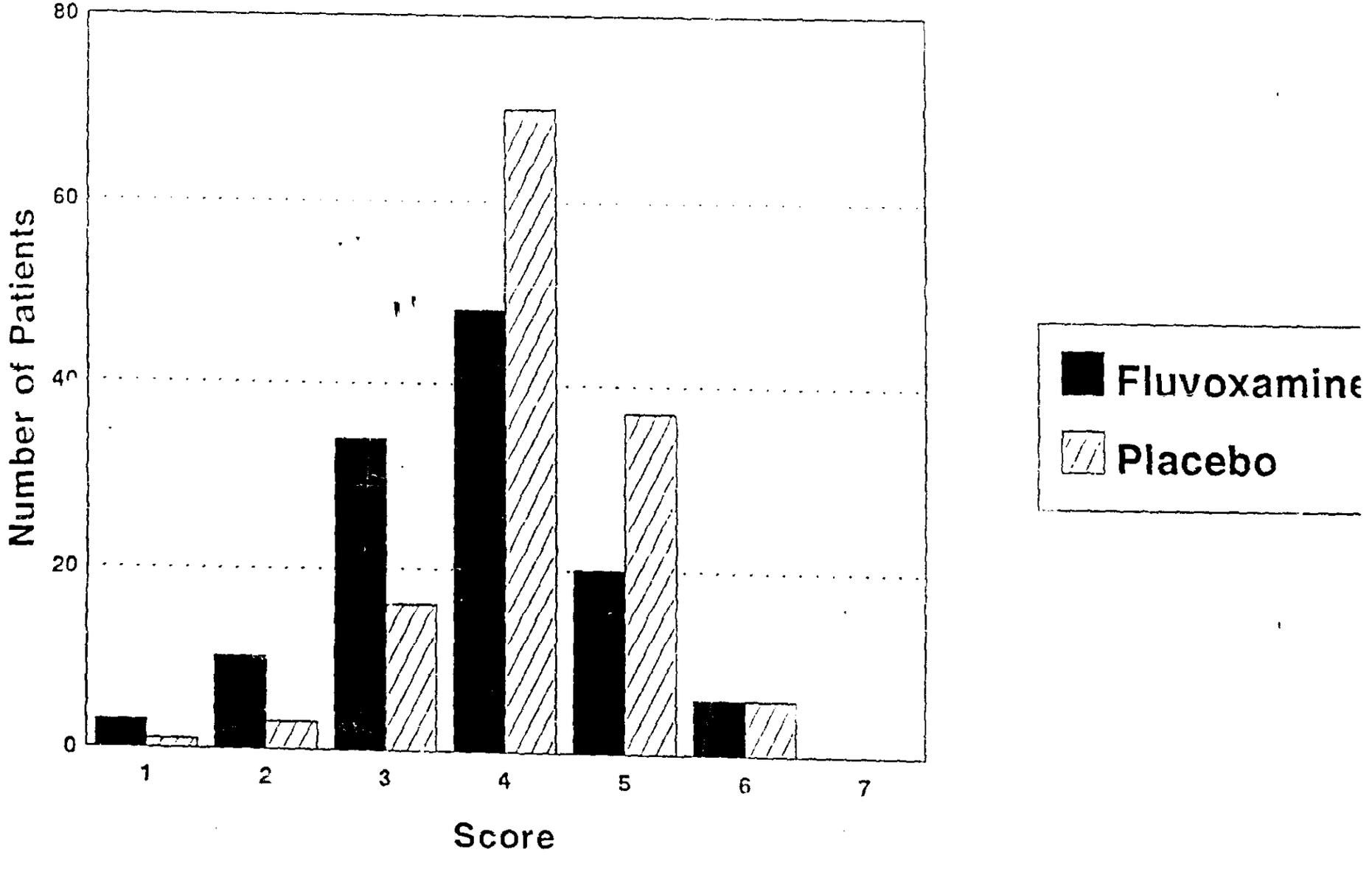
Frequency (/-)CS Total Scores at Week 10 for 10 Week Completers Studies H.114.5529 and H.114.5534



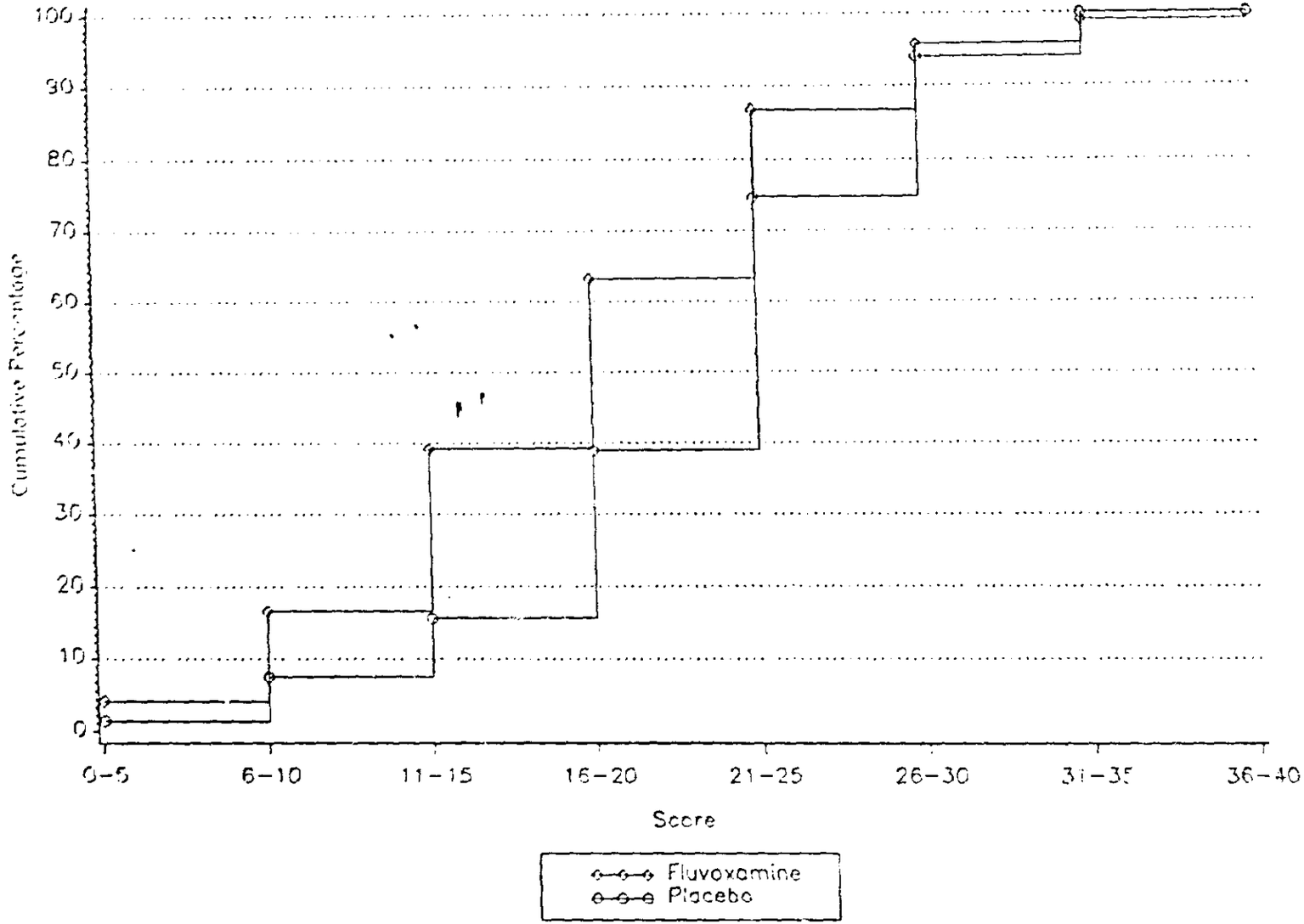
Frequency ( ) MH_OC Scores at Week 10 for 10 Week Completers Studies H.114.5529 and H.114.5534



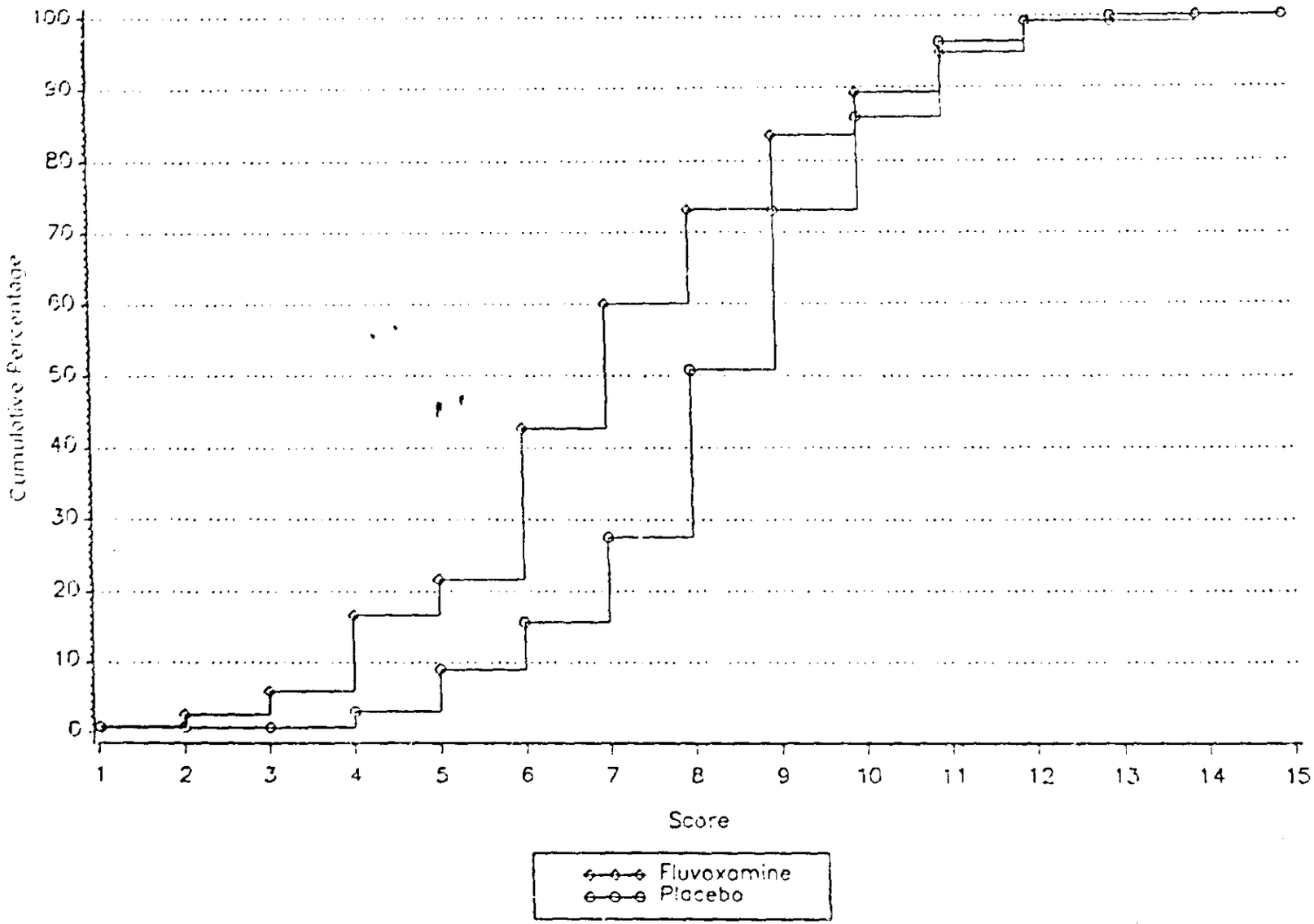
Frequency of CG ,e erity of Illness Scores at Week 10 for 10 Week Completers Studies H.114.5529 and H.114.5534



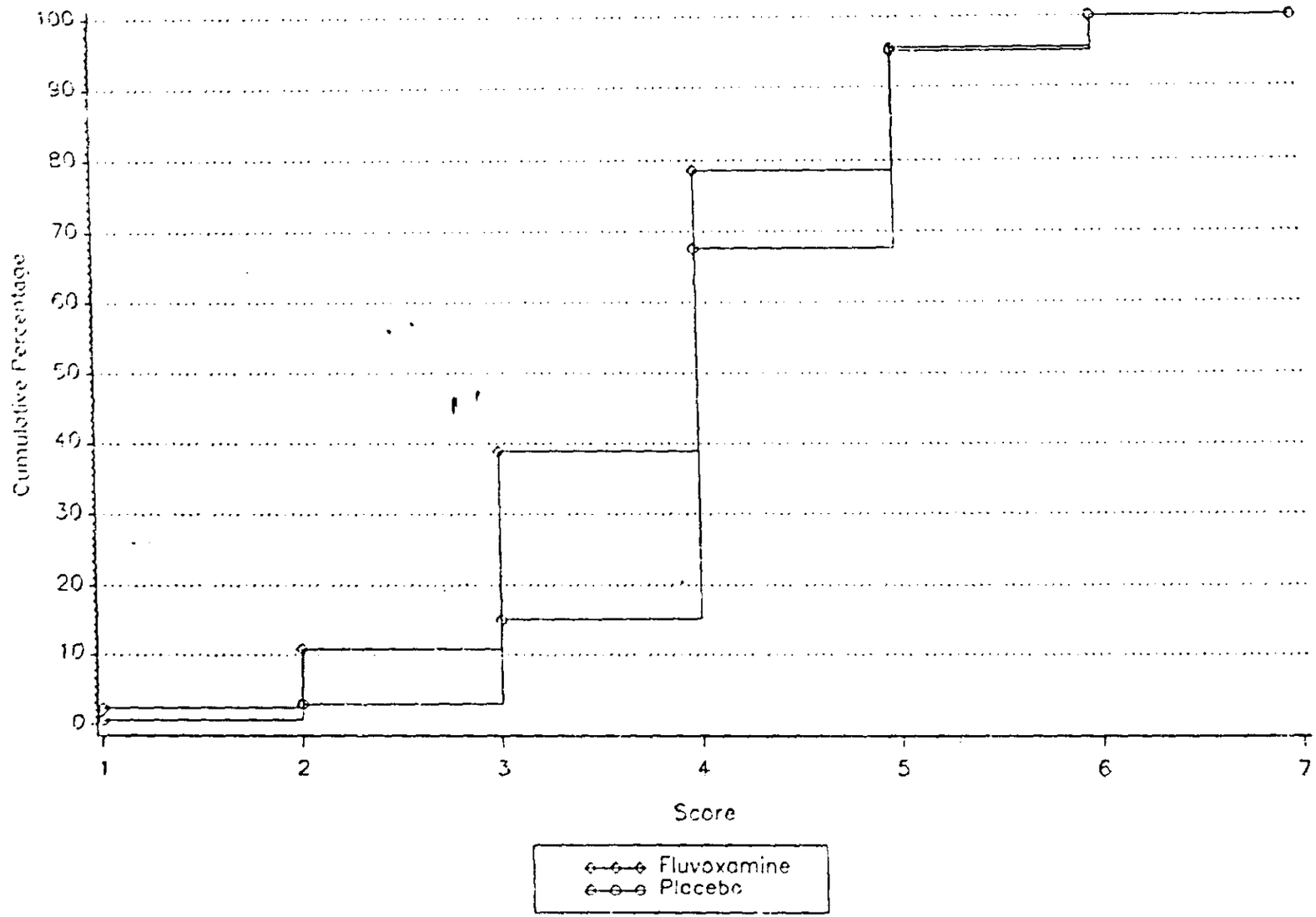
Cumulative Distribution Function of Y-BOCS Total Scores
at Week 10 for Week 10 Completers
Studies H.114.5529 and H.114.5534 Combined



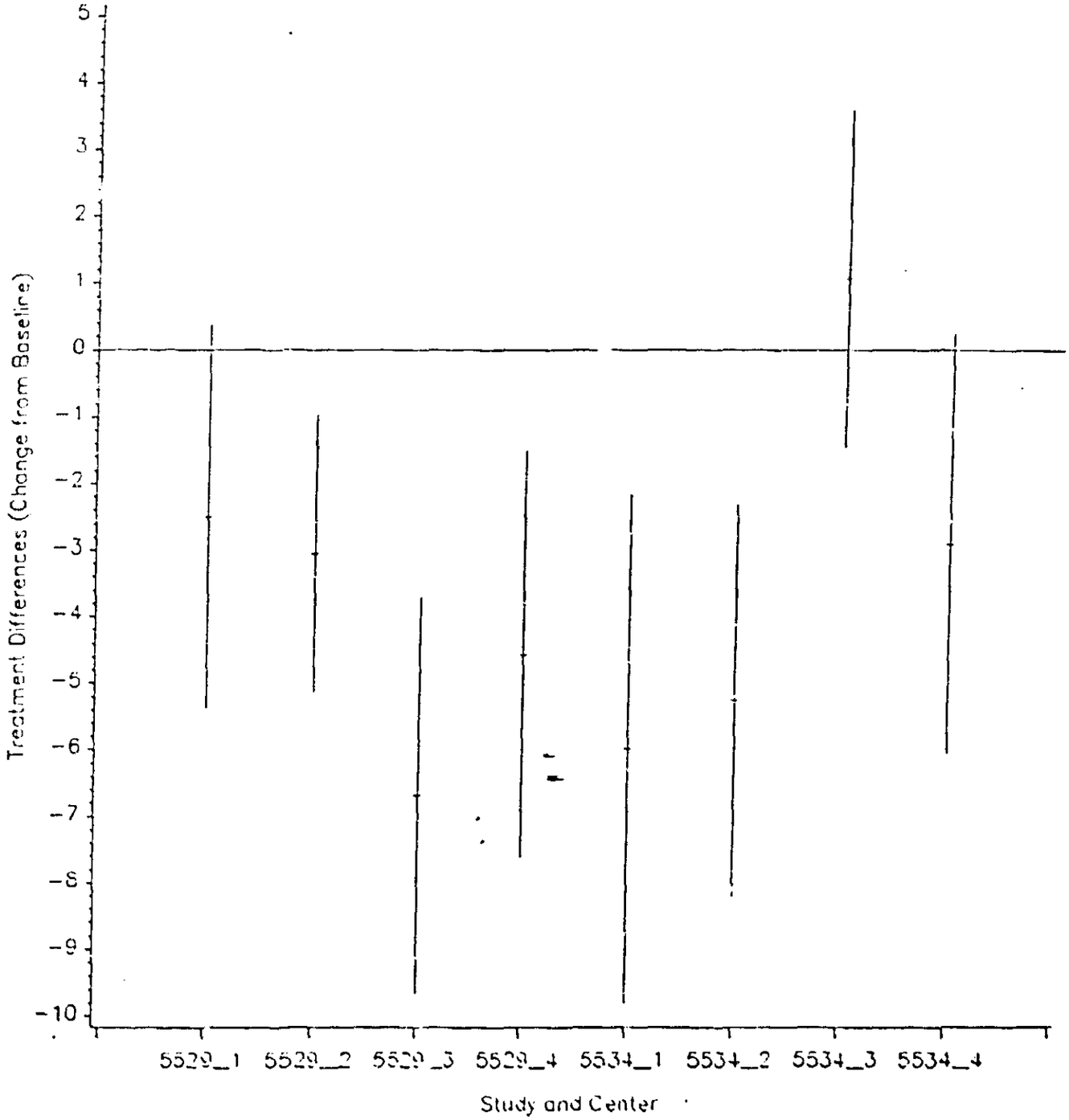
Cumulative Distribution Function of NIMH_OC Scores at Week 10 for Week 10 Completers Studies H.114.5529 and H.114.5534 Combined



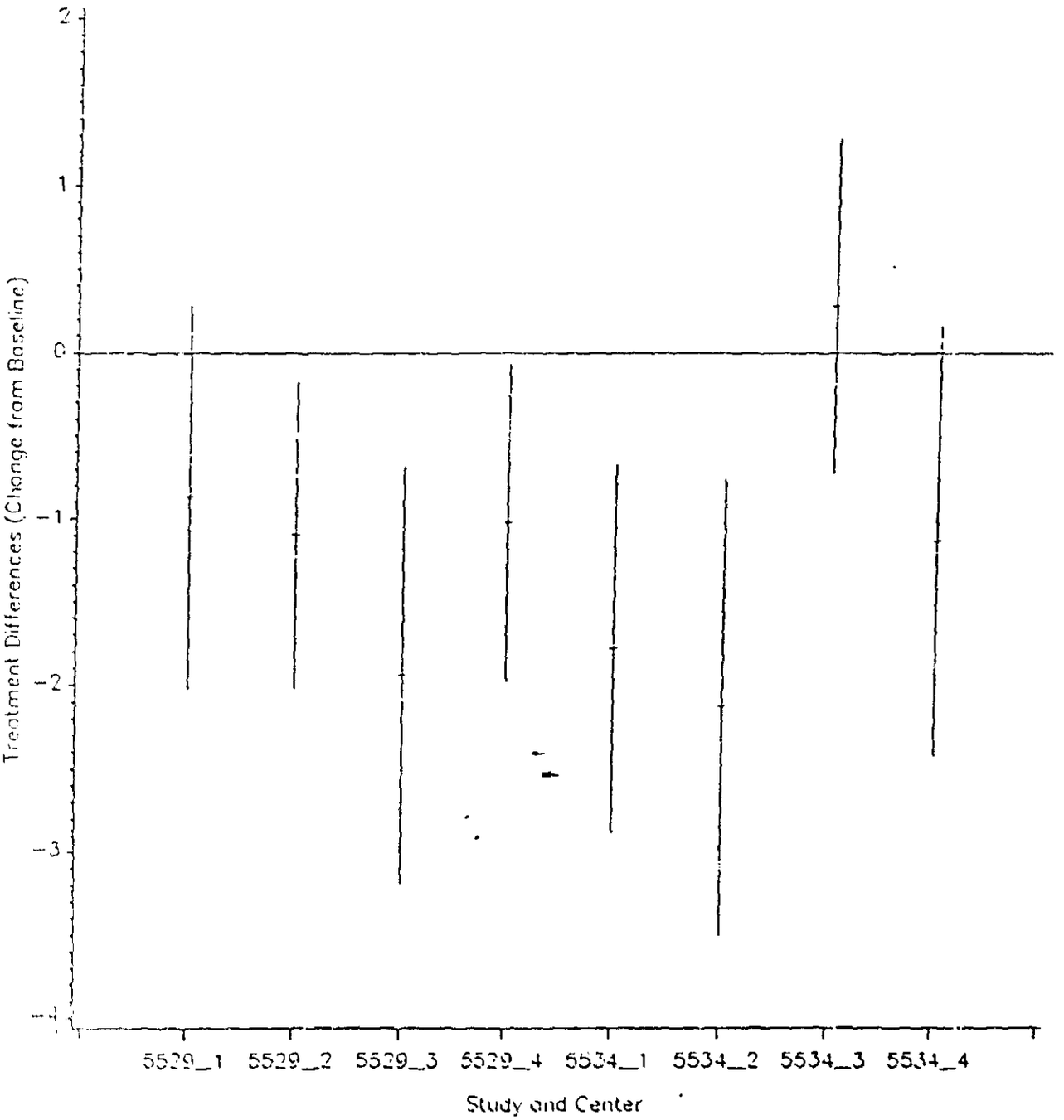
Cumulative Distribution Function of CGI–Severity of Illness Items at Week 10 for Week 10 Completers Studies H.114.5529 and H.114.5534 Combined



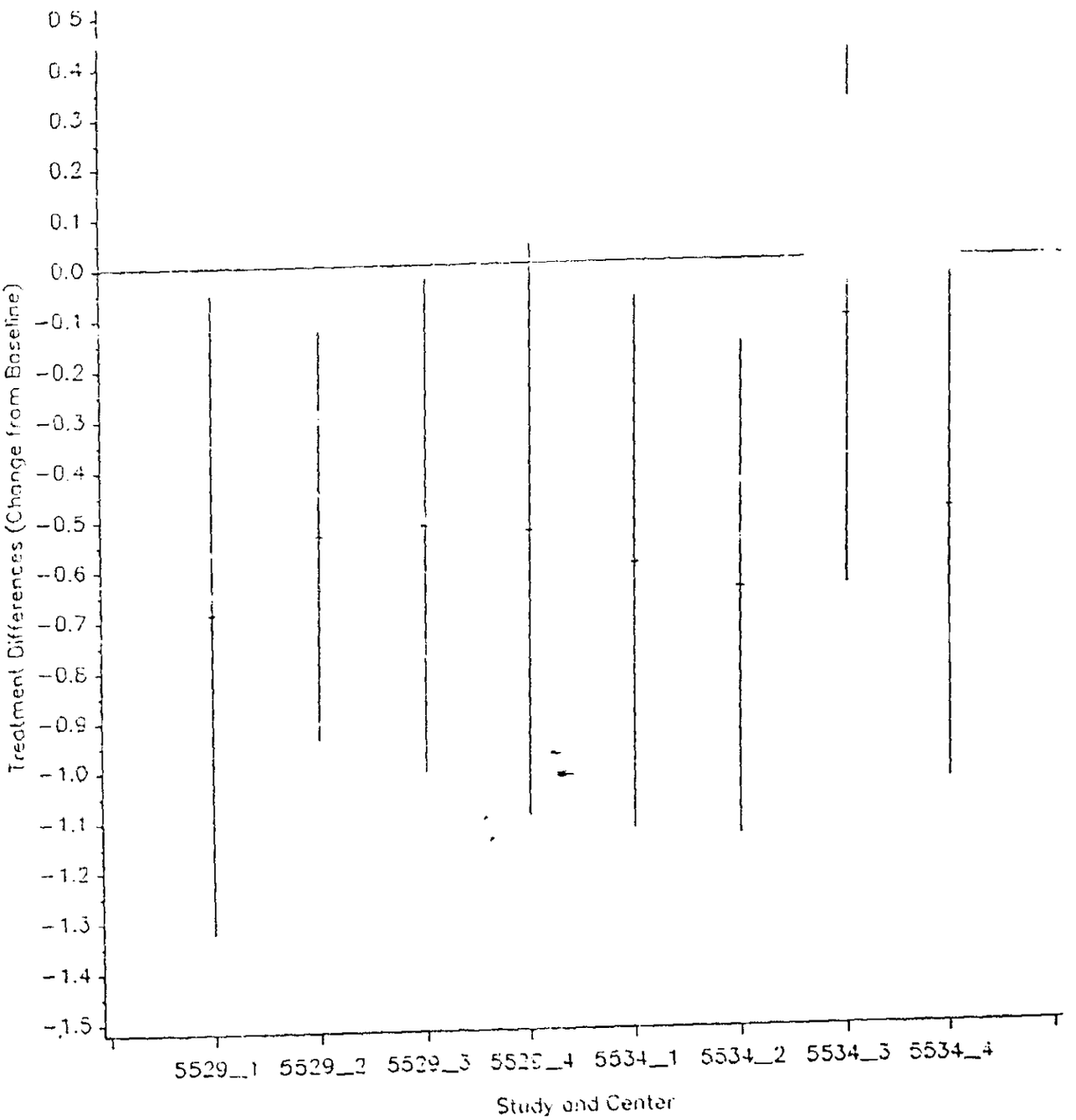
Y-BOCS Total Score Treatment Differences (Change from Baseline) at Week 10 for Week 10 Completers Studies H.114.5529 and H.114.5534 Combined



NIMH_OC Score Treatment Differences (Change from Baseline) at Week 10 for Week 10 Completers Studies H.114.5529 and H.114.5534 Combined



CGI–Severity of Illness Item Treatment Differences (Change from Baseline) at Week 10 for Week 10 Completers Studies H.114.5529 and H.114.5534 Combined



Dawn
HFD-120

Statistical Review and Evaluation

NDA: 20-243

Date: OCT 15 1993

Applicant: Solvay Pharmaceuticals
Marietta, Georgia 30062

Name of Drug: Luvox (Fluvoxamine Maleate) tablets

Documents Reviewed: Original NDA volume 1 of 1 dated 12/27/91, 'Oncogenicity of Fluvoxamine Maleate given by dietary administration to the wister rat for two and a half years' by R.L.F. Dawes (undated), and 'The effects of the dietary administration of Fluvoxamine Maleate (DU 23000) to male and female syrian hamsters during their life-span' by Richard Adams Ph.D., Study director for Bio-research consultants, Inc. (undated). Data on floppy diskette supplied by the sponsor.

I. Background: In this NDA submission two animal carcinogenicity studies, one in rats and one in hamsters, were included. These two studies were intended to assess the carcinogenicity potential of Luvox (Fluvoxamine Maleate) tablets in rats and hamsters when administered orally through dietary mixture using some selected dose levels and time periods. Dr. Berry Rosloff, HFD-120, who is the reviewing pharmacologist of this NDA requested the Division of Biometrics to perform the statistical review and evaluation of these studies. The results of this review have been discussed with Dr. Rosloff.

II. The rat study

IIa. Design: Two separate experiments, one in male and one in female rats, were conducted. In each of these experiments there were three treated groups known as low, medium, and high, and a control group. For each sex one hundred and sixty SPF Wister rats were randomly divided into equal groups of forty animals to form the treatment groups. The dose levels for treated groups were 10, 40, and 160* mg/kg/day for low, medium, and high dose group, respectively. The control groups received normal diet. The study lasted for 122** weeks for males and 128** weeks for females.

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* The high dose level was 160 mg/kg/day at the start of the test, but was increased to 200 mg/kg/day after 39 weeks, and to 240 mg/kg/day after 53 weeks.

** The study was initially designed to run for 104 weeks, but due to high survival rates, it was prolonged until a 40% survival was reached.

The animals were observed daily for signs of ill-health or toxicity. The results being recorded weekly. The time of onset, dimension and location of palpable tumors were recorded monthly starting after 24 weeks of dosing. A complete histopathological examination was conducted on all animals died during the study, killed moribund, or sacrificed at the end of the study.

IIb. Snonsor's analyses

Survival data analysis: Stem and leaf diagram (Tukey J.W., Exploratory data analysis, Addison-Wesley, Reading, Massachusetts, 1977) giving times in weeks to deaths during the study were presented for all treatment groups in male mice. Box and whisker chart (Tukey J.W., 1977) showing distributions of weeks of deaths during the study were plotted for all treated groups seperately for each sex. It was concluded that there was no statistically significant difference in the mortality among treament groups.

Tumor data analyses: It was concluded that neoplastic lesions with greater than 5% incidence rate per group did not show any treatment or dose dependent relationship. No statistical analyses were performed on the tumor data.

IIc. Reviewer's analyses

The reviewer independently performed analyses on the survival and tumor data. The survival data were analyzed using the method described in the papers of Cox (Regression models and life tables, Journal of the Royal Statistical Society, B, 34, 187-220, 1972), and of Gehan (A generalized Wilcoxon test for comparing arbitrarily singly censored samples, Biometrika, 52, 203-223, 1965). The tumor data were analyzed using the methods described in the paper of Peto (Guidelines for sample sensitive significance test for carcinogenic effects in long-term animal experiments, Long term and short term screening assays for carcinogens: A critical appraisal, International agency for research against cancer monographs, Annex to supplement, World Health Organization, Geneva, 311-426, 1980), and the method of exact permutation trend test developed by the Division of Biometrics. The data used in the reviewer's analysis were provided by the sponsor on a floppy diskette.

Survival data analyses: The intercurrent mortality data of the rat study are given in Table 1. The plots of Kaplan-Meier estimates of the survival distributions of the treatment groups for male and female rats are given in Figures 1a and 1b, respectively. The homogeneity of survival distributions of all four groups (Control, Low, Medium, and High) was tested separately for male and female rats using the Cox test and the Generalized Wilcoxon test.

The tests did not show any statistically significant positive

linear trend or increment in mortality in the treatment groups when compared with the control. The p-values of the trend and the pairwise tests are given in Tables 2a and 2b.

Tumor data analyses: The reviewer performed the trend test on data of all tumor types and the pairwise comparisons of the treated groups with the control for some selected tumor types. Since the sponsor classified the tumor types as 'cause of death' or 'not a cause of death', following Peto et al. (1980), the reviewer applied the 'death rate method' and the 'prevalence method', respectively for testing positive linear trend in these two categories of tumor types. For tumor types occurring in both categories (i.e. same tumor found as cause of death for some animals and not cause of death for some other animals) a combined test was performed. The exact permutation trend test was used to calculate the p-values of all trend tests, except for tumors which were found in both categories, in which cases the continuity corrected normal test was used. The scores used were 0, 10, 40, and 200 for control, low, medium, and high dose groups, respectively. The score 200 for the high dose group is the average of 160, 200, and 240. The time intervals used were 0-52, 53-78, 79-100, 101-114, 115-122 weeks, and terminal sacrifice.

The incidence rates of tumor types with p-values less than .05 are listed below.

		Tumor rate				P-value	
Sex	Organ/Tumor	C	L	M	H	Trend	Pairwise
		40	40	40	40		
Male	Pancreas/Adenocarcinoma	0	0	0	3	.0109	.0656 (C,H)
Female	Thyroid/Adenoma Parafollicular cell	2	4	3	7	.0466	.1041 (C,H)

Multiple testing adjustment: The rule proposed by Haseman was used to adjust the effect of multiple testings. Haseman's rule states that in order to keep the false-positive rate at the nominal level of approximately five percent, tumor types with a spontaneous tumor rate of no more than one percent should be tested at .05 level, otherwise the level should be set at .01 (Haseman, (1983), A re-examination of false-positive rates for carcinogenesis studies, Fundamental and Applied Toxicology, 3: 334-339).

On the basis of Haseman's rule the positive linear trend in adenocarcinoma in pancreas is considered to be statistically significant. The incidence rates and P-values of tumor types tested for positive linear trends and pairwise comparisons are given in Table 3.

III. The Hamster study

IIa. Design: Two separate experiments, one in male and one in female Hamsters, were conducted. In each of these experiments there were three treated groups known as low, medium, and high, and a control group. For each sex two hundred and eighty five Syrian golden hamster were randomly divided into four treatment groups. In both sexes the three treated groups had 60 animals each while the control group had 105 animals. The dose levels for treated groups were 9, 36, and 144* mg/kg/day for low, medium, and high dose groups, respectively. The control groups received normal diet. The study lasted for 111 weeks for males, and 83 weeks for females. In both sexes an interim sacrifice of 15 animals from control and 10 animals from each treated group was performed between week 51-54.

The animals were checked twice daily for any abnormal physical or behavioral changes. A physical examination for palpable masses and other general conditions were conducted every week. A complete histopathological examination was conducted on all animals died during the study, killed moribund, sacrificed intermily or at the end of the study.

IIb. Snonsor's analyses

Survival data analysis: Cumulative percentage mortality tables and cumulative percentage survival plots of both male and female hamsters were presented. It was concluded that there was no adverse effect of fluvoxamine treatment on mortality rates. No other statistical analyses were presented.

Tumor data analyses: Tumor data were analyzed using the methods described in the paper of Peto et al. (1980).

The tests did not show any statistically significant positive linear trend for tumor types tested in either sex.

IIc. Reviewer's analyses

The reviewer independently performed analyses on the survival and tumor data. In the survival data analysis the methods described in the papers of Cox (1972), and of Gehan (1965) were used. The tumor data analyses were done using the method described in the paper of Peto et al. (1980), and the method of exact permutation trend test, developed by the Division of Biometrics. The data used in the

* The high dose level was 144 mg/kg/day at the start of the study, but was increased to 180 mg/kg/day on day 98, and to 240 mg/kg/day on day 133.

reviewer's analysis were provided by the sponsor on a floppy diskette.

Survival data analyses: The intercurrent mortality data of the hamster study are given in Table 4. The plots of Kaplan-Meier estimates of the survival distributions of the treatment groups for male and female hamsters are given in Figures 2a and 2b, respectively. The homogeneity of survival distributions of all four groups (Control, Low, Medium, and High) was tested separately for male and female hamsters using the Cox test and the generalized Wilcoxon test.

The tests did not show any statistically significant positive linear trend or increment in mortality in the treatment groups when compared with the control. The p-values for the positive linear trend tests and the pairwise tests are given in Tables 5a and 5b.

Tumor data analyses: The reviewer performed the trend test on data of all tumor types and the pairwise comparisons of the treated groups with the control for some selected tumor types. Since the sponsor classified the tumor types as 'cause of death' or 'not a cause of death', following Peto et al. (1980), the reviewer applied the 'death rate method' and the 'prevalence method', respectively for testing positive linear trend in these two categories of tumor types. For tumor types occurring in both categories (i.e. same tumor found as cause of death for some animals and not cause of death for some other animals) a combined test was performed. The exact permutation trend test was used to calculate the p-values of all trend tests, except for tumors which were found in both categories, in which cases the continuity corrected normal test was used. The scores used were 0, 9, 36, and 188 for control, low, medium, and high dose groups, respectively. The score 188 for the high dose group is the average of 144, 180, and 240. The time intervals used were 0-52, 51-54 (interim sacrifice), 53-78, 79-100, 101-111 weeks, and terminal sacrifice for males, and 0-52, 51-54 (interim sacrifice), 53-72, 73-83 weeks, and terminal sacrifice for females.
The incidence rates of tumor types with p-values less than .05 are listed below.

		Tumor rate				P-value	
Sex	Organ/Tumor	C	L	M	H	Trend	Pairwise
		105	60	60	60		
Female	Spleen/Hemangioma	0	0	1	2	.0365	.1354

Multiple testing adjustment: On the basis of Haseman's rule the positive linear trend in spleen hemangioma is considered to be statistically significant. The incidence rates and P-values of tumor types tested for positive linear trends and pairwise comparisons are given in Table 6.

IV. Evaluation of validity of the design

The reviewer's analyses showed that except for pancreas adenocarcinoma in male rats and spleen hemangioma in female hamsters none of the tested tumor types either in the rat or in the hamster study showed statistically significant positive linear trend. However, before drawing the conclusion that the drug is not carcinogenic in rats or hamsters, it is important to look into the following two issues as having been pointed out in the paper by Haseman (Statistical issues in the design, analysis and interpretation of animal carcinogenicity studies, Environmental Health Perspectives, Vol. 58, pp 385-392, 1984).

(i) Were enough animals exposed, for a sustained amount of time, to the risk of late developing tumor?
(ii) Were dose levels high enough to pose a reasonable tumor challenge to the animals?

There is no consensus among experts regarding the number of animals and length of time at risk, although most carcinogenicity studies are designed to run for two years with fifty animals per treatment group.

The following are some rules of thumb regarding these two issues as suggested by experts in this field:

Haseman (Issues in carcinogenicity testing: Dose selection, Fundamental and Applied Toxicology, Vol. 5, pp 66-78, 1985) has done an investigation on the first issue. He gathered data from 21 studies using Fischer 344 rats and B6C3F1 mice conducted at the National Toxicology Program (NTP). It was found that, on an average, approximately 50% of the animals in the high dose group survived the two-year study period. Also, in a personal communication with Dr. Karl Lin of Statistical Application and Research Branch, Division of Biometrics, Haseman suggested that, as a rule of thumb, a 50% survival of 50 initial animals in the high dose group, between weeks 80-90, would be consider as a sufficient number and adequate exposure.

In addition Chu, Cueto and Ward (Factors in the evaluation of 200 national cancer institute carcinogen bioassay, Journal of Toxicology and environmental Health. Vol. 8, pp 251-280, 1981), suggested that " To be considered adequate, an experiment that has not shown a chemical to be carcinogenic should have groups of animals with greater than 50% survival at one-year."

It appears, from these three sources, that the proportions of survival at 52 weeks, 80-90 weeks, and two years are of interest in determining the adequacy of exposure and number of animals at risk.

Regarding the question of adequate dose levels, it is generally

accepted that the high dose should be close to the MTD (maximum tolerated dose). In the paper of Chu, Cueto and Ward (1981), the following criteria are mentioned for dose adequacy.

i) "A dose is considered adequate if there is a detectable loss in weight gain of up to 10% in a dosed group relative to the controls."
ii) "The administered dose is also considered an MTD if dosed animals exhibit clinical signs or severe histopathologic toxic effects attributed to the chemical."
iii) "In addition, doses are considered adequate if the dosed animals show a slight increased mortality compared to the controls."

We will now investigate the validity of the experimental designs of the Luvox rat and hamster carcinogenicity studies, in the light of the above guidelines.

Rat study

The following are summary survival data of rats in the high dose group.

	End of 52 weeks	End of 85 weeks
Male	100%	97.5%
Female	100%	92.5%

Based on the survival criteria mentioned above, it can be concluded that enough rats in both sexes were exposed to the drug for a sufficient amount of time.

The following are summary data of body weight gains of the rat study.

		Mean body weight(gms)			
Sex	Group	Beginning of study	End of study	Weight gain	Percentage of Control
Male	Control	98.00	391.00	293.00	
	Low	98.00	383.00	285.00	97.27
	Medium	97.00	407.00	310.00	105.80
	High	97.00	360.00	263.00	89.76
Female	Control	88.00	274.00	186.00	
	Low	86.00	266.00	180.00	96.77
	Medium	87.00	257.00	170.00	91.39
	High	87.00	241.00	154.00	82.79

Therefore, relative to the control, male and female rats in the high dose group had decrements of body weight gain equal to 10.24% and 17.21%, respectively.

The mortality rates at the end of the experiment are as follows:

	Control	Low	Medium	High
Male	52.50%	55.00%	60.00%	37.50%
Female	55.00%	40.00%	60.00%	47.50%

In both sexes the morality rates of the high dose group are lower than those of the control.

Thus, from the weight gain criterion it can be concluded that the used high dose was somewhat over MTD. However, to draw any final conclusion in this regard all clinical signs and histopathological effects must be taken into consideration.

Hamster study

The following are summary survival rates* data of rats in the high dose group.

	End of 52 weeks	End of 83 weeks
Male	98%	96%
Female	96%	34%

Based on the survival criterion Haseman proposed, it is concluded that not enough female hamsters were exposed to the drug for a sufficient amount of time.

The following are summary data of body weight gains in the hamster study.

		Mean body weight(gms)			
Sex	Group	Beginning of study	End of study	Weight gain	Percentage of Control
Male	Control	93.10	124.90	31.80	
	Low	93.10	126.30	33.20	104.40
	Medium	94.20	130.00	35.80	112.57
	High	93.50	127.40	33.90	106.60
Female	Control	87.40	143.50	56.10	
	Low	87.90	144.20	56.30	100.34
	Medium	88.40	145.60	57.20	101.96
	High	87.70	146.40	58.70	104.63

Therefore, relative to the animals in the control group the animals in high dose group in both sexes had increments in body weight gain of 6.6% and 4.63% in male and female, respectively.

The mortality rates* at the end of the experiment are as follows:

	Control	Low	Medium	High
Male	70%	76%	56%	66%
Female	68%	62%	58%	66%

* These rates were calculated excluding the animals killed in the interim sacrifice during weeks 51-54.

In both sexes the morality rates in the high dose group at the end of the experiment are lower when compared with the controls.

Thus, from the body weight gain and the mortality criteria it can be concluded that the used high dose in both sexes is below the MTD. However, to draw any final conclusion in this regard all clinical signs and histopathological toxic effects must be taken into consideration.

V. Summary

The rat study: No statistically significant positive linear trend or differences in mortality among the treatment groups were detected. Adenocarcinoma in pancreas in male rats showed a statistically significant (at .05 level) positive linear trend.

Based on the survival data it can be concluded that enough rats in both sexes were exposed to the drug for a sufficient amount of time. From the weight gain criterion it can be concluded that the used high dose was somewhat over MTD. However, to draw any final conclusion in this regard all clinical signs and histopathological effects must be taken into consideration.

The hamster study: The tests did not show any statistically significant positive linear trend or differences in mortality among the treatment groups.

Spleen hemangioma in female hamsters showed a statistically significant (at .05 level) positive linear trend.

Based on the survival data, it is concluded that not enough female hamsters were exposed to the drug for a sufficient amount of time. From the body weight gain and the mortality criteria it can be concluded that the used high dose in both sexes is below MTD. However, to draw any final conclusion in this regard all clinical signs and histopathological toxic effects must be taken into consideration.

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HFD-715/SARB Chron
HFD-715/DRU 2.1.1 NDA 20-184 Luvox Rat and Hamster carcinogenicity studies.
HFD-502/Assistant Director (Pharmacology)
HFD-715/Diskette Rahman-2/LUVOX.CAR
HFD-400/Dr. Contrera

Table 1

Intercurrent mortality rates in rat study

Sex	Time(wks)	Control	Low	Medium	High
MALE					
	0 - 52	0/ 40 (0.00)	0/ 40 (0.00)	0/ 40 (0.00)	0/ 40 (0.00)
	53- 78	4/ 40 (10.00)	4/ 40 (10.00)	1/ 40 (2.50)	1/ 40 (2.50)
	79-100	5/ 36 (22.50)	6/ 36 (25.00)	9/ 39 (25.00)	0/ 39 (2.50)
	101-114	6/ 31 (37.50)	8/ 30 (45.00)	8/ 30 (45.00)	6/ 39 (17.50)
	115-122	6/ 25 (52.50)	4/ 22 (55.00)	6/ 22 (60.00)	8/ 33 (37.50)
	TERM. SACR	19/ 40 (47.50)	18/ 40 (45.00)	16/ 40 (40.00)	25/ 40 (62.50)
FEMALE					
	0 - 52	0/ 40 (0.00)	0/ 40 (0.00)	0/ 40 (0.00)	0/ 40 (0.00)
	53- 78	1/ 40 (2.50)	1/ 40 (2.50)	3/ 40 (7.50)	2/ 40 (5.00)
	79-100	6/ 39 (17.50)	4/ 39 (12.50)	6/ 37 (22.50)	4/ 38 (15.00)
	101-114	11/ 33 (45.00)	9/ 35 (35.00)	7/ 31 (40.00)	11/ 34 (42.50)
	115-122	4/ 22 (55.00)	2/ 26 (40.00)	8/ 24 (60.00)	2/ 23 (47.50)
	TERM. SACR	18/ 40 (45.00)	24/ 40 (60.00)	16/ 40 (40.00)	21/ 40 (52.50)

Note: Except the TERM. SACR. row, an entry of this table =number of animals dying or sacrificed in the time interval/number of animals entering the time interval. An entry in parenthesis = cumulative mortality rate;i.e. cumulative percent of animals dying up to the end of the time interval. An entry in the TERM. SACR. row = number of animals surviving to terminal sacrifice / initial number of animals. An entry in parenthesis in this row = percent of animals (of the initial number) surviving to terminal sacrifice.

Table 2a

P-values of tests for homogeneity and positive linear trend in mortality in rat study

Test of homogeneity

Sex	Test	P-value (One tail Chi-Sqr.)
Male	Cox	.1316
	Wilcoxon	.0733
Female	Cox	.4612
	Wilcoxon	.6318

Test of Positive linear trend

Sex	Test	P-value (One tail Normal)
Male	Cox	.9853
	Wilcoxon	.9938
Female	Cox	.5999
	Wilcoxon	.5930

Table 2b

P-values of pairwise tests for the differences in mortality between treatment groups in rat study

Male rats

PAIRWISE COMPARISONS (1 D.F. CHI-SQUARES, WITH CONT CORR) DSNAME: B:LTA.MRT

GROUP		EXACT ONE TAIL TEST	2X2 CHI-SQUARE USING N IN DEN	DIRECTION OF 2X2 CHI-SQ	COX'S TEST EXACT INVERSE	COX'S TEST CONSERVATIVE	GENERALIZED K/W ANALYSIS EXACT INVERSE	GENERALIZED K/W ANALYSIS CONSERVATIVE
0 VS. 1	CHISQ		.0000	POS	.0132	.0132	.0706	.0706
	PROB	.5000	1.0000		.9085	.9086	.7905	.7905
0 VS. 2	CHISQ		.2032	POS	.1351	.1349	.1288	.1287
	PROB	.3262	.6522		.7132	.7134	.7196	.7198
0 VS. 3	CHISQ		1.2626	NEG	2.2214	2.2156	3.6024	3.5910
	PROB	.1305	.2612		.1361	.1366	.0577	.0581
1 VS. 2	CHISQ		.0512	POS	.0000	.0000	.0068	.0068
	PROB	.4106	.8211		.9983	.9983	.9342	.9343
1 VS. 3	CHISQ		1.8102	NEG	3.4498	3.4325	5.5568	5.5243
	PROB	.0891	.1785		.0633	.0639	.0184*	.0188*
2 VS. 3	CHISQ		3.2020	NEG	4.7088	4.6856	6.5054	6.4716
	PROB	.0365*	.0735		.0300*	.0304*	.0108*	.0110*

Female rats

PAIRWISE COMPARISONS (1 D.F. CHI-SQUARES, WITH CONT CORR) DSNAME: B:LTA.FRT

GROUP		EXACT ONE TAIL TEST	2X2 CHI-SQUARE USING N IN DEN	DIRECTION OF 2X2 CHI-SQ	COX'S TEST EXACT INVERSE	COX'S TEST CONSERVATIVE	GENERALIZED K/W ANALYSIS EXACT INVERSE	GENERALIZED K/W ANALYSIS CONSERVATIVE
0 VS. 1	CHISQ		1.2531	NEG	.9682	.9656	.8808	.8794
	PROB	.1316	.2630		.3251	.3258	.3480	.3484
0 VS. 2	CHISQ		.0512	POS	.0098	.0098	.0138	.0138
	PROB	.4106	.8211		.9211	.9211	.9065	.9065
0 VS. 3	CHISQ		.2001	NEG	.1860	.1859	.2432	.2431
	PROB	.3275	.6546		.6662	.6664	.6219	.6220
1 VS. 2	CHISQ		2.4500	POS	1.9671	1.9604	1.7269	1.7234
	PROB	.0585	.1175		.1608	.1615	.1888	.1893
1 VS. 3	CHISQ		.2032	POS	.1191	.1189	.1397	.1396
	PROB	.3262	.6522		.7301	.7303	.7086	.7087
2 VS. 3	CHISQ		.8045	NEG	.5466	.5482	.4773	.4771
	PROB	.1849	.3697		.4589	.4590	.4896	.4897

Table 3

Tumor rates and P-values of the tested tumor types for positive linear trend test and pairwise comparisons in rat study

Organ/tumor	Tumor rates				P-value	
	C	L	M	H		
Male	40	40	40	40	Trend	Pairwise
Adrenal/Pheochromocytoma	3	1	2	3	.2754	
Pancreas/Adenocarcinoma	0	0	0	3	.0109	.0656 (C,H)
Skin/Lipoma	0	1	2	2	.2069	
Skin/Lymphosarcoma	0	0	0	2	.0801	
Spleen/Splenoma	0	0	1	1	.2331	
Testis/Leydig cell tumor	0	3	3	0	.9201	.1008 (C,M)
Thyroid/Adenocarcinoma	0	0	0	2	.1014	
Thyroid/Adenoma	0	1	1	1	.2392	
Thyroid/Adenoma parafollicular cell	3	4	6	7	.2904	.2781 (C,H)
Urinary bladder/Papilloma	0	0	4	1	.2496	.0904 (C,M)
Female						
Adrenal/Adenoma	0	0	1	1	.1772	
Adrenal/Pheochromocytoma	0	0	0	2	.0769	
Liver/Carcinoma	0	0	1	1	.2039	
Lung/Carcinoma	0	0	1	1	.2039	
Pituitary/Adenoma	14	17	12	20	.0704	.1136 (C,H)
Skin/Lipoma	0	0	1	2	.0639	.2834 (C,H)
Thyroid/Adenoma parafollicular cell	2	4	3	7	.0466	.1041 (C,H)

Table 4

Intercurrent mortality rates in hamster study

Sex	Time(wks)	Control	Low	Medium	High
MALE					
	0 - 52	3/105 (2.86)	1/ 60 (1.67)	0/ 60 (0.00)	1/ 60 (1.67)
	51-54 (I.S.)	15/102 (17.14)	10/ 59 (18.33)	10/ 60 (16.67)	10/ 59 (18.33)
	53 - 78	8/ 87 (24.76)	5/ 49 (26.67)	3/ 50 (21.67)	0/ 49 (18.33)
	79 - 100	19/ 79 (42.86)	10/ 44 (43.33)	8/ 47 (35.00)	12/ 49 (38.33)
	101 - 111	33/ 60 (74.29)	22/ 34 (80.00)	17/ 39 (63.33)	20/ 37 (71.67)
	Term. Sac.	27/105 (25.71)	12/ 60 (20.00)	22/ 60 (36.67)	17/ 60 (28.33)
FEMALE					
	0 - 52	2/105 (1.90)	2/ 60 (3.33)	0/ 60 (0.00)	2/ 60 (3.33)
	51-54 (I.S.)	15/103 (16.19)	10/ 58 (20.00)	10/ 60 (16.67)	10/ 58 (20.00)
	53 - 72	14/ 88 (29.52)	8/ 48 (33.33)	5/ 50 (25.00)	11/ 48 (38.33)
	73 - 83	45/ 74 (72.38)	21/ 40 (68.33)	24/ 45 (65.00)	20/ 37 (71.67)
	Term. Sac.	29/105 (27.62)	19/ 60 (31.67)	21/ 60 (35.00)	17/ 60 (28.33)

Note: Except the TERM. SACR. row, an entry of this table =number of animals dying or sacrificed in the time interval/number of animals entering the time interval. An entry in parenthesis = cumulative mortality rate;i.e. cumulative percent of animals dying up to the end of the time interval. An entry in the TERM. SACR. row = number of animals surviving to terminal sacrifice / initial number of animals. An entry in parenthesis in this row = percent of animals (of the initial number) surviving to terminal sacrifice.

I.S.= Interim Sacrifice

Table 5a

P-values of tests for homogeneity and positive linear trend in mortality in hamster study

Test of homogeneity

Sex	Test	P-value (One tail Chi-Sqr.)
Male	Cox	.1325
	Wilcoxon	.0900
Female	Cox	.7254
	Wilcoxon	.6620

Test of Positive linear trend

Sex	Test	P-value (One tail Normal)
Male	Cox	.8028
	Wilcoxon	.8586
Female	Cox	.3358
	Wilcoxon	.2525

Table 5b

P-values of pairwise tests for the differences in mortality between treatment groups in hamster study

Male hamsters

PAIRWISE COMPARISONS (1 D.F. CHI-SQUARES, WITH CONT CORR) DSNAME: b:tta.mhm

GROUP		EXACT ONE TAIL TEST	2X2 CHI-SQUARE USING N IN DEN	DIRECTION OF 2X2 CHI-SQ	COX'S TEST EXACT	COX'S TEST INVERSE	COX'S TEST CONSERVATIVE	GENERALIZED K/W ANALYSIS EXACT	GENERALIZED K/W ANALYSIS INVERSE	GENERALIZED K/W ANALYSIS CONSERVATIVE
0 VS. 1	CHISQ		.0659	POS	.0080		.0080	.1218		.1216
	PROB	.4000	.7975		.9287		.9287	.7271		.7273
0 VS. 2	CHISQ		2.2317	NEG	3.8511		3.8337	5.3204		5.3008
	PROB	.0677	.1352		.0497*		.0502	.0211*		.0213*
0 VS. 3	CHISQ		.2137	NEG	.7178		.7173	1.7203		1.7191
	PROB	.3213	.6439		.3969		.3970	.1897		.1898
1 VS. 2	CHISQ		2.7273	NEG	3.7986		3.7829	3.7824		3.7723
	PROB	.0491*	.0986		.0513		.0518	.0518		.0521
1 VS. 3	CHISQ		.5519	NEG	.7032		.7025	.7864		.7858
	PROB	.2289	.4575		.4017		.4019	.3752		.3754
2 VS. 3	CHISQ		.5335	POS	.9611		.9586	1.2026		1.1999
	PROB	.2327	.4651		.3269		.3275	.2728		.2733

Female hamsters

PAIRWISE COMPARISONS (1 D.F. CHI-SQUARES, WITH CONT CORR) DSNAME: b:tta.fhm

GROUP		EXACT ONE TAIL TEST	2X2 CHI-SQUARE USING N IN DEN	DIRECTION OF 2X2 CHI-SQ	COX'S TEST EXACT	COX'S TEST INVERSE	COX'S TEST CONSERVATIVE	GENERALIZED K/W ANALYSIS EXACT	GENERALIZED K/W ANALYSIS INVERSE	GENERALIZED K/W ANALYSIS CONSERVATIVE
0 VS. 1	CHISQ		.4056	NEG	.0921		.0920	.0470		.0470
	PROB	.2619	.5242		.7616		.7616	.8284		.8284
0 VS. 2	CHISQ		1.1002	NEG	.7494		.7490	.9002		.8999
	PROB	.1471	.2942		.3867		.3868	.3427		.3428
0 VS. 3	CHISQ		.0497	NEG	.0067		.0067	.2000		.1999
	PROB	.4111	.8236		.9349		.9349	.6547		.6548
1 VS. 2	CHISQ		.0333	NEG	.1175		.1175	.3946		.3944
	PROB	.4276	.8551		.7317		.7318	.5299		.5300
1 VS. 3	CHISQ		.0335	POS	.1587		.1586	.3526		.3525
	PROB	.4275	.8548		.6904		.6904	.5527		.5527
2 VS. 3	CHISQ		.3003	POS	.7519		.7513	1.5065		1.5054
	PROB	.2919	.5837		.3859		.3861	.2197		.2198

Table 6

Tumor rates and P-values of the tested tumor types for positive linear trend test and pairwise comparisons in hamster study

Organ/tumor	Tumor rates				P-value	
	C	L	M	H		
Male	105	60	60	60	Trend	Pairwise
Adrenal/Lymphoma	0	0	1	1	.2393	
Bone Marrow/Lymphoma	2	2	1	2	.3747	
Colon/Polyp	4	0	4	4	.4547	
Epididymus/Lymphoma	0	0	1	1	.1378	
Esophagus/Lymphoma	1	1	0	1	.4556	
Forestomach/Lymphoma	0	0	0	1	.2449	
Harderian Gland/Carcinoma	0	0	1	1	.1490	
Kidney/Lymphoma	1	2	0	1	.5221	
Pancreas/Adenoma(Islet cell)	5	6	5	3	.2821	
Pancreas/Lymphoma	1	0	1	1	.3339	
Spleen/Hemangioma	1	0	0	2	.1299	
Thymus/Lymphoma	0	2	1	1	.3133	
Female						
Adrenal/Adenoma	3	2	4	5	.0507	
Lung/Adenomatosis (focal)	1	2	1	3	.0990	.1589 (C,H)
Skin/Lymphoma	0	0	2	1	.1519	
Spleen/Hemangioma	0	0	1	2	.0365*	.1354 (C,H)

Figure 1a

Kaplan-Meier Estimates of the survival distributions
(Male rats)

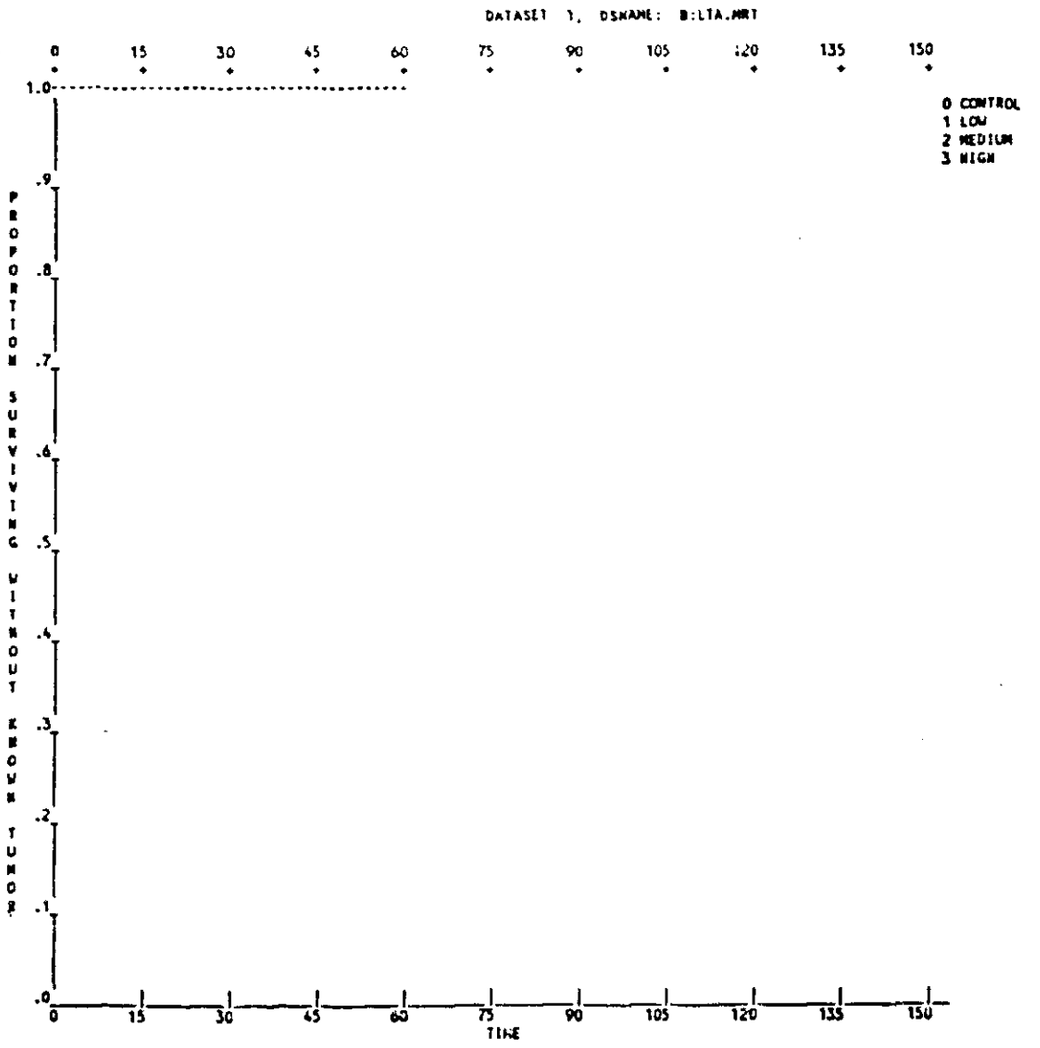


Figure 1b

Kaplan-Meier Estimates of the survival distributions
(Female rats)

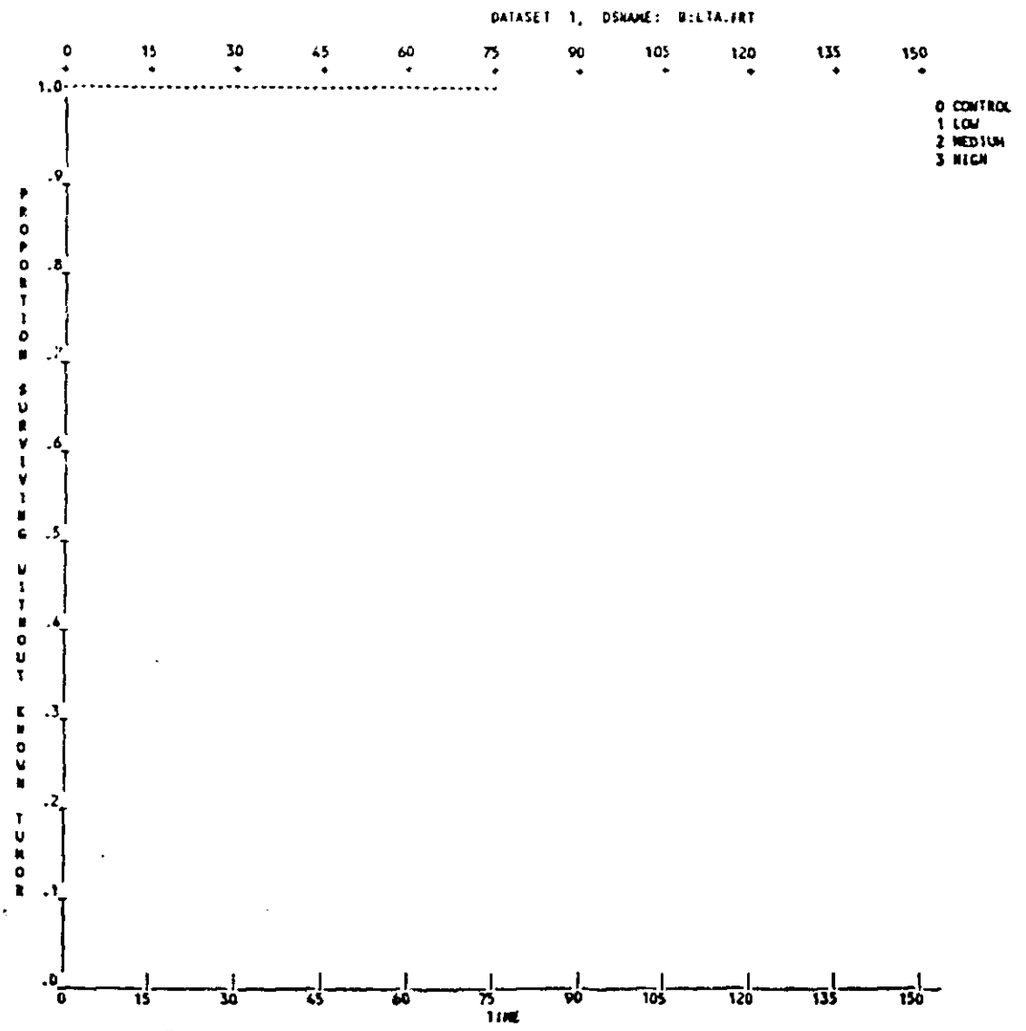


Figure 2a

Kaplan-Meier Estimates of the survival distributions
(Male hamsters)

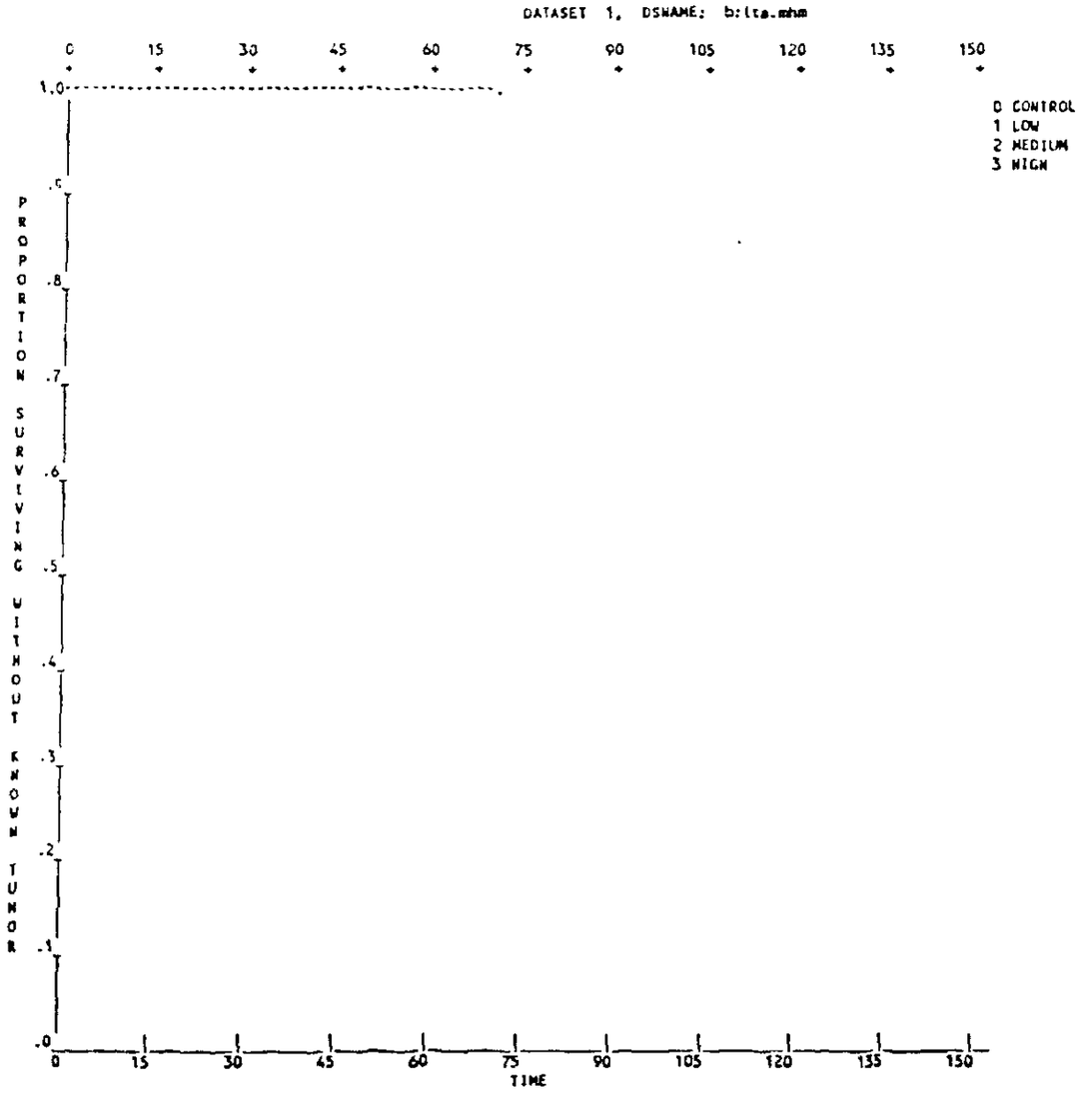
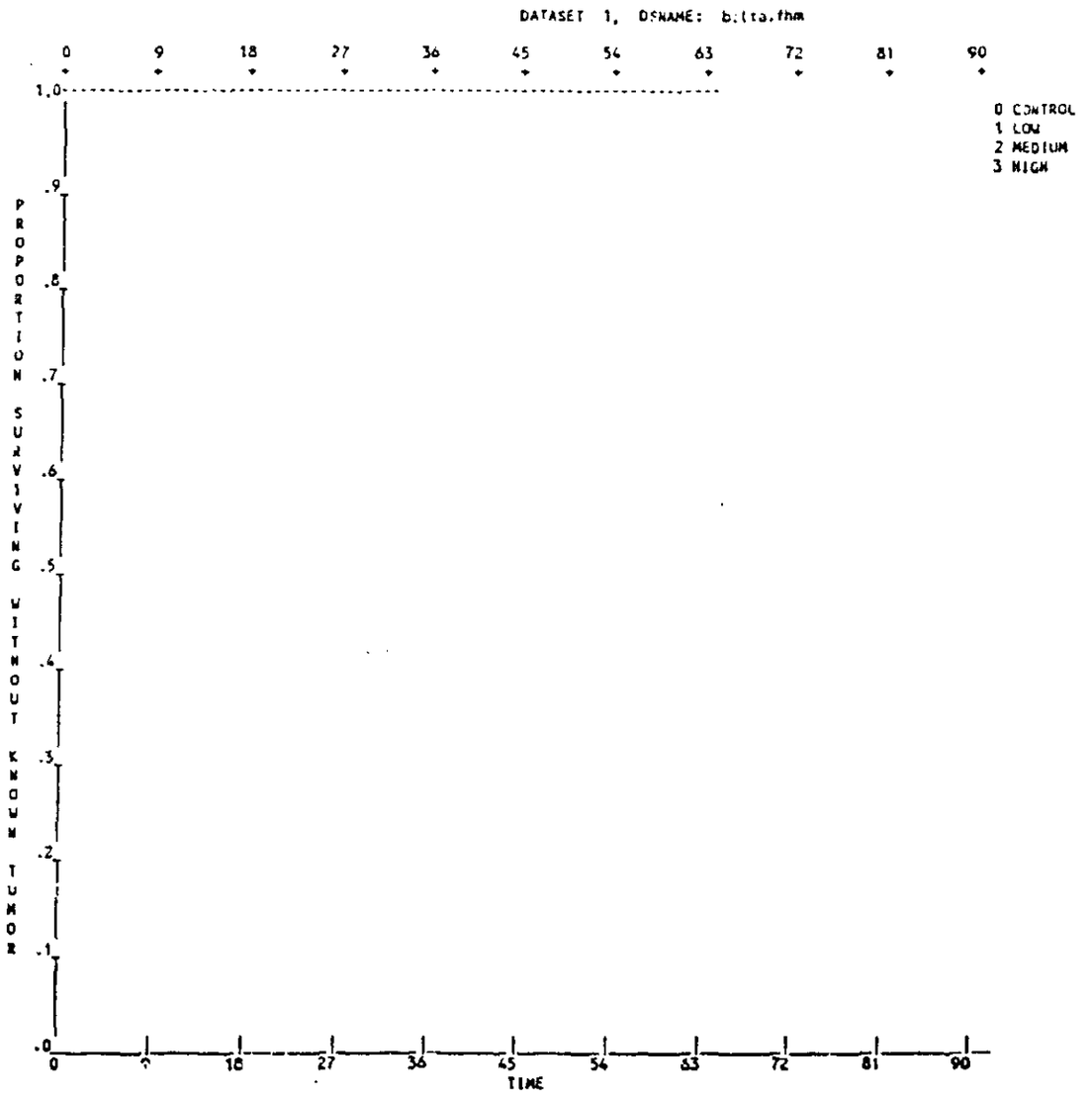


Figure 2b

Kaplan-Meier Estimates of the survival distributions
(Female hamsters)



Statistical Review and Evaluation

(Addendum)

NDA: 20-243 Date: MAY 2 1994

Applicant: Solvay Pharmaceuticals
Marietta, Georgia 30062

Name of Drug: Luvox (Fluvoxamine Maleate) tablets

Documents Reviewed: Original NDA volume 1 of 1 dated 12/27/91, 'Oncogenicity of Fluvoxamine Maleate given by dietary administration to the wister rat for two and a half years' by R.L.F. Dawes (undated), and 'The effects of the dietary administration of Fluvoxamine Maleate (DU 23000) to male and female syrian hamsters during their life-span' by Richard Adams Ph.D., Study director for Bio-research consultants, Inc. (undated). Data on floppy diskette supplied by the sponsor.

I. Background

A report of statistical review and evaluation on the hamster and the rat carcinogenicity studies of this NDA was issued by the Division of Biometrics on October 15. 1993. In that review the rat tumor data were analyzed for male and female separately. The analysis showed a statistically significant positive linear trend in the incidence of pancreas adenocarcinoma in male rats. In a telephone conversation Dr. Glenna Fitzgerald (HFD-120) requested this reviewer to analyze the pancreas adenocarcinoma data after combining the data from both male and female rats. This addendum contains the requested review.

II. Analysis of pancreas adenocarcinoma data combining two sexes

Combining data: As a first step data form male and female experiments were put together to form one single experiments with 80 animals (40+40) in each treatment group. This new data set was used in the following analysis.

Data analysis: The reviewer performed the positive linear trend test and pairwise comparison of the high dose group with the control. Since the sponsor classified the tumor types as 'cause of death' or 'not a cause of death', following Peto et al. (1980), the reviewer applied the 'death rate method' and the 'prevalence method', respectively for testing positive linear trend in these two categories of tumor types. For tumor types occurring in both categories (i.e. same tumor found as cause of death for some animals and not cause of death for some other animals) a combined test was performed. The exact permutation trend test was used to calculate the p-values of all trend tests, except for tumors which were found in both categories, in which cases the continuity

corrected normal test was used. The scores used were 0, 10, 40, and 200 for control, low, medium, and high dose groups, respectively. The score 200 for the high dose group is the average of 160, 200, and 240. The time intervals used were 0-52, 53-80, 31-104, 105-120, 121-128 weeks, and terminal sacrifice. The pairwise comparison was performed using the age-adjusted Fisher Exact test.

The incidence rates and the p-values are listed below.

Organ/Tumor	Tumor rate C	L	M	H	P-value Trend	Pairwise
	80	80	80	80		
Pancreas/Adenocarcinoma	1	1	0	3	.0197	.2060 (C,H)

Multiple testing adjustment: The rule proposed by Haseman was used to adjust the effect of multiple testings. Haseman's rule states that in order to keep the false-positive rate at the nominal level of approximately five percent, tumor types with a spontaneous tumor rate of no more than one percent should be tested at .05 level, otherwise the level should be set at .01 (Haseman, (1983), A re-examination of false-positive rates for carcinogenesis studies, Fundamental and Applied Toxicology, 3: 334-339).

On the basis of Haseman's rule the positive linear trend in pancreas adenocarcinoma in the combined sex population is not considered to be statistically significant.

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Mathematical Statistician

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HFD-715/SARB Chron
HFD-715/DRU 2.1.1 NDA 20-184 Luvox Rat and Hamster carcinogenicity studies
HFD-502/Assistant Director (Pharmacology)
HFD-715/Diskette Rahman-2/LUVOX.CAR
HFD-400/Dr. Contrera

Che

Chem. Review #10 does not exist. It was inadvertantly Omitted by the reviewing Chemist

DIVISION OF NEUROPHARMACOLOGICAL DRUG PRODUCTS
Review of Chemistry, Manufacturing, and Controls

NDA #: 20-243 **CHEM.REVIEW #** 1 **REVIEW DATE:** 23-DEC-92

SUBMISSIONTYPE	DOCUMENT DATE	CDER DATE	ASSIGNED DATE
ORIGINAL	24-DEC-91	30-DEC-91	08-JUL-92

NAME & ADDRESS OF APPLICANT: **Solvay Pharmaceuticals**
901 Sawyer Road
Marietta, GA 30062

DRUG PRODUCT NAME
Proprietary: **LUVOX™**
Nonproprietary/USAN: Fluvoxamine Maleate
Code Name/#: DU23000; MK264
Chem.Type/Ther Class:

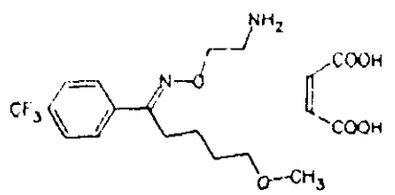
PHARMACOL.CATEGORY/INDICATION: Obsessive & Compulsive Disorder

DOSAGE FORM: Tablet
STRENGTHS: 25 mg; 50 mg; 100 mg & 150 mg
ROUTE OF ADMINISTRATION: oral route
DISPENSED: XXXXX Rx_____OTC

CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

5-methoxy-4'-(trifluoromethyl)valerophenone (E)-O-(2-aminoethyl)oxime maleate (1:1)

$C_{15}H_{21}N_2O_2F_3 \cdot C_4H_4O_4$ ***Molecular Weight:*** 434.4; **CAS # 61718-82-9**



SUPPORTING DOCUMENTS: IND NDA 19-189; DMF

RELATED DOCUMENTS: US Patent 4,085,225 (18-APR-78)

CONSULTS:

REMARKS/COMMENTS: See the attached review of the DMF). See REVIEW NOTES.

CONCLUSIONS & RECOMMENDATIONS: In its present form the **DMF does not support the NDA 20-243.** Recommend the NDA 20-243 **NOT APPROVABLE** due to the deficiencies in the CM&C part of the application. **SEE THE REVIEW NOTES.**

cc:
Orig. NDA 20-243
HFD-120
HFD-120/WJRzeszotarski/**23-DEC-92**
HFD-120/PDavid
HFD-120/SWBlum
HFD-102/CKumkumian[#1 only]
R/D Init by:SWB

W. Janusz Rzeszotarski, Ph.D.,Chemist
filename: N020243.000

SWB 3/26/94

DIVISION OF NEUROPHARMACOLOGICAL DRUG PRODUCTS
Review of Chemistry, Manufacturing, and Controls

NDA #: 20-243 **CHEM.REVIEW # 2** **REVIEW DATE: 06-JAN-93**

SUBMISSION TYPE	DOCUMENT DATE	CDER DATE	ASSIGNED DATE
ORIGINAL AMENDMENT	24-NOV-92	27-NOV-92	01-DEC-92

NAME & ADDRESS OF APPLICANT: **Solvay Pharmaceuticals**
901 Sawyer Road
Marietta, GA 30062

DRUG PRODUCT NAME
Proprietary: **LUVOX™** MAR 28
Nonproprietary/USAN: Fluvoxamine Maleate
Code Name/#: DU23000; MK264
Chem.Type/Ther.Class:

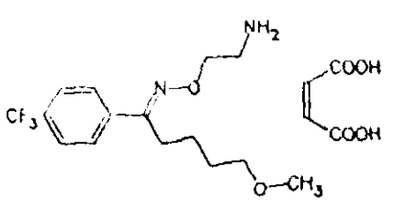
PHARMACOL.CATEGORY/INDICATION: Obsessive & Compulsive Disorder

DOSAGE FORM: Tablet
STRENGTHS: 25 mg; 50 mg; 100 mg & 150 mg
ROUTE OF ADMINISTRATION: oral route
DISPENSED: XXXXX Rx_____OTC

CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

5-methoxy-4'-(trifluoromethyl)valerophenone (E)-O-(2-aminoethyl)oxime maleate (1:1)

$C_{15}H_{21}N_2O_2F_3 \cdot C_4H_4O_4$ ***Molecular Weight: 434.4;*** ***CAS # 61718-82-9***



SUPPORTING DOCUMENTS: IND NDA 19-189; DMF

RELATED DOCUMENTS: US Patent 4,085,225 (18-APR-78)

CONSULTS:

REMARKS/COMMENTS: **The amendment provides the response to a review of DMF and the new drug substance part of the NDA summarized by a list of deficiencies faxed to applicant on 24-SEP-92. See REVIEW NOTES.**

CONCLUSIONS & RECOMMENDATIONS: In its present form the **DMF does not support the NDA 20-243 and the sponsor will update the DMF**. The additional information provided in the amendment is limited in scope and only partially acceptable. Recommend the NDA 20-243, as amended, **NOT APPROVABLE** due to the deficiencies in the CM&C part of the application. **SEE THE REVIEW NOTES.**

cc:
Orig. NDA 20-243
HFD-120
HFD-120/WJRzeszotarski/06-JAN-93
HFD-120/PDavid
HFD-120/SWBlum
HFD-102/CKumkumian[#1 only]
R/D Init by:SWB

JWR 3/26/94

W. Janusz Rzeszotarski, Ph.D.,Chemist
filename: N020243.001

DIVISION OF NEUROPHARMACOLOGICAL DRUG PRODUCTS
Review of Chemistry, Manufacturing, and Controls

NDA #: 20-243.002 **CHEM.REVIEW # 3** **REVIEW DATE: 06-JAN-93**

SUBMISSIONTYPE	DOCUMENT DATE	CDER DATE	ASSIGNED DATE
ORIGINAL AMENDMENT	17-SEP-92	21-SEP-92	24-SEP-92

NAME & ADDRESS OF APPLICANT: **Solvay Pharmaceuticals**
901 Sawyer Road
Marietta, GA 30062

DRUG PRODUCT NAME
Proprietary: **LUVOX™**
Nonproprietary/USAN: Fluvoxamine Maleate
Code Name/#: DU2300C; MK264
Chem.Type/Ther.Class:

MAR 28 1994

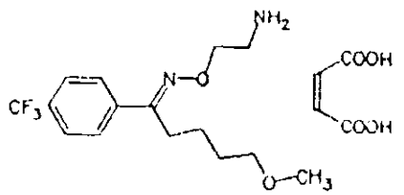
PHARMACOL.CATEGORY/INDICATION: Obsessive & Compulsive Disorder

DOSAGE FORM: Tablet
STRENGTHS: 25 mg; 50 mg; 100 mg & 150 mg
ROUTE OF ADMINISTRATION: oral route
DISPENSED: XXXXX Rx_____OTC

CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

5-methoxy-4'-(trifluoromethyl)valerophenone (E)-O-(2-aminoethyl)oxime maleate (1:1)

$C_{15}H_{21}N_2O_2F_3 .C_4H_4O_4$ ***Molecular Weight: 434.4;*** ***CAS # 61718-82-9***



SUPPORTING DOCUMENTS: IND NDA 19-189; DMF

RELATED DOCUMENTS: US Patent 4,085,225 (18-APR-78)

CONSULTS:

REMARKS/COMMENTS: The amendment provides the results of Tier 0 tests which were based on the Environmental Assesment Test Matrix. Solubility in water, vapor pressure, dissociation constant and octanol/water partition coefficient have been determined. The results indicate localization of fluvoxamine maleate in the aquatic compartment.

CONCLUSIONS & RECOMMENDATIONS: Information generated for presentation at a meeting with Dr Phillip Vincent. **N.A.I.**

cc:
Orig. NDA 20-243
HFD-120
HFD-120/WJRzeszotarski/06-JAN-93
HFD-120/PDavid
HFD-120/SWBlum
HFD-102/CKumkumian[#1 only]
R/D Init by:SWB

3/26/94

W. Janusz Rzeszotarski, Ph.D.,Chemist
filename: N020243.002

DIVISION OF NEUROPHARMACOLOGICAL DRUG PRODUCTS
Review of Chemistry, Manufacturing, and Controls

NDA #: 20-243.002 **CHEM.REVIEW # 4** **REVIEW DATE: 18-DEC-92**

SUBMISSION TYPE	DOCUMENT DATE	CDER DATE	ASSIGNED DATE
ORIGINAL			
AMENDMENT	03-DEC-92	04-DEC-92	05-DEC-92

NAME & ADDRESS OF APPLICANT: **Solvay Pharmaceuticals**
901 Sawyer Road
Marietta, GA 30062

DRUG PRODUCT NAME
Proprietary: **LUVOX™**
Nonproprietary/USAN: Fluvoxamine Maleate
Code Name/#: DU23000; MK264
Chem.Type/Ther.Class:

MAR 2 8 1994

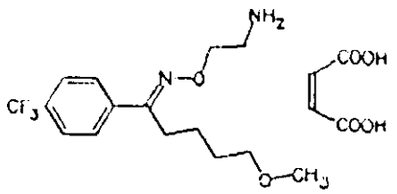
PHARMACOL.CATEGORY/INDICATION: Obsessive & Compulsive Disorder

DOSAGE FORM: Tablet
STRENGTHS: 25 mg; 50 mg; 100 mg & 150 mg
ROUTE OF ADMINISTRATION: oral route
DISPENSED: XXXXX Rx_____OTC

CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

5-methoxy-4'-(trifluoromethyl)valerophenone (E)-O-(2-aminoethyl)oxime maleate (1:1)

$C_{15}H_{21}N_2O_2F_3 .C_4H_4O_4$ Molecular Weight: 434.4; CAS # 61718-82-9



SUPPORTING DOCUMENTS: IND NDA 19-189; DMF

RELATED DOCUMENTS: US Patent 4,085,225 (18-APR-78)

CONSULTS:

REMARKS/COMMENTS: The amendment provides for a copy of the subsection entitled "Drug Formulation" (Vol 1.25) which has been incorporated as part of Human Pharmacokinetics and Bioavailability Section of the Original NDA 20-243. The information has been requested by the chemistry reviewer. (See enclosed)

CONCLUSIONS & RECOMMENDATIONS: A thorough presentation of formulation development from capsules to present tablets. **N.A.I.**

cc:
Orig. NDA 20-243
HFD-120
HFD-120/WJRzeszotarski/**18-DEC-92**
HFD-120/PDavid
HFD-120/SWBlum
HFD-102/CKumkumian[#1 only]
R/D Init by:SWB

3/28/94

W. Janusz Rzeszotarski, Ph.D.,Chemist
filename: N020243.003

DIVISION OF NEUROPHARMACOLOGICAL DRUG PRODUCTS
Review of Chemistry, Manufacturing, and Controls

NDA #: 20-243 **CHEM.REVIEW # 5** **REVIEW DATE: 18-JUN-93**

SUBMISSION TYPE	DOCUMENT DATE	CDER DATE	ASSIGNED DATE
NEW CORRESPONDENCE	07-JUN-93	10-JUN-93	11-JUN-93

NAME & ADDRESS OF APPLICANT: **Solvay Pharmaceuticals**
901 Sawyer Road
Marietta, GA 30062

DRUG PRODUCT NAME
Proprietary: **LUVOX™**
Nonproprietary/USAN: Fluvoxamine Maleate
Code Name/#: DU23000; MK264
Chem.Type/Ther.Class:

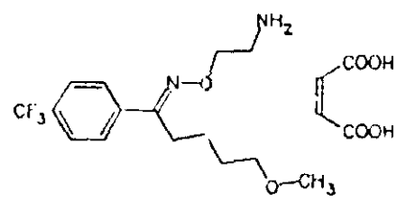
PHARMACOL.CATEGORY/INDICATION: Obsessive & Compulsive Disorder

DOSAGE FORM: Tablet
STRENGTHS: 25 mg; 50 mg; 100 mg & 150 mg
ROUTE OF ADMINISTRATION: oral route
DISPENSED: XXXXX Rx_____OTC

CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

5-methoxy-4'-(trifluoromethyl)valerophenone (E)-O-(2-aminoethyl)oxime maleate (1:1)

$C_{15}H_{21}N_2O_2F_3 \cdot C_4H_4O_4$ Molecular Weight: 434.4; CAS # 61718-82-9



SUPPORTING DOCUMENTS: IND NDA 19-189; DMF

RELATED DOCUMENTS: US Patent 4,085,225 (18-APR-78)

CONSULTS:

REMARKS/COMMENTS: The amendment provides for the sponsor's understanding of the discussion of particle size as discussed with the Agency on 12-MAY-93. **SEE MEMO N020243.T01.**

CONCLUSIONS & RECOMMENDATIONS: N.A.I. The NDA 20-243 as amended (See Reviews # 1, 2, 3, & 4) is **NOT APPROVABLE.**

cc:
Orig. NDA 20-243
HFD-120
HFD-120/WJRzeszotarski/**18-JUN-93**
HFD-120/PDavid
HFD-120/SWBlum
HFD-102/CKumkumian[#1 only]
R/D Init by:SWB

W. Janusz Rzeszotarski, Ph.D.,Chemist
filename: N020243.004

SWB 3/20/94

DIVISION OF NEUROPHARMACOLOGICAL DRUG PRODUCTS
Review of Chemistry, Manufacturing, and Controls

NDA #: 20-243 **CHEM.REVIEW # 6** **REVIEW DATE: 03-AUG-93**

SUBMISSION TYPE	DOCUMENT DATE	CDER DATE	ASSIGNED DATE
ORIGINAL AMENDMENT	21-JUL-93	23-JUL-93	26-JUL-93

NAME & ADDRESS OF APPLICANT: **Solvay Pharmaceuticals**
901 Sawyer Road
Marietta, GA 30062

DRUG PRODUCT NAME
Proprietary: **LUVOX™**
Nonproprietary/USAN: Fluvoxamine Maleate
Code Name/#: DU23000; MK264
Chem.Type/Ther.Class:

MAR 2 8 1994

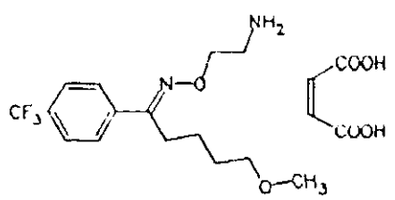
PHARMACOL.CATEGORY/INDICATION: Obsessive & Compulsive Disorder

DOSAGE FORM: Tablet
STRENGTHS: 25 mg; 50 mg; 100 mg & 150 mg
ROUTE OF ADMINISTRATION: oral route
DISPENSED: XXXXX Rx_____OTC

CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

5-methoxy-4'-(trifluoromethyl)valerophenone (E)-O-(2-aminoethyl)oxime maleate (1:1)

$C_{15}H_{21}N_2O_2F_3 \cdot C_4H_4O_4$ ***Molecular Weight: 434.4;*** ***CAS # 61718-82-9***



SUPPORTING DOCUMENTS: IND NDA 19-189; DMF

RELATED DOCUMENTS: US Patent 4,085,225 (18-APR-78)

CONSULTS:

REMARKS/COMMENTS: The amendment provides for the sponsor's RESPONSE TO THE DEFICIENCIES IN THE ENVIRONMENTAL ASSESSMENT as listed in the letter of 07-JUL-92. Further reference is made to a meeting with Dr Philip Vincent on 27-OCT-92.

CONCLUSIONS & RECOMMENDATIONS: **N.A.I.** The NDA 20-243 as amended (See Reviews # 1, 2, 3, 4 & 5) is **NOT APPROVABLE** due to unanswered CM&C deficiencies.

cc:
Orig. NDA 20-243
HFD-120
HFD-120/WJRzeszotarski/**03-AUG-93**
HFD-120/PDavid
HFD-120/SWBlum
HFD-102/CKumkumian[#1 only]
R/D Init by:SWB

W. Janusz Rzeszotarski, Ph.D., Chemist
filename: N020243.005

3/26/94

DIVISION OF NEUROPHARMACOLOGICAL DRUG PRODUCTS
Review of Chemistry, Manufacturing, and Controls

NDA #: 20-243 **CHEM.REVIEW # 7** **REVIEW DATE: 20-AUG-93**

SUBMISSIONTYPE	DOCUMENT DATE	CDER DATE	ASSIGNED DATE
ORIGINAL AMENDMENT	30-JUL-93	04-AUG-93	05-AUG-93

NAME & ADDRESS OF APPLICANT: **Solvay Pharmaceuticals**
901 Sawyer Road
Marietta, GA 30062

DRUG PRODUCT NAME
Proprietary: **LUVOX™**
Nonproprietary/USAN: Fluvoxamine Maleate
Code Name/#: DU23000; MK264
Chem.Type/Ther.Class:

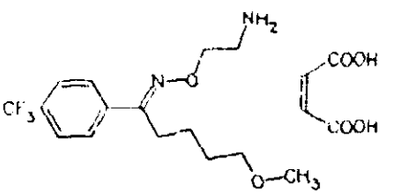
PHARMACOL.CATEGORY/INDICATION: Obsessive & Compulsive Disorder

DOSAGE FORM: Tablet
STRENGTHS: 25 mg; 50 mg; 100 mg & 150 mg
ROUTE OF ADMINISTRATION: oral route
DISPENSED: XXXXX Rx_____OTC

CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

5-methoxy-1-[4-(trifluoromethyl)phenyl]-1-pentanone, O-(2-aminoethyl)oxime, (E), 2-butene dioic acid, (Z), (1:1)

$C_{15}H_{21}N_2O_2F_3 . C_4H_4O_4$ ***Molecular Weight: 434.4;*** ***CAS # 61718-82-9***



SUPPORTING DOCUMENTS: IND NDA 19-189; DMF

RELATED DOCUMENTS: US Patent 4,085,225 (18-APR-78)

CONSULTS:

REMARKS/COMMENTS: The amendment provides for a response to the correspondence of 22-APR-93 from the Agency providing comments on the chemistry, manufacturing and control section of this NDA. (See enclosed)

CONCLUSIONS & RECOMMENDATIONS: The issues have been cleared and the NDA 20-243 is now recommended **APPROVABLE.**

cc:
Orig. NDA 20-243
HFD-120
HFD-120/WJRzeszotarski/**20-AUG-93**
HFD-120/PDavid
HFD-120/SWBlum
HFD-102/CKumkumian[#1 only]
R/D Init by:SWB

SWB 8/26/94

W. Janusz Rzeszotarski, Ph.D.,Chemist
filename: N020243.006

DIVISION OF NEUROPHARMACOLOGICAL DRUG PRODUCTS
Review of Chemistry, Manufacturing, and Controls

NDA #: 20-243 **CHEM.REVIEW # 8** **REVIEW DATE: 30-AUG-93**

SUBMISSIONTYPE	DOCUMENT DATE	CDER DATE	ASSIGNED DATE
ORIGINAL AMENDMENT	23-AUG-93	24-AUG-93	24-AUG-93

NAME & ADDRESS OF APPLICANT: **Solvay Pharmaceuticals**
901 Sawyer Road
Marietta, GA 30062

MAR 2 8 1994

DRUG PRODUCT NAME
Proprietary: **LUVOX™**
Nonproprietary/USAN: Fluvoxamine Maleate
Code Name/#: DJ23000; MK264
Chem.Type/Ther.Class:

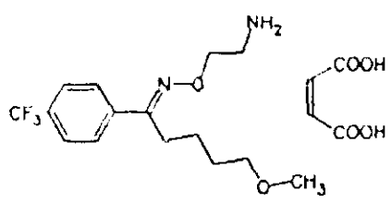
PHARMACOL.CATEGORY/INDICATION: Obsessive & Compulsive Disorder

DOSAGE FORM: Tablet
STRENGTHS: 25 mg; 50 mg; 100 mg & 150 mg
ROUTE OF ADMINISTRATION: oral route
DISPENSED: XXXXX Rx_____OTC

CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

5-methoxy-4'-(trifluoromethyl)valerophenone (E)-O-(2-aminoethyl)oxime maleate (1:1)

$C_{15}H_{21}N_2O_2F_3 .C_4H_4O_4$ Molecular Weight: 434.4; CAS # 61718-82-9



SUPPORTING DOCUMENTS: IND NDA 19-189; DMF

RELATED DOCUMENTS: US Patent 4,085,225 (18-APR-78)

CONSULTS:

REMARKS/COMMENTS: The amendment provides for the manufacturing and control information on scored LUVOX Tablets of the 50 and 100 mg strength. Additionally, it contains updated SOP summary, corrected blister packaging description, corrected specifications for colloidal silicon dioxide and labels for various blister packages and revised labels for bottle packaging.

CONCLUSIONS & RECOMMENDATIONS: Recommend the NDA 20-243 as amended (See Reviews # 1, 2, 3, 4, 5, 6 & 7) **APPROVABLE** .

cc:
Orig. NDA 20-243
HFD-120
HFD-120/WJRzeszotarski/**30-AUG-93**
HFD-120/PDavid
HFD-120/SWBlurn
HFD-102/CKumkumian[#1 only]
R/D Init by:SWB

MB 3/20/94

W. Janusz Rzeszotarski, Ph.D.,Chemist
filename: NO20243.007

DIVISION OF NEUROPHARMACOLOGICAL DRUG PRODUCTS
Review of Chemistry, Manufacturing, and Controls

NDA #: 20-243 **CHEM.REVIEW # 9** **REVIEW DATE: 01-OCT-93**

SUBMISSIONTYPE	DOCUMENT DATE	CDER DATE	ASSIGNED DATE
ORIGINAL AMENDMENT	21-SEP-93	24-SEP-93	27-SEP-93

NAME & ADDRESS OF APPLICANT: **Solvay Pharmaceuticals**
901 Sawyer Road
Marietta, GA 30062

DRUG PRODUCT NAME
Proprietary: **LUVOX™**
Nonproprietary/USAN: Fluvoxamine Maleate
Code Name/#: DU23000; MK264
Chem.Type/Ther.Class:

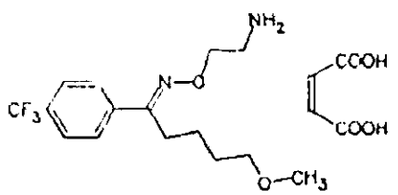
PHARMACOL.CATEGORY/INDICATION: Obsessive & Compulsive Disorder

DOSAGE FORM: Tablet
STRENGTHS: 25 mg; 50 mg; 100 mg & 150 mg
ROUTE OF ADMINISTRATION: oral route
DISPENSED: XXXXX Rx_____OTC

CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

5-methoxy-4'-(trifluoromethyl)valerophenone (E)-O-(2-aminoethyl)oxime maleate (1:1)

$C_{15}H_{21}N_2O_2F_3 \cdot C_4H_4O_4$ ***Molecular Weight: 434.4;*** ***CAS # 61718-82-9***



SUPPORTING DOCUMENTS: IND ; NDA 19-189; DMF

RELATED DOCUMENTS: US Patent 4,085,225 (18-APR-78)

CONSULTS:

REMARKS/COMMENTS: The amendment provides for the response to the drug product deficiencies communicated to the sponsor and includes the requested IR identification procedure for the finished dosage form. Also included are 12 months stability data for the bottle packaging of LUVOX 25, 50, 100 and 150 mg Tablets and the corrected master formula record for 50 mg scored LUVOX tablets dosage units).

CONCLUSIONS & RECOMMENDATIONS: Recommend the NDA 20-243 as amended (See Reviews # 1, 2, 3, 4, 5, 6, 7 & 8) **APPROVABLE** .

cc:
Orig. NDA 20-243
HFD-120
HFD-120/WJRzeszotarski/01-OCT-93
HFD-120/PDavid
HFD-120/SWBlum
HFD-102/CKumkumian[#1 only]
R/D Init by:SWB

W. Janusz Rzeszotarski, Ph.D.,Chemist
filename: N020243.008

DIVISION OF NEUROPHARMACOLOGICAL DRUG PRODUCTS
Review of Chemistry, Manufacturing, and Controls

NDA #: 20-243 **CHEM.REVIEW # 11** **REVIEW DATE: 10-DEC-93**

SUBMISSIONTYPE	DOCUMENT DATE	CDER DATE	ASSIGNED DATE
ORIGINAL			
AMENDMENT	23-NOV-93	26-NOV-93	30-NOV-93

NAME & ADDRESS OF APPLICANT: **Solvay Pharmaceuticals**
901 Sawyer Road
Marietta, GA 30062

DRUG PRODUCT NAME
Proprietary: **LUVOX™**
Nonproprietary/USAN: Fluvoxamine Maleate
Code Name/#: DU23000; MK264
Chem.Type/Ther.Class:

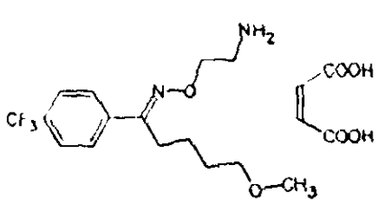
PHARMACOL.CATEGORY/INDICATION: Obsessive & Compulsive Disorder

DOSAGE FORM: Tablet
STRENGTHS: 25 mg; 50 mg; 100 mg & 150 mg
ROUTE OF ADMIN.STRATION: oral route
DISPENSED: XXXXX Rx_____OTC

CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

5-methoxy-1-[4-(trifluoro methyl)phenyl]-1-pentanone, O-(2-aminoethyl)oxime, (E), 2-butene dioic acid, (Z), (1:1)

$C_{14}H_{21}N_2O_2F_3 . C_4H_4O_4$ ***Molecular Weight: 434.4;*** ***CAS # 61718-82-9***



SUPPORTING DOCUMENTS: IND NDA 19-189; DMF

RELATED DOCUMENTS: US Patent 4,085,225 (18-APR-78)

CONSULTS:

REMARKS/COMMENTS: The amendment provides for a response to the issues raised in review # 7 (assay limits), batch information on the drug substance and drug product used in clinical studies. Also attached is the test procedure used in identifying packaged LUVOX tablets from the packager

CONCLUSIONS & RECOMMENDATIONS: Recommend the NDA 20-243 as amended (See reviews 1 to 10) **APPROVABLE.**

cc:
Orig. NDA 20-243
HFD-120
HFD-120/WJRzeszotarski/**10-DEC-93**
HFD-120/PDavid
HFD-120/SWBlum
HFD-102/CKumkumian[#1 only]
R/D Init by:SWB

3/22/94

W. Janusz Rzeszotarski, Ph.D.,Chemist
filename: N020243.010

DIVISION OF NEUROPHARMACOLOGICAL DRUG PRODUCTS
Review of Chemistry, Manufacturing, and Controls

NDA #: 20-243 **CHEM.REVIEW # 12** **REVIEW DATE: 07-JAN-94**

SUBMISSION TYPE	DOCUMENT DATE	CDER DATE	ASSIGNED DATE
ORIGINAL			
AMENDMENT	20-DEC-93	23-DEC-93	30-DEC-93

NAME & ADDRESS OF APPLICANT: **Solvay Pharmaceuticals**
901 Sawyer Road
Marietta, GA 30062

DRUG PRODUCT NAME
Proprietary: **LUVOX™**
Nonproprietary/USAN: Fluvoxamine Maleate
Code Name/#: DU23000; MK264
Chem.Type/Ther.Class:

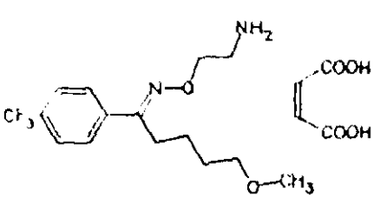
PHARMACOL.CATEGORY/INDICATION: Obsessive & Compulsive Disorder

DOSAGE FORM: Tablet
STRENGTHS: 25 mg; 50 mg; 100 mg & 150 mg
ROUTE OF ADMINISTRATION: oral route
DISPENSED: XXXXX Rx_____OTC

CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

5-methoxy-1-[4-(trifluoromethyl)phenyl]-1-pentanone, O-(2-aminoethyl)oxime, (E), 2-butene dioic acid, (Z), (1:1)

$C_{15}H_{21}N_2O_2F_3 \cdot C_4H_4O_4$ ***Molecular Weight:*** 434.4; **CAS # 61718-82-9**



SUPPORTING DOCUMENTS: IND NDA 19-189; DMF

RELATED DOCUMENTS: US Patent 4,085,225 (18-APR-78)

CONSULTS:

REMARKS/COMMENTS: The amendment provides for a response to the issues raised in review # 7 (assay limits), batch information on the limits of impurities in the drug substance.

CONCLUSIONS & RECOMMENDATIONS: Recommend the NDA 20-243 as amended (See reviews 1 to 11) **APPROVABLE.**

cc:
Orig. NDA 20-243
HFD-120
HFD-120/WJRzeszotarski/**07-JAN-94**
HFD-120/PDavid
HFD-120/SWBlum
HFD-102/CKumkumian[#1 only]
R/D Init by:SWB

W. Janusz Rzeszotarski, Ph.D.,Chemist
filename: N020243.011

Bio

FEB 9 1994

Fluvoxamine Maleate (LUVOX®)
Tablets 25, 50, 100 and 150 mg

Solvay Pharmaceuticals, Inc
901 Sawyer Road
Marietta, Georgia 30062
Submission Dates: 12/24/91, 5/21/93, 7/30/93, 8/23/93, 10/13/93

Reviewers: Chandrahas Sahajwaila, Ph.D.
Safaa Ibrahim, Ph.D.
Vijay Tammara, Ph.D.

Type of Submission: NDA 20-243 (NME)

= =

Review of an NDA

SYNOPSIS

Fluvoxamine maleate is a potent and selective serotonin reuptake inhibitor indicated for use in the treatment of obsessive compulsive disorder. The recommended dose is 100 to 300 mg daily. Fluvoxamine is nearly completely absorbed when administered as a tablet, capsule or oral solution. Fluvoxamine is metabolized in the liver by the cytochrome P450 system, and may be a competitive inhibitor for the IA2 and IIIA4 isoenzymes. Steady-state plasma concentrations are achieved after 4 to 6 days of consecutive 50 mg BID to 150 mg BID dosing. Over the therapeutic dose range of 100 to 300 mg per day, fluvoxamine exhibits non-linear pharmacokinetics. The absolute bioavailability is approximately 53%, protein binding is approximately 80% and the volume of distribution is approximately 25 L/kg. There is a slight reduction in fluvoxamine AUC (14%) in the presence of food, following a single 50 mg tablet dose administration of fluvoxamine. Age-related increases in C_{max}, AUC and T½ were observed after multiple 50 and 100 mg doses. This study also indicated possibility of sub-population due to genetic polymorphism of cytochrome P450 enzyme system particularly CYP450IID6. Fluvoxamine administered as 50 mg bid for 6 weeks to patients with renal impairment was found to be safe and well tolerated. Patients with liver impairment had decreased clearance (30%) and increased T1/2 (60%) following a single 100 mg dose. When co-administered with fluvoxamine, plasma concentrations of warfarin (about fold), theophylline fold), propranolol fold) and alprazolam fold) were increased in healthy volunteers. In presence of fluvoxamine, antipyrine clearance decreased (63%) and T1/2 fold) increased. Fluvoxamine coadminstration did not alter the single dose pharmacokinetics of digoxin. Increased fluvoxamine metabolism (about 25%) has been observed due to cigarette smoking. The mean plasma concentration for females was about 29% greater than males. There appears to be no relationship between fluvoxamine plasma

concentrations and therapeutic or adverse effect. Pharmacokinetic differences due to race have not been studied.

LUVOX™ (fluvoxamine maleate) tablets are available in four dosage strengths (25, 50, 100 and 150 mg). In composition, they are qualitatively the same and quantitatively proportional to each other. The 50 mg and 100 mg dosages will be marketed in scored tablet form, while the 25 mg and 150 mg tablets will be unscored. The proposed commercial fluvoxamine maleate 50-mg film-coated tablet has been shown to be bioequivalent to the capsule formulation used in clinical trials.

RECOMMENDATION:

The sponsor's NDA 20-243 appears to be acceptable for meeting the Biopharmaceutics requirements, provided comments are addressed satisfactorily by the sponsor.

Dissolution specifications recommended by DOB are:
Medium: mL Purified Water at °C ± °C.
Apparatus: USP Apparatus (Paddles) at RPM.
Specification: Not less than % dissolved in minutes.

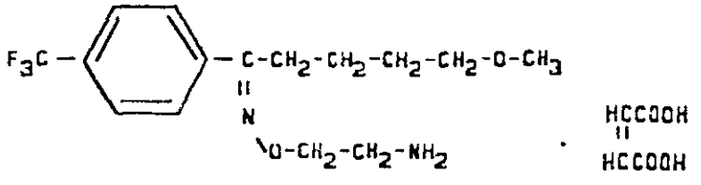
TABLE OF CONTENTS:

Appendix 1 and 2 contain more detailed/data information. These appendices are being retained by the Division of Biopharmaceutics, and can be obtained upon request.

BACKGROUND

Fluvoxamine maleate (LUVOX®) is a potent and selective 5-hydroxytryp-tamine (hereafter referred to as serotonin) reuptake inhibitor (SSRI) indicated for use in the treatment of obsessive-compulsive disorder (OCD) in humans. Preclinical pharmacology studies indicate that fluvoxamine is devoid of anticholinergic, antihistaminic, stimulant, sedative, monamine oxidase inhibitory, proconvulsive, hypertensive or cardiotoxic properties.

Fluvoxamine maleate is a compound in the series of 2-aminoethyl oximeters of aralkylketones. The chemical structure is shown below.



The chemical name is 5-methoxy-4'-(trifluoromethyl)valerophenone-(E)-O-(2 aminoethyl)oxime maleate (1:1). The empirical formula is $C_{15}H_{21}O_2N_2F_3 \bullet C_4H_4O_4$ and the gram molecular weight is 434.4.

SUMMARY OF BIOAVAILABILITY, PHARMACOKINETICS AND PHARMACODYNAMICS

I. BIOAVAILABILITY AND BIOEQUIVALENCE

A. Absolute Bioavailability

In a single dose 3-way crossover pharmacokinetic study (Report 56638/18/92) of fluvoxamine maleate administered intravenously (10 mg and 30 mg) and orally (50 mg capsule) to 17 healthy male volunteers, the mean absolute bioavailability was 53% ± 21%

B. Pivotal Bioequivalence

Twenty-three (23) healthy male subjects completed this open, balanced, randomized, 3-period single dose crossover study (Report CR100.0007). Each subject received, in random order, the proposed commercial 50-mg fluvoxamine maleate tablet, a 50-mg capsule and a 50-mg oral solution. The mean C_{max} value for the 50 mg tablet (17.6 ± 4.58 ng/ml) was significantly greater ($p < 0.05$) than the value observed for the reference 50 mg capsule (16.3 ± 4.89 ng/ml). There were no significant

differences in mean values for $AUC_{(0-t)}$, $AUC_{(0-inf)}$, T_{max}, K_{el}, and $T^{1/2}$, between tablet and capsule. Sufficient power (>0.80) was present to detect ±20% differences in mean values for all comparisons except T_{max} ($p>0.61$). The mean T_{max} values were within a range of ±20%. The 90% confidence limits calculated from the two, one-sided t-test procedure for all pharmacokinetic parameters were within a range of % to %. Based on these results, the 50 mg fluvoxamine tablet is considered bioequivalent to the 50 mg reference capsule used in the clinical efficacy trials.

C. Food Effect

The influence of food on the bioavailability of a 50 mg fluvoxamine maleate tablet formulation (not the marketed tablet) was studied in 8 males and 4 females in a single dose, two-period (fasting and fed) open, balanced, randomized crossover study (Report H.114.6501). Although considerable intersubject variability (about 50%) is observed in C_{max} and T_{max} values, mean values are similar between fed and fasting conditions for both parameters. The mean AUC value was 14% lower in the fed state, compared to the fasting condition. This effect is not considered to be clinically important. From the data given, it was observed that females have a greater AUC (about 35%) in comparison to males both in fed and fasting state.

II. GENERAL PHARMACOKINETICS AND DOSE PROPORTIONALITY

A. Single and Multiple Dose Pharmacokinetics

The study designed to evaluate fluvoxamine pharmacokinetics was single dose trial using healthy volunteers (9 males and 1 female), ages 20 to 25 years (Report 56654/22/76). The dosage consisted of 100 mg fluvoxamine maleate administered as 2 hard gelatin capsules. The C_{max} values ranged from ng/mL. The T_{max} value ranged from hours. The mean AUC, corrected to a dose of 1 mg/kg, was approximately 800 ng x mL/hr. The mean elimination half-life was 15 hours, varying from 12.7 to 19 hours.

The pharmacokinetics of single-dose intravenously and orally administered fluvoxamine maleate in seventeen (17) healthy male subjects was evaluated in a single-dose 3-way crossover study (Report 114.6006/56638/18/92). Each subject received 10 mg and 30 mg intravenous (i.v.) fluvoxamine administered over 60 minutes in normal saline and a 50 mg fluvoxamine capsule in an open, randomized, three-period crossover design.

Following a 60 minute intravenous infusion of 10 and 30 mg, plasma levels of fluvoxamine declined biexponentially with a mean half-life of approximately 12 to 13 hours (range . Systemic clearance for 10 mg and 30 mg i.v. dose was about 23 mL/min/kg. The apparent mean volume of distribution for fluvoxamine was approximately 25 L/kg for both i.v. doses, indicating that the drug has extensive

tissue binding. This study also indicated that only about 2% of the administered dose was excreted unchanged.

Renal clearance for both the i.v. doses and oral dose was about 0.45 mL/min/kg. The plasma concentrations obtained after oral dosing with the 50 mg capsules were comparable to the concentrations observed after the 30 mg i.v. dose. The absolute bioavailability for fluvoxamine was 53.3%, supporting the existence of systemic first pass metabolism for fluvoxamine. The mean half-life observed after oral dosing was 12.8 hours, which was comparable to the i.v. results.

B. DOSE PROPORTIONALITY

The relationship between dose and fluvoxamine plasma concentrations was first examined in a three-way crossover study in twelve (12) healthy male volunteers (Report H.114.614). Each subject received, in random fashion, single doses of 25, 50, and 100 mg of fluvoxamine maleate in an aqueous solution.

The ANOVA for C_{max} showed no significant difference between the dose levels of the dose-normalized C_{max} ($p=0.706$). In addition, the two one-sided t-test procedure using the 25 mg dose as the reference showed that both the 50 mg dose-normalized C_{max} and the 100 mg dose-normalized C_{max} were within the % range. The two, one-sided t-test procedure using the 25 mg dose as the reference found that both the 50 mg dose-normalized AUC and the 100 mg dose-normalized AUC were within the % range and were not significantly different. Analysis of variance (ANOVA) showed no difference between the three doses in T_{max} ($p=0.485$). There was a statistically significant period effect on T_{max}; however, there was no significant sequence effect.

Based on this analysis, fluvoxamine maleate exhibited linear pharmacokinetics over dosing range of 25, 50 and 100 mg given as oral solution. However, this was a single dose study. In another study (Report 100.0098) single and multiple dose (25 and 50 mg) pharmacokinetic of fluvoxamine was evaluated in young and elderly subjects and it was concluded that pharmacokinetics at these doses were not dose proportional. The difference in the two studies was that the study concluding dose proportional pharmacokinetics utilized oral solution whereas, study concluding not dose proportional used fluvoxamine capsules.

A study was conducted in thirty healthy male volunteers comparing three fluvoxamine dose levels of 100 mg/day, 200 mg/day and 300 mg/day (Report CR 100.0008). These doses cover the range of doses recommended for the OCD indication. The subjects were titrated sequentially up to 100 mg fluvoxamine (50 mg b.i.d.) initially and then up to 200 mg (100 mg b.i.d.) and finally 300 mg (150 mg b.i.d.) according to the titration schedule shown below. Doses in this study were given at 8 AM and

8 PM with approximately a week at each of the target doses.

Study Days	Morning Dose (8 AM)	Evening Dose (8 PM)
1-3	0	50 mg
4-10	50 mg	50 mg
11-13	50 mg	100 mg
14-20	100 mg	100 mg
21-23	100 mg	150 mg
24-30	150 mg	150 mg
31	150 mg	0

Analysis of the mean Cmin values confirmed that after 4 days of dosing at 100 mg/day, steady-state plasma concentrations were achieved. For the 200 mg/day and 300 mg/day doses, steady-state was achieved by 6 days of dosing. No circadian effect was observed in fluvoxamine pharmacokinetic parameters. While steady state plasma concentrations were achieved at all dosage regimens, the mean C_{min}, C_{max}, C_{ss} and AUC values were not proportional to dose. Dose normalized AUC, Cmax and Cmin for 300 mg daily dose were about twice as would be predicted from 100 mg daily dose. The disposition of fluvoxamine appeared to follow elimination pharmacokinetics with a mean (%CV) V_{max} value of 330 mg/12 h (38%) and K_m value of 610 ng/mL (93%). However, Km values should be used with caution, since these were computed from three data points and data was highly variable (C.V. of 93%).

III. METABOLISM

A. RADIOLABEL DISPOSITION

The first human trial with fluvoxamine maleate was a radiolabeled study (Report 56654/15/74). The drug was administered in hard gelatin capsules to five healthy male volunteers as a single oral dose of 5 mg (5 subjects) and 1 mg (1 subject). Blood samples collected at 1, 3, 8 and 25 hours and urine collected upto 71 hours.

The excretion of total radicactivity in urine ranged from % (mean 94%) of the total dose administered. About 77% of the radioactivity was recovered within 24 hours. Excretion rate was shown to be biphasic with a terminal half-life ranging from hours. The plasma half-life from the last two time points were roughly estimated to be 14 to 22 hours. The results of this study led to the conclusion that orally administered fluvoxamine is virtually completely absorbed.

B. ISOLATION AND IDENTIFICATION OF METABOLITES

The isolation and identification of fluvoxamine metabolites was conducted using pooled urine collected from the first disposition study using ^{14}C-labeled fluvoxamine (Report 56654/15/74; 5 mg radiolabelled dose) and from a study in which subjects were administered a 100 mg dose of unlabeled drug (Report 56654/22/76).

Nine metabolites were identified, constituting approximately 85% of the urinary excretion products of fluvoxamine (metabolism scheme Figure 1 and Table 1 attached). The main routes of metabolism were demethylation and deamination. The main human metabolite is fluvoxamine acid in which the methoxyl side-chain is oxidized to a valeric acid group and which together with the N-acetylated analog, accounts for about 60% of the urinary excretion products. A third metabolite, fluvoxethanol, formed by oxidative deamination, accounts for about 10%. Both fluvoxamine acid and fluvoxethanol have been reported to be tested for:

1. tetrabenzine antagonism
2. 5-HTP potentiation
3. inhibition of serotonin uptake by rat brain synaptosomes

and have shown no serotonin reuptake inhibitory activity (Report H.114.101).

C. PROTEIN BINDING

The protein binding of fluvoxamine was investigated by equilibrium dialysis of the ^{14}C-labeled drug (Report 56630/54/77). It was demonstrated that fluvoxamine is about 77% bound to human plasma proteins and of that the greatest percentage (69%) is bound by the albumin fraction. A second protein binding study was conducted (since

first study utilized diluted plasma) using equilibrium dialysis to measure the protein binding of fluvoxamine in undiluted heparinized human plasma (Report H.114.630). The concentrations were chosen to cover most of the range that can be encountered in clinical use. The results showed that in the observed concentration range of approximately ng/mL to ng/mL in plasma, about 80% of fluvoxamine is bound to protein. At concentrations lower than ng/ml. high variability in percent bound was observed which ranged from %. Above ng/mL percent bound to protein was about %.

D. ISOMERISM

The chemical structure of fluvoxamine permits isomerization of the active E-isomer to the inactive Z-isomer. This isomerization can also occur during metabolism. The potential formation of the Z-isomer of fluvoxamine and of the major metabolites was studied using the urinary samples from five healthy volunteers who received three single doses of 50 mg at 4 hour intervals (Report H114.624). It was shown that, of the administered fluvoxamine maleate which contained less than % of the Z-isomer, excreted fluvoxamine and the major metabolites contained % of the Z-isomers. Thus interconversion does not seem to be of concern.

E. CYTOCHROME P450 METABOLISM

Multiple hepatic Cytochrome P450 (CYP450) enzymes are involved in the oxidative biotransformation of a large number of structurally different drugs and endogenous compounds. The available knowledge concerning the relationship of fluvoxamine and the CYP450 enzyme system has been obtained from the pharmacokinetic interaction studies conducted in healthy volunteers. Based on the results of these studies, fluvoxamine appears to inhibit the metabolism of several drugs that are oxidatively metabolized by the hepatic CYP450 system.

The drug interaction profile, summarized by CYP450 isoenzyme, is presented in the following table:

IA2	IIC9	IIIA4
Antipyrine	Warfarin	Antipyrine
Theophylline		Alprazolam
Propranolol		
Warfarin		

Antipyrine clearance decreased (63%), propranolol C_{min} serum concentrations increased folds), Warfarin plasma concentrations increased %), Alprazolam pharmacokinetic parameters (AUC, C_{max}, $T^{1/2}$) showed a % increase and

Theophylline plasma concentrations and elimination half life increased folds). Further details are provided in the drug interaction section of this review.

It is not known whether fluvoxamine cosegregates with CYP450 IID6 metabolism in humans. To date, no pharmacokinetic studies of fluvoxamine have been conducted in extensive and poor metabolizers of dextromethorphan. Sponsors are presently conducting in-vitro studies to determine specific isoenzymes involved in the metabolism of fluvoxamine.

IV. SPECIAL POPULATIONS

A. SINGLE DOSE AND STEADY-STATE PHARMACOKINETICS IN THE ELDERLY

To investigate the pharmacokinetics of fluvoxamine in the elderly, 50 mg of the drug was administered twice daily to a group of 14 elderly healthy volunteers, 13 of whom completed the study (Report H.114.625). The drug was administered for 28 days. Steady state plasma concentrations were achieved in 5 to 10 days. Mean AUC, Cmax and Tmax values did not differ on Days 14 and 28. Comparing the mean data results from this elderly study to studies in young subjects did not indicate any differences in the pharmacokinetic parameters of elderly vs young. However, individual data indicates a subpopulation of slow metabolizers of fluvoxamine (4 slow vs 9 fast).

B. SINGLE AND MULTIPLE DOSE PHARMACOKINETICS-ELDERLY/YOUNG

The single-dose (25 mg, 50 mg) and multiple-dose (50 mg, 100 mg) pharmacokinetics of fluvoxamine was evaluated in healthy elderly and young subjects (Report 100.0098). Twenty-three (23) healthy male subjects (11 elderly, 12 young) completed this open-label parallel group multiple dose study. Each subject received a single 25-mg fluvoxamine tablet on Day 1, a single 50-mg tablet on Day 3, a 50-mg tablet once daily on Days 5 to 13 and two 50-mg tablets once daily on Days 14 to 20.

Compared to the young subjects, AUC(0-inf), Cmax and T½ in the elderly group were greater by 56%, 6% and 52% ($p < 0.05$), respectively. Mean Tmax values were 66 to 236 min longer for the elderly, compared to the young subjects. At steady state, mean AUC(0-TAU), Cmax and T½ were greater in the elderly subjects by 55%, 35% and 28%, respectively, during the 100 mg multiple dose treatment. Mean Tmax values for the elderly were higher by 54 minutes at steady state, compared to the young group.

The results of the present study indicate steady-state plasma concentrations in elderly and young subjects were achieved after about 7 consecutive days of 50 mg and 100 mg doses. The increase in plasma concentrations and pharmacokinetic parameters observed in the elderly group at all dose levels is most likely due to age-related

decreases in hepatic oxidation and cardiac output, resulting in decreased efficiency of drug elimination. This study also indicated possibility of subpopulation due to genetic polymorphism of cytochrome p450 enzyme system, particularly CYP450IID6.

C. SAFETY/TOLERANCE IN RENALLY-IMPAIRED PATIENTS

Twenty-five (25) patients with decreased renal function (creatinine clearance of 5 to 45 mL/min) were enrolled in an open, baseline controlled study (two centers) and were treated for six weeks with fluvoxamine (Report H114.5097/MC1 + MC2/M). The volunteers were administered 50 mg of fluvoxamine maleate in the evening for three days. For the remainder of the study, dosing consisted of one 50-mg tablet in the morning and one in the evening, both doses with meals.

Fluvoxamine maleate at a dose of 50 mg twice a day did not appear to cause any serious problems when dosed in these patients. The range of plasma concentrations was ng/mL. These values are not higher than in subjects with normal renal clearance and support the conclusion that for unchanged fluvoxamine, renal clearance is not an important route of fluvoxamine elimination. Furthermore, the mean plasma concentrations at Week 6 (122.1 ± 84 ng/mL, $n = 13$) were similar to those at Week 4 (122.7 ± 79 ng/mL, $n = 11$). This suggests that no accumulation occurs in patients with renal failure once steady-state conditions have been achieved and therefore no dosage adjustment may be necessary.

D. PHARMACOKINETICS IN HEPATICALLY-IMPAIRED PATIENTS

A pharmacokinetic study was conducted in 13 patients with chronic liver disease (Report H.114.011.85). Each patient received a single dose of 100 mg of fluvoxamine maleate in the form of two 50-mg tablets.

The mean C_{max} value in patients with hepatic impairment was comparable to that observed in healthy volunteers. There was, however, an increase in the elimination half-life by about 60% and AUC by about 30% for the liver failure patients, indicative of a lower clearance in these patients.

V. DRUG INTERACTIONS

A. ALPRAZOLAM

The pharmacokinetic/pharmacodynamic evaluation of the combined administration of alprazolam and fluvoxamine to steady-state was performed in healthy male volunteers (Report TR7215-92016). The study was conducted in sixty, healthy, young, male volunteers ranging in age from 20 to 44 years old and weighing 59 to 100 kg. The study utilized a double-blind parallel design such that 20 subjects were randomly assigned into one of three treatments:

TREATMENT A: Days 1-3 - One 50-mg fluvoxamine maleate capsule at 8 AM
Days 4-6 - Two 50-mg fluvoxamine maleate capsules at 8 AM
Days 7-10 - Two 50-mg fluvoxamine maleate capsules at 8 AM and one placebo tablet at 8 AM, 1 PM, 6 PM, and 11 PM

TREATMENT B: Days 1-3 - One placebo capsule at 8 AM
Days 4-6 - Two placebo capsules at 8 AM
Days 7-10 - Two placebo capsules at 8 AM and one Xanax 1.0-mg tablet at 8 AM, 1 PM, 6 PM, and 11 PM.

TREATMENT C: Days 1-3 - One 50-mg fluvoxamine maleate capsule at 8 AM.
Days 4-6 - Two 50-mg fluvoxamine maleate capsules at 8 AM.
Days 7-10 - Two 50-mg fluvoxamine maleate capsules at 8 AM and one Xanax 1.0-mg tablet at 8 AM, 1 PM, 6 PM, and 11 PM.

Psychomotor performance was evaluated using Symbol Digit Substitution (SDS), Continuous performance (CPT) tests. Co-administration of alprazolam and fluvoxamine resulted in plasma concentrations and pharmacokinetic parameters (AUC, C_{max}, $T^{1/2}$) of alprazolam which were approximately twice those observed when alprazolam was administered alone; oral clearance was decreased to one half. The elevated plasma alprazolam concentrations resulted in increased decrements in psychomotor performance and memory, compared to alprazolam given alone. In presence of alprazolam, mean fluvoxamine plasma concentrations decreased by about 25%.

It should be noted that in this study 100 mg daily dose of fluvoxamine was administered whereas, 300 mg daily dose is recommended; hence greater interaction with alprazolam may be expected at the highest recommended dose of fluvoxamine. The results of this study indicate that alprazolam dose should be reduced and patients titrated to lowest effective dose of alprazolam.

SMOKERS vs NONSMOKERS

In alprazolam study each group had 10 smokers and 10 nonsmokers. Day 10 results for the fluvoxamine treatment group suggest that fluvoxamine AUC in smokers (2094 ± 1027 ng*hr/mL) was lower than that in nonsmokers (2716 ± 913 ng*hr/mL) by about 25%. The results indicate increased fluvoxamine metabolism due to smoking.

B. THEOPHYLLINE

The effect of steady state fluvoxamine on the pharmacokinetics of a single dose of theophylline was evaluated in healthy male volunteers (Report 56638/29/92). The study was conducted as a non-randomized crossover in 12 healthy non-smoking, male volunteers. The eleven subjects who completed the study ranged in age from 20 to

35 years of age and weighed 64 to 85 kg.

was administered orally and consisted of fluvoxamine as 50 mg 442 mg of aminophylline dissolved in 100 mL water. The subjects were a single dose of aminophylline on two separate occasions, prior to and ady state levels of fluvoxamine had been achieved. The subjects were given xamine 50 mg every 12 hours for 13 consecutive days to attain steady-state plasma concentrations. Aminophylline was administered as a single dose of aminophylline solution. This solution contained 442 mg of aminophylline, equivalent to 375 mg theophylline.

The clearance of theophylline was significantly decreased ($p < 0.05$), and theophylline AUC was increased fold. The elimination half-life of theophylline also demonstrated approximately a fold increase. Therefore, if theophylline has to be co-administered with fluvoxamine, the dose has to be reduced to one third of the usual daily maintenance dose and plasma concentrations of theophylline should be monitored.

C. PROPRANOLOL

To investigate whether fluvoxamine has any effect on the pharmacodynamics and pharmacokinetics of propranolol, a double-blind, placebo-controlled, drug interaction study was conducted (Report H.114.5092). Twelve healthy volunteers (6 males and 6 females) were stabilized on propranolol 160 mg Q.D. (Inderal LA®) for 15 days and were administered fluvoxamine 50 mg bid (or placebo) on Days 4-15. The crossover treatment was identical, except that the fluvoxamine and placebo treatments were reversed.

Propranolol alone produced its expected reduction in heart rate and blood pressure. Fluvoxamine had no additive effect on lowering blood pressure with the exception of a small but significant ($p < 0.05$) decrease in mean diastolic blood pressure during exercise on the treadmill. Heart rate was also slightly reduced by approximately 3 beats/minute and 8 beats/minute during exercise. Compared with placebo, the differences were statistically significant at the 5% level.

For most of the volunteers, steady-state concentrations of fluvoxamine were reached 1 week after the start of treatment. After concurrent treatment with fluvoxamine, the steady-state trough plasma levels of propranolol increased an average of fold. Although mean of 26.3 vs 131.1 ng/mL were reported; two of the subjects were outliers; that is, one subject had fold higher and other subject had fold higher propranolol concentrations.

In order to investigate whether a similar pharmacokinetic interaction occurs between fluvoxamine and immediate release propranolol tablets, a small open-label study with a similar study design as above was conducted (Report H.114.5095). In this study

collected for 72 hours following a 1.25 mg intravenous dose of digoxin over a 15-minute period on day 15 of the two treatments.

No statistically significant difference in digoxin pharmacokinetics was found between the fluvoxamine and placebo treatments, based on similar AUC (0.25 to 72 hours) values for two treatments. Further, this difference was only about 5%.

It was concluded that there was no effect of fluvoxamine on single-dose pharmacokinetics of digoxin after IV dosing.

G. ATENOLOL

Twelve healthy volunteers (six males and six females), ages 20-50 years old, participated in this study (H.114.5096) to evaluate the effect of fluvoxamine on the pharmacokinetics of atenolol, only six subjects completed the study. The design of this study was identical to that of the study with propranolol (Section C), with 100 mg of atenolol administered daily instead.

In contrast to propranolol, concomitant administration of fluvoxamine with atenolol did not influence plasma levels of atenolol.

H. ALCOHOL

Two studies were conducted to assess the potential pharmacokinetic and pharmacodynamic interaction between fluvoxamine and alcohol administered orally or intravenously.

Twelve healthy male volunteers took part in a cross-over study (Report H.114.627) designed to assess the interaction between twice daily oral doses of fluvoxamine maleate (50 mg) or placebo and single doses of alcohol (ethanol, 40 grams). Volunteers received fluvoxamine maleate (50 mg) or placebo once daily for 3 days and then 50 mg twice daily for 9 additional days with a final 50 mg dose on the morning of day 13. On Day 1 of each treatment period all volunteers received a single dose of alcohol. On Days 10 and 13 of each treatment period all volunteers received either alcohol or a placebo resembling alcohol. All alcohol doses were given 2 hours after the morning dose of fluvoxamine. On days 1, 10 and 13, blood samples were taken for the measurement of blood alcohol concentration. Assessments of cognitive function and measurement of breath alcohol concentrations were also made. On Days 10 and 13 blood samples were taken for the measurement of plasma fluvoxamine levels.

In Study H.114.6002 (Report Number H.114.627), a single dose of fluvoxamine maleate (50 mg) on Day 1 had no effect on blood alcohol pharmacokinetics. After repeated twice daily dosing with fluvoxamine, the mean AUC for a single dose of alcohol was significantly ($p = 0.025$) higher (11% on Day 13) than in the presence of

placebo. This difference is not considered to be clinically significant. Likewise, alcohol had no effect on fluvoxamine pharmacokinetics.

The pharmacokinetic interaction between fluvoxamine and intravenously administered alcohol was studied in 12 healthy, male subjects (Report H.114.628). On two occasions, one week apart and in a randomized cross-over design, they received 50 mg fluvoxamine maleate (capsule) or a placebo capsule. Two hours after capsule intake, an intravenous infusion of ethanol 8% v/v in saline (40 grams in 2 hours) was given. On Days 9-11 all subjects took 50 mg fluvoxamine maleate in the morning, and on Days 12-21 50 mg fluvoxamine twice daily. On Day 22 the third study session took place. After the morning dose of 50 mg fluvoxamine maleate the participants received again an i.v. dose of 40 grams alcohol between 2 and 4 hours after capsule intake. On Days 1, 8 and 22 blood samples were drawn for measurement of blood alcohol and plasma fluvoxamine concentrations.

In Study H.114.6001 (Report H.114.628), the plasma levels of fluvoxamine were in the range observed in other pharmacokinetics studies. The pharmacokinetics of intravenously administered alcohol was not significantly affected by concomitant multiple-dose administration of fluvoxamine as compared to alcohol (i.v) alone. A minor increase in Cmax of alcohol was observed when single-dose fluvoxamine was co-administered.

From the results of these two studies, it can be concluded that there is no significant influence of the administration of fluvoxamine on the pharmacokinetics of alcohol. Likewise alcohol had no effect on the pharmacokinetics of fluvoxamine.

VI. CONCENTRATION-EFFECT RELATIONSHIPS

In the two double-blind studies in obsessive compulsive disorder, fluvoxamine plasma samples were collected for analysis at the final double-blind assessment (Day 70 or earlier) as a measure of compliance (as per protocol H.114.5529 and H.114.5534). The samples were collected from 217 of the 320 patients enrolled in the two studies. Seventy-nine (77%) of the 103 fluvoxamine-treated patients were included in the analysis. Twenty-four fluvoxamine-treated patients were excluded because the plasma concentration and Y-BOCS score changes from baseline to endpoint did not show any correlation. Relationship between fluvoxamine plasma concentration and demographics (age, sex and dose weight ratio) and clinical efficacy were assessed. However, since plasma samples collected were not in a controlled fashion inferences drawn by the following analysis may not be useful or conclusive.

AGE: There was no consistent trend or relationship between age and plasma concentration. However, patients in the age group greater than 65 (N = 2) had plasma concentrations fold higher than the patients in the age group of less than 30 years.

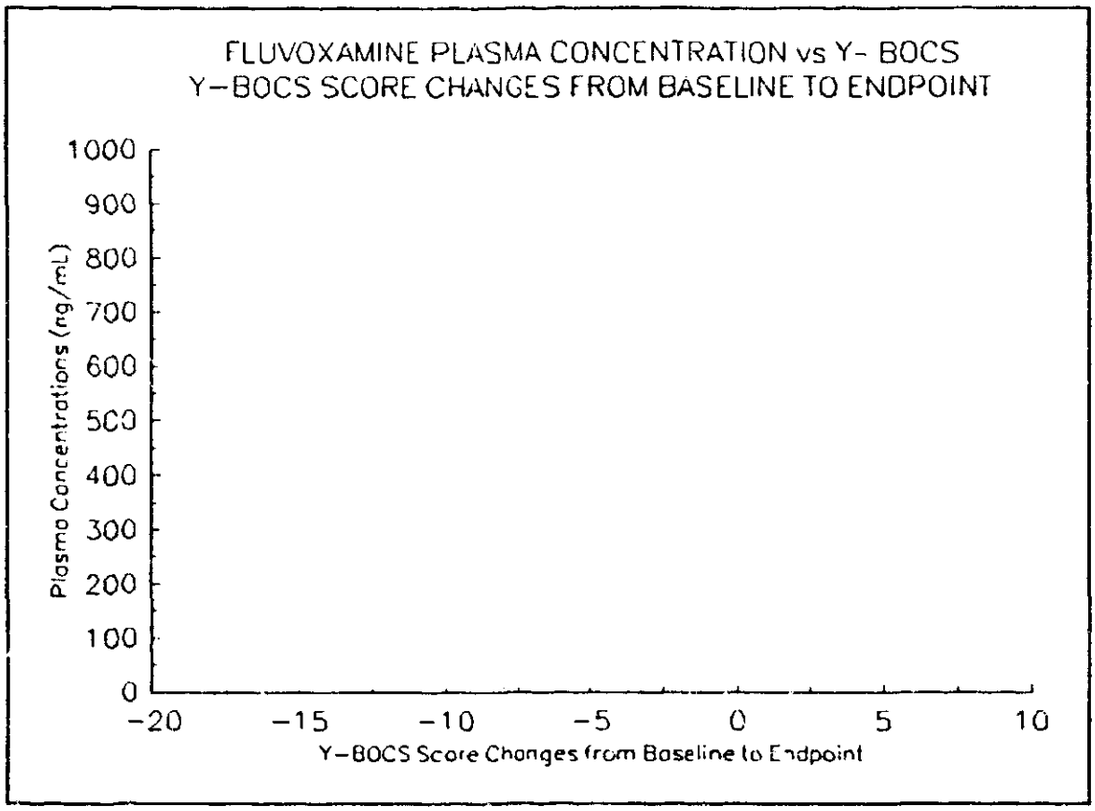
SEX: The mean plasma concentration for females was about 29% greater than males

for data combined from protocols 114.5529 and 114.5534. The mean plasma concentrations for females in protocol 114.5529 were greater by 69% whereas, in protocol 114.5534 males had plasma concentrations higher by %.

Dose Weight Ratio: There does not appear to be any trend or relationship between plasma concentrations of fluvoxamine and dose/weight ratio in the combined group.

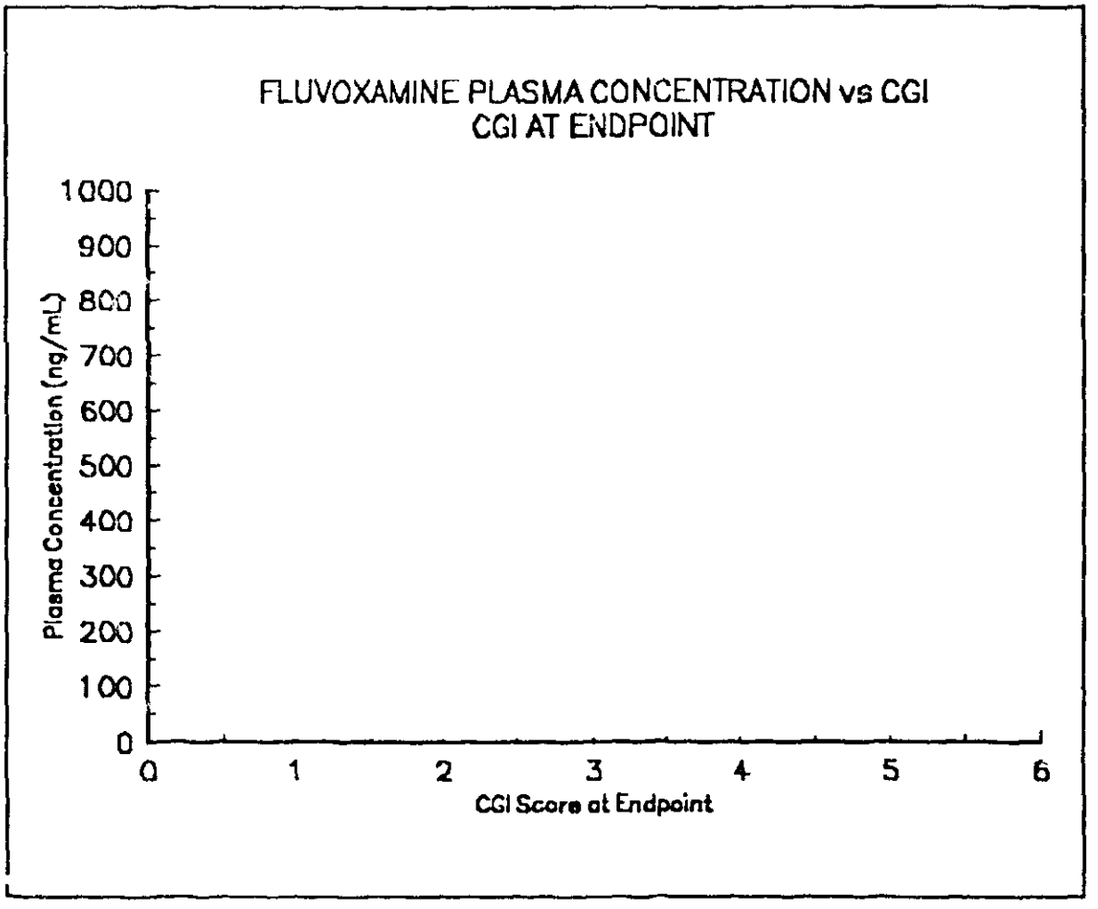
Clinical Response: As described below there appears to be no correlation between fluvoxamine plasma concentrations and CGI global improvement data or YBOCS score changes.

A plot of the fluvoxamine plasma concentration (ng/mL) versus change in Y-BOCS score from baseline to endpoint, as shown in the following figure, revealed a widely scattered display of data points, thus indicating there was no relationship between the two parameters. The Pearson correlation coefficient was -0.008, with a p-value of 0.9-1, confirming that no correlation can be found between the fluvoxamine plasma concentration and Y-BOCS score changes.



Fluvoxamine plasma concentration vs Y-BOCS score (changes from baseline to endpoint for studies H.114.5529 and H.114.5534). r = p-value = 0.94

Fluvoxamine plasma concentration versus the global improvement item of the CGI at endpoint was also plotted. As shown in the next figure, most of the plasma values fell into the low plasma concentration range with only a few exceptions. Using the criteria describing therapeutic response, i.e., scores 8 obtained from the global improvement item of the CGI of 1 or 2 (response), and scores of 3 to 7 (non-response), there was not enough evidence to show any correlation between fluvoxamine plasma concentration and the CGI global improvement data.



Plasma concentration vs CGI score at endpoint for studies H.114.5529 and H.114.5534. Patients with CGI of 1 or 2 were responders. Those patients with CGI of 3 to 7 were considered as non-responders.

Because of the lack of consistent timing of blood sample collection in relation to study drug administration and the flexible dose design of the clinical studies, the inability to find a correlation between fluvoxamine plasma concentrations and response is not surprising. Thus from these data no conclusion can be drawn about this relationship.

VII. FORMULATION

All strengths of fluvoxamine maleate tablets (25, 50, 100, and 150 mg) are compressed from a common granulation. The proposed market presentation for the 50 and 100 mg dosage strengths are in the form of scored tablets, while the 25 and 150 mg strengths are unscored. The original NDA submission provides for the manufacture, control, packaging, holding and labeling of the unscored form of the tablets. In an amendment subsequently submitted on August 23, 1993, the same information for scored 50 mg and 100 mg tablets is provided.

VIII. DISSOLUTION

During the course of *in vitro* dissolution profile investigation of fluvoxamine maleate tablets, three different media (de-aerated water, simulated gastric fluid (SGF) without enzymes and simulated intestinal fluid (SIF) without enzymes) were studied with respect to identical dissolution test parameters. The dissolution profiles for the 50, 100 and 150 mg tablets appeared to be quite similar for each dosage strength, with the amount of fluvoxamine released being highest in SIF (approximately '%), followed by SGF (approximately %), and water (approximately %) within minutes. Similar prompt release profiles were also observed for the tablet and capsule (clinical formulation) batches that were used in the *in vivo* bioequivalence and dose-proportionality studies.

The dissolution methodology currently provided in the NDA of all strengths for release control purposes is outlined as follows:

Medium:	mL Purified Water at °C ± °C.
Apparatus:	USP Apparatus 2 (Paddles) at RPM.
Specification:	Not less than 85% dissolved in 45 minutes.

The dissolution specification proposed by sponsor has been set at 85% (Q) in 45 minutes. However, dissolution data of film coated tablets suggests that about 95% of the drug was dissolved within 30 minutes. **Division of Biopharmaceutics recommends that the dissolution specification be set at:**

Medium:	900 mL Purified Water at 37°C ± 0.5°C.
Apparatus:	USP Apparatus (Paddles) at 50 RPM.
Specification:	Not less than '% dissolved in minutes.

GENERAL COMMENTS TO THE MEDICAL REVIEWER (Need not be sent to the firm):

1. Alprazolam drug interaction study was performed with fluvoxamine 100 mg daily dose administered QD, whereas, the recommended maximum dose of fluvoxamine is 300 mg daily. It is possible that there might be greater drug interaction with alprazolam when coadministered with 300 mg daily dose of fluvoxamine.

2. It should be noted that fluvoxamine significantly interacted with theophylline and propranolol.

COMMENTS TO BE SENT TO THE FIRM

Division of Biopharmaceutics recommends the following Dissolution specifications for for all strengths of fluvoxamine tablets:

Medium: mL Purified Water at °C ± °C.
Apparatus: USP Apparatus (Paddles) at RPM.
Specification: Not less than % dissolved in minutes.

Chandrahas G. Sahajwalla, Ph.D.
Pharmacokinetics Evaluation Branch

Safaa Ibrahim, Ph.D.
Pharmacokinetics Evaluation Branch

Vijay Tammara, Ph.D.
Pharmacokinetics Evaluation Branch

Biopharm Day: October 8, 1993

Review Completed: 12/16/93

Revisions Completed: 1/5/94

RD/FT initialed by Raman Baweja, Ph.D. R. Baweja 1/7/94.

cc: NDA 20-243, HFD-120, HFD 426 (Sahajwalla, Tammara, Ibrahim, Baweja, Fleischer), Chron, Division, Drug, Reviewer Files. HFD-340(Visk);

1 page

purged

Table 1

PHARMACOKINETIC AND PHARMACODYNAMIC PROFILE OF FLUVOXAMINE AND ITS METABOLITES

Compound[a]	Percentage Radioactivity in Urine[b]	Plasma Half Life (hr)	Ratio of Metabolite to Fluvoxamine in AUC or Cmax	Pharmacologic Activity Relative to Serotonin Re Uptake Inhibition[e]	Percent Bound to Plasma Protein	Monitor in PK/BE Studies	Enzyme System Responsible for Formation[f]
Total Radioactivity	94%	Oral $t_{1/2\alpha}$ = 2.5 hr[c] Oral $t_{1/2\beta}$ = 14.8 hr[c] Oral $t_{1/2\beta}$ = 14.22 hr[d]	...	...	...	...	...
Fluvoxamine	0%	UNKNOWN	...	ACTIVE	77-80% (mostly to albumin)	YES	...
Fluvoxamine Acid (B)	35%	UNKNOWN	UNKNOWN	INACTIVE	UNKNOWN	NO	UNKNOWN
Fluvoxethanol (F1)	5%	UNKNOWN	UNKNOWN	INACTIVE	UNKNOWN	NO	UNKNOWN
N Acetylated Fluvoxamine (D)	8%	UNKNOWN	UNKNOWN	UNKNOWN	UNKNOWN	NO	UNKNOWN
G	6%	UNKNOWN	UNKNOWN	UNKNOWN	UNKNOWN	NO	UNKNOWN
C2	7%	UNKNOWN	UNKNOWN	UNKNOWN	UNKNOWN	NO	UNKNOWN
F	10%	UNKNOWN	UNKNOWN	UNKNOWN	UNKNOWN	NO	UNKNOWN
C1	4%	UNKNOWN	UNKNOWN	UNKNOWN	UNKNOWN	NO	UNKNOWN
A1	8%	UNKNOWN	UNKNOWN	UNKNOWN	UNKNOWN	NO	UNKNOWN
C3	3%	UNKNOWN	UNKNOWN	UNKNOWN	UNKNOWN	NO	UNKNOWN

[a] See accompanying figure for structures of fluvoxamine and metabolites.
[b] No plasma radioactivity data available.
[c] Based on urinary excretion rate profiles
[d] Two point determination based on decline of total plasma radioactivity between t = 8 and 25 hr.
[e] No known relationship exists between plasma concentration of metabolites and observed toxicity
[f] No direct evidence exists for metabolizing enzymes, although Cyt P450 2D6 implicated from human drug interaction studies

FEB 10 1994

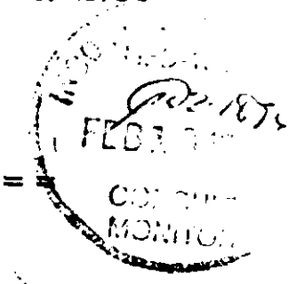
Fluvoxamine Maleate (LUVOX®)
Tablets 25, 50, 100 and 150 mg

Solvay Pharmaceuticals, Inc
901 Sawyer Road
Marietta, Georgia 30062
Submission Dates: 10/29/93

Reviewers: Chandrahas Sahajwalla, Ph.D.

NDA 20-243

Type of Submission:



Review of a Submission

BACKGROUND

Fluvoxamine maleate (LUVOX®) is a potent and selective 5-hydroxytryptamine reuptake inhibitor (SSRI) indicated for use in the treatment of obsessive-compulsive disorder (OCD) in humans. The recommended dose is 100 to 300 mg daily.

Fluvoxamine is metabolized in the liver by the cytochrome P450 system, and may be a competitive inhibitor for the IA2 and IIIA4 isoenzymes. It has been suggested that a sub-population due to genetic polymorphism of cytochrome P450 enzyme system particularly CYP450IID6 exists. When co-administered with fluvoxamine, plasma concentrations of warfarin (about fold), theophylline fold), propranolol fold) and alprazolam fold) were increased in healthy volunteers. In presence of fluvoxamine, antipyrine clearance decreased (63%) and T1/2 fold) increased. Fluvoxamine coadminstration did not alter the single dose pharmacokinetics of digoxin. Increased fluvoxamine metabolism (about 25%) has been observed due to cigarette smoking.

NDA for fluvoxamine (NDA 20-243) has been reviewed by the Division of Biopharmaceutics. This submission deals with an in-vitro drug metabolism study and drug interaction of fluvoxamine with lorazepam and bromazepam.

In-Vitro Drug Metabolism

Distinguishing Serotonin-Specific Reuptake Antidepressants via Effects on Drug Metabolism in Vitro:

Serotonin-specific reuptake inhibitors (SSRI) antidepressants have the property to impair the activity of hepatic drug metabolizing enzymes. The study submitted by the sponsor evaluated the effects of fluvoxamine on drug-metabolizing activity in human liver microsomal preparations in vitro. Two of the cytochrome subfamilies evaluated were p450-3A4 (reflected by parallel hydroxylation of alprazolam) and p450-2D6 (reflected by hydroxylation of desipramine to form 2-hydroxy-desipramine). The effects of fluvoxamine were compared to those of other SSRIs and their principal

metabolites. Inhibiting properties of ketoconazole and quinidine, established as highly potent and relatively specific inhibitors of p450-3A4 and p450-2D6, respectively, were also studied. Results are provided in Table 1 and Figures 1-3. It appears from the in-vitro data that fluvoxamine is a potent inhibitor of alprazolam metabolite formation (3A4) and that it is relatively weak towards inhibiting 2-OH-DMI formation (2D6). Details of methods for experiment and data analysis are provided in the Appendix.

In humans, alprazolam clearance decreased by about 55% when it was coadministered with fluvoxamine compared to alprazolam given alone. In vitro partitioning of fluvoxamine between liver homogenate and water yielded a ratio of 26.6. Based on in vitro data, expected decrease in clearance of alprazolam was 43%. Thus sponsor concludes that in vitro findings are predictive of in vivo drug interactions (refer comments 3-5).

Lorazepam and Bromazepam

The Influence of Multiple-Dose Administration of Fluvoxamine on the Pharmacokinetics of the Benzodiazepines Bromazepam and Lorazepam. A Randomized, Cross-over Study (Protocol H. 1 14.6004/P).

OBJECTIVE

The objective of this study was to determine the influence of fluvoxamine on the pharmacokinetics and pharmacodynamics of bromazepam and lorazepam in healthy male subjects.

STUDY DESIGN

Thirteen healthy male subjects participated in this randomized, four period, crossover study. One subject withdrew for personal reasons and was replaced by a subject who completed the pharmacokinetics portion of the study. Pharmacodynamic measurements were obtained for 11 of the 12 subjects who completed the study.

Serial blood samples for the determination of plasma bromazepam and lorazepam concentrations were collected up to 96 hours after benzodiazepine administration. Immediate and delayed word recall, simple and choice reaction times, number vigilance task, memory scanning task and delayed word recognition tests were performed at frequent intervals during each treatment period.

DOSAGE FORMS:

Fluvoxamine 50-mg capsule (Batch No. FCA89JO4A, OP No. 13294)
Bromazepam 12-mg capsule (Batch No. FCA9OCI2B, OP No. 13335)
Lorazepam 4-mg capsule (Batch No. FCA9ODI 1 A, OP No. 13338)

RESULTS:

Steady-state plasma fluvoxamine concentrations were achieved during all the study sessions. The mean bromazepam (single dose) and lorazepam (single dose) pharmacokinetics parameters alone and in the presence of fluvoxamine are presented in the following tables.

Geometric and Harmonic Mean Pharmacokinetics Parameters and 90% Confidence Intervals (CI) for Bromazepam and Lorazepam Alone and With Fluvoxamine

Bromazepam Parameter	Bromazepam	Bromazepam (plus fluvoxamine)
Median Tmax (hours)	2.0	2.75
Cmax (ng/mL) (90% CI)*	158 (131-190)	215 (176-263)
AUC (nghr/mL) (90% CI)	3879 (3081-4883)	9195 (7132-11854)
Harmonic $T_{1/2}$ (hr) (90% CI)	18.8 (17.1-20.8)	36.0 (31.1-42.8)
Lorazepam Parameter	**Lorazepam**	**Lorazepam (plus fluvoxamine)**
Median Tmax (hours)	1.75	1.75
Cmax (ng/mL) (90% CI)	36 (32-40)	38 (35-42)
AUC (ng hr/ml) (90% CI)	669 (574-781)	749 (625-897)
Harmonic $T_{1/2}$ (hr) (90% CI)	14.6 (13.1-16.4)	16.3 (14.6-18.5)

* 90% CI is around the Treatment Mean.

The ratio of the geometric mean values of AUC for bromazepam with fluvoxamine to the AUC of bromazepam alone was 2.39. The ratio of the geometric mean values of Cmax for bromazepam with fluvoxamine to the Cmax of bromazepam alone was 1.36. The harmonic mean elimination half-life (T1/2) of bromazepam was significantly increased ($p<0.05$) in the presence of fluvoxamine, compared to bromazepam given

alone.
The geometric mean AUC and harmonic mean T1/2 for lorazepam in the presence of fluvoxamine were increased by 12%, compared to lorazepam given alone. The geometric mean Cmax and median Tmax were not greatly affected by concomitant administration of fluvoxamine.

Impairment in the cognitive function tests when bromazepam and fluvoxamine were administered concomitantly appeared 16 and 24 hours after dosing when lorazepam and fluvoxamine were administered in combination. After 24 hours, impairments in the primary or secondary variables were observed on 26 occasions during bromazepam and fluvoxamine co-administration, compared to four occasions where bromazepam was given alone.

The effects of lorazepam alone on cognitive function had subsided at 12 hours post dose, but there was a return of widespread impairment at 1 6 hours post dose suggesting a possible interaction between minimal impairment and fatigue. After 24 hours, impairments in the primary or secondary cognitive function variables were observed on four occasions with lorazepam alone and on 16 occasions during fluvoxamine and lorazepam concomitant administration.

Fluvoxamine effects on cognitive function as assessed from fluvoxamine baseline data (pretreatment) indicated significant improvements in speed of memory scanning, speed of detections on the vigilance task and accuracy of delayed verbal recall. Trends for improvements were also seen in simple reaction time, choice reaction time, and accuracy of vigilance.

CONCLUSIONS

The above results suggest that fluvoxamine inhibits the metabolism of benzodiazepines which are metabolized by hepatic oxidative pathways (bromazepam), but does not affect the metabolism of benzodiazepines which are metabolized by glucuronide conjugation (lorazepam). The increased plasma concentrations of bromazepam which were observed in the presence of fluvoxamine were accompanied by increased impairment of cognitive function, compared to bromazepam given alone. The overall increase in impairments during fluvoxamine co-administration was greater with bromazepam than with lorazepam.

The AUC and $T_{1/2}$ of bromazepam increased about fold suggesting that fluvoxamine interferes with metabolism of bromazepam. Pharmacodynamic evaluation showed that from 16 hours onwards, fluvoxamine co-administration with both benzodiazepines caused an increased number of cognitive impairments. The overall increase in impairments was greater with bromazepam than with lorazepam.

Labelling Comments:

1. Lorazepam in combination with fluvoxamine produces marked impairment of attention, vigilance, memory and subjective alertness. Fluvoxamine has shown significant drug interaction with Bromazepam and Alprazolam hence, When these drugs are administered concurrently, the starting dose of **benzodiazepines** should be reduced and the patient titrated to the lowest dose.

General Comments:

2. The agency appreciates and encourages the efforts by the sponsor for conducting the in-vitro drug metabolism study to predict possible drug interactions.

3. The method for determining Ki values for various SSRIs was not described in the report. Dixon plots would be helpful in this regard.

4. The Ki values of different SSRIs for known Cyt-P450 probes are indicative of possible interactions, however, these are not conclusive unless experiments are properly designed.

5. In vitro partition ratio of fluvoxamine between liver homogenate and water was used to predict the net decrement in alprazolam clearance based on the in vitro data. This fails to represent proper physiologic conditions. The partition ratio between hepatocytes or liver tissue slices and plasma would be more relevant in this assessment.

Recommendation:

Please incorporate comment 1 in the labelling of fluvoxamine. Please forward comments 1-5 to the sponsor.

Chandrahas G. Sahajwalla, Ph.D.
Pharmacokinetics Evaluation Branch

RD/FT initialed by Raman Baweja, Ph.D. R. Baweja 2/10/94.

cc: **IND , HFD-120, HFD 426 (Sahajwalla, Baweja, Fleischer), Chron Division, Drug, Reviewer Files,** HFD 340(VSL).

Draft dated 2/8/94

TABLE 1

SUMMARY OF *IN VITRO* INHIBITION STUDIES

Mean (±SE) K_i values in μM (n=3-6):

	Alprazolam		Desipramine
	4-OH-ALP formation	α-OH-ALP formation	2-OH-DMI formation
SSRIs			
Fluvoxamine	10.2(±1.3)	8.2(±3.3)	16.6(±6.5)
Fluoxetine	83.3*	47.2(±13.7)	3.0(±0.7)
Norfluoxetine	11.1*	8.8(±3.5)	3.5(±1.1)
Sertraline	23.8*	159(±83)	22.7(±7.0)
Desmethylsertraline	20.4*	56(±22)	16.0(±4.5)
Paroxetine	39.4(±5.2)	36.7(±7.2)	2.0(±0.8)
Index compounds			
Ketoconazole	.046(±.013)	.076(±.013)	10.3(±1.8)
Quinidine	626*	82(±27)	0.053(±0.037)

*indicates harmonic mean value

FIGURE 1

FIGURE 2

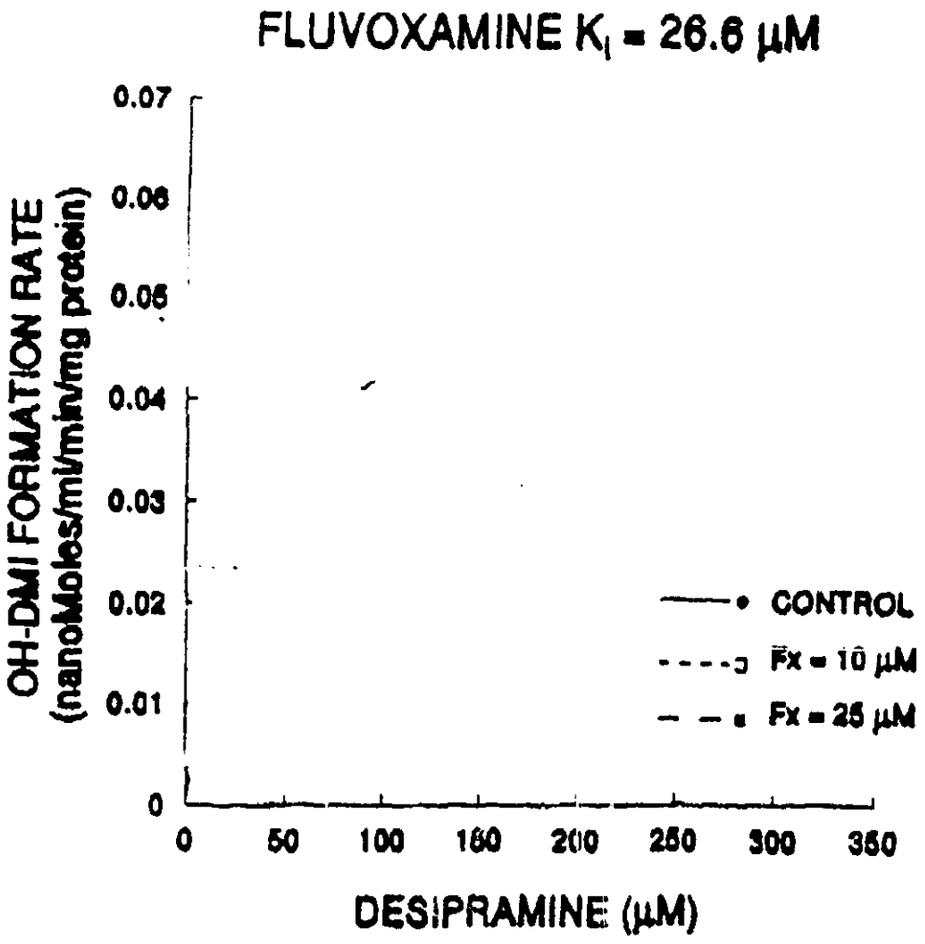
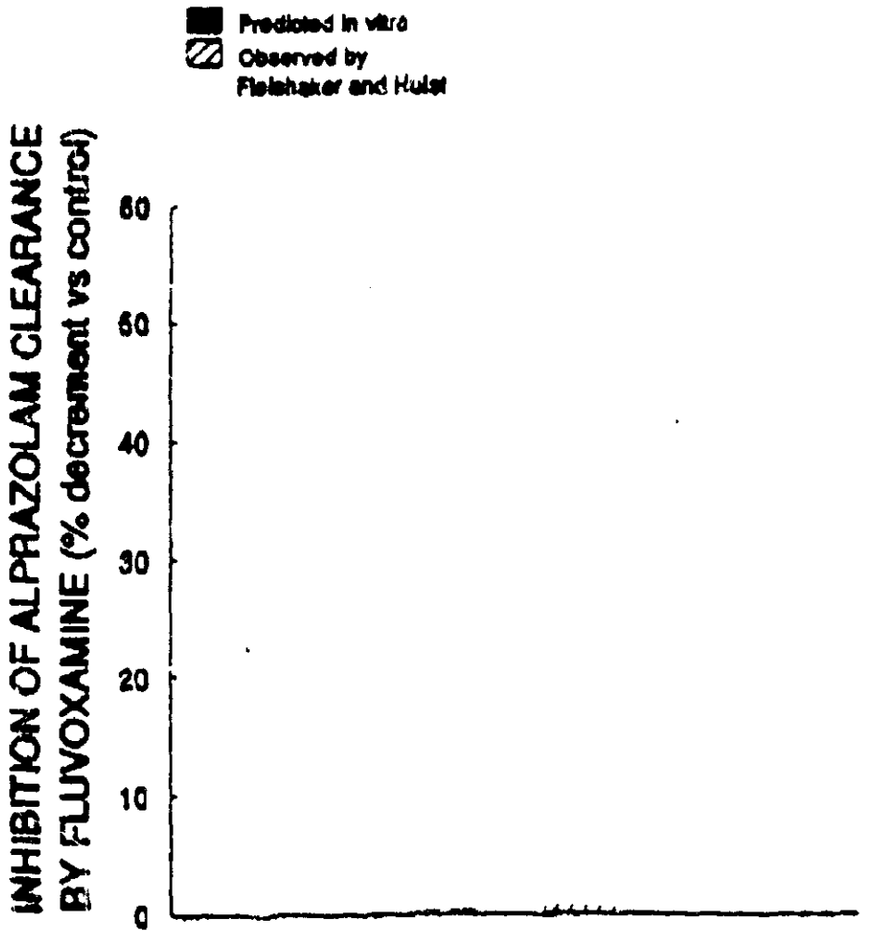

FLUVOXAMINE K_i = 26.6 µM
OH-DMI FORMATION RATE (nanoMoles/ml/min/mg protein)
0.07
0.06
0.05
0.04
0.03
0.02
0.01
0
0
50
100
150
200
250
300
350
DESIPRAMINE (µM)
CONTROL
Fx = 10 µM
Fx = 25 µM

FIGURE 3


Predicted in vitro
Observed by
Fleishaker and Hulst
INHIBITION OF ALPRAZOLAM CLEARANCE
BY FLUVOXAMINE (% decrement vs control)
60
50
40
30
20
10
0

Lisa L. von Moltke, M.D.
David J. Greenblatt, M.D.
Jerold S. Harmatz, B.A.
Richard I. Shader, M.D.

Department of Pharmacology and
Experimental Therapeutics,
Tufts University School of Medicine and
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Boston, MA

SUMMARY SCIENTIFIC REPORT

DISTINGUISHING SEROTONIN-SPECIFIC REUPTAKE INHIBITOR ANTIDEPRESSANTS VIA EFFECTS ON DRUG METABOLISM *IN VITRO*

Background and Objectives

Serotonin-specific reuptake inhibitor (SSRI) antidepressants have the additional pharmacologic property of impairing the activity of hepatic drug-metabolizing enzymes. Many clinical reports have described pharmacokinetic drug interactions of actual or potential clinical importance as a consequence of this property.[1,2] However it is clear that there are significant differences among SSRIs in their capacity to inhibit cytochrome activity; likewise, not all cytochrome subfamilies are equally susceptible to inhibition by SSRIs.[3,4]

The present study evaluated the effects of fluvoxamine on drug-metabolizing activity in human liver microsomal preparations *in vitro*. Two of the most important cytochrome subfamilies were assessed: P450-3A4 and P450-2D6. The index reaction reflecting P450-3A4 activity was the parallel hydroxylation of the benzodiazepine alprazolam (ALP) to its metabolites, 4-hydroxy- and α-hydroxy-alprazolam (4-OH-ALP, α-OH-ALP).[5] The index reaction reflecting P450-2D6 activity was the hydroxylation of desipramine (DMI) to form 2-hydroxy-desipramine (2-OH-DMI).[6] The effects of fluvoxamine were compared to those of other SSRIs and their principal metabolites. Also studied were the inhibiting properties of

ketoconazole and quinidine, established as highly potent and relatively specific inhibitors of P450-3A4 and P450-2D6, respectively.[3,4,7,8]

Methods

Liver samples from human donors were used to prepare microsomes by ultracentrifugation as described previously.[9-11] Microsomal pellets were suspended in potassium phosphate buffer containing % glycerol and stored at -80°C until use. Incubation mixtures contained mM phosphate buffer, mM Mg^{++}, mM $NADP^{+}$, and an isocitrate/isocitric dehydrogenase regenerating system. Reactions were initiated by addition of microsomal protein mg/ml). After 20-30 minutes at 37°C, reactions were stopped by and addition of µl of acetonitrile. The appropriate internal standard was added, the incubation mixture was centrifuged, and the supernatant transferred to an autosampling vial for HPLC analysis. All incubations were performed in duplicate.

The HPLC system used a reverse-phase C-18 Microbondapack column, with effluent monitored by ultraviolet absorbance.[9-11] Incubation mixtures were analyzed along with calibration standards containing known quantities of metabolites. For analysis of 4-OH-ALP and α-OH-ALP, the internal standard was nitrazepam or acetaminophen, and the absorbance wavelength was nm; for 2-OH-DMI, the internal standard was hydroxy-clomipramine and the wavelength was 254 nm.

For studies of ALP,[9,10] incubation tubes contained ALP concentrations ranging from µM. Inhibitor studies included incubation tubes containing individual SSRIs (up to µM), ketoconazole (up to M), or quinidine (up to µM), along with ALP.

For studies of DMI,[11] incubation tubes contained DMI ranging from

μM. Inhibitor tubes contained SSRIs μM), ketoconazole (up to μM) or quinidine (up to μM).

Reaction velocities were expressed in units of nanoMoles/ml/min/mg protein.

Data Analysis

Reaction velocities (V) at varying concentration of substrate (S) and inhibitor (I) were analyzed (without transformation) by nonlinear least squares regression analysis.[12] Data points were fitted to the following function:

$$V = \frac{V_{max} \cdot S}{S + K_m \cdot (1 + I/K_i)} \qquad \text{(Equation 1)}$$

Iterated variables were: V_{max}, the maximum reaction velocity, K_m, the half-maximum substrate concentration; and K_i, the inhibition constant.

Results and Discussion

Figures 1 and 2 show representative kinetic curves for ALP and DMI, and the effect of fluvoxamine on the reaction rates. Table 1 summarizes all K_i values.

Fluvoxamine and norfluoxetine had similar potency as inhibitors of alprazolam metabolite formation, while the other SSRIs had somewhat lower potency. Consistent with the presumed role of P450-3A4, ketoconazole was a highly potent inhibitor of both pathways, while quinidine was a weak inhibitor.

Paroxetine, fluoxetine and norfluoxetine were the most potent inhibitors of 2-OH-DMI formation, while fluvoxamine, sertraline, and desmethylsertraline were relatively weak. Human pharmacokinetic studies have yielded results consistent with the *in vitro* findings. Paroxetine[13] and fluoxetine/norfluoxetine[14] cause very large increases in steady-state DMI levels during coadministration, while cotherapy of DMI with sertraline/desmethylsertraline causes relatively small changes in steady-state DMI levels.[14] *In vitro* studies

of the index compounds (Table 1) demonstrated that quinidine was a highly potent inhibitor of 2-OH-DMI formation, with a K_i value in the nanomolar range. Although much less potent than quinidine, ketoconazole had a mean K_i of 10.3 μM.

The relation of the *in vitro* findings for fluvoxamine to actual drug administration in humans was evaluated using the data of Fleishaker and Hulst.[15] In that study, coadministration of fluvoxamine with alprazolam caused a 55% reduction in alprazolam clearance compared to alprazolam given alone. The mean steady-state fluvoxamine concentration was 80.3 ng/ml (.2525 μM). We measured the *in vitro* partitioning of fluvoxamine between liver homogenate and water; the mean partition ratio was 26.6. This, multiplied by the plasma concentration from above, yields an expected liver tissue concentration of μM. Using Equation 1, above, it can be shown that the fractional decrement of *in vitro* reaction velocity at any concentration of inhibitor relative to the velocity with no inhibitor is:

$$\text{fractional decrement} = \frac{I}{I+K_i} \qquad \text{(Equation 2)}$$

under the assumption that the concentration of substrate (alprazolam) is much smaller than the reaction K_m. Entering μM as the inhibitor concentration in Equation 2, the mean predicted net decrement in alprazolam clearance based on the *in vitro* data was 43% ± 3.8% (Figure 3). Thus the in vitro findings are of predictive value in the context of human drug interactions.

ACKNOWLEDGEMENTS

The authors are grateful for the contributions of Dr. Michael H. Court and Ms. Su Xiang Duan.

ENVIRONMENTAL ASSESSMENT

AND

FINDING OF NO SIGNIFICANT IMPACT

FOR

Luvox
(fluvoxamine maleate)

Tablets
(25, 50, 100, and 150 mg)

NDA 20-243

FOOD AND DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH

FINDING OF NO SIGNIFICANT IMPACT

NDA 20-243

Luvox

(fluvoxamine maleate)

Tablets
(25, 50, 100, and 150 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 Luvox, Solvay Pharmaceuticals 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 cannot determine that Luvox may not be toxic to organisms in the human environment due to limited ecotoxicity data. Therefore the applicant shall be required to collect contaminated-drug substance wash water associated with equipment

cleaning during the manufacture of Luvox tablets treating the same as pharmaceutical waste. The firm shall transport this waste off-site for destruction by high temperature incineration. The firm has provided letters from their foreign manufacture assuring compliance with applicable law.

Luvox is extensively metabolized in humans and therefore will probably not be discharged to any significant extent to the environment.

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.

12-5-94
DATE

Approved
Phillip G. Vincent, Ph. D.
Environmental Assessment Officer
Center for Drug Evaluation and Research

12/5/94
DATE

Concurred
Charles S. Kumkumian, Ph. D.
Assistant Director (Chemistry)
Office of Drug Evaluation I
Center for Drug Evaluation and Research

Attachment: MSDS
Environmental Assessment

CC: Original NDA 20-243/HFD-120 P. David
FONSI File 20243
Docket File
FOIA HFD-019

Environmental Assessment for LUVOX™ (Fluvoxamine Maleate) Tablets

1.0 DATE

September 20, 1994

2.0 NAME OF APPLICANT

Solvay Pharmaceuticals, Inc.

3.0 ADDRESS

901 Sawyer Road
Marietta, Georgia 30062

4.0 DESCRIPTION OF THE PROPOSED ACTION

4.1 Requested Approval

Solvay Pharmaceuticals, Inc., is requesting approval to manufacture, package, distribute, and market LUVOX™ (fluvoxamine maleate) Tablets for the treatment of obsessive-compulsive disorder (OCD) in humans. Finished tablets will be packaged in high density polyethylene (HDPE) bottles and foil backed plastic blister packs. LUVOX™ Tablets will be administered daily, by the oral route, to affected individuals. Approved tablets will contain 25, 50, 100, and 150 mg of active ingredient. The marketed product will be dispensed only on the order of a licensed physician.

4.2 Need for the Action

Safer and more effective therapies are needed for individuals affected with obsessive-compulsive disorder. OCD is a serious and potentially disabling disease that is associated with depression and an increased risk of suicide. Currently available therapies may cause a number of side effects including fatigue, somnolence, vomiting, nausea, dry mouth, sexual dysfunction and may be associated with an increased risk of seizures (Jenike et al., 1990). These side effects limit the use of these compounds in OCD affected individuals.

Fluvoxamine maleate is effective in the treatment of OCD and has few associated side effects (Tamimi et al., 1991). The mechanism of action of fluvoxamine maleate is thought to be linked to the inhibition of serotonin re-uptake in neurons. In preclinical studies, it was found that fluvoxamine maleate inhibited neuronal re-uptake of serotonin *in vitro*. In contrast to clomipramine, fluvoxamine maleate produces no sedative activity or amphetamine-like stimulating activity, and possesses limited anticholinergic activity. Moreover, fluvoxamine maleate does not promote seizure activity. Fluvoxamine maleate will provide a therapeutic option for patients affected by OCD.

4.3 Locations Where the Products will be Produced, Tested, or Distributed

The drug substance, fluvoxamine maleate, will be manufactured and packaged in bulk for export by Solvay Duphar B.V. at its facility in Weesp, The Netherlands. Tablets for distribution in the United States will be manufactured at Solvay Pharmaceuticals, Inc., in Baudette, Minnesota, and packaged in HDPE bottles or shipped in bulk to a contractor for blister packaging. Upon completion of bulk packaging in Baudette, tablets will be transferred to PACO Pharmaceutical Services, Inc. in Lakewood, New Jersey, for blister packaging. Stability testing, limited quality assurance analysis and final distribution to physicians and pharmacies will take place at Solvay Pharmaceuticals', Inc., facility in Marietta, Georgia.

Drug Substance Manufacturing Site:

Solvay Duphar B.V. (Weesp Facility)
C.J. Van Houtenlaan 36
1381 CP Weesp
The Netherlands

An environmental assessment report for the drug substance manufacturing site is included in Confidential Appendix 2.

Drug Product Manufacturing, Bottle Packaging, and QC/QA Site:

Solvay Pharmaceuticals, Inc.
210 Main Street West
Baudette, MN 56623

Blister Packaging Site:

The tablets will be packaged for final distribution at:

PACO Pharmaceutical Services, Inc.
1200 Paco Way
Lakewood, NJ 08701

An environmental assessment report for the blister packaging site is included in Confidential Appendix 3.

Stability Testing, Alternate QC/QA Analysis, and Distribution Site:

Solvay Pharmaceuticals, Inc.
901 Sawyer Road
Marietta, GA 30062

4.4 General Dispersement of Finished Product

LUVOX™ Tablets will be used in private residences, hospitals, and clinics throughout the United States. Returned and rejected goods will be accumulated at Solvay Pharmaceuticals', Inc., facility in Marietta, Georgia and incinerated at facilities permitted to handle pharmaceutical wastes.

4.5 Types of Environments Present at and Adjacent to Corporate Locations

Solvay Duphar B.V. (Weesp Facility)

The drug substance will be manufactured at the Solvay Duphar facility in the town of Weesp. The facility is served by city water and an off-site sewage treatment facility. The manufacturing site for fluvoxamine maleate consists of 423,845 square meters total area and is surrounded by meadows, private housing, and warehouses. Buildings occupy a space of 148,005 square meters. The climate is cool and temperate. The surrounding terrain is flat and the upper soil is a silty clay typical of the Netherlands. The site is partially adjacent to surface water (ditches). The Amsterdam-Rhine canal, a small harbor, and a waterway called 'Smal Weesp' are nearby. The rainwater from the chemical production area is collected in a rainwater sewer system and treated in the sewage treatment facility. The rainwater from other areas of the site flows to ditches or the municipal sewer system (city of Weesp).

Solvay Pharmaceuticals, Inc., Baudette, Minnesota

LUVOX™ Tablets will be manufactured, tested, and packaged in HDPE bottles at the Solvay Pharmaceuticals', Inc., facility in Baudette, Minnesota. This area has a cool, temperate climate. The site is one block west of the main business district, and is surrounded by other light industrial and commercial properties. The site is serviced by the city water supply and city sewer. All water and sewage from the plant buildings and adjacent open areas drain into the city sewer.

The facility, which is approximately 105,000 square feet, provides administrative offices, including Human Resources, Accounting, Materials Management, Purchasing, Production, Packaging, Warehousing, and Shipping; support facilities for Engineering and Maintenance; and laboratory facilities for Quality Control and Assurance.

PACO Pharmaceutical Services, Inc.

LUVOX™ Tablets will be blister packaged by PACO Pharmaceutical Services Inc. in Lakewood, New Jersey. The facility is located on a five acre level site which is surrounded by other light industry, woods, and residential communities. It is served by city water and sewer and is located within the 100-year flood plain of Ceder Creek, a tributary of the Metedeconk River. The one building on the site occupies approximately 200,000 square feet. The climate is temperate and the soil varies from sandy loam to sandy gravel.

Solvay Pharmaceuticals, Inc., Marietta, Georgia

Distribution of the finished and packaged drug product will occur at Solvay Pharmaceuticals, Inc., in Marietta, Georgia. This area has a warm, temperate climate. The facility supports Administration, Manufacturing, Research and Development, and Quality Control/Quality Assurance (QC/QA). The Marietta facility will serve as an alternate QC/QA site for LUVOX™ Tablets and for stability testing. Solvay Pharmaceuticals, Inc., is located in a suburban area and is surrounded by other light industrial businesses, undeveloped commercially zoned property, and apartments. The site is served by city water and sewer. The total site comprises 44 acres of lawns, wooded areas, and moderately sloping hills. Buildings and parking lots occupy approximately 376,000 square feet. The upper soil layer is clay.

5.0 IDENTIFICATION OF CHEMICAL SUBSTANCES THAT ARE THE SUBJECT OF THE PROPOSED ACTION

The chemical substances that are the subject of the proposed action can be divided into six categories: (1) drug substance and related impurities, (2) drug substance manufacturing waste products, (3) tablet manufacturing waste products, (4) quality control testing materials, (5) packaging materials and package disposal waste products, and (6) drug substance metabolites.

5.1 Drug Substance Description

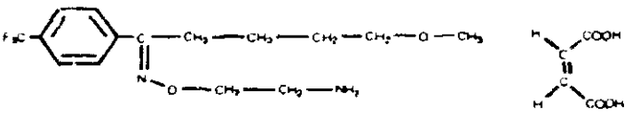
Chemical Name: 5-methoxy-4'(trifluoromethyl)valerophenone(E)-O-(2-aminoethyl)oxime maleate (1:1)

Generic Name: fluvoxamine maleate

INN: fluvoxamine maleate

CAS Registry Number: 61718-82-9

Structural Formula:



Molecular Weight: 434.4

Molecular Formula: $C_{15}H_{21}O_2N_2F_3 \bullet C_4H_4O_4$

Physical Description: White to almost white crystalline powder.

Melting Point: Approximately 122°C (with decomposition)

Purity: 98.0 - 102.0 percent

Impurities

Chemical structures and specifications for impurities of fluvoxamine maleate are presented in Figure 1 in Confidential Appendix 1.

5.2 Drug Substance Manufacturing

Drug substance manufacturing wastes are those substances that can be released in the course of manufacturing fluvoxamine maleate and the materials used in cleaning and maintaining the production facilities. These substances include fluvoxamine maleate, organic solvents, alcohols, reagents, purified water, inert gases, surfactants, cleaning reagents, and commercial detergents typically found in a pharmaceutical manufacturing facility. Table 1 in Appendix 1 lists the solvents, chemicals and reagents used in the production of fluvoxamine maleate.

5.3 Drug Product Manufacturing

Tablet manufacturing wastes are substances that can be released during the tablet manufacturing processes. These substances include fluvoxamine maleate, granulating and binding agents, color additives, sugars, coating agents, and pharmaceutical grade water, as well as cleaning agents, surfactants, and commercial detergents. Table 2 in Appendix 1 presents the substances and amounts used to produce one batch of LUVOX™ Tablets at the Baudette, Minnesota facility.

5.4 Quality Assurance Testing

Materials involved in quality control analysis of fluvoxamine maleate drug substance and tablets are standard pharmaceutical analytical materials and laboratory chemicals. Table 3 in Appendix 1 presents the chemical compounds and amounts used in quality control analysis of the drug substance before the granulation stage of production. Table 4 in Appendix 1 presents the chemical compounds and amounts used in the analysis of the finished tablets.

5.5 Drug Product Packaging

LUVOX™ Tablets will be packaged in high density polyethylene (HDPE) bottles and foil backed plastic blister packs. These packaging materials will enter the waste stream as a result of product use, and when rejected or expired materials are returned. Table 1 presents the types of plastic materials used in the packaging for LUVOX™ Tablets.

TABLE 1
PACKAGING MATERIALS FOR LUVOX™ TABLETS

Plastic Blister Packages	
Polyvinyl chloride	74.6%
Polyvinylidene chloride	17.9%
High density polyethylene	7.5%
Plastic Bottles	
High density polyethylene	100%

Source: PACO Pharmaceutical Services, Inc.

5.6 Drug Product Use

The metabolic products of fluvoxamine maleate in humans have been investigated (Overmars et al. 1983). Fluvoxamine maleate is extensively metabolized and excreted in the urine. Eleven metabolites have been isolated, nine of which have been identified. The molecular characteristics of the metabolites of fluvoxamine maleate and their proportions in urine are presented in Figure 2 in Appendix 1.

6.0 INTRODUCTION OF SUBSTANCES INTO THE ENVIRONMENT

Fluvoxamine maleate and the chemical substances associated with its manufacture and use can potentially enter the environment from five sources: (1) the fluvoxamine maleate drug substance production facility, (2) the fluvoxamine maleate tableting and testing facility, (3) the finished dosage form stability testing and distribution facility, (4) the sites of intended use, and (5) waste disposal sites for discarded product and packaging materials.

6.1 Drug Substance Manufacturing, Solvay Duphar, B.V. (Weesp Facility)

Introduction of fluvoxamine maleate and its manufacturing by-products into the environment can occur from the manufacturing facility in Weesp, The Netherlands. Under Dutch law, the introduction of substances into the environment is controlled by several national and local governmental authorities. These laws are in accordance with European Community guidelines. Solvay Duphar sites reduce emissions through process optimization and waste minimization strategies, implementing recovery

operations where this is technically and economically feasible, and ensuring a high standard of general housekeeping.

Dutch environmental laws, expected emissions, emission controls, compliance with emission requirements, and occupational safety activities are discussed below.

Environmental and Occupational Health Laws and Regulations in The Netherlands

Solvay Duphar's facilities operate under the environmental and occupational laws and subsequent regulations of the Netherlands. These laws and regulations cover the handling of emissions to air, water and soil, chemical waste disposal, noise regulation, as well as worker health and safety.

The primary legislation regulating environmental concerns in the Netherlands is the Environmental Control Act of 1992 (ECA). Until March of 1993, the major environmental law in the Netherlands was the Public Nuisance Act. The ECA provides improved integration of environmental laws in the Netherlands and when fully in place will replace the Public Nuisance Act, Soil Protection Act, Waste Substances Act, and the Chemical Waste Act, and all of their required permits. Permits granted under the Public Nuisance Act, however, remain in force although the authority to grant such permits has been repealed. New permits, when required, will be granted under the ECA. Appendix 2, Attachment A, contains information about the ECA.

In 1987, the Weesp Local Council granted Solvay Duphar B.V. general license for the manufacture and processing of chemical pharmaceutical compounds under the Public Nuisance Act (Permit HW-7-85). Sections of this authorization were updated in 1989 (Permit HW-5-88). These permits have no date of expiration. Copies of the covering letters of these permits are presented in Appendix A.

In compliance with the Public Nuisance Act, the Weesp facility operates under a number of regulations that pertain to:

- storage and processing of chemical compounds, including wastes
- prevention of soil contamination
- prevention of unnecessary discharge into the waste water treatment system
- prevention/restrictions of emissions into the air
- prevention of excessive noise and odor.

Environmental Emissions, Emission Controls, and Compliance

Emissions into the Air

Air emissions to the atmosphere resulting from the manufacture of fluvoxamine maleate are controlled by identifying the specific substance or process to be controlled and utilizing several different types of control technology. In general, reaction vessels are vented to scrubbers and a cryogenic solvent recovery unit which are monitored on a regular basis. Particulate emissions are controlled via HEPA filters and wet scrubbing of relevant equipment where appropriate. Less than 1 kg of fluvoxamine maleate dust is generated and collected per metric ton of drug substance produced. Collected fluvoxamine maleate is disposed of via incineration by AVR Chemie C.V. in Rotterdam in accordance with the Chemical Waste Act discussed below.

Solvay Duphar B.V. is licensed by the City of Weesp, under the Public Nuisance Act, to emit solvents into the air (Permit HW-7-85). The permits set general limits on 3 specific non-water soluble compounds (toluene, hexane and petroleum ether) and 1 water soluble compound (methyl ethyl ketone). The permitted limit is 120 metric tons annually for these 4 solvents combined. Dutch environmental authorities do not "certify" the emission values placed in permits. Appendix A contains a copy of the relevant section of permit HW-7-85 with calculations supporting the 120-metric-ton limit. The production of fluvoxamine maleate involves the release of toluene and hexane.

Solvay Duphar B.V. is in compliance with its permitted limit to emit solvents into the air. Estimated emissions in 1993 of non-water soluble solvents totaled 33 metric tons, with fluvoxamine maleate production accounting for approximately 15 metric tons of non-water soluble solvents. In addition, an estimated 19 metric tons of methyl ethyl ketone was emitted in 1993 by other activities not related to fluvoxamine maleate production. A total of approximately 52 metric tons of the regulated 120 metric tons of solvent were released into the air in 1993.

The Weesp facility is expected to remain in compliance with its permitted air emissions limit. Approval of the proposed action would add approximately 15 additional metric tons of non-water soluble solvents to the total released during the 5th year of production for the U.S. market. Thus, approximately 67 metric tons of regulated solvents would be emitted. This amount is below the estimated maximum emission limits established by the permit.

Emissions into Water

Solvay Duphar B.V. has been licensed by the Ministry of Transport and Water Management, in accordance with the Surface Waters Pollution Act, (Wet Verontreiniging Oppervlakte Water) to discharge treated waste water under specified conditions into Dutch surface waters (Permit 10803 RFR) via the AWZI waste water treatment facility in Weesp. In addition, Solvay Duphar has a permit according to the Public Nuisance Act to operate the AWZI waste water treatment facility (Permit HW-13-80). The permits have no date of expiration. The AWZI facility is operated, by agreement with Solvay Duphar B.V., by the City of Weesp.

The AWZI waste water treatment facility in Weesp is an advanced sewage treatment facility. Influent enters the facility into a contact tank where the waste water is mixed with return sludge which contains bacterial flakes. The waste water then enters the aerators where activated sludge is introduced and biological degradation occurs. Following aeration, waste water is then sent to sedimentation tanks where sludge is removed and treated effluent is discharged into the Amsterdam-Rhine Canal.

Measurements of the input and effluent streams are made daily. Reports are generated every 3 months for the Ministry. An annual report summarizes the operations of the WWTP for the Ministry of Transport and Water Management.

The AWZI waste water treatment facility and Solvay Duphar are in compliance with its discharge permit. Appendix A contains a copy of the permit letters for the AWZI facility. A summary of the performance of the waste water treatment facility from 1987 until 1993 is provided in Appendix 2, Attachment C.

There is substantial reserve waste water treatment capacity available at the Weesp facility, and it and Solvay Duphar are expected to remain in compliance if the proposed action is approved. The changes in emissions resulting from approval of the proposed action are described in Appendix 2.

Chemical and Solid Wastes

The release of chemical waste materials from chemical and pharmaceutical production in The Netherlands is governed by the Chemical Waste Act (Wet Chemische Afvalstoffen). Under the law, all chemical liquid and solid wastes generated at the facility are incinerated at the Rotterdam AVR-Chemie C.V. Waste Handling Facility. The facility

is a four stage incinerator which meets the most stringent requirements in the world. The first stage consists of an electrostatic filter to remove fly-ash, metals and, dioxins. These materials are removed to a safeguarded dump site. The second stage consists of wet scrubbers to remove hydrogen chloride, heavy metals, sulphur dioxide, and hydrogen fluoride. The water used in this process is cleaned in a treatment plant and the contaminants removed are stored in a safeguarded site. Next an active carbon filter is implemented to remove dioxins and other remaining contaminants. Finally, a deNO_x plant removes any oxides of nitrogen. AVR Chemie, in compliance with the Chemical Waste Act, has granted Solvay Duphar B.V. permission to send an unlimited amount of these materials to the incinerator. Appendix A contains a copy of a letter from AVR Chemie indicating allocated waste streams, numbers and tariffs.

With approval of the proposed action, fluvoxamine production would increase the amount of chemical waste incinerated by approximately 101 metric tons during the 5th year of production of fluvoxamine maleate for the U.S. market. Appendix 2, Attachment D contains an example report of waste removal filed with the Dutch Ministry of Housing, Planning, and Environment.

Employee Protection

Worker health and safety in The Netherlands is protected by the Occupational Safety Act which is administered by the Labor Inspectorate. The act sets standards for worker protection and training that must be adhered to by the employing company. Inspections are carried out randomly by the authorities to insure worker safety.

Personnel working in the Weesp facility are provided with safety glasses/goggles, uniforms, safety shoes, and gloves as their norm protective equipment. If conditions warrant, workers have at their disposal air breathing systems, air suits, aprons, and boots. Directions for the safe use of equipment and required operations are written and posted in the appropriate work area. Moreover, employees are trained in the proper operation of equipment to minimize potential safety, health, or environmental risks. In addition, Material Safety Data Sheets are available on site for all chemicals handled at the facility.

6.2 Description of LUVOX™ Tableting Facility, Baudette, Minnesota

The final manufacturing process for LUVOX™ Tablets will take place at Solvay Pharmaceuticals, Inc., in Baudette, Minnesota. Potential discharges of fluvoxamine maleate may occur during manufacturing and packaging runs, quality control testing, and equipment and facility cleaning. Emissions of other chemical substances may also occur throughout manufacturing, packaging, and quality control activities. Except for certain analytical reagents, all compounds used in the manufacturing process are pharmaceutical grade compounds intended for human consumption and are readily biodegradable. All emissions are minimized through engineering controls, Standard Operating Procedures, and Good Manufacturing Practices.

Substances expected to be emitted and their CAS numbers are listed below:

- Fluvoxamine maleate - 61718-82-9
- Starch NF (corn) - None assigned
- Pregelatinated starch NF - None assigned
- Mannitol USP - 69-65-8
- Purified water USP - 7732-18-5
- Colloidal silicon dioxide NF - 7631-86-9
- Sodium stearyl fumarate NF - 4070-80-8
- Opadry® Yellow YS-1-2053 (25 mg tablet only) - None assigned
- Opadry® Yellow YS-1-2013 (50 mg tablet only) - None assigned
- Opadry® Beige YS-1-8325 (100 mg tablet only) - None assigned
- Opadry® Red YS-1-1891 (150 mg tablet only) - None assigned
- Opadry® Clear YS-1-7006 - 117698-04-1
- Carnauba Wax NF - 8015-86-9
- Methanol - 67-56-1
- Ethanol - 64-17-5
- 0.01 N Sodium hydroxide in methanol - 1310-73-2
- Sodium heptane sulfonate - 22767-50-6
- Ammonium hydrogen phosphate - 7783-28-0
- Ammonium hydroxide solution 25% - 1336-21-6
- Phosphoric acid 85% - 7664-38-2
- Drug Product - None assigned

Expected emissions, environmental control practices, and occupational safety practices are discussed in the following sections.

Emissions into the Air

The expected air emissions at this facility include water vapor from the tablet manufacturing processes. Very small amounts of ethanol and methanol could be released to the atmosphere in the quality control testing of fluvoxamine maleate raw materials and finished tablets.

Applications for air emission facility permits for volatile organic compounds (VOCs) are pending for the facility in Baudette. The current level of VOC emissions is 183,331 lbs/year. The approval of this proposed action will have no effect on this permit because there are no VOCs used in the production of LUVOX™ Tablets and the QC/QA activities are not expected to release these compounds into the environment.

The analytical methods for LUVOX™ Tablets utilize a closed system that does not require extraction or evaporation. Therefore, any emissions from these activities would only occur as a result of broken glassware or other inadvertent release. Given the current volume of VOCs released from the Baudette facility, the impact of QC/QA activities on total VOC emissions from the facility would be immeasurable.

The heating, ventilation, and air conditioning (HVAC) system for the Baudette facility incorporates the use of a filter system. Fluvoxamine maleate dust will enter the controlled air space within the LUVOX™ Tablet production area during the manufacturing and testing processes in very limited amounts. All air effluent generated from the processes involved in the manufacture of LUVOX™ Tablets (i.e., weighing, mixing, tableting, and quality control testing) will be captured via exhaust systems in HEPA (High-Efficiency Particulate Absolute) filters with collection efficiencies greater than 99.99 percent for all the particle sizes normally encountered. The filtered air in these systems is vented outside.

The waste material collected in the air filtration systems will be handled as solid waste, as described below. Possible maximum emissions to workplace or ambient air would be less than 0.01 percent of these amounts.

Appropriate engineering controls are utilized to minimize employee exposure to airborne dusts (e.g., dust collection pick-ups, vacuum transfer equipment). In addition, personal protective equipment (PPE) is worn by employees to minimize potential exposure (e.g., HEPA respirators, Air Helmet, supplied air). During all other manufacturing operations, including coating, a dust mask is worn by employees in the processing room.

Air emissions that are generated from the production of LUVOX™ Tablets are regulated by the Minnesota Pollution Control Agency (MPCA) in compliance with section 112 of the Federal Clean Air Act. Specifically, these include Minnesota Rules (MR) 7001.0010 - 7001.0210 (Air Quality Permits); MR 7002.0005 - 70002.0095 (Permit Fees); and, MR 7005.0010 - 7005.0117 (Ambient Air Quality Standards).

As noted above, Solvay Pharmaceuticals, Inc., has applied for facility air emission permits. However, issuance has been delayed twice by the Minnesota Pollution Control Agency in order to comply with the Clean Air Act of 1990. Solvay Pharmaceuticals, Inc., expects to be issued one permit:

> Part 70 (for ozone protection) which specifically addresses air emission of organic solvents which are generated from the manufacture of other products. Note: Although the Part 70 permits do address the emissions of particulate matter (PM-10), the threshold limit for regulation is 70 tons or greater on an annual basis.

Based on the total fifth year projections of 1352 kg of waste, assuming a [1]99.99% air filtration efficiency, we can determine that less than 0.14 kilograms of fluvoxamine maleate and less than 1 kilogram of other substances would be emitted to the environment for that year. Calculations for the emission of fluvoxamine maleate into the air are shown in Appendix 1, Tables 6 and 7. Air emissions resulting from Quality Assurance testing would be less. Furthermore, because the Part 70 permit is based upon tonnage, one can reasonably say that there will be no impact on the impending permits.

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[1]99.99% Particulate filtration - Section 6 Emissions into the Air.

Water Emissions

Waste liquids generated from the production of LUVOX™ Tablets come from the washing of equipment after use in the manufacturing facility and quality control laboratory. All equipment parts and room surfaces (such as floors, walls, and ceilings) involved in the manufacture of LUVOX™ Tablets are vacuumed; the solid waste is collected for incineration. Waste liquids contaminated with fluvoxamine maleate during cleaning procedures are collected for disposal as pharmaceutical waste. Fluvoxamine maleate will not discharged to the municipal sewer system. Chemical reagents used in the QC/QA analytical testing procedures are stored and disposed of as hazardous waste at an EPA permitted disposal facility.

The Baudette sewage treatment facility consists of two large settling ponds, screens and appropriate pumps. The influent is screened to remove large solid debris (e.g. rocks, bottles, etc.), and pumped into the primary pond which has a capacity of 46.9 million gallons and receives an average daily flow of 243,000 gallons. The primary pond feeds a secondary pond with a capacity of 14.96 million gallons. The secondary pond is discharged into the Rainy River after a detention time of no less than 195 days and after meeting the following criteria:

COD	-	25mg/l (monthly average)
BOD	-	234 mg/l (weekly average)
TSS	-	45 mg/l (monthly average)
Fecal Coliform Bacteria	-	200/100 ml March 31 to October 31
pH	-	6.0 to 9.0

Due to the size and utilization rate of the facility, the ponds have never been cleaned and no sludge has been removed for disposal. Moreover, none of these activities are planned in the foreseeable future.

Baudette Light and Water, which operates the waste water treatment plant, NPDES permit MN0029599, is regulated by the Minnesota Department of Environmental Protection under Minnesota Rule 7001.1000 - 7001.1100, as subject to regulations under Section 307b of the Federal Clean Water Act, 40 CFR 439. The liquid wastes from the Baudette facility require no pretreatment under the above regulations because of the small amounts of chemical substances involved (Minnesota Rule 7045.102, subpart 2, section F), and their release is in compliance with the above referenced laws and regulations.

Solid Wastes

Municipal solid wastes (e.g., office wastes and packaging wastes) are disposed of in the Lake of the Woods County Sanitary Landfill, Williams, Minnesota 56686. This municipal landfill is regulated by the Minnesota Department of Environmental Protection under Minnesota Rule 7035.300 -7035.2805.

Solid wastes containing fluvoxamine maleate and other substances used in manufacturing and quality control activities will be collected and destroyed via incineration. These materials consist of floor sweepings, residual solid materials collected during equipment cleaning, and airborne dust collected from the air filtration system. The maximum total amount of fluvoxamine maleate dust expected to be generated per batch of product manufactured is shown in Appendix 1, Table 5. The maximum total amount of fluvoxamine maleate waste expected to be generated during the fifth production year is 1352 kilograms. In addition, approximately, 5400 kilograms of other manufacturing wastes (i.e., granulation wastes not including fluvoxamine maleate) during the same time period will be generated. The calculations detailing these emissions may be found in Appendix 1, Table 7.

Collected solid waste is stored and then transported off-site and incinerated by an Environmental Protection Agency (EPA)-registered, non-hazardous waste disposal company equipped to dispose of pharmaceutical "rejects" of dosage forms, raw materials, and infectious/medical wastes. No products, wastes, or by-products are currently land-filled. Two incineration facilities have been identified by Solvay Pharmaceuticals, Inc., for the destruction of fluvoxamine maleate dust and other associated waste products:

(1) Ogden Martin Systems of Lake, Inc., 3830 Rogers Industrial Park Road, Okahumpka, Florida 34762

(2) Midway Environmental Management, Highway 66, P.O. Box 728, Stroud, Oklahoma 74079.

The waste disposal firms and their processes are discussed below.

Ogden-Martin Systems of Lake, Inc.

Ogden-Martin Systems operate a typical waste to energy incinerator. Refuse collection trucks are weighed at the scalehouse and monitored for safety. An overhead crane mixes the waste in the pit and lifts the waste up into a feed chute leading to the furnace.

From the feed chute, waste is pushed by hydraulic ram feeders onto a stoker grate. Waste is constantly agitated to insure proper burning. A forced draft fan supplies the primary combustion air and overfire air is injected through the front and rear walls of the furnace. Heat from the combustion process converts water to steam which is used to produce electricity.

From the boiler, the cooled gases enter the advanced air pollution control system. Using lime slurry, the dry scrubber neutralizes any acid-forming gases, such as sulfur oxides and hydrogen chloride. Particulates are captured by a high-efficiency electrostatic precipitator or by a baghouse. As the gas stream travels through these filter devices, more than 99 percent of particulate matter is removed. The ash residue is then conveyed to an enclosed conveyor to an enclosed building where it is tested and loaded into covered, leak-proof trucks and taken to a landfill designed to protect against groundwater contamination. Ash residue from the furnace is then processed for removal of recyclable scrap iron.

All aspects of the plant's operation are monitored from a central control room 24-hours a day, seven days a week, 365 days a year.

Ogden Martin Systems operates under permit number AO35-193817 issued by the Florida Department of Environmental Regulation. The permit expires on October 25, 1996. A copy of the facility permit may be found in Confidential Appendix 4.

Midway Environmental Management Company, Inc.

The Midway Incinerator is a Basic 700 - Pulsing Hearth unit with three (3) heating stages. Prior to the acid bath bag house, the heat is used to generate commercial steam (for energy recovery) and recirculated through an economizer and heat exchange unit for maximum use of energy. The ash is water cooled and tested (TCLP) along with the filtered material to ensure it is non-hazardous and landfilled.

Midway Environmental operates under permit number 87-066-0 issued by Air Quality Service, Oklahoma State Department of Health. The permit has no date of expiration. A copy of the facility permit may be found in Appendix 4.

Hazardous Wastes

Hazardous wastes, including solvents that are not recycled, are poured into waste drums, documented, and then accumulated in a storage area. Approximately 1,600 liters of solvents and reagents listed in Appendix 1, Table 3 will be generated during the fifth year of production.

The waste will be stored for a limited time, as determined by regulation 40 CFR 262.34 (d) for small quantity generators and Minnesota Rule 7045.0219, until scheduled pick-up (Facility ID #MND148515737). The EPA generation permit and facility ID# number has no date of expiration or specific limits. At that time, the waste will be removed from Solvay Pharmaceuticals, Inc., and transported to an off-site facility for incineration:

Trade Waste Incineration
#7 Mobile Avenue
Sauget, IL 62201

Trade Waste Incineration (TWI) operates under permit number ILDO 98642424 - 29 issued by the Illinois Environmental Protection Agency. The permit expires on May 5,1998. TWI incinerates hazardous waste in two free-standing fixed-hearth incinerators and one rotary kiln. Emissions are controlled by maintaining proper combustion temperatures, feed rate and maintenance of the dry scrubber and lime slurry baghouse. A copy of the facility permit may be found in Appendix 4.

Table 2 details the current permits applicable to the Solvay facility.

TABLE 2
CURRENT PERMITS, EXPIRATION DATES AND LIMITS APPLICABLE TO SOLVAY PHARMACEUTICALS, INC., BAUDETTE MINNESOTA

NAME	PERMIT NUMBER	EXPIRATION	LIMITS
EPA Generator I.D. Number	MNI[illegible]7	None	None
National Pollution Discharge Elimination System (NPDES)	[illegible]	8/30/98	temperature 86F (max) pH. 6-9 (range) residual chlorine 0.04 mg/l TSS 30 mg/l

TSS = Total suspended solids.

Worker Protection

Employees who work in the production and packaging areas wear protective clothing, filtered-air helmets, and dust respirators as needed. Laboratory personnel wear eye shields and other appropriate protective clothing. All necessary steps are taken to assure compliance with Occupational Safety and Health Administration (OSHA) standards and hazard communication requirements (29 CFR 1903.1 - 1910.1450) and Minnesota regulations (MR 5205.0010 - 5206.2000). The Material Safety Data Sheet for fluvoxamine maleate is located in Appendix B.

Calculation of Environmental Exposure

The amount of fluvoxamine maleate released into the air is negligible. Fluvoxamine maleate will not be discharged into the sanitary sewer and, therefore, will not be released into surface water. Approximately 1,352 kilograms of waste fluvoxamine maleate will be collected as solid waste and incinerated during the fifth production year (Appendix 1, Table 7).

All other waste compounds used in the production, testing, and packaging of LUVOX™ Tablets will enter the environment in amounts within the limits allowed by the applicable laws, regulations, and permits.

The procedures, implementation, supervision, and overall responsibility for the control of emissions and waste disposal are handled by Solvay Pharmaceuticals, Inc., Health, Safety, and Environmental Department.

6.3 Quality Control Testing and Distribution, Solvay Pharmaceuticals, Inc., Marietta, Georgia

A limited amount of quality control and stability testing of finished LUVOX™ Tablets will take place at the Solvay Pharmaceuticals, Inc., facility in Marietta, Georgia. Environmental discharges of fluvoxamine maleate, and chemical substances and reagents used in the testing laboratory, could occur only during product testing and laboratory equipment cleaning. All emissions are minimized through engineering controls, Standard Operating Procedures, and Good Manufacturing Practices.

Substances expected to be emitted and their CAS numbers are listed below:

- Drug Product - None assigned
- Methanol - 67-56-1
- Ethanol - 64-17-5
- 0.01 N Sodium hydroxide in methanol - 1310-73-2
- Sodium heptane sulfonate - 22767-50-6
- Ammonium hydrogen phosphate - 7783-28-0
- Ammonium hydroxide solution 25% - 1336-21-6
- Phosphoric acid 85% - 7664-38-2

Expected emissions, environmental control practices, and occupational safety practices are as follows:

<u>Air Emissions</u>

Air emissions associated with the testing of LUVOX™ Tablets contain no hazardous materials regulated by the state of Georgia; therefore, the state does not require a permit. Air from the laboratory is exhausted through fume hoods located throughout the work area. The exhaust system meets the requirements set forth in the applicable OSHA Standards (29 CFR 1910.1450). As stated above, the analytical methods for LUVOX™ Tablets utilize a closed system; therefore, no emissions of any kind are expected from these procedures.

Water Emissions

Waste liquids generated from the analytical testing of LUVOX™ Tablets consist of small amounts of water, fluvoxamine maleate, reagents, and solvents from the analysis and from the cleanup of laboratory equipment. All hazardous waste are collected, stored, and disposed of in a manner consistent with all federal, state, and local laws and regulations. Solvay Pharmaceuticals, Inc., Health, Safety and Environmental Department monitors effluent water from the dilution basin at least annually. Wastes from the dilution basin are transported via sewer line to the waste water treatment plant which serves the facility.

Waste water from the facility is treated by the R. L. Sutton Waste Water Treatment Plant (NPDES Permit GA0026140) regulated by the Georgia Environmental Protection Division (EPD) under section 307b of the Clean Water Act, 40 CFR 439 (Rules and Regulations of the State of Georgia, Title 391, Chapter 3, Rule 6). Liquid waste from the Solvay Pharmaceuticals, Inc., facility requires no pretreatment and is in compliance with the above referenced laws and regulations.

Solid Wastes

Municipal solid wastes (e.g., office wastes and packaging wastes) are disposed of in the Cobb County Landfill, 1772 County Farm Road, S.W., Marietta, Georgia. This municipal landfill is regulated by the Georgia EPD under Title 391, Article 3, Chapter 4 of the Rules and Regulations of Georgia. Approximately 300 grams of waste drug substance and 60 kilograms of other waste will be generated during the fifth production year.

Solid wastes containing fluvoxamine maleate and other substances used in analyses will be collected and destroyed via incineration at one of the two previously identified non-hazardous waste handling facilities. Fluvoxamine maleate waste and other waste chemical substances used in the laboratory for QC/QA activities are minimal.

Hazardous Wastes

Approximately 210 liters of solvents and reagents listed in Appendix 1, Table 4 will be released during the fifth production year. All hazardous wastes are collected, stored, and disposed of in accordance with federal, state and local laws and regulations. The waste will be stored for a limited time, as determined by regulation 40 CFR 262.34 (d) for small quantity generators and Title 391, Article 3, Chapter 11 of the Rules and Regulations of the State of Georgia (Facility ID #GAD981251945).

Ultimately, the waste will be removed from Solvay Pharmaceuticals, Inc., and transported to the hazardous waste incinerator identified above.

Table 3 lists the applicable permits, expiration dates and applicable limits for the Marietta facility.

TABLE 3
PERMITS, PERMIT NUMBERS, EXPIRATION DATES AND LIMITS AT SOLVAY PHARMACEUTICALS, INC., MARIETTA, GEORGIA

NAME	PERMIT NUMBER	EXPIRATION	LIMITS
EPA Generator ID Number	GAD981251945	None	None
Georgia Stormwater Permit	GAR000000	5/31/98	None

Worker Protection

Employees who work in the laboratory wear eye shields and other appropriate protective clothing. All necessary steps are taken to assure compliance with the applicable OSHA standards, 29 CFR 1903 - 1910.1450.

Calculation of Environment Exposure

The amount of fluvoxamine maleate released into air and water is negligible. Only about 300 grams of fluvoxamine maleate will be used in quality assurance testing during the fifth year of production. All wastes will enter the environment in amounts within the limits allowed by the applicable laws, regulations, and permits.

The procedures, implementation, supervision, and overall responsibility for the control of emissions and waste disposal are handled by the Health, Safety, and Environmental Supervisor.

6.4 Institutional and General Patient Population Use

Administered fluvoxamine maleate and its metabolites will enter the environment primarily through waste water treatment facilities. The calculations carried out to provide an estimate of the quantity of fluvoxamine maleate to enter the environment as a result of use may be found in Appendix 1, Table 8. The Maximum Expected Emitted Concentration (MEEC) is 0.00036 ppm based on the formula and assumptions recommended in the PMA Interim Guidance for Environmental Assessment Compliance Requirements. The actual amounts of fluvoxamine maleate entering the environment will be

significantly lower because fluvoxamine maleate is extensively metabolized by the liver into pharmacologically inactive metabolites. Following administration of fluvoxamine maleate tablets, less than 4 percent of the drug is excreted unchanged in the urine (Overmars et al., 1983; Grahnen and Eckernas, 1992). The MEEC for patient use is more appropriately expressed as 0.000014 ppm.

6.5 Waste Disposal Sites for Discarded Product and Packaging Materials

LUVOX™ Tablets and components of the HDPE bottle and closure packaging and the plastic blister packaging materials will enter the environment upon approval of this action.

Foil backed blister packs consist of a clear laminated plastic film containing rigid polyvinyl chloride (PVC), polyethylene, and polyvinylidene chloride (PVDC) bonded to a backing of paper and aluminum foil. Laminated plastic packaging is not currently recycled on a commercial basis. When incinerated, PVC and PVDC may contribute to the generation of many types of chlorinated and unchlorinated organic and inorganic compounds. Much of the concern regarding emissions from incinerators associated with chlorinated plastics has focused on their potential contribution to the generation of polychlorinated dibenzodioxins and dibenzofurans (PCDDs and PCDFs), and hydrochloric acid (HCl). Although there is considerable controversy regarding the contribution of halogenated plastics to emissions from incinerators, the results from a number of studies have suggested that there is not a relationship between the chlorinated plastics content of municipal solid waste and the levels of PCDDs and PCDFs (Lisk, 1988; Marcus and Milis, 1988; Yakowitz, 1990; Yasuhara and Morita, 1988). This has been attributed to the presence of sufficient naturally occurring chlorine in other components of the incinerator waste stream to generate these compounds. It appears that incinerator operating conditions are more important to PCDD/PCDF formation than the presence or absence of any single municipal solid waste constituent. Although HCl emissions may be correlated with the amount of chlorine-containing plastics in the waste stream, many other materials also contribute to the production of HCl, and efficient emissions controls generally are required. When landfilled, these plastic packaging materials degrade extremely slowly (EPA 1990a).

HDPE bottles may be recycled in many communities. When incinerated, HDPE contributes to the generation of many types of organic compounds, including polycyclic aromatic hydrocarbons, simpler organic compounds, carbon dioxide, and water (EPA 1990a, Hawley-Fedder et al. 1984, Hoff 1984). These types of compounds also are generated by incineration of

many other components of the incinerator waste stream. Emissions of these products of incomplete combustion generally depend more on incinerator operating conditions than on the presence or absence of any single municipal solid waste component. When disposed of in a landfill, HDPE degrades extremely slowly (EPA 1990a).

A total of approximately 14,150 kilograms of plastic blister packaging will be used during the fifth production year. Returned, rejected, and expired LUVOX™ Tablets and their packaging will be accumulated at Solvay Pharmaceuticals, Inc., in Marietta, Georgia and shipped periodically to the disposal sites identified previously for incineration. It is estimated that 2 - 3 percent of the packaged LUVOX™ Tablets will be incinerated annually after return to Solvay Pharmaceuticals, Inc. Based on the fifth year production information, a maximum of approximately 354 kilograms of blister packaging material, containing 7.5 percent HDPE, 74.6 percent polyvinyl chloride (PVC) and 17.9 percent polyvinylidene chloride (PVDC) by weight, will be incinerated along with the LUVOX™ Tablets if all returned material is in blister packaging.

Approximately 13,796 kilograms of blister packaging material from used product will enter municipal solid waste disposal facilities around the United States based on fifth year production information. These materials will be either landfilled, incinerated, or recovered depending upon disposal location. It is estimated that 73 percent, 14 percent and 13 percent of municipal wastes are disposed of by landfill, incineration, and recovery, respectively (EPA 1990b).

The types and amounts of chemical substances expected to enter the environment due to the disposal of blister packaging for LUVOX™ Tablets are detailed in Table 4.

A total of approximately 18,513 kilograms of HDPE bottle packaging material will be used during the fifth production year. If the 2-3 percent of LUVOX™ Tablets returned to Solvay Pharmaceuticals, Inc., is packaged in HDPE bottles, approximately 463 kilograms of HDPE will be incinerated by Solvay Pharmaceuticals, Inc., based on fifth year production estimates. Approximately 18,050 kilograms of HDPE bottle packaging material from used product will enter solid waste disposal facilities around the United States.

Calculation of Environmental Exposure

Plastics are extremely resistant to degradation and, as a result, their contribution to landfill leachate is not typically considered to be an environmental concern (EPA 1990a).

TABLE 4
CHEMICAL SUBSTANCES EXPECTED TO ENTER THE ENVIRONMENT AS A RESULT OF THE DISPOSAL OF BLISTER PACKAGING FOR LUVOX™ TABLETS

Chemical	Amount
Disposal of Returned LUVOX™ and Packaging	
Incineration	
Fluvoxamine maleate	2-3 percent of total produced
HDPE	27 kg
PVC	264 kg
PVDC	63 kg
Disposal of Used LUVOX™ Packaging	
Landfill	
HDPE	745 kg
PVC	7516 kg
PVDC	1778 kg
Incineration	
HDPE	145 kg
PVC	1442 kg
PVDC	346 kg
Recovery	
HDPE	135 kg
PVC	1338 kg
PVDC	321 kg

Plastics may contribute to the emissions of a large variety of compounds from municipal and hazardous waste incinerators. It has been estimated that approximately 14 billion kilograms of plastics will enter the United States municipal solid waste stream in 2000 (EPA 1990). A total of approximately 14,150 kilograms of plastic blister packaging and 18,513 kilograms of HDPE bottle packaging will be used during the fifth production year of LUVOX™ Tablets. Together, this represents approximately 0.0002 percent of the total amount of plastic entering the municipal solid waste stream.

Approval of this action would result in a negligible amount of additional HCl, PCDDs, PCDFs, and other compounds entering the environment as a result of incineration. These compounds would enter the environment via emissions from EPA licensed incinerators into the atmosphere. Proper operation of these incinerators and dilution of the feedstock for hazardous waste or municipal incinerators would significantly reduce the potential for release to the environment. The HCl would be largely captured in the effluent air scrubbers which regulate air flowrate, pH, and temperature.

Pathways governing the chemical fate and degradative pathways of fluvoxamine maleate are presented in Section 7 of this Environmental Assessment report, Fate of Emitted Substances.

By signing this environmental assessment, Solvay Pharmaceuticals, Inc., confirms that it is in compliance with, or on an enforceable schedule to be in compliance with, all applicable emission requirements set forth in permits, consent decrees and administrative orders, as well as emission requirements set forth in applicable federal, state, and local statutes and regulations at its facilities discussed above.

7.0 FATE OF EMITTED SUBSTANCES IN THE ENVIRONMENT

The fate of fluvoxamine maleate and the other chemical substances associated with the proposed action is determined by the physical, chemical, and biological characteristics of the compounds involved. In the case of LUVOX™ Tablet production and use, information presented in Section 6 of this Environmental Assessment report indicates that only the drug substance, fluvoxamine maleate, should be considered for the purposes of this environmental assessment. Other potentially emitted compounds are introduced into the environment from a wide variety of sources other than those associated with the proposed action. The amounts of these compounds expected to enter the environment as a result of approval of the proposed action are negligible and are not expected to result in any adverse environmental effects.

7.1. Metabolism in Man

When administered to humans, fluvoxamine maleate is extensively metabolized. Eleven metabolites have been isolated, all of which are excreted in the urine (Overmars et al., 1983). Less than 4 percent of the administered dose of fluvoxamine maleate is eliminated unchanged (Overmars et al., 1983; Grahnen and Eckernas, 1992). Information presented in Overmars et al. (1983) indicates that metabolites B and E are excreted at levels of 10 percent or greater. However, these

compounds are more polar than the parent compound, and are therefore not expected to be more environmentally persistent than fluvoxamine maleate. Accordingly, these compounds are not considered significant for the purposes of this environmental assessment and will not be further evaluated.

7.2 Fate Studies

The fate of fluvoxamine maleate in the environment is largely influenced by its chemical and physical properties. A brief discussion of these properties is presented below and summarized in Table 5.

TABLE 5
SUMMARY OF ENVIRONMENTAL FATE STUDIES

Dissociation Constant (pK_a)	5.8, in aqueous solution 6.91 and 9.00, in ethanolic solution
Log Octanol/Water Partition Coefficient	1.59
Water Solubility	15.26 mg/mL 15.239 mg/mL, based on density of 1.0014 g/mL of saturated solution at 25°C
Vapor Pressure	1.33×10^{-6} Pascal

Dissociation Constant

The dissociation constants for fluvoxamine maleate were determined in laboratory studies conducted in accordance with the Food and Drug Administration (FDA) Environmental Assessment Technical Assistance Handbook, 3.04. The study report and data summary charts can be found in Confidential Appendix 5.

In an aqueous titration study fluvoxamine maleate showed one well-defined average pK_a of 5.8. A second poorly-defined apparent pK_a appeared between pH 7.5 and pH 10 in the aqueous titration study. It was not possible to quantitatively characterize this value due to the appearance of a precipitate at pH values of 8.5 and higher (the test solution appeared cloudy at these elevated pH levels). As recommended in applicable test methods for determination of dissociation constants, a second titration study was carried out using a water-miscible solvent to resolve the precipitation problems that occurred in the pure water system.

This second titration study, carried out in a 30% ethanol solution, showed two pK_as, with average values of 6.91 and 9.00. No precipitation was observed under the study conditions from pH 2 to pH 12.

Results of these studies suggest that at pH 2 one carboxylate group on the maleate, as well as the primary amine on the fluvoxamine, are protonated. The second carboxylic acid on the maleate is also at least partially protonated, but appears to be a sufficiently strong acid that it is completely protonated only at pH <2 (i.e., outside the scope of the study). In the pH range containing the lower observed pK_as, 5.8 in the aqueous system and 6.91 in the mixed solvent system, completion of the deprotonation of the more acidic carboxylate group occurs and deprotonation of the less acidic carboxylate group begins. In the pH range containing the higher observed pK_a, 9.00 in the mixed solvent system, completion of the deprotonation of the less acidic carboxylate group occurs and slow deprotonation of the primary amine begins. In the aqueous titration study, at pH 8.5, fluvoxamine free base presumably was present in excess of its solubility in water (the tests were conducted using fluvoxamine maleate at concentrations of approximately 4,500 mg/liter) and, thus, began to precipitate out of solution.

It should be noted that alcohols, in general, weaken both acids and bases. For example, the average pK_a of amines is lowered by about 0.5 in 50% ethanol (Albert and Serjeant, 1984). Thus, based on the information discussed above, at pH 9 no more than half of the total fluvoxamine present in an aqueous solution would be present as the free base, and it is likely that less than this amount would actually be present. Waste water treatment facilities typically operate at pH levels in the range of 6 to 9, probably skewed to lower values (i.e., closer to neutral pH 7) (Merrit, 1983; Metcalf and Eddy, 1979, AWA, 1990). Values higher than this generally occur only for specialized separation processes (e.g., addition of lime to coagulate and collect specific waste components). Similarly, receiving water bodies for waste water treatment plant effluent streams also are generally in a pH range of 6 to 9, also probably skewed to lower values (Britton et al., 1983). Accordingly, under most environmentally relevant conditions, the majority of the total fluvoxamine present would occur as ionized fluvoxamine maleate. For example, at pH 8.5, 8, and 7, the molar fractions of fluvoxamine free base present at equilibrium would be approximately 0.24, 0.09, and 0.01, respectively.

Octanol/Water Partition Coefficient

The log octanol/water partition coefficient for fluvoxamine maleate is 1.59. This value was determined in a study conducted in accordance

with the FDA Environmental Assessment Technical Assistance Handbook, 3.02. The study report and data summary charts are presented in Confidential Appendix 6.

Water Solubility

The water solubility of fluvoxamine maleate is 15.26 mg/ml or 15,239 ppm based upon a density determination of 1.0014 g/ml of saturated solution at 25°C. The water solubility of the compound was determined in a study conducted in accordance with the FDA Environmental Assessment Technical Assistance Handbook, 3.01. The study report and data summary charts can be found in Confidential Appendix 7.

Vapor Pressure

The vapor pressure of fluvoxamine maleate is less than 1.33×10^{-5} Pascal (10^{-7} torr). The vapor pressure of the compound was determined in a study conducted in accordance with the FDA Environmental Assessment Technical Assistance Handbook, 3.03. A study report and data summary charts can be found in Confidential Appendix 8.

Environmental Significance of Fate Studies

Fluvoxamine maleate is expected to enter the environment as a result of patient use. Fluvoxamine maleate excreted after patient use will enter the environment primarily via sanitary sewer systems throughout the United States, with release to WWTPs and subsequent discharge to receiving surface water bodies. Under typical expected environmental conditions at these types of locations, fluvoxamine maleate is expected to be the predominant molecular species of this compound. The high water solubility, low octanol/water partition coefficient, and low vapor pressure of this compound indicate that it will localize primarily into the aquatic environmental compartment. Thus, based on consideration of the PMA Interim Guidance for Environmental Assessment Compliance Requirements and requirements under 21 CFR 25.31a (a), the results of these initial fate studies indicate that the aquatic compartment is of primary concern with regard to the potential environmental effects of fluvoxamine maleate. Transport of fluvoxamine maleate into the air and terrestrial compartments is expected to be negligible by comparison.

7.3 Fate of Fluvoxamine Maleate in Freshwater, Estuarine, and Marine Ecosystems

The major determinant of the fate of fluvoxamine maleate in this environmental compartment is its rate of degradation. In this case, the

aerobic biodegradability in water of the compound was determined because it will enter the aquatic compartment primarily via waste water treatment plants.

Aerobic Biodegradability in Water

The biodegradability of fluvoxamine maleate was determined using the modified OECD test for ready biodegradability, shake flask test, CO_2 evolution method. CO_2 evolution and soluble organic carbon reduction were measured as indicators of biodegradability. In this test, 23.8 percent of the compound was degraded over the 28-day test period. Thus, although fluvoxamine maleate is degradable in water, it does not meet the current PMA recommended criteria for ready biodegradation.

The biodegradability of fluvoxamine maleate was determined in a study conducted in accordance with the FDA Environmental Assessment Technical Assistance Handbook, 3.11. A study report and data summary charts can be found in Confidential Appendix 9.

7.4 Summary of Fate Studies Regarding the Degradation of Fluvoxamine Maleate

Information presented in the above discussion indicates that fluvoxamine maleate will partition primarily into the aquatic compartment and that it eventually will biodegrade in that environmental compartment. However, the modest degradation rate observed in this study suggests that the ability of the compound to inhibit microbial activity in the environment should be evaluated and compared to the MEEC.

8.0 ENVIRONMENTAL EFFECTS OF RELEASED SUBSTANCES

No formal studies evaluating the potential toxic effects of fluvoxamine maleate in the environment were identified. The primary environmental receptors of concern with regard to fluvoxamine maleate production and use are microorganisms in WWTP sludges. Although some fluvoxamine maleate may escape degradation in WWTP and discharge to surface waters, the concentrations in these effluent waters would be extremely low. Therefore, the potential for the compound to inhibit microbiological activity in the environment was evaluated using a 7-day microbial inhibition study as the most appropriate and relevant evaluation of potential adverse effects in the environment.

8.1 Environmental Hazard Assessment

The microbial inhibition study was conducted in accordance with the FDA Environmental Assessment Technical Assistance Handbook, 4.02. The study report and data summary charts can be found in Confidential Appendix 10. The findings of the study are summarized in Table 6.

The potential microbial inhibition activity of fluvoxamine maleate was tested in seven microbial species: two aerobic bacteria, one anaerobic bacterium, three fungi, and one alga. Nine fluvoxamine maleate concentrations ranging from 4 to 1000 ppm were tested. Minimum inhibitory concentrations ranging from 63 to >1000 ppm for the individual species were identified.

TABLE 6
SUMMARY OF 7-DAY MICROBIAL INHIBITION STUDY RESULTS

Organism	Minimum Inhibitory Concentration (MIC)* (ppm)	No Observed Effect Level (NOEL) (ppm)
Pseudomonas aeruginosa	500	250
Bacillus cereus	500	250
Clostridium sporogenes	500	250
Gliochladium virens	500	250
Penicillium funiculosum	500	250
Aspergillus niger	>1000	>1000
Oscillatoria prolifera	63	31

* All organisms were tested at fluvoxamine maleate concentrations of 0, 4, 8, 16, 31, 63, 125, 250, 500, and 1000 ppm.

8.2 Evaluation of Environmental Effects

Emissions Associated With Production of LUVOX™ Tablets

Solid and liquid wastes are collected for disposal by incineration. Therefore, no fluvoxamine maleate is expected to enter the environment as a result of the manufacture of LUVOX™ Tablets.

Emissions Associated With Use of LUVOX™ Tablets

Small amounts of fluvoxamine maleate may be excreted by individuals using LUVOX™ Tablets and ultimately may enter the aquatic environment through WWTPs. Based upon the estimated maximum emissions of fluvoxamine maleate to the aquatic compartment and a formula and assumptions recommended in the PMA Interim Guidance for Environmental Assessment Compliance Requirements, a Maximum Expected Emitted Concentration (MEEC) of 0.00036 ppm for the aquatic compartment was calculated for this environmental pathway (Appendix 1, Table 9). It is known that fluvoxamine is extensively metabolized by the liver into pharmacologically inactive metabolites. Following administration of fluvoxamine maleate tablets, less than 4 percent of the drug is excreted unchanged (Overmars et al, 1983). The MEEC for patient use is, therefore, more appropriately expressed as 0.000014 ppm. This MEEC is more than six orders of magnitude less than the minimum inhibitory concentrations identified for fluvoxamine maleate.

Summary of Environmental Effects

The data presented above and summarized in Table 7 indicate that fluvoxamine maleate, at maximum expected environmental concentrations, is unlikely to adversely affect microbial activity and ultimately would be expected to biodegrade in the environment. Maximum potential environmental concentrations of this compound are more than six orders of magnitude lower than MICs for all microorganisms tested in a relevant screening evaluation. It should be noted that algae are likely to be of limited concern for maintenance of a healthy waste water treatment system.

TABLE 7
QUANTITATIVE ENVIRONMENTAL HAZARD ASSESSMENT

Emission to Waste Water Treatment Plant from LUVOX™ Tablet Manufacturing Facility:

There will be no discharge of fluvoxamine maleate to waste water treatment plant.

Emissions to Waste Water Treatment Plants from Patient Use of LUVOX™ Tablets:

MEEC: 0.000014 ppm

MIC/NOEL:

Alga	63 ppm/31 ppm
Bacteria	500 ppm/250 ppm

Margin of Safety: Approximately 1,000,000 to 10,000,000

9.0 USE OF RESOURCES AND ENERGY

The proposed action will be performed within existing facilities and with the present work force. No additional buildings, equipment, landscaping, or construction will be necessary. Therefore, land use will be unaffected. The raw materials used in the production of LUVOX™ Tablets and the chemicals used as excipients in the final dosage form are readily available. The production of this drug product and the use of electric energy in this process will not cause significant depletion of any natural resources, including energy, minerals, and land.

Energy and water use as a result of approval of this action has been estimated based upon a percentage of total facility usage for the manufacture and distribution of LUVOX™ Tablets. Manufacture of the drug substance accounts for 1.2% and 2.0% of Solvay Duphar's energy and water use, respectively. These percentages are expected to double if the proposed action is approved. It is anticipated, based on marketing projections of sales in the fifth year, that approximately 90,270 kilowatt hours of electricity and 45,000 gallons of water will be used at the Baudette, Minnesota facility in the production of LUVOX™ Tablets. This comprises 2 percent and 1.2 percent, respectively, of the total annual electricity and water used at this site. It is anticipated that approximately 7,297 kilowatt hours of electricity and 3,159 gallons of water will be used at the Marietta, Georgia facility in connection with the testing and

distribution of LUVOX™ Tablets. This comprises approximately 0.1 percent each of the total electricity and water used at this site.

No effects are expected to occur in endangered or threatened species, or upon property listed in, or eligible for listing in, the National Register of Historic Places.

10.0 MITIGATION MEASURES

No mitigation measures are necessary since no adverse environmental effects have been identified in this environmental assessment. However, Solvay Pharmaceuticals, Inc., will employ the measures documented in Section 6 of this Environmental Assessment report to remain in compliance with all cited regulations and enforcement agencies and to minimize releases into the environment. Should a hazardous materials release occur, each Solvay Pharmaceuticals, Inc., facility will utilize its Facility Emergency Action Plans (FEAPs) to handle such an event.

Waste minimization at all Solvay Pharmaceuticals, Inc., facilities is achieved through strict accounting control systems which ensure that any significant decreases in yield are investigated and corrected. Procedures are in place to collect and incinerate contaminated solid and liquid waste associated with the manufacture of LUVOX™ Tablets, thereby minimizing environmental exposure to fluvoxamine maleate.

Material Safety Data Sheets are available for employees who work in the production areas. In addition, employees in the production and packaging areas and in laboratories wear protective clothing as needed, to assure compliance with OSHA occupational health standards.

11.0 ALTERNATIVES TO THE PROPOSED ACTION

The only alternative to the proposed action is no action. The alternative action would result in OCD-affected individuals being denied a safe and effective treatment for their condition. However, no adverse environmental effects have been identified in this environmental assessment and none are expected as a result of the proposed action.

12.0 INDIVIDUALS WHO PREPARED THIS ENVIRONMENTAL ASSESSMENT

The following persons prepared this document.

Solvay Pharmaceuticals, Inc., Personnel

Kenneth F. Anderson
Supervisor, Health, Safety and Environmental
B.S., Biology, North Georgia College
Eight years' experience with the disposal of hazardous wastes and SARA Title III activities as well as development and administration of corporate health and safety programs.

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Thirteen years' experience in preclinical research and development, three years in regulatory affairs.

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B.A., Chemistry, West Georgia College
Ph.D., University of Georgia College of Pharmacy-Medicinal Chemistry
Ten years' experience in the research and development of drugs and biologics.

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S. Thomas Golojuch
B.S., Biology, Georgetown University
M.S., Biology, George Mason University
More than 15 years experience in human health and environmental risk assessment.

Carl G. Osborne, D.V.M.
B.S., Zoology/Ecology, East Tennessee State University
D.V.M., Virginia-Maryland Regional College of Veterinary Medicine
Sixteen years experience in the development and review of environmental assessments and environmental impact statements.

13.0 CERTIFICATION

The undersigned responsible officials certify that the information presented in this document is true, accurate, and complete, to the best of the knowledge of Solvay Pharmaceuticals, Inc.

David G. Powell — Date 12-1-94

David Powell, Ph.D.
Senior Vice President
Operations Division

14.0 REFERENCES

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15.0 APPENDICES

15.0 APPENDICES (continued)

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Letter dated 1.4.87 from Municipality of Weesp to Duphar

Our ref. WV 7-85
Subject: Despatch of Nuisance Act Licence

In accordance with the provisions of Article 31,subsections (1) and (5), of the Environmental Protection (General Provisions) Act, we enclose herewith a copy of the decision and also of the notification, referred to in subsection (2)(c) of that Article, relating to your application (registered under the number quoted above) for a licence pursuant to the Nuisance Act.

Within one month of receiving this letter, please transfer into our giro account No. 9088 in the name of the Municipality of Weesp, or into account No. 48.49.25.377 with the Amro-Bank in Weesp, the fee of NLG 74,637.04.

Burgomaster and Aldermen of Weesp
per pro

Director of Technical Services

(signed)
Ir. H. Dooijes

NUISANCE ACT

The Burgomaster and Aldermen of Weesp;

having regard to Article 31 of the Environmental Protection (General Provisions) Act;

hereby announce that, under provisions to remove danger, damage or nuisance to the environment, on 24 March 1987 they granted a licence pursuant to the Nuisance Act in response to the application from Duphar B.V. in Weesp for a new licence, covering the entire plant, in respect of a plant for the manufacture, treatment and processing of chemical/ pharmaceutical products, situated at C.J. van Houtenlaan 36 in Weesp.

For one month from 3 April 1987, the decision and all relevant documents will be available for inspection in the Town Hall (Information Centre) every working day from 8.15 a.m. to midday, and also in the Public Library at Oudegracht 67 every Monday, Wednesday and Friday from 5.30 p.m. to 8.30 p.m.

In accordance with Article 44(2) of the Environmental Protection (General Provisions) Act, up to 4 May 1987 the following shall be able to appeal to the Crown:

(a) the applicant;

(b) the advisers involved;

(c) anyone who has raised objections in accordance with Articles 20, 21, 22(2) or 28(1)(c) of the Environmental Protection (General Provisions) Act;

(d) any other interested party who shows that he was not reasonably able to raise objections in accordance with Articles 20, 21, 22(2) or 28(1)(c) of the Environmental Protection (General Provisions) Act.

The decision shall come into effect upon expiry of the time limit for appeal, unless an appeal has been lodged prior to that date and, applying Article 60a of the Council of State Act, a request has been made for the decision to be suspended or for an interim provision to be adopted.

Any appeal must be addressed to Her Majesty the Queen and sent to the Council of State, Administrative Disputes Division, P.O. Box 20019, 2500 EA 's-Gravenhage.

Any request for suspension or for an interim provision must be addressed to the Chairman of the Administrative Disputes Division of the Council of State.

The decision shall not take effect before such request has been decided.

Weesp, 2 April 1987

Notification a.

HW-7-85 Municipality of Weesp

Nuisance Act Licence

The Burgomaster and Aldermen of Weesp;

in view of the application received on 12 April 1985 from Duphar B.V. in Weesp for a new licence pursuant to the Nuisance Act, covering the entire plant, in respect of a plant for the manufacture, treatment and processing of chemical/ pharmaceutical products, situated at C.J. van Houtenlaan 36 in Weesp, registered in the Land Register under the Municipality of Weesp, sections B and D, numbers 1195 and 2510;

whereas the procedure in accordance with the provisions of Section 3 of the Environmental Protection (General Provisions) Act has been carried out;

objections to the aforementioned application for a licence have been raised by Mr L.H. van Stuivenberg of Weesp;

the objections are mainly to the pilot plants, the concentrations of chemical waste in the air and the surface water;

with regard to the pilot plants it is requested that there should be reliable monitoring of the products which are to be made in the pilot plants and a ban on extending the pilot plants;

it is further requested that part of the population of Weesp should be medically examined once the plant is in operation and that there should be an absolute ban on the production and/or testing of prohibited chemical products such as insecticides and defoliants;

with regard to the objections raised to the pilot plants and the emissions in the air and the surface water, it may be stated that by laying down regulations the objections may reasonably be overcome;

with regard to the requested medical examination for part of the population of Weesp it must be judged that there is no causal link between the complaints made and the operation of the plant;

on the basis of the Nuisance Act there is therefore no reason to carry out such an examination and nor can this lead to the requested licence being refused;

with regard to the request for an absolute ban on the production and/or testing of prohibited chemical products it may be stated that, considering the purpose of the Nuisance Act, there is no reason to do so;

objections have been raised by Mr L.H. van Stuivenberg to the issuing of the draft decision;

the objections centre mainly on the pilot plants, on the emission of chemical waste into the air in the form of vapours, from which the health of the inhabitants of

Weesp could (already) suffer detriment in the form of headaches, asthmatic disorders and tiredness, and nuisance from bad smells;

with regard to the emission of chemical waste into the air, a regulation is requested stipulating the construction of a large chimney about 70 metres tall to which all pilot plants are connected, so that all vapours can blow away better and in higher layers of air;

it is further requested that medical research be carried out among the population into the existence of physical complaints in the form of headaches, asthmatic disorders and tiredness in relation to the plant's operation with at the same time a comparison being made with other places in the Netherlands having a similar number of inhabitants with respect to the number of cases of cancer occurring during the last 15 years;

it is pointed out that any disaster would have catastrophic consequences for the population;

it is requested that there be reliable monitoring of all pilot products, including the quantities produced per product, and the relevant codes used, so that no banned products may be produced,

it is also asked whether there is any possibility of being able to close the pilot plant for sound reasons in the event of banned products being produced;

it is pointed out that incomplete or out-of-date lists of the substances used are issued for inspection;

it is further requested that an investigation be carried out by an independent body into the lists and codes of the relevant products;

with regard to the objection concerning the emission of chemical waste into the air by the pilot plants in the form of vapours, from which the health of the inhabitants could suffer detriment, it may be stated that, through dilution, the concentration of these vapours at living levels is reduced to such an extent that the aim of the Nuisance Act, namely to prevent or limit danger, damage or nuisance, is fulfilled and a link between the emission of these vapours and any detrimental consequences for the health of the inhabitants cannot be established;

with regard to the objection concerning the nuisance from bad smells, it may be stated that if the regulations contained in the Nuisance Act licence are complied with, such smells cannot arise;

concerning the request to include a regulation stipulating the construction of a large chimney about 70 metres tall to which all pilot plants are connected, so that all vapours can blow away better and in higher layers of air, it may be stated that the inclusion of such a regulation is not necessary, since in Section M (emissions) measures/arrangements for reducing emissions from pilot plants and production plants have been elaborated in detail;

with regard to the request for medical research to be carried out among the population into the existence of physical complaints in the form of headaches, asthmatic disorders and tiredness in relation to the plant's operation, with at the same time a comparison being made with other

places in the Netherlands having a similar number of inhabitants with respect to the number of cases of cancer occurring during the last 15 years, it may be stated that, from information from the District Health Service, the Weesp Group of Family Practitioners and the Regional Inspectorate for Public Health and Environmental Protection, it appears that these bodies do not have any data pointing to an increased pattern of complaints in, specifically, the Aetsveld district, or in any other part of Weesp in connection with the operation of the plant;

in TNO Report G.1348 - "Measurements of emissions of organic compounds in the synthesis of vitamin D at Duphar B.V. in Weesp from 11 to 19 October 1984" - dated April 1985, it is stated on page 13 that the maximum emission concentration was not exceeded anywhere;

whereas, on the basis of the above considerations it has to be judged that there is no causal link between the complaints made and the plant's operation;

on the basis of the Nuisance Act there is therefore no reason to carry out such examinations and nor can this lead to the requested licence being refused;

it may be stated that through the regulations incorporated in the licence and the monitoring thereof, the circumstances in which aspects of danger, damage and/or nuisance can arise are reasonably limited, so that the chance of a disaster is greatly reduced;

with regard to the request that there should be reliable monitoring of all pilot products, including the quantities produced per product, and the relevant codes used, so that no banned products may be produced, it can be stated that the request is reasonably accommodated through the regulations included in Section Q (production changes/production development);

with regard to the question whether there is any possibility of being able to close the pilot plant for sound reasons in the event of banned products being produced, it can be stated that failure to observe the regulations, or action which is in contravention of the licence, should result in the provisions of Article 28 or Article 28a of the Nuisance Act being applied;

with regard to the assertion that incomplete or out-of-date lists of the substances used are issued, it has to be stated that this assertion is not corroborated by the facts;

whereas, moreover, changes in production may only be made if no increase in the aspects of danger, damage and/or nuisance as a result of the change in production may reasonably be expected, while for any other changes in production it will be necessary to apply for a licence under the Nuisance Act;

with regard to the requested investigation by an independent body into the reliability of the lists issued and the codes for the relevant products, it may be judged on the basis of the Nuisance Act that there is no reason to carry out such an investigation;

having regard to the provisions of the relevant articles of the Nuisance Act and the Environmental Protection (General Provisions) Act,

hereby decide:

I to dismiss the objections to the application for a licence;

II to dismiss the objections to the draft decision;

III to grant the requested licence in accordance with the certified annexes belonging to this decision.

Weesp, 24 March 1987 Fee: NLG 74,637.04
despatched: 1 APR 1987

The said Burgomaster and Aldermen,
the Secretary, the Burgomaster,

(signed) (signed)
Mr. R.H. Engel A. Visser

Letter dated 13.4.89 from Municipality of Weesp to Duphar

Our ref. SO5/HV-5-88b
Subject: Despatch of Nuisance Act Licence

In accordance with the provisions of Article 31, subsections (1) and (5), of the Environmental Protection (General Provisions) Act, we enclose herewith a copy of the decision and also of the notification, referred to in subsection (2)(c) of that Article, relating to your application (registered under the number quoted above) for a licence pursuant to the Nuisance Act.

You will receive a bill from the Financial and Economic Affairs department for the fee due.

Burgomaster and Aldermen of Weesp
per pro

Head of the Urban Development Department

(signed)
Drs. G.M. Wortman

Encs.

SO5/HW-1-5-7-11-12-13-15/88

Nuisance Act Licence

The Burgomaster and Aldermen of Weesp:

having regard to Article 31 of the Environmental Protection (General Provisions) Act;

hereby announce that, under provisions to remove danger, damage or nuisance to the environment, on 2 and 9 May 1989 they granted a licence pursuant to the Nuisance Act in response to applications from:

1. Shipshape Jachtservice Weesp, of Weesp, for a new licence, covering the entire establishment, for the maintenance and storage of boats/yachts (approx. 15 metres long), and also a metal-working establishment for shipyard activities, situated at Nijverheidslaan 18 in Weesp;

2. Mr E. Vink, of Huizen, for a licence to set up and operate a repair establishment for motor vehicles, situated at Nijverheidslaan 40a in Weesp;

3. AL-DRUK, of Weesp, for a new licence, covering the entire establishment, in respect of an establishment having electrically-driven tools for a printing works, situated at Middenstraat 49 in Weesp;

4. Bleijenberg Weesp B.V., of Weesp, for a licence to extend/modify a metal-working establishment for the use of an engineering and construction firm, situated at Hogeweyselaan 203 in Weesp;

5. ABR Afvalverwerking Nederland B.V., of Weesp, for a licence to set up and operate a metal-working establishment and also to store chemicals, all for commercial purposes, situated at Pampuslaan 147 in Weesp;

6. Ruitenbeek Weesp B.V., of Weesp, for a new licence, covering the entire establishment, in respect of an establishment having electrically-driven tools, and for the storage of flammable liquids, all for the use of a printing works, situated at Bloemendalerweg 14 in Weesp;

7. Duphar B.V., of Weesp, for a licence to

extend/modify an establishment for the manufacture, treatment and processing of chemical pharmaceutical products, situated at C.J. van Houtenlaan 36 in Weesp.

For one month from 26 May 1989, the decision and all relevant documents will be available for inspection in the Town Hall (Information Centre) every working day from 8.15 a.m. to midday, and also in the Public Library at Oudegracht 67 every Monday, Wednesday and Friday from 5.30 p.m. to 8.30 p.m.

In accordance with Article 44(2) of the Environmental Protection (General Provisions) Act, up to 26 June 1989 the following shall be able to appeal to the Administrative Disputes Division of the Council of State:

(a) the applicant;

(b) the advisers involved;

(c) anyone who has raised objections in accordance with Articles 20, 21, 22(2) or 28(1)(c) of the Environmental Protection (General Provisions) Act;

(d) any other interested party who shows that he was not reasonably able to raise objections in accordance with Articles 20, 21, 22(2) or 28(1)(c) of the Environmental Protection (General Provisions) Act.

The decision shall come into effect upon expiry of the time limit for appeal, unless an appeal has been lodged prior to that date and, applying Article 107 of the Council of State Act, a request has been made for the decision to be suspended or for an interim provision to be adopted. Any appeal must be addressed to the Council of State, Administrative Disputes Division, P.O. Box 20019, 2500 EA 's-Gravenhage. Any request for suspension or for an interim provision must be addressed to the Chairman of the Administrative Disputes Division of the Council of State. The decision shall not take effect before such request has been decided.

Weesp, 25 May 1989

HW-5-88 Municipality of
Weesp

Nuisance Act Licence

The Burgomaster and Aldermen of Weesp;

in view of the application received on 15 March 1988 from Duphar B.V. in Weesp for a licence pursuant to the Nuisance Act to extend/modify a plant for the manufacture, treatment and processing of chemical pharmaceutical products, situated at C.J. van Houtenlaan 36 in Weesp, registered in the Land Register under the Municipality of Weesp, sections B and D, numbers 2817 and 1215;

whereas the procedure in accordance with the provisions of Section 3 of the Environmental Protection (General Provisions) Act has been carried out;

no objections have been raised to the issue of the decision requested;

no objections have been raised to the draft decision,

any danger, damage or nuisance which might be caused by the plant can be sufficiently overcome by the certified regulations belonging to this Decision;

having regard to the provisions of the relevant articles of the Nuisance Act and the Environmental Protection (General Provisions) Act;

hereby decide:

to grant the requested licence in accordance with the certified annexes belonging to this Decision.

Fee: You will receive a bill from the Financial and
Economic Affairs department for the fee due.

Weesp, 9 May 1989

The said Burgomaster and Aldermen,
the Secretary, the Burgomaster,

(signed) (signed)
W.A. Bakker, deputy A. Visser

Letter dated 31.3.81 from Municipality of Weesp to Duphar

Our ref. HW-13-80
Subject: Despatch of Nuisance Act Licence

In accordance with the provisions of Article 31, subsections (1) and (5), of the Environmental Protection (General Provisions) Act, we enclose herewith a copy of the decision and also of the notification, referred to in subsection (2)(c) of that Article, relating to your application (registered under the number quoted above) for a licence pursuant to the Nuisance Act.

Within 5 days of receiving this letter, please transfer into our giro account No. 9088 in the name of the Municipality of Weesp, or into account No. 48.49.25.377 with the Amro-Bank in Weesp, the fee of NLG 1,415.00.

Burgomaster and Aldermen of Weesp
the Secretary, the Burgomaster,

(signed) (signed)
G. Biesheuvel H.J. Over de Linden

APPENDIX B

Material Safety Data Sheet for Fluvoxamine Maleate

SOLVAY PHARMACEUTICALS

MATERIAL SAFETY DATA SHEET

IDENTITY (As used on Label and List) **Fluvoxamine Maleate**

Note: Blank spaces are not permitted. If any item is not applicable, the space must be marked to indicate that.

Section I

Manufacturer's Name	Emergency Telephone Number
Solvay Pharmaceuticals	(404) 578-9000
Address (Number, Street, City, State and Zip Code)	**Telephone Number for Information**
901 Sawyer Road, Marietta, GA 30062	(404) 578-9000

Signature of Preparer (optional)

Section II - Hazardous Ingredients/Identity Information

Hazardous Components (specific chemical identity, common names)	OSHA PEL	ACGIH TLV	Other Limits Recommended	Chemical Abstract No.
Fluvoxamine Maleate	None	None	N/A	61718-82-9

Section III - Physical/Chemical Characteristics

Boiling Point - See Note*

Specific Gravity (H_2O = 1) - 1.3034-1.3202

Vapor Pressure (mm Hg.) - $<1.33x10^{-6}$ pascal
$<1.33x10^{-7}$ torr

Melting Point - 122°C

Vapor Density (AIR = 1) - See Note*

Evaporation Rate - See Note*
(Butyl Acetate = 1) - N/A

Solubility in Water - 20 grams per liter at 20°C

Appearance and Odor - White powder

*Note: Due to the material being a solid and the very low vapor pressure ($< 1.33x10^{-7}$ torr) the boiling point, vapor density and evaporation rate are not considered significant characteristics of this material.

Section IV - Fire and Explosion Hazard Data

Flash Point (Method Used) - Combustible Flammable Limits - See Note* LEL - 300°C (dust)

Extinguishing Media - Carbonic acid, powder, halogens, atomized water, foam, water

Special Fire Fighting Procedures - None

Unusual Fire and Explosion Hazards - None

*Note: Many normally non-flammable powders can become explosive when excessive quantities are suspended in a confined atmosphere. Whenever possible, powders should be contained and not allowed to become airborne (NFPA 497B).

Section V - Reactivity Data

Stability - Stable Conditions to Avoid - None

Incompatibility (Materials to Avoid) - None

Hazardous Decomposition or Byproducts - None

Hazardous Polymerization - Will Not Occur Conditions to Avoid - None

Section VI - Health Hazard Data

ACUTE TOXICITY:
LD50 oral rat: 1470 - 2000 mg per kg
LD50 dermal rat: more than 5000 mg per kg
LC50 inhalation rat: 1030 mg/m^3/4 hours

IRRITATION:
Skin-irritation guinea pig (5 ml of 50% suspension/16 h/covered): not irritating
Eye-irritation rabbit (100 mg): severely irritating and corrosive
Lung-irritation rat: RD50 150 - 200 mg per m^3: severely irritating

SENSITIZATION:
Causes slight sensitization in guinea pigs.

(SUB)CHRONICAL TOXICITY
At dosages from 10 mg per kg and up, effects on the fat metabolism have been found in mice and hamsters. A no-effect level is not known for this effect in these species.
In rats and dogs effects on the fat metabolism were found from 15 mg/kg/day.

FERTILITY:
At dosages of 20 and 80 mg/kg/day, an increased pup-mortality after birth was seen in rats.

TERATOGENICITY:
No teratogenic effects were seen in rats and rabbits.

MUTAGENICITY:
Not mutagenic in the Ames test, micro nucleus test and chromosome aberration test.

CARCINOGENICITY:
Not carcinogenic in rats and hamsters.

HUMAN EFFECTS:
Nausea, somnolence, constipation, loss of appetite and agitation have been seen after short-term oral administration of the recommended human dose (100-300 mg/day).

ENVIRONMENTAL TOXICITY:
Fluvoxamine maleate at maximum expected environmental concentrations is unlikely to adversely affect microbial activity and ultimately would be expected to biodegrade in the environment.

EMERGENCY AND FIRST AID PROCEDURES - If symptoms of exposure are present, seek medical attention.

Section VI: - Precautions for Safe Handling and Use

Steps to be Taken in Case Material is Released or Spilled: Suck up spilled material with an explosion-protected industrial vacuum cleaner. Carefully collect remainder, (extra personal protection: protective gloves, protective clothes and air stream helmet).

Waste Disposal Method - Dispose of in a manner consistent with federal, state and local regulations.

Precautions to Be Taken in Handling and Storing - Use engineering practices to control any airborne powders (e.g., dust collection systems).

Other Precautions - Use engineering practices to control worker and environmental exposure

Section VIII - Control Measures

Respiratory Protection (Specify Type) - Full-face HEPA respirator, supplied air respirator, air stream helmet.

Ventilation
Local Exhaust - Consistent for the control of airborne powders
Mechanical (General) - Same as above)
Special - None
Other - None

Protective Gloves - latex rubber

Eye Protection - goggles/full-face respirator

Other Protective Clothing or Equipment - Lab coat, protective coveralls. Whenever possible, workers should be protected by engineering practices.

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: April 21, 1994

FROM: Barry Rosloff, Ph.D.

SUBJECT: NDA 20-234 (Fluvoxamine for Obsessive-Compulsive Disorder) - Addendum to review of 3/10/92

TO: NDA 20-234 Original and Division File
Dr. Fitzgerald
Dr. Laughren
Dr. Dubitsky
Dr. Rosloff
Paul David

Two issues have arisen since my review of NDA 20-234 was completed:

1) As indicated in my previous reviews of fluvoxamine, there was a concern that the doses used in the Segment I and II rat reproduction studies were set too low, although it concluded at the time that the studies were acceptable. However, a subsequently submitted (12/17/93 to IND Japanese subacute gavage study in rats (apparently done in support of development of the drug in Japan) indicates that rats can adequately tolerate gavage doses several fold higher than those used in the reproduction studies. For this reason, and also for the reason that in the Segment III studies there were increases in pup deaths at birth and decreases in postnatal pup weight and survival which could not totally be explained by maternal toxicity (see attached memo by Dr. Fisher), we will recommend additional reproduction studies at higher doses. (See Dr. Fisher's memo for suggested studies).

2) The rat and hamster carcinogenicity studies were reviewed by the Executive Committee of the Carcinogenicity Assessment Committee on 4/5/94. Based on a new statistical review by Biometrics (10/15/93, copy attached) the Committee originally considered the occurrence of a small number of pancreatic tumors in high dose male rats as "marginally significant" and that this finding should probably be included in the labelling; however, after the Committee was subsequently provided with supplementary information by myself it concurred (with one dissension) with my recommendation to not include this in the labelling. (Relevant memos attached).* The Committee also agreed that results in other organs showed no clear evidence of a drug-related increase in tumors..

(5/2/94)

*Note added in proof: A new analysis by Biometrics, combining the sexes, found no significant effect on pancreatic adenocarcinoma (copy attached).

RECOMMENDATIONS:

In view of the fact that the doses used in the rat reproduction studies appeared to be too low (particularly in view of the 2 week rat gavage study submitted to IND on 12/17/93), it is recommended that they be repeated post-marketing. Doses should be based on rangefinding studies and/or other relevant data to insure adequate exposure. A suggestion for a segment II or combined segment II/III study, which could help determine whether the adverse effects on pups were due to in utero or postnatal effects, has been made by Dr. Fisher (see attached memo).

Barry Rosloff

Barry N. Rosloff, Ph.D.

cc: NDA 20-350
HFD-120
HFD-120/GFitzgerald
/BRosloff
/CSO
rd/ejs/4/26/94
ft/ejs/5/2/94
N:\Rosloff\memo

M E M O R A N D U M

DATE: April 22, 1994

FROM: Ed Fisher

SUBJECT: Developmental toxicity of Fluvoxamine

TO: Glenna Fitzgerald

Standard segment I, II, and III studies were conducted in rats with doses of 0, 5, 20 and 80 mg/kg, administered orally. No evidence of maternal toxicity was observed at these doses in any study, so the choice of the high dose should be questioned. No adverse effects on embryo/fetal development were seen in litters examined prior to parturition (gestational day 20 in the segment I and II studies). Effects noted in litters evaluated after birth in the segment I study included decreased litter size from birth through weaning in all drug treatment groups (means 10-15% below C) and increased pup mortality between days 4 and 21 of lactation in the MD and HD groups (23% cumulative mortality in each vs. 18% in C, n.s., but the C value is high). In the segment III study, decreases in total and viable pups born (11 and 16% below controls, n.s.), increased pup mortality from birth (7% fetal loss on postnatal day 0 vs. 2% in C, n.s.) through day 12, and decreased litter size from birth through day 21 (- 28%, $p<.01$) were seen at the HD. Increased pup mortality was seen in all drug treatment groups over 21 days post partum; cumulative mortality was 17, 17, and 25% in LD, MD, and HD groups, resp., vs. 4% in C (statistically significant at all doses).

A second segment III type study with a cross-fostering design was performed using two groups (50 rats/grp) dosed with either 0 or 160 mg/kg. No obvious adverse effects were seen in drug treated dams during gestation, but several experienced dystocia (3; 2 died) or delayed parturition (2) at term. A decrease in viable pups (16% below C, $p<.01$) and increased pup mortality (11% fetal loss vs. 0.9% in C, $p<.05$) were seen in the drug treatment group at birth, while mean pup weight was slightly increased in the treated group. All 48 pregnant control dams reared their own or a fostered treatment group litter to day 21 post partum. The cumulative pup mortality from day 1, when litters were equalized and cross-fostered, through day 21 was 6% for control litters raised by control mothers and 8% for treatment group litters raised by control mothers. In contrast, a statistically significant proportion of pregnant drug treated dams (15/46) failed to rear any young. Furthermore, after cross-fostering, total litter losses for drug treated dams occurred almost twice as often (but n.s.) with non-fostered (i.e., prenatally exposed) litters (8/23) as with fostered (control) litters (4/20). All but one of these were seen by postnatal day 4. For treated dams rearing some young to weaning, pup mortality was about twice that seen in litters reared by control dams (12 and 14% cumulative mortality after day 1 for control and treated litters, resp.; group differences n.s.).

The cross-fostering results certainly indicate that much of the increased peri/postnatal pup mortality associated with the drug is secondary to maternal drug effects. However, direct effects of postnatal drug exposure during lactation cannot be ruled out, and several n.s. trends suggest an interaction between pre- and postnatal effects: both fostered and non-fostered offspring from drug treated dams gained less weight than control offspring over 21 days post partum, although the effect only reached statistical significance in the non-fostered pups; the pup mortality rate among treatment group young reared by control dams was higher than that for control litters reared by control dams, and the pup mortality rate for treatment group pups reared by treated dams was higher than that in control litters reared by treated dams; and total litter loss for treated dams occurred more often with non-fostered than with fostered litters. In addition, while a maternal role in the increased pup mortality at birth in treatment group litters is implied, this effect could not be addressed by cross-fostering. Evaluation of the embryo/fetal toxicity of a dose as high as that used in the fostering study prior to parturition might help to discriminate between direct and indirect fetal effects. Since the high dose used in the existing segment II study was too low, this could be done in a prolonged segment II or combined segment II/segment III study with a HD of at least 160 mg/kg and fetal examination on day 20.

I N T E R O F F I C E M E M O R A N D U M

Date: 21-Apr-1994 02:01pm DST
From: Barry Rosloff
ROSLOFF
Dept: HFD-120
Tel No: 443-4152

TO: Alan Taylor (TAYLORA)

CC: Joseph F. Contrera (HFD-400) (CONTRERAJF)
CC: Joseph DeGeorge (DEGEORGE)
CC: Charles Resnick (RESNICK)
CC: Glenna Fitzgerald (FITZGERALD)
CC: Zulema Miguele (MIGUELE)

Subject: CACEC Mtg. 4/5/94 -- NDA 20-234 (Luvox)

The Committee agreed with the reviewer (Dr. Rosloff) that the hamster study showed no clear drug-related increase in tumors.

Regarding the rat study, although the reviewer concluded there was no clear drug-related increase in tumors, it was noted that a recent statistical evaluation by Biometrics concluded that there was a staistically significant trend for an increase in pancreatic adenocarcinomas in males. The numbers of tumors seen were 0,0,0, and 3 in controls, LD, MD, and HD, resp. (N=40/sex/group). Dr. Rosloff noted that although the tumor type is relatively rare, it is not extremely rare with a recently published historical control mean of about 0.5% with a range of 0-2%. Furthermore, a pancreatic adenocarcinoma was also seen in 1 control female (i.e. 2.5%); none in the other female groups. The committee concluded that the result in males was "marginally significant" and that it should probably go in the labelling. Part of the Committee's reasoning was based on the fact that the study was rather old, had a relatively low N (40/sex/group, although Dr. Rosloff noted that survival was extremely good and treatment continued for 2.5 years), and used an HD which did not cause pronounced toxicity aside from decreased wieght gain for which decreased palatability as a cause could not be ruled out. (At the meeting I incorrectly stated that the HD was 15x the highest clinical dose; the correct number is 50. There were no exposure data for comparison with humans.) Dr Rosloff noted that there was an 18 month rat study, using 20/sex/group at the same doses and in the same strain as in the CA study. The committee noted that the results of this study might shed light on the pancreatic problem. (I noted that my review of this study indicated no such problems although I no longer had this study in my possession and would request it in order to look at the individual animal data. I received a copy of the study from the sponsor this week: there were no pancreatic tumors in any animal and no drug-related effects of any kind in pancreas.)

Does any of this new information change anyone's mind about the significance of the pancreatic tumors? The new information is as follows:

1. There were no pancreatic tumors in the 18 month study.
2. The multiple of the clinical dose is 50, not 15. (Also, although I noted at the meeting that overt signs at HD were minimal, I neglected to mention that vacuolated hepatocytes and/ or centrilobular degeneration, and foci of pneumonia were clearly increased at HD, possibly indicating adequate exposure.)

I N T E R O F F I C E M E M O R A N D U M

Date: 21-Apr-1994 04:54pm DST
From: Alan Taylor
TAYLORA
Dept: HFD-502 PKLN 13B28
Tel No: 301-443-2544

TO: Barry Rosloff (ROSLOFF)

CC: Joseph F. Contrera (HFD-400) (CONTRERAJF)
CC: Joseph DeGeorge (DEGEORGE)
CC: Charles Resnick (RESNICK)
CC: Glenna Fitzgerald (FITZGERALD)
CC: Zulema Miguele (MIGUELE)

Subject: RE: CACEC Mtg. 4/5/94 -- NDA 20-234 (Luvox)

Barry,
A couple of points you may need to clarify for us:

1. Is the 50X multiple based on mg/kg or mg/m2?

2. What was the survival and tox profile in the 18 month study?

In general, I think the additional data and clarifications in your memo would lead me to agree with your recommendation that we leave this out of labeling. However, if you can get the answers to the above it would be helpful.

Thanks, Alan.

I N T E R O F F I C E M E M O R A N D U M

Date: 21-Apr-1994 05:31pm DST
From: Joseph DeGeorge
DEGEORGE
Dept: HFD-150 WOOD 400SC
Tel No: 301-295-9135

TO: Barry Rosloff (ROSLOFF)

CC: Alan Taylor (TAYLORA)
CC: Joseph F. Contrera (HFD-400) (CONTRERAJF)
CC: Charles Resnick (RESNICK)
CC: Glenna Fitzgerald (FITZGERALD)
CC: Zulema Miguele (MIGUELE)

Subject: RE: CACEC Mtg. 4/5/94 -- NDA 20-234 (Luvox)

Given that the main study appears (based on the toxicity) to have used an appropriate MTD dose, and that there were no additional tumors in the shorter/smaller study, and that in females it could not be considered a rare tumor (greater than 2%). I would support that the findings not be required to be in the labeling. The reasoning should be carefully and completely documented in the review.
Joseph DeGeorge

I N T E R O F F I C E M E M O R A N D U M

Date: 22-Apr-1994 12:45pm DST
From: Barry Rosloff
ROSLOFF
Dept: HFD-120
Tel No: 443-4152

TO: Alan Taylor (TAYLORA)

CC: Joseph F. Contrera (HFD-400) (CONTRERAJF)
CC: Joseph DeGeorge (DEGEORGE)
CC: Charles Resnick (RESNICK)
CC: Glenna Fitzgerald (FITZGERALD)
CC: Zulema Miguele (MIGUELE)

Subject: NDA 20-234--Your memo of 4-21-94

1. The 50x multiple is based on mg/kg. (Sorry)

2. The tox profile in the 18 month study was similar to that in the CA study: decreased weight gain/food consumption at HD, and similar liver and lung pathology (but the former only in males in the 18 month study) at HD and sometimes MD; in addition there were kidney changes(chronic inflammation, distended tubules, basophilic tubules), mainly but not exclusively in males, at the higher doses in the 18 month study. Mortality in the 18 momth study was low (overall about 7%) and not drug-related.

I N T E R O F F I C E M E M O R A N D U M

Date: 25-Apr-1994 07:51am DST
From: Alan Taylor
TAYLORA
Dept: HFD-502 PKLN 13B28
Tel No: 301-443-2544

TO: Barry Rosloff (ROSLOFF)

CC: Joseph F. Contrera (HFD-400) (CONTRERAJF)
CC: Joseph DeGeorge (DEGEORGE)
CC: Charles Resnick (RESNICK)
CC: Glenna Fitzgerald (FITZGERALD)
CC: Zulema Miguele (MIGUELE)

Subject: RE: NDA 20-234--Your memo of 4-21-94

Barry,
I agree with Joe's email and I concur with your recommendations based on the additional analyses performed. Since other committee members have not responded, we assume they concur. (If not, please make this known ASAP.)
Please write up draft final report and send by email.
Thanks, Alan.

I N T E R O F F I C E M E M O R A N D U M

Date: 25-Apr-1994 09:48am DST
From: Joseph F. Contrera (HFD-400)
CONTRERAJF
Dept: HFD-400 PKLN 13B19
Tel No: (301)443-4750

TO: Alan Taylor (TAYLORA)

CC: Barry Rosloff (ROSLOFF)
CC: Joseph DeGeorge (DEGEORGE)
CC: Charles Resnick (RESNICK)
CC: Glenna Fitzgerald (FITZGERALD)
CC: Zulema Miguele (MIGUELE)

Subject: RE: NDA 20-234--Your memo of 4-21-94

I agree with Dr. Rosloff's conclusions also.

I N T E R O F F I C E M E M O R A N D U M

Date: 25-Apr-1994 11:04am DST
From: Charles Resnick
RESNICK
Dept: HFD-110
Tel No: 443-0316

TO: Barry Rosloff (OSLOFF)

CC: Alan Taylor (TAYLORA)
CC: Joseph F. Contrera (HFD-400) (CONTRERAJF)
CC: Joseph DeGeorge (DEGEORGE)
CC: Glenna Fitzgerald (FITZGERALD)
CC: Zulema Miguele (MIGUELE)

Subject: RE: CACEC Mtg. 4/5/94 -- NDA 20-234 (Luvox)

Guess I'm the only holdout. I do not see how an 18 month study can be used to refute a finding from a 28-29 month study.

I still think that the significant trend in pancreatic adenocarcinoma occurrence in male rats belongs in labeling, described as an equivocal finding. The statement should include the observation that, based on additional data from an 18 month study in the same strain of rat, exposure durations in excess of 18 months were required.

The new information is not impressive in terms of documenting MTD. In my view, the most impressive non-neoplastic finding in the carcinogenicity study was the better survival in the high dose male group.

I N T E R O F F I C E M E M O R A N D U M

Date: 25-Apr-1994 12:36pm DST
From: Barry Rosloff
ROSLOFF
Dept: HFD-120
Tel No: 443-4152

TO: Alan Taylor (TAYLORA)

CC: Joseph F. Contrera (HFD-400) (CONTRERAJF)
CC: Joseph DeGeorge (DEGEORGE)
CC: Charles Resnick (RESNICK)
CC: Glenna Fitzgerald (FITZGERALD)
CC: Zulema Miguele (MIGUELEZ)

Subject: CACEC mtg. 4/5/94---NDA 20-234 (Luvox)

As indicated in the previous memos on this subject the Committee (with one dissension, Dr. Resnick) agrees with the reviewer that the animal studies performed provided no clear evidence of drug-related carcinogenicity; the occurrence of a small number of pancreatic tumors in high dose males is too equivocal to ascribe to drug and include in the labelling.

Barry Rosloff

I N T E R O F F I C E M E M O R A N D U M

Date: 25-Apr-1994 01:51pm DST
From: Alan Taylor
TAYLORA
Dept: HFD-502 PKLN 13B28
Tel No: 301-443-2544

TO: Barry Rosloff (ROSLOFF)

CC: Joseph F. Contrera (HFD-400) (CONTRERAJF)
CC: Joseph DeGeorge (DEGEORGE)
CC: Charles Resnick (RESNICK)
CC: Glenna Fitzgerald (FITZGERALD)
CC: Zulema Miguele (MIGUELEZ)

Subject: RE: CACEC mtg. 4/5/94---NDA 20-234 (Luvox)

In theory, if there is not unanimous agreement on recommendations, the full committee should be consulted. However, this case may be somewhat different.

My reading is that all agree that the findings are equivocal and the studies, though problematic, are ultimately acceptable. If this is the case, the only real stickler is the recommendation on labeling. Labeling recommendations are really the pervue of the division. While the CAC often comments on this, it is not critical to the assessent of the study design, interpretation, etc., which is real charge of the committee. Therefore, with the concurrence of the committee, I'd suggest that the division have the option of taking the split decision on the labeling recommendation, making their own final determination. Alternatively, the division may request a full CAC meeting to get broader input.

Glenna, please let me know your decision ASAP.

Barry, printed copies of all emails regarding this issue should be appended to the report of the executive committee deliberations which is submitted for the file maintained in HFD-502.

Thanks, Alan.

I N T E R O F F I C E M E M O R A N D U M

Date: 03-May-1994 03:00pm DST
From: Alan Taylor
TAYLORA
Dept: HFD-502 PKLN 13B28
Tel No: 301-443-2544

TO: Glenna Fitzgerald (FITZGERALD)
TO: Barry Rosloff (ROSLOFF)
TO: Joseph F. Contrera (HFD-400) (CONTRERAJF)
TO: Charles Resnick (RESNICK)

Subject: NDA 20234 CAC review draft final report

Please reply by COB tomorrow if modifications are needed in this report. Otherwise, I will sign and issue on Thursday. Thanks, Alan

CAC Executive Committee Minutes

Application: NDA 20-234
Division: HFD-120
Date: April 5, 1994
Reviewer: Barry Rosloff
Chairperson: Taylor
Members: Contrera, Resnick, Fitzgerald

The committee reviewed the results of carcinogenicity studies in hamsters and rats. The hamster study was considered acceptable in design and outcome.

The rat study was controversial for a number of reasons. The study showed an increased incidence of pancreatic adenocarcinomas (0, 0, 0, 3/40), a relatively rare tumor in males. However, historical data from the published literature indicated an incidence of 0-2%. Furthermore, one pancreatic adnocarcinoma was also reported in one female control animal. Based on the data provided at the meeting the committee agreed that the findings were marginally significant and should probably be included in labeling because the study itself was of marginal quality. Study conduct issues of concern included, the low numbers of animals tested per dose group, and the lack of definitive toxicity endpoints (aside from decreased body wt. and food consumption) indicative of testing at the MTD. It is noted however, that the study was carried out for 29 months rather than the usual 24 months. In addition, Dr. Rosloff recalled that there was data from a shorter 18 month study in the same strain of rats that suggested no similar effect. The committee requested that Dr. Rosloff review this data in detail and provide any additional comments by email.

Rosloff's analysis of the 18 month study showed that no increase in pancreatic adenocarcinomas. In addition, Dr. Rosloff noted after further review that evidence of toxicity including vacuolated hepatocytes, centrilobular degeneration in liver of both studies, evidence of pneumonia in the 29 month study and renal toxicity (chronic inflammation, distended tubules, basophilic

tubules) in the 18 month study may be indicative of adequate exposure in the two studies chronic studies. There was good survival in both studies further supporting the adequacy of exposure to carcinogenic challenge.

Based on the total information provided, the committee agreed that the findings in the pancreas were "equivocal" but did not warrant repeat testing. Unanimous agreement could not be achieved on whether or not the finding should be included in the labeling. Therefore, this was left to the discretion of the review division.

cc:
NDA 20-234
HFD-120/div file
/Fitzgerald
/Rosloff
HFD-502/CAC file

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: August 16, 1994

FROM: Glen Jon Smith, HFD-647

THROUGH: Phillip G. Vincent, Ph.D.
Environmental Assessment Officer, HFD-102

SUBJECT: Environmental Assessment, NDAs 20-243, 20-350 Luvox™ Tablets (Fluvoxamine Maleate).

TO: Paul David, HFD-120

The Center has reviewed the environmental assessments for the subject NDAs.

Action: INADEQUATE

Please transmit the following to the firm and copy HFD-102.

Your environmental assessment has been carefully reviewed. Please address the following deficiency.

1. Item 4: Please revise this item to include descriptions of the environments present and adjacent to the manufacturing facility in the Netherlands and the packaging facility in New Jersey.

2. Item 5: Please revise this item to include all impurities in addition to the (Z) isomer and appropriate limits.

3. Regarding Item 6:

   A. Regarding manufacture of the drug substance:

      1. We note that all environmental assessment information regarding the manufacture of the drug substance was submitted in an confidential appendix. The Environmental Assessment (EA) is a public document which will be available for review per 21 CFR 25.31. Information defined in the formats per 21 CFR 25.31a should be contained in the EA. Confidential or proprietary information should be placed in appendices which are clearly marked as confidential at the end of the EA. However, confidential information should be

summarized to the extent possible and included as part of the EA in accordance with 21 CFR 25.30(b).

2. You indicated that limits for the emission of specific organic solvents were included in the applicable permits. The documents submitted did not contain a list of specific organic solvents or applicable limits. Please submit this information along with certification from the appropriate regulatory authorities confirming the accuracy of the information.

3. Please include in the assessment a discussion of controls used to limit gaseous and particulate air emissions.

4. You have indicated that due to the multiproduct nature of the manufacturing facility, accurate determination of the impact of the action on compliance with wastewater stream limits was not possible. However, the increase in the amount of wastewater along with reasonable assumptions (e.g. the COD/BOD of the influent remains relatively constant over time) may be used to estimate the increase in influent COD/BOD in order to demonstrate that sufficient reserve capacity does exist for wastewater treatment. Please submit this type of estimate along with the appropriate assumptions.

5. Please include in the assessment a brief description of the controls used at your wastewater treatment plant.

6. Please include in the assessment a brief description of the incineration equipment and process (e.g. two stage, emission controls) used for the disposal of solid and chemical wastes.

7. Please note that all statements of compliance with applicable environmental regulations and laws must be included in the Environmental Assessment and not in confidential appendices.

B. Regarding manufacture of the drug product:

1. Please include in the assessment a brief description of the incineration equipment and process (e.g. two stage, emission controls) used at both proposed facilities for the disposal of solid and chemical wastes.

2. Please submit calculations showing the potential impact the action may have on compliance with permit limits for air emissions.

3. Please revise the listings and descriptions of all of permit numbers to include expiration dates and applicable limits. Do not send copies of the actual permits unless specifically requested.

4. Regarding Items 7 and 8:

A. The testing reports submitted in support of this assessment contained significant discrepancies (See Comment 8). The information based on these studies must therefore be considered inadequate to support any conclusions regarding fate of emitted substances and environmental effects of released substances. You have therefore failed to comply with the regulations for these items per 21 CFR 25.31a(a). Your EA must address all topics included for these items and contain testing results to support any conclusions. The items may reference confidential appendices where necessary, but may not be composed solely of such references.

B. You have stated that the drug substance was not found to be biodegradable by the test model employed and have failed to identify a mechanism for removal of the drug substance from the environment. Failure to identify such a mechanism may necessitate chronic toxicity studies. Please submit estimates of when such studies would be required as well as proposed testing. Please note also that identification of a mechanism for the rapid removal of the drug substance from the environment could possibly negate the need for chronic toxicity studies and it is strongly recommended that a mechanism be identified if possible.

C. You have referred to the "PMA/FDA Environmental Assessment Technical Test Matrix" and the "PMA/FDA Interim Environmental Assessment Guidance" in your assessment. Please be advised that this interim PMA document is not an FDA document and has not been sanctioned by the Agency. The phraseology used in your assessment should be modified accordingly.

5. Item 10: Please note that the purpose of this item is to address measures taken if available information indicates that adverse environmental impacts may be associated with the proposed action. Should the assessment indicated no adverse impact, please state that it is your conclusion that there will be no adverse impact and that mitigation is therefore not necessary.

6. Item 11: The determination of whether an alternative action is "not warranted" is the decision of the Agency. Please revise your statement to remove this phrase.

7. Item 14: Please revise this item to include all references, including OECD and FDA testing procedures as well as the PMA interim document.

8. Regarding Item 15:

   A. You failed to include Data Summary Charts in your Environmental Assessment. Please note that these charts should be part of the assessment and not placed solely within confidential appendices.

   B. The study submitted for the determination of dissociation constants is inadequate.

      1. The report was revised to indicate that the constant observed in the range of pH 10 - 12 was due to excess base and not a true inflection point without submitting supporting data.

      2. The report indicated that the inflection points at lower pH values were due in part to the protonation of the carboxylate groups on the maleate as well as the primary amine group on fluvoxamine. Data resolving these was not submitted.

      3. The report indicated that analysis in aqueous solutions at pH > 8 was complicated by the precipitation of the free base. This observation strongly suggests that the fluvoxamine is dissociated from the maleate, with the potential for precipitation in the environment. Dissociation constant studies should therefore be conducted on fluvoxamine free base and not fluvoxamine maleate.

   C. The study submitted for the determination of octanol/water partition coefficients is inadequate.

      1. The study indicated that the partition coefficient at 10^{-4}M differed from that obtained at lower concentrations. However, association or dissociation effects were not addressed as required in the Technical Assistance Document 3.02.

      2. The above observation, along with the precipitation of the free base at pH values >8 indicate that the study should have been conducted

at pH values of 5, 7 and 9 using fluvoxamine free base instead of at pH 7 using fluvoxamine maleate.

D. The study submitted for the determination of water solubility is inadequate. In view of the above observations, the solubility study should have been conducted at pH values of 5, 7 and 9 using fluvoxamine free base.

E. The study submitted for the determination of vapor pressure is inadequate. In view of the above observations, the study should have been conducted using fluvoxamine free base in order to determine the Henry's Law constant for the molecule.

F. The study submitted for the determination of aerobic biodegradation is inadequate in that significant deviations from OECD Procedure 301E were made without the submission of validation for the changes. The changes included:

1. Storage of soil samples for up to 30 days instead of same day use.

2. Storage of activated sludge for up to 48 hours instead of same day use.

3. The use of raw sewerage in the combined inoculum.

4. The acclimation of the combined inoculum to the test substance for 14 days prior to initiation of the study.

5. The use of sealed biometer flasks containing $Ba(OH)_2$ scrubbers. Note that the OECD procedure requires closure which allows for exchange between the flask and the atmosphere.

In addition, the testing results for CO_2 evolution were described as lower than expected for the control substance. The extent, potential cause and significance of the deviation was not addressed.

G. The study submitted for the determination of microbial inhibition is inadequate.

1. The general protocol submitted did not include detailed information regarding the testing procedure used, to include specific media and preparation, and incubation conditions.

2. The incubation conditions reported in the testing results did not include observed temperature

ranges and were not consistent with the time periods shown in the procedure section of the report.

In addition, the study indicated that a % dimethyl sulfoxide solution was needed to reach the required drug substance concentration of ppm, since the sample was not soluble in water at this level. This observation is not consistent with the value of ppm reported in the water solubility study. Please explain the discrepancy.

Endorsements:

HFD-102/GJSmith 8/17/94

HFD-102/PGVincent

CC: Original NDA 20-243, 20-350
EA File 20243.REV
Division File/HFD-120
Supervisory Chemist/HFD-120

AUG 18 1994

20243E00.LGS/GJSEA#01

F/T by GJS/8.17.94

Memorandum

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

DATE: July 8, 1994

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

SUBJECT: Approvable Action Memorandum
NDA 20-243: Luvox (fluvoxamine)
for Obsessive Compulsive Disorder

TO: File NDA 20-243
&
Robert Temple, M. D.
Director,
Office of Drug Evaluation I
HFD-100

This memorandum conveys my endorsement of the conclusion of the Division's review team, headed by Dr. Thomas Laughren, that the evidence submitted to the file of NDA 20-243 supports the issuance of an approvable action letter for the use of Luvox in the management of Obsessive Compulsive Disorder (OCD).

Background:

Fluvoxamine has been in development for an unusually long time; a comment or two about its regulatory history, accordingly, seems appropriate.

Initial interest in selective serotonin re-uptake inhibitors [SSRIs] like fluvoxamine was focused on their potential for use as antidepressants. The first member of the SSRI class to be marketed as a treatment for depression was zimelidine [Zelmid™] (Sweden, 1982). At the time of its introduction, zimelidine was hailed as a major advance in the treatment of depression: equipotent to tricyclics, but free of their troublesome anticholinergic side effects and their adverse effects on cardiovascular function.

Unhappily, within a year of its marketing, a Guillian Barre like syndrome was reported in association with zimelidine's use. Although the number of patients affected were few relative to the numbers exposed, zimelidine's sponsor, Astra, concluded the liability of continued marketing was too great

and in September of 1983, voluntarily withdrew the product from marketing, worldwide. Pari passu, Merck, zimelidine's domestic sponsor, withdrew its then pending NDA , for the product.

The 'zimelidine syndrome' cast a cloud over the safety of other SSRIs then in development. Was the syndrome a consequence of selective 5HT re-uptake inhibition or was it a 'hypersensitivity' reaction caused by some unique physical and/or chemical property of the zimelidine molecule?

Fluvoxamine was one of the products affected. It had been approved in Switzerland in August of 1983, just prior to zimelidine's withdrawal, but the pace of subsequent approvals in other countries was undoubtedly slowed by concerns about the possibility that the 'zimelidine syndrome' might be a generic liability of all SSRI's. Eventually, these concerns diminished. In 1987, Favarin™ became the first SSRI after zimelidine to be marketed in the UK for the treatment of depression. It is now marketed in more than 40 countries, primarily as an antidepressant.

At the time of zimelidine's withdrawal, fluvoxamine was widely considered a likely candidate to become the first antidepressant SSRI to be marketed in the United States. Attempts to document fluvoxamine's efficacy in depression however, failed[1] and fluoxetine won the race to be the first SSRI marketed domestically. Subsequently, two other SSRIs (sertraline and paroxetine) were approved for use as antidepressants. In February of this year, fluoxetine was granted an indication for the management of OCD.

Effectiveness in use.

The review team's conclusion that fluvoxamine is effective in the management of OCD is based on the results of two adequate and well controlled clinical investigations (Studies 5529 and 5534) which were conducted under a identical protocols. Although the two studies

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unequivocally document that fluvoxamine has a clinically beneficial effect on the symptoms/signs of OCD, the estimate of the mean effect is relatively modest. Indeed, as Dr. Laughren notes, after 10 weeks of therapy, (the end of the studies), a substantial proportion of the fluvoxamine treated patients, including those who improved, were still sick enough to meet the entry criteria for these trials.

Despite the modest size of the estimated mean effect, our advisors unanimously concluded that the results of the two clinical trials documented fluvoxamine's effectiveness as a bona fide anti-obsessional treatment.

Comments about the nature of the fluvoxamine safety data base.

Although not directly relevant to Solvay's claims for the use of fluvoxamine in OCD, the firm's prior efforts to develop it as an antidepressant (mentioned earlier) have had an effect on the current submission and review. The earlier antidepressant development programs exposed more than 35,000 patients to fluvoxamine and this experience had to be considered in the regulatory assessment of fluvoxamine's safety in use.

The quality of the clinical evidence available from the depression development programs is not uniform, however. The Division, therefore, agreed to allow Solvay to adjust the detail of description of the clinical safety data presented in the fluvoxamine NDA to reflect the relative reliability of the source from whence they were derived. Accordingly, clinical data were partitioned into three strata:

> Stratum 1: 2601 subjects who participated in randomized controlled trials (2 in OCD patients and 11 in depressed patients).
> Stratum 2: 2546 subjects who participated in 70 North American uncontrolled and European controlled and uncontrolled trials. Sixty enrolled depressed patients, 4 enrolled subjects with OCD.
> Stratum 3: 35,368 subjects (almost all on fluvoxamine) drawn from a subset (N=66) of (N=92) 'marketing studies' for which ' case reports' of some type were available.

The primary focus of the division's safety review is based on reports derived from Strata I and II which, together, represent experience gained with some 2737 fluvoxamine treated patients, 90% of whom were exposed at doses in the range of 100 to 300 mg/day.

Data from Stratum III were also assessed, but primarily for signals of unusual and/or unexpected drug associated risk (i.e., Stratum III was treated much in the way reports from spontaneous post-marketing sources are treated). The review of Stratum III data, therefore, focused on serious adverse events: deaths and dropouts. The review relied primarily upon line listings, generated by the firm, for each patient who died or discontinued prematurely. Dr. Dubitsky, the medical reviewer, checked a sample of the line listings against the case reports and found the former acceptably representative of the latter. He did not, however, perform an audit to determine the reliability of the firm's case finding. (i.e., he did not review case reports from an entire study to determine whether or not he agreed with the firm about the classification of all cases.)

Reports for Strata I and II were handled as usual.

Safety in use

The reports submitted reasonably document that fluvoxamine will be safe for use if marketed under the conditions of use recommended in the labeling developed by the division's review team and attached to the approvable action letter being forwarded to the Office in the company of this memorandum.

As is my custom, I note for the record, that 'safe for use' is a term of art. No drug is absolutely safe; accordingly, the review team's conclusion represents a judgment that the benefits of fluvoxamine outweigh the risks that, at the time the judgment is being offered, are known or believed to be associated with its use. The judgment takes into account the risks of untreated depression and the risks associated with currently marketed alternative treatments.

Labeling

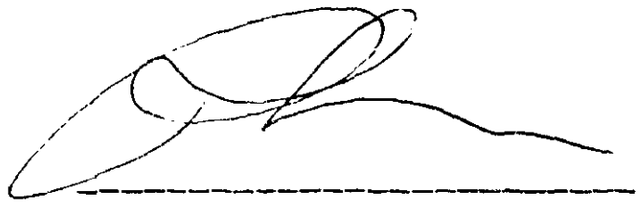
I have no substantive comments.

Action letter.

The approvable action letter forwarded to the Office makes a number of requests. None are exceptional.

Recommendation:

Issue the approvable action letter.



Paul Leber, M.D.
July 8, 1994

cc: NDA 20-243
HFD-100
Temple
HFD-120
Laughren
Katz
David

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: August 23, 1994

FROM: Thomas P. Laughren, M.D.
Group Leader, Psychiatric Drug Products
Division of Neuropharmacological Drug Products
HFD-120

SUBJECT: Luvox (fluvoxamine) Approvable Package/NDA 20-243

THROUGH: Paul Leber, M.D.
Director, DNDP (HFD-120)

TO: Robert Temple, M.D.
Director, ODE-I (HFD-100)

Labeling Modifications

We have made most of the labeling changes you proposed in the Luvox labeling mark-up attached to your 8-19-94 memo. I have only a few commencs:

-Seizures (p. 8): We ordinarily have not included seizure rates for placebo and active control because of a perception that estimates may not be as reliable as for the NDA drug. Here, for example, there was only 1 placebo seizure (1/1055), compared to 6 fluvoxamine seizures (6/2737). For active control, although there were 5 seizures (5/979), there were 6 different active control drugs, so it isn't clear what 0.5% would represent.

-Drug Interactions (p. 12): We have added a new paragraph on an apparent interaction with methadone.

-Incidence in Controlled Trials (pp. 15-18): We've asked them to create a new 1% table using a pool of the 2 OCD studies and the 6 6-week depression studies, and then make the changes we have proposed for their existing 1% table.

-Other Events...: We've made most of your proposed changes, and we have proposed that they generate a new table using your rule of having at least 2 patients with less serious events for inclusion.

-Non-US Postmarketing Reports: We have added a few more terms to this subsection since the original draft of labeling.

Changes to CMC Section of Letter

The CMC section is now greatly expanded due to the addition of 2 subsections, based on reviews we have just received: (3) Nomenclature (a minor issue), and (4) Environmental Assessment (a long list of apparently major deficiencies).

cc:
Orig NDA 20-243
HFD-120/DivFile
HFD-120/PLeber/TLaughren/GDubitsky/PDavid

DOC: MEMFLUVX.AE2

Memorandum

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

DATE: November 17, 1994

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

SUBJECT: Approval Action Memorandum
NDA 20-243: Luvox (fluvoxamine)
for Obsessive Compulsive Disorder

TO: File NDA 20-243
&
Robert Temple, M. D.
Director,
Office of Drug Evaluation I
HFD-100

This memorandum represents my formal endorsement of the review team's recommendation that Luvox (fluvoxamine maleate) be approved for use for "the treatment of obsession and compulsion in patients with obsessive-compulsive disorder (OCD), as defined in DSM-III-R" under the conditions of use described in the proposed draft labeling attached to the approval action letter forwarded to ODE 1 for issuance.

I have no comments to offer beyond those already enumerated in my July 8, 1994 approvable action memorandum.

Paul Leber, M.D.

cc: NDA 20-243
HFD-100
Temple
HFD-120
Laughren
Katz
David

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: 11-9-94

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 Luvox (fluvoxamine), for OCD

TO: File, NDA 20-243
[**Note:** This memo should be filed with the 12-24-91 original submission.]

1.0 BACKGROUND

The agency issued an approvable letter for this NDA on 8-30-94. Solvay responded with a 9-9-94 amendment, as well as subsequent amendments. In addition, we held a teleconference with the sponsor on 11-9-94 to discuss final labeling and additional phase 4 committments.

2.0 SAFETY UPDATE

Our safety review upon which the approvable action was based focused on data included in the original submission and all subsequent amendments up to and including a 11-23-93 safety update. The final safety update included in the 9-9-94 submission focused on serious events reported to Solvay between 10-2-93 and 8-31-94. These reports came from Solvay sponsored studies, postmarketing experience, and the published literature. These reports included 12 deaths and 148 nonfatal serious events. This safety update was reviewed by Dr. Greg Dubitsky (review dated 9-26-94). He concluded that this safety update revealed no new safety concerns that would preclude the final approval of this product, and I agree with that conclusion. Nevertheless, this expanded database necessitated several minor modifications of labeling.

3.0 WORLD LITERATURE UPDATE

The 9-9-94 amendment included a literature update, as well as a warrant by Solvay that their review of the updated literature did not reveal any findings that would adversely affect conclusions

about the safety of fluvoxamine, with the exception of a reported interaction with clozapine that we were already aware of and had incorporated into labeling. Dr. Dubitsky reviewed the literature update and concluded that all the relevant findings had already been adequately addressed in our proposed labeling.

4.0 REGULATORY STATUS UPDATE

Since the previous update, fluvoxamine has been approved for the treatment of depression in 3 additional countries. Otherwise, there is apparently no important new information to report regarding the worldwide status of fluvoxamine.

5.0 LONG-TERM EFFICACY DATA

In the 9-9-94 amendment, Solvay has committed to conducting, subsequent to approval, an adequate and well-controlled relapse prevention trial for fluvoxamine in the maintenance treatment of OCD.

6.0 PEDIATRIC OCD INFORMATION

In the 9-9-94 amendment, Solvay has indicated that their placebo controlled trial in children and adolescents with OCD is almost complete, and they have committed to submitting a report on this study as part of a labeling supplement.

7.0 PHARMACOLOGY/TOXICOLOGY ISSUES

In the 9-9-94 amendment, Solvay has committed to repeating the Segment I and II rat studies, however, only if rangefinding and/or toxicokinetic studies indicate that the doses in the original studies were inadequate. In addition, Solvay has agreed to work with FDA in designing studies to explore whether or not the effects on rat pup weight and survival were due to in utero or postnatal factors.

8.0 BIOPHARMACEUTICS ISSUES

In the 9-9-94 amendment, Solvay has (1) committed to conducting additional studies to clarify the metabolism of fluvoxamine, and (2) agreed to the dissolution specifications proposed in our 8-30-94 approvable letter. In addition, in a 11-9-94 teleconference, Solvay committed to (1) conducting a clinical study to examine the possible effect of the combined use of fluvoxamine and terfenadine on parent terfenadine plasma levels and/or QT intervals, and (2) conducting an additional study to establishing the elimination

half-life of fluvoxamine at steady state after multiple oral doses of 300 mg/day.

9.0 CHEMISTRY, MANUFACTURING, AND CONTROLS ISSUES

Environmental Assessment: FDA's position on the acceptability of Solvay's environmental assessment is not finalized at the time of preparation of this memo. In anticipation of the assessment being considered acceptable for approval, with a committment for a post-approval repair of the deficiencies, we are forwarding an approval package to the Office. In a 11-9-94 teleconference, Solvay committed to repairing the identified deficiencies in phase 4.

Nomenclature: Solvay has committed to seeking, subsequent to approval, adoption by the USAN Council of the established name for this product, i.e., fluvoxamine maleate.

25 and 150 mg Formulations: The sponsor is not planning to market the 25 and 150 mg formulations at this time, nevertheless, we are approving these forms. Consequently, we have noted the approval of these formulations in the approval letter, along with an acknowledgement that they are not planning to market them at present.

Methods Validation: Methods validation has been successfully completed.

Establishment Inspection: A satisfactory FUR has been received.

10.0 FINAL LABELING

In a 9-9-94 teleconference with Solvay, we reached final agreement on the labeling that is included with the approval letter.

11.0 CONCLUSIONS AND RECOMMENDATIONS

I believe that Solvay has submitted sufficient data to support a conclusion that fluvoxamine is effective and acceptably safe in the treatment of OCD, and I recommend that we issue the attached approval letter with labeling.

cc:
Orig NDA 20-243
HFD-120/DivFile
HFD-120/TLaughren/PLeber/GDubitsky/PDavid
HFD-100/RTemple

DOC: MEMFLUVX.AP1

MEMO OF TELEPHONE CALL

Date: November 1, 1994
NDA: 20-243
Subject: Information Request
Firm: Solvay Pharmaceuticals
Drug: Fluvoxamine Maleate Tablets
Contact: Don Ruggirello, Regulatory Affairs
Phone #: (404) 578-5658

At the request of Dr. Laughren, I contacted Mr. Ruggirello to inform him that I intended to fax the environmental assessment deficiencies noted by the Agency reviewer from Solvay's resubmission dated September 20, 1994 (see attached deficiencies).

I requested that Solvay respond to these deficiencies as soon as possible. Mr. Ruggirello acknowledged understanding of the above and thanked me in advance for the faxed deficiencies.

Paul A. David, R.Ph.
Regulatory Management Officer

Attachment

NDA:ORIG 20-243
NDA:DIV FILE
HFD-120/PLeber/TLaughren/GDubitsky
HFD-120/YRzeszotarski/SBlum/PDavid
HFD-005/MJones
HFD-102/PVincent
F:\DAVID\FLUVOX\TE-5
INFORMATION REQUEST

EA REVIEW #2, NDA 20-243

1. GENERAL ISSUES:

a. The segregation of confidential and non-confidential information in the EA is not appropriate. Much of the non-confidential appendices. We suggest you get an example of an available Environmental Assessment/Finding of No Significant Impact to use as a guide. A listing of recent EA's/FONSI's can be seen in the Dockets Management Branch (HFA-305), Food and Drug Administration, room 1-23, 12420 Parklawn Drive, Rockville, Maryland 20857. They also can be obtained through the Freedom of Information Office (HFI-35), Food and Drug Administration, 5600 Fisher Lane, Rockville, Maryland 20857. Some examples of information which should be included in confidential appendices are all test reports, the EA for the drug substance facility as long as it is adequately summarized in the environmental document (certification of compliance with environmental laws must be in non-confidential section), impurity/degradant specifications and identification of the impurities and degrdants if considered confidential.

b. Data based on structure-activity based chemical modeling is not acceptable in environmental assessments. Please delete all references and information relating to the QSAR program.

c. Much of the testing including deviations from the test protocols. Strict adherence to standard accepted test protocols is encouraged and facilitates the review process.

2. Since no rapid removal mechanism has been identified, at a minimum, acute aquatic toxicity testing in organisms is needed. Please refer to U.S. FDA Technical Assistance Documents 4.01, 4.08 and 4.11 for tests that may have to be performed. Based on the data generated on these tests, chronic toxicity data may also have to be provided. You are encouraged to contact the Center if you have any questions.

doc# N:\David\N20243.EA

MEMORANDUM

TO: Solvay Pharmaceuticals
Regulatory Affairs
ATTN: Mr. Don Ruggirello
901 Sawyer Road
Marietta, GA 30062

FROM: Food and Drug Administration
Center for Drug Evaluation & Research/ODEI
Division of Neuropharmacological Drug Products
HFD-120
Psychiatric Drug Products Group
5600 Fishers Lane
Rockville, MD 20857

RE: NDA 20,243: Labeling.

DATE: October 26, 1994

Your two recent communications, one of which was FAX'd to us on October 24 and the other on October 26, 1994, have been reviewed. To further assist us in formulating a revised labeling proposal for LUVOX, please provide the following items.

1) Attachment I, pages 19-21 of your 10/24 FAX, contains a revised "Other Events" table. A number of changes in this table are indicated before finalization.

a) It appears that all adverse events which occurred in one patient, regardless of seriousness, have been excluded from this table. Please note that any events considered serious, even if observed in one patient, should be included in this table, as discussed with Dr. Eric Phillips on 10/25/94.

b) It was requested that vague adverse events in this table be clarified by substitution, and not by footnoting. That is, the more specific events are to be listed in the body of the table according to their individual frequencies and the general term is to be deleted entirely. Please revise this table accordingly.

c) Our August 30, 1994, approvable letter requested substitution of the terms "abdomen enlarged" and "cerebrovascular disorder" with more specific terms. It does not appear that this has been done. Please make the appropriate substitutions.

d) We would like to combine the events "duodenal ulcer," "peptic ulcer," "peptic ulcer syndrome," and "stomach ulcer" under the term gastrointestinal ulcer. Please determine the number of unique patients who experienced any of these events in the Strata I/II study pool and make this replacement accordingly.

e) Similarly, we would like to combine the terms "face edema," "peripheral edema," and "edema" under the term edema.

f) Likewise, we ask that you combine the terms "arthritis" and "rheumatoid arthritis" under the term arthritis.

g) Please list the term "tendinous contracture" separately from the vague term "tendon disorder" and clarify the latter term by substitution if feasible.

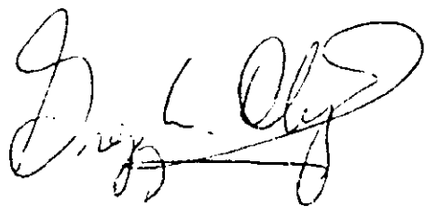
2) Attachment I, pages 9-11 of your 10/26 FAX, includes a revised adverse event incidence table. Two changes in this table are indicated:

a) We plan to combine "tooth extraction and abscess" with "toothache" and "tooth caries" under the COSTART term Tooth Disorder, with footnote clarification. Please provide us with the total number of unique patients who experienced any of these events in the fluvoxamine group and in the placebo group. "Toothache" may then be omitted from the "Other Events" table.

b) The rationale for tabulating "URI/URTI" separately from "Cold/Flu" is unclear. Again, please provide us with the total number of unique patients who experienced any of these events in each treatment group so that these events may be pooled under the COSTART term Upper Respiratory Infection.

3) Regarding item #2 on pages 3-5 of your 10/26 FAX, it must be emphasized that the process of substituting these investigator terms for COSTART terms in the "Other Events" table must be based on all data in Strata I/II combined dataset and not just on the six short-term depression and two pivotal OCD trials. Events listed in this table are intended to convey the safety experience in this much larger study pool. Please prepare a revised "Other Events" table accordingly.

Your timely response to this request is appreciated. If any questions arise, please contact Dr. Dubitsky at (301) 594-2850.



Gregory M. Dubitsky, M.D.
Medical Reviewer
Psychiatric Drug Products Group

cc: GDubitsky
TLaughren
PDavid

MEMO OF TELEPHONE CALL

Date: October 21, 1994
NDA: 20-243
Subject: Information Request
Firm: Solvay Pharmaceuticals
Drug: Fluvoxamine Maleate Tablets
Contact: Greg Perkins, Ph.D., Regulatory Affairs
Phone #: (404) 578-5509

At the request of Dr. Laughren, I contacted Dr. Perkins to inform him that the Division would be faxing him a list of requests and modifications pertaining to their proposed labeling (see attachment).

Dr. Perkins acknowledged understanding of the above, and stated that Solvay would respond to the fax as soon as possible.

Paul A. David, R.Ph.
Regulatory Management Officer

NDA:ORIG 20-243
NDA:DIV FILE
HFD-120/PLeber/TLaughren/GDubitsky
HFD-120/PDavid
Doc #FLUVOX\10-21-94.TE
INFORMATION REQUEST

MEMORANDUM

TO: Solvay Pharmaceuticals
Regulatory Affairs
ATTN: Mr. Don Ruggirello
901 Sawyer Road
Marietta, GA 30062

FROM: Food and Drug Administration
Center for Drug Evaluation & Research/ODEI
Division of Neuropharmacological Drug Products
HFD-120
Psychiatric Drug Products Group
5600 Fishers Lane
Rockville, MD 20857

RE: NDA 20,243: Labeling.

DATE: October 21, 1994

Your labeling modification, which was submitted on September 9, 1994, has been reviewed and a revision of our proposed labeling is currently in preparation. To facilitate this process, we request the following items:

1) The table of treatment-emergent adverse events, on pages 22-24 of your labeling modification, contains a number of adverse event terms which are too vague to be useful in labeling. Please provide clarification for the terms listed below **by means of footnotes** consisting of a summary statement of the more specific terms embraced by the tabulated term. For example, if 20 of the 24 patients enumerated in the table with infection had "colds" based on the investigator terms for these events, the following footnote would be appropriate: Mostly "colds."

Thinking abnormal
Vasodilatation
Abnormal dreams
CNS stimulation
Tooth Disorder
Infection
Pain
Amblyopia
Abnormal ejaculation

2) Footnote #2 of the above referenced table (on page 25), which lists infrequent adverse events in the TESS study pool, should be deleted and these events should be incorporated into the "Other Events" table on pages 31-32, using the same rules for exclusion of adverse events as described on pages 29-30. Likewise, several of

these adverse events, which are listed below, are too vague to be helpful to practicing clinicians and should be clarified **by substitution** of more specific terms.

Hangover effect
Electrocardiogram abnormal
Peripheral vascular disorder
Rectal disorder
Sleep disorder
Speech disorder
Lung disorder
Pleural disorder
Voice alteration
Skin disorder
Abnormal vision
Ear disorder
Eye disorder
Eye pain
Urine abnormality
Prostatic disorder
Testis disorder
Menstrual disorder

3) The last two paragraphs on page 28 describe significant differences in adverse event incidence between the OCD and depression study pools. As above, a few of these terms warrant clarification **by footnotes**.

Amblyopia
Abnormal ejaculation
Thinking abnormal
Tooth disorder

4) The "Other Events" table on pages 31-32 also includes a number of imprecise adverse events terms, which should be clarified **by substitution** with more descriptive investigator terms. Also, it appears that some terms in our proposed labeling have been replaced with less specific terms, specifically leukopenia was replaced with WBC abnormal, thrombocytopenia with abnormal platelets, and hypothyroidism with goiter. Please replace these with more precise terms.

Nervous System:	neurosis
	abnormal gait
	personality disorder
Digestive System:	gastrointestinal disorder
	liver damage
	tongue disorder
Body as a Whole:	lab test abnormal

Cardiovascular System:	arrhythmia hemorrhage
Musculoskeletal:	joint disorder
Hematic and Lymph:	blood dyscrasia abnormal platelets WBC abnormal
Endocrine System:	goiter

Again, as noted above, the events listed in Footnote #2 on page 25 should be included in this table.

Note that this substitution of investigator terms for COSTART terminology process will necessitate a small change to the introduction to the "Other Events" table, which now indicates that COSTART terms are used. A suggested rewording of the second introductory paragraph on page 30 is as follows: In the tabulations which follow, a standard COSTART-based Dictionary terminology has been used to classify reported adverse events. The COSTART terms are listed except in cases where the COSTART term is too imprecise to be clinically meaningful; in these cases, the more descriptive investigator term was substituted. .....

As we have suggested in our approvable letter, adverse events considered extremely unlikely to be drug related as well as those events judged not to be potentially serious and which were experienced by only one patient have been excluded.

Please provide us with the specific events that have been excluded from this table, listed by reason for exclusion, in addition to the criteria you used to determine seriousness.

5) We note that the Precautions section of labeling describes a modest pharmacodynamic interaction between fluvoxamine and lorazepam. Our review of this study indicates a marked impairment of attention, vigilance, memory, and subjective alertness when these drugs were coadministered. Please provide a copy of the study report for H.114.6004, entitled "The Influence of Multiple-Dose Administration of Fluvoxamine on the Pharmacokinetics of the Benzodiazepines Bromazepam and Lorazepam. A Randomized Crossover Study" to assist us in evaluating this discrepancy.

Your timely response to this request is much appreciated. Should any questions arise, please contact Dr. Dubitsky at (301) 594-2850.

MEMORANDUM OF TELEPHONE CALL

Date:	October 21, 1994
NDA:	20,243
Subject:	PK issues in labeling
Firm:	Solvay
Drug:	Fluvoxamine Maleate (LUVOX)
Point of Contact:	Raman Baweja, Ph.D.
Phone #:	594-5466

Dr. Baweja contacted the undersigned to convey responses to questions which were presented to him on October 20, 1994, regarding LUVOX labeling. The questions are repeated in bold print below, followed by the responses. Reference is made to the sponsor's September 9, 1994, submission, Attachment II (Labeling Modification).

1) Page 3, third paragragh: The sponsor has not determined the half-life of fluvoxamine with steady-state doses of 300 mg/day. Given that doses up to 300 mg/day are recommended and that fluvoxamine exhibits non-linear pharmacokinetics over the dose range 100-300 mg, this information is useful for labeling. Can this be studied post-approval as a Phase IV study?

Yes, this data may be obtained from a Phase IV study or from a literature source, which the sponsor may elect to provide.

2) Page 8, sponsor's second comment: It is suggested by the sponsor that, when fluvoxamine and theophylline are co-administered, it may be clinically prudent to increase the theophylline dosing interval rather than reduce the dose, since Cmax did not substantially change with the addition of fluvoxamine to theophylline. What is your opinion?

Dr. Baweja, after consultation with a colleague who is experienced in theophylline pharmacokinetics, stated that the recommendation to decrease the dose should remain as stated; we should <u>not</u> recommend increasing it.

3) Page 9, Warfarin paragraph: The sponsor claims that warfarin plasma levels increased by 65% when fluvoxamine and warfarin were given concurrently; the biopharm reviewer stated that levels increased by 98%. Which figure is correct?

This appears to be a matter of which reference point is taken as baseline. This study evaluated warfarin levels under three

conditions: with warfarin alone, with warfarin + placebo, and with warfarin + fluvoxamine. Since mean warfarin levels for the two treatment periods without fluvoxamine are somewhat different, the percentage increase with fluvoxamine depends on which comparison is used. Dr. Baweja recommends that the contrast yielding the larger difference (warfarin alone versus warfarin + fluvoxamine or 98%) be used.

4) Page 15, Lorazepam paragraph: **The sponsor claims that there was modest impairment of cognitive function with fluvoxamine and lorazepam concomitantly compared to lorazepam alone; the biopharm reviewer stated that the impairment was marked. Which is correct?**

Available data is insufficient to answer this question. It was decided that we (DNDP) would request the study report for the supporting trial and examine the specific data upon which this claim is based.

Gregory M. Dubitsky, M.D.
October 24, 1994

cc: HFD-120/GDubitsky
TLaughren
PDavid

David

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: May 26, 1994

FROM: Thomas P. Laughren, M.D. TPL
Group Leader, Psychiatric Drug Products
Division of Neuropharmacological Drug Products
HFD-120

SUBJECT: Recommendation for Approvable Action for
Luvox (fluvoxamine)

TO: File NDA 20-243
[**Note**: This overview should be filed with the 12-24-91 original submission.]

1.0 BACKGROUND

Fluvoxamine is one of 4 selective serotonin reuptake inhibitors (SSRI) that has been the subject of an NDA in the Psychopharmacology Group in recent years. Fluvoxamine is being proposed in this NDA for use in the treatment of OCD. The other SSRIs in this series are fluoxetine, sertraline, and paroxetine, all of which are approved for use in the treatment of depression. Fluoxetine was also the subject of a recent meeting of the PDAC considering its use in the treatment of Obsessive Compulsive Disorder (OCD), and has now been approved for this indication as well. Clomipramine is the only other drug approved for OCD in the US. Like the others it the SSRI series, fluvoxamine's pharmacological action can be characterized predominantly as selective serotonin reuptake inhibition.

IND for fluvoxamine was originally submitted 10-25-75.

NDA 19-189 for fluvoxamine in the treatment of depression was submitted 12-20-83. A nonapprovable letter was issued for this NDA on 9-25-86, primarily on the basis of inadequate efficacy data to support the claim. The current sponsor has chosen to focus on OCD as the initial indication for which to seek approval. However, they have also had a development program for depression ongoing simultaneously, and for fluvoxamine in the treatment of depression was submitted 6-10-93.

Several critical meetings were held during the development of fluvoxamine for OCD:

5-21-90: This was a pre-NDA meeting, including all the disciplines. The focus was on clinical data, with an emphasis on structuring the integrated safety summary.

4-4-91: This was a followup meeting to discuss in detail the format and content of the integrated safety summary.

The original NDA 20-243 for fluvoxamine in the treatment of OCD was submitted 12-27-91. Major safety updates were submitted 2-23-93 and 4-8-93.

Fluvoxamine was the subject of a 10-18-93 meeting of the PDAC, and the Committee voted in favor of both its efficacy (6 for, 0 against) and safety (6 for, 0 against).

2.0 CHEMISTRY

Methods validation has not been completed at this time, however, this is not needed for an approvable action. It is my understanding that all the manufacturing sites have passed inspection, but that FURs may be needed. Finally, our review of the environmental assessment has not been completed as of the data of this memo. Otherwise, there are no remaining chemistry issues that need resolution.

3.0 PHARMACOLOGY

Fluvoxamine is a selective serotonin reuptake inhibitor with no significant affinity for histaminergic, alpha or beta adrenergic, muscarinic, or dopaminergic receptors. There are several toxicity issues that need to be resolved for this NDA:

Pregnancy Category:

We have proposed category C for fluvoxamine, based on findings of increased pup mortality and decreased pup weights and survival in reproduction studies in which pregnant rats were dosed through weaning. We have offered the sponsor the option of doing additional crossfostering studies to further clarify these findings and possibly revise this categorization.

Dosing in Reproduction Studies:

There is a lingering concern that the dosing was not high enough in the rat reproduction studies. Consequently, we will recommend additional reproduction studies at higher doses post-approval.

Carcinogenicity Findings:

There were three pancreatic adenocarcinomas in the high dose male rats. In a 4-5-94 meeting of the Executive Committee of the CAC, a recommendation was made to consider this a marginally significant finding that should be included in labeling. However, the Executive Committee has subsequently decided not to recommend inclusion of this finding in labeling. However, there was a discrepancy regarding the actual number of tumors (2 vs 3) and insufficient information regarding specificity of the cell types. Consequently, we will ask for clarification of these issues before making a final decision about labeling for this finding.

4.0 BIOPHARMACEUTICS

Fluvoxamine has a moderate first pass effect (absolutebioavailability = 53%), and apparently no active metabolites. There is little food effect on bioavailability and fluvoxamine is approximately 80% protein bound. It is widely distributed with a volume of distribution of 25 L/kg. Although there is modest nonlinearity within the recommended dose range of 100-300 mg/day, this is not likely to be of clinical importance. The elimination half-life is roughly 16 hours and steady state is reached in approximately 1 week. Clearance is diminished in the elderly and in patients with hepatic impairment.

Fluvoxamine is metabolized by several P450 isozymes and has the potential for several important drug interactions. Formal interaction studies have suggested important increases in propranolol, warfarin, theophylline, and alprazolam in association with concomitant fluvoxamine administration. In addition, there have been published reports suggestive of very pronounced increases in plasma levels of tricyclic antidepressants (and parent:metabolite ratios) in association with the combined use of fluvoxamine with TCAs. These data suggest that fluvoxamine may inhibit several P450 isoenzymes, including IA2, IIC9, IIIA4, and probably IID6. Preliminary in vitro data support the view that fluvoxamine may be an important IIIA4 inhibitor, but they suggest only weak IID6 inhibition. Given the potentially serious risks of fluvoxamine coadministration with either terfenidine or astemizole, we have proposed contraindication of these combinations.

The Division of Biopharmaceutics has recommended several changes to the pharmacokinetics sections of labeling, and we have incorporated many of these proposed changes, with some modification.

In the approvable letter, we will propose dissolution specifications and also ask the sponsor to do additional studies to better understand the effects of fluvoxamine on the various P450 isoenzymes.

5.0 CLINICAL DATA

5.1 Efficacy Data

5.1.1 Overview of Studies Pertinent to Efficacy

There were a total of 16 studies reported in the NDA that were of potential relevance to the question of the effectiveness of fluvoxamine in the treatment of OCD.

(1) Five of these studies were placebo controlled, including 2 identically designed US studies (5529 and 5534) conducted under the same protocol. Published reports were available on 3 other small, placebo controlled non-IND studies of fluvoxamine in the treatment of OCD. (a) Perse, et al: This was a crossover study involving 20 patients with OCD. Treatment periods were 8 weeks and fluvoxamine doses were titrated within a range of 50 to 300 mg/day. There were statistically significant differences favoring fluvoxamine over placebo on 4/5 OCD measures. (b) Goodman, et al: This was a parallel group study involving 50 patients with OCD. The treatment period was 8 weeks and fluvoxamine doses were titrated within a range of 50 to 300 mg/day. Fluvoxamine was statistically significantly superior to placebo on the Y-BOCs and on the number of responders. (c) Cottraux, et al: This was a 3-way, 24-week study comparing fluvoxamine (with or without behavior therapy) and placebo (with behavior therapy) in 60 patients with OCD. There were only scattered between group differences in this study.

(2) A report was available on 1 small, active control non-IND study comparing fluvoxamine and desipramine (100-300 mg/day) for 8 weeks in the treatment of OCD (Goodman, et al). There were 11 fluvoxamine responders compared to only 2 desipramine responders.

(3) Reports were also available on 10 uncontrolled studies of fluvoxamine in the treatment of OCD. These studies were not reviewed with regard to efficacy.

Our efficacy review focused on the 2 placebo controlled US studies (5529 and 5534) for which we had full reports and complete access to the data.

Studies 5529 and 5534

Studies 5529 and 5534 were conducted under identical protocols. These were 4-center, double-blind, placebo controlled, parallel group, 10-week studies comparing fluvoxamine and placebo in outpatients meeting DSM III-R criteria for OCD. [Note: A division of the 8 centers into the 2 independent studies was accomplished prior to the conduct of these studies.] A total of 360 patients were randomized for these studies combined, i.e., 160 for each of fluvoxamine and placebo (20 patients/group/study center). Patients

had to meet the following entrance criteria: at least 18 years of age; OCD diagnosis for at least 1 year; NIMH-OC Global Rating Scale score of $\geq$ 7 at screening and at baseline. Patients with HAMD total scores $\geq$ 20 (or item 1 $\geq$ 2) were excluded.

Patients were titrated to a daily fluvoxamine dose of 150 mg/day over the first 2 weeks of the trial, following which dose was adjusted within a range of 100-300 mg/day (on a bid schedule), on the basis of response and tolerance.

The efficacy assessments (obtained q 2 weeks) included: (1) Y-BOCS, a 10-item scale including 5 items for obsessions and 5 for compulsions (each item scored 0-4, i.e., a total range of 0 to 40); (2) NIMH OC Scale, a 15-point global rating [(1-3), minimal/normal; (4-6), subclinical symptoms; (7-9), clinical symptoms; (10-12), severe; (13-15, very severe]; and (3) CGI.

There were roughly equal numbers of males and females in this population, the average age was 35-36, and they were predominantly caucasian. Groups were comparable on demographic and efficacy variables at baseline.

Completion rates were very high for these studies. Combining the two trials, 76% of fluvoxamine patients and 87% of placebo patients completed these 10-week studies.

Fluvoxamine doses rose to a plateau at week 6, and the mean dose at week 10 (for completers) in both studies was 250 mg/day.

Study 5529 Results

Summary of Efficacy Results for Study 5529
Mean Baseline and Mean Change from Baseline to Endpoint (LOCF) for Y-BOCS and NIMH-OCS Scores

	Fluvoxamine	Placebo	P-Value
Y-BOCS			
Baseline	23.3	22.8	
Change/BL	-4.9	-1.7	0.0002
NIMH-OCS			
Baseline	8.9	8.9	
Change/BL	-1.7	-0.7	0.0003

Observed cases analyses by visit revealed significant fluvoxamine/placebo differences by week 6 for YBOCS and by week 4 for NIMH-OCS, both of which persisted until the end of the study.

Study 5534 Results

Summary of Efficacy Results for Study 5534 Mean Baseline and Mean Change from Baseline to Endpoint (LOCF) for Y-BOCS and NIMH-OCS Scores			
	Fluvoxamine	Placebo	P-Value
Y-BOCS			
Baseline	22.6	23.8	
Change/BL	-3.9	-1.7	0.013
NIMH-OCS			
Baseline	8.9	9.0	
Change/BL	-1.3	-0.4	0.004

Observed cases analyses by visit revealed significant fluvoxamine/placebo differences by week 6 for YBOCS and by week 4 for NIMH-OCS, both of which persisted until the end of the study.

5.1.2 Comment on Efficacy Data

In their reviews, Drs. Dubitsky and Hoberman concluded that studies 5529 and 5534 provided evidence for the effectiveness of fluvoxamine in the treatment of OCD, and I agree with that conclusion. I have additional comments on several issues pertinent to efficacy:

Evidence Bearing on the Question of Dose/Response for Efficacy

Since the 2 key efficacy trials (5529 and 5534), as well as the 3 supportive studies reported in the published literature, utilized dose titration within a range of 100-300 mg/day for fluvoxamine, there is no basis upon which to estimate any possible dose response relationship for fluvoxamine in the treatment of OCD. Dr. Hoberman did a preliminary exploration of dose by looking at final fluvoxamine dose at 10 weeks (in completers) vs week 10 therapeutic response. This analysis yielded what was suggestive of a dose/response relationship up to 250 mg/day, but then turned down sharply at 300 mg/day. This result may reveal the hazard of attempting to extract dose/response information from titration studies, i.e., nonresponders may end up with the highest doses. The sponsor collected plasma samples for fluvoxamine levels in studies 5529 and 5534, however, the timing of sampling was not consistent and was not recorded. Given this failing, in addition to the problem of the titration design, it is not surprising that no correlation between plasma level and clinical response was seen. Consequently, the best advice we will be able to offer is to dose

patients as they were dosed in the 2 trials supporting the efficacy claim.

Clinical Predictors of Response

Both Dr. Hoberman and the sponsor conducted several analyses to explore for clinical predictors of response.

Dr. Hoberman's explorations included the following: (1) A regression of response on age yielded a non-significant slope. (2) Distributions of response by sex were essentially identical, suggesting no predictive value of gender. (3) Explorations of baseline Y-BOCS and HAMD scores did not suggest either was predictive of outcome.

The sponsor conducted several subgroup analyses to explore for marital status, previous resistance to SSRI treatment, and secondary depressive symptoms as predictors of response. None of these analyses identified any potential predictors.

Size of Treatment Effect

The size of the treatment effect in the two positive fluvoxamine studies, as measured by the fluvoxamine-placebo differences in the mean changes from baseline on the Y-BOCS total score (LOCF), were less than those seen for one of the two drugs approved in the US for the treatment of OCD, i.e., clomipramine. The treatment effect size was roughly 10 units on the Y-BOCS for the clomipramine studies, compared to changes ranging from roughly 2 to 3 units for the fluvoxamine studies. The fluvoxamine effect size as measured by YBOCS changes was similar to that seen for fluoxetine/OCD, another SSRI that was the subject of a recent PDAC meeting. However, the patient population studied for clomipramine may have been somewhat sicker, with baseline Y-BOCS scores ranging from 26 to 28, compared to 22 to 24 for the fluvoxamine studies.

It is interesting to note that, given (1) the entry criterion for the fluvoxamine studies of 7 on the NIMH-OCS, (2) mean baseline NIMH-OCS scores of 9 in both studies, and (3) changes from baseline of the magnitude observed (-1.7 for 5529 and -1.3 for 5534, on the NIMH-OC Scale), many patients even after 10 weeks of treatment would have had NIMH-OC Scale scores high enough to qualify for entry into these studies. Nevertheless, it is only fair to point that this was also the case for the clomipramine and fluoxetine OCD studies, and furthermore, these modest changes must be compared with the fairly small change seen in placebo patients. In any case, I think the rating scale changes observed in the fluvoxamine studies represent a sufficiently clinically important change to justify the approval of this product for the treatment of OCD.

Duration of Treatment

One of the failings of this program was the absence of adequate relapse prevention data. We have come to expect some credible relapse prevention data from examples set by recent antidepressant NDAs, and the PDAC is also increasingly focused on this issue. OCD is, of course, a chronic condition, and the clinician is faced with the question of what to do following response to acute treatment. While there were some data available for open and uncontrolled extensions from Studies 5529 and 5534, these data were inadequate for analysis and they do not shed much useful light on this question. In the absence of adequate data bearing on this question, I have recommended that we take the same approach for labeling that we have with the antidepressants for which we have inadequate data, i.e., acknowledge the absence of data, yet suggest that it would not be unreasonable to continue responding patients beyond the acute treatment phase. We will ask the sponsor to consider future studies to address this important question.

Alternative Displays of Efficacy Data

One concern that was raised at the PDAC meeting for Prozac in the treatment of OCD was focused on the difficulty for clinicians in interpreting the efficacy results presented as mean change from baseline. For clinicians, the suggestion was made that it might be of additional value to have the data presented as distributions of patient responses at baseline and endpoint so that one might obtain a better sense of how individual patients do, relative to where they start out, e.g., on a measure like CGI severity. To address this concern for fluvoxamine we asked Solvay to provide some displays of the efficacy data, with the hope of arriving at some alternative presentations of data to include in labeling. Specifically we asked them to develop displays for three variables, i.e., the Y-BOCS total score, the NIMH-OCS score, and CGI severity, for the pool of completers from studies 5529 and 5534. We asked for and received the following displays: (1) scatter plots, BL vs 10 weeks; (2) cross tabulations, BL vs 10 weeks, for each treatment arm; (3) bar graphs for week 10 data, including fluvoxamine and placebo on the same display; and (4) cumulative distribution functions.

I found these displays useful in providing alternative summaries of the effectiveness of fluvoxamine compared to placebo. To illustrate, I have used data from the NIMH-OCS score cross-tabulations, baseline vs 10 weeks, for completers, to generate a classification of % responders for fluvoxamine vs placebo. The cross tabulations (shift tables) upon which the classification is based are presented first:

Shift Table for NIMH-OC Scale Scores (Baseline vs Week 10) Fluvoxamine Completers (N = 120)					
NIMH-OC Category (BL)	NIMH-OC Category (Week 10)				
	Normal	Subclin.	Clinical	Severe	Very Sev
Normal	0	0	0	0	0
Subclin	0	1	0	0	0
Clinical	6	34	34	4	0
Severe	1	9	14	14	0
Very Sev	0	0	1	1	1

Shift Table for NIMH-OC Scale Scores (Baseline vs Week 10) Placebo Completers (N = 134)					
NIMH-OC Category (BL)	NIMH-OC Category (Week 10)				
	Normal	Subclin.	Clinical	Severe	Very Sev
Normal	0	0	0	0	0
Subclin	0	0	0	0	0
Clinical	1	18	60	6	0
Severe	0	2	17	29	1
Very Sev	0	0	0	0	0

The classification is based on movements between NIMH-OC categories from baseline to 10 weeks, as follows: 'worse' and 'no change' are self evident; 'slight improvement' = an improvement by 1 category, e.g., movement from 'severe' to 'clinical;' 'moderate improvement' = movement across 2 categories; and 'marked improvement' = movement across 3 categories. The results of this classification are as follows:

Outcome Classification (%) on NIMH-OC Scale for Completers in Pool of Two OCD Studies (5529 & 5534)		
Outcome Classification	Fluvoxamine (N = 120)	Placebo (N = 134)
Worse	3%	5%
No Change	42%	67%
Slight Improvement	41%	26%
Moderate Improvement	13%	2%
Marked Improvement	1%	0

It would appear from this display that, for a majority of fluvoxamine responders, the effect is fairly modest. However, most of the moderate improvement was associated with drug treatment. Almost no patients were markedly improved.

Absence of Efficacy Data for Children and Adolescents with OCD

The other important deficiency in this development program was the absence of efficacy data for children and adolescents. This is a problem for OCD because of the very early age of onset for this disorder (peak age of onset is 9 for males and 12 for females). It is likely that many children and adolescents would be treated with fluvoxamine for OCD if it were approved for treating adults with this disorder. Although it is true that Solvay has not specifically sought approval for this indication in these age groups, ideally we would have data to support (or refute) what is likely to occur in clinical practice following approval. In fact, we are aware of an ongoing study by Solvay involving a comparison of fluvoxamine and placebo for 10 weeks in children/adolescents ranging in age from 8 to 17 that should generate useful information regarding this population.

5.2 Safety Data

5.2.1 Original Submission and Early Safety Updates

Clinical Data Sources for Safety Review

The safety data for fluvoxamine, including the original submission, the 2-23-93 and 4-8-93 safety updates, and the numerous amendments in response to our requests for additional information, were reviewed by Dr. Greg Dubitsky (review dated 10-22-93). This original review was based on an unusually large integrated database including 37,975 exposures to fluvoxamine in clinical trials that were part of the fluvoxamine pre- and post-marketing development program for which case report forms were available. The phase 2-3

studies were separated into 3 strata (I-III) on the basis of the reliability and completeness of the data. Strata I included North American, controlled, pre-marketing studies; Strata II included North American uncontrolled, European controlled and uncontrolled pre-marketing studies; Strata III included worldwide post-marketing studies (almost exclusively uncontrolled). Cutoff dates for the integrated database were as follows: 12-31-90 for strata I and II; 7-1-92 for strata III. In addition, Dr. Dubitsky evaluated IND reports for serious adverse events submitted to the IND as late as July, 1993.

As noted, 37,975 human subjects were exposed to fluvoxamine in the sponsor's development program (in the integrated database available with the two safety updates), including 651 in phase 1 studies and 37,324 in phase 2-3 studies. Explorations for more common adverse events were based on pools from the strata I/II database, since this database included active and placebo controls, and it provided reliable duration of exposure data for all patients.

The strata I/II database included 2737 fluvoxamine exposures (N=492 for OCD and N=2245 for Depression). Patients in the strata I/II database were 62% female, predominantly white, and predominantly middle-aged. There were approximately 225 patients over age 65 exposed to fluvoxamine in the strata I/II database. Approximately 90% of fluvoxamine-treated patients in the strata I/II database received modal fluvoxamine doses in a range of 100 to 300 mg/day, and approximately 75% of exposures were for 6 months or less. Nevertheless, there were approximately 600 patients who received fluvoxamine for 6 months or more in the strata I/II database.

In addition, some post-marketing data were available (1425 reports for an estimated exposure to fluvoxamine worldwide of 4.5 million patients).

Deaths

There were 76 deaths among fluvoxamine-treated patients overall in strata I-III, including 18 in the strata I/II integrated database for which the denominator and full exposure data were available. When adjusted for duration of exposure, the mortality rates were comparable for fluvoxamine and active control, however, both groups were numerically greater than placebo. 7 of the fluvoxamine deaths were due to suicide, not an unusual or unexpected finding for this population (more about this later). The remaining 11 deaths were due to a variety of medical reasons, none of which suggested any causal linkage to fluvoxamine use. There were 58 deaths reported for strata III patients, and 67 deaths among the numerous post-marketing reports. None of these cases was particularly suggestive of a causal role for fluvoxamine, except perhaps two cases of overdose death in patients presumably taking fluvoxamine alone.

Adverse Dropouts

Strata I studies were explored to identify the common and drug-related adverse events leading to dropout for fluvoxamine, and these included the following: for the 2 OCD studies (insomnia, somnolence, anxiety, nausea, asthenia, and infection); for 6 depression studies (insomnia, somnolence, nervousness, dizziness, agitation, anxiety, nausea, vomiting, diarrhea, anorexia, dyspepsia, headache, asthenia, and abdominal pain).

Serious Events Search

A search for serious events, using FDA's definition, identified 888 fluvoxamine-treated patients with serious events among the 37,324 patients in the phase 2-3 studies [Does not include the deaths discussed above.]. In addition, 483 serious events were identified by a similar search of the 1425 reports in the spontaneous post-marketing reports database. Given the large number of serious events in this very large clinical trials and postmarketing experience database, Dr. Dubitsky developed a strategy for selecting which of these events to review in some detail. Most of these events were not examined in detail, including those psychiatric events not unexpected in this population and relatively common medical events that were not seen in unusual numbers given the very large database. All other events were looked at in detail, including 149 cases. In the reviewer's judgement, 26 could be considered possibly drug-related. Specific events are discussed later.

Other Searches

Other special searches were conducted for suicidality, aggression/hostility, bleeding symptoms, serotonin syndrome, allergic reactions, and zimelidine syndrome. No fluvoxamine/placebo differences were seen in the searches for suicidality, aggression/hostility, bleeding symptoms, and allergic reactions. No cases of serotonin syndrome or zimelidine syndrome were detected in the database.

Other Safety Findings

Common/Drug-Related AEs. The common and drug-related adverse event profiles for fluvoxamine were derived separately for Strata I OCD and depression trials. For OCD, the profile included the following: insomnia, somnolence, nervousness, dry mouth, thinking abnormal, tremor, decreased libido, nausea, anorexia, asthenia, sweating, abnormal ejaculation, anorgasmia, urinary frequency, rhinitis, taste perversion. For depression, the profile included: nausea, dyspepsia, anorexia, vomiting, somnolence, insomnia, nervousness, asthenia, and sweating.

LAB:

No clinically important fluvoxamine/placebo differences were observed in comparisons within Strata I pools on (1) median change from baseline and (2) incidence of potentially clinically significant changes from baseline for various serum chemistry, hematology, or urinalysis variables.

There were no fluvoxamine/active control differences in incidence of dropout for serum chemistry changes in the Strata I/II database, however, both active drugs had rates of dropout roughly 2-3 times the placebo rate. Most of the dropouts were for liver function abnormalities, including 12 of 14 fluvoxamine dropouts (see Liver Dysfunction later under important and possibly drug related adverse events). Fluvoxamine had fewer dropouts than either placebo or active control for hematological abnormalities, and there were no dropouts in the Strata I/II database for urinalysis changes.

Vital Signs:

No clinically important fluvoxamine/placebo differences were observed in comparisons within Strata I pools on (1) median change from baseline and (2) incidence of potentially clinically significant changes from baseline for various vital signs variables.

Fluvoxamine had an incidence roughly one-half the active control incidence and roughly 10-fold the placebo incidence on dropout for vital signs changes in the Strata I/II database. However, there was no consistent pattern of findings to suggest a risk of specific vital signs changes with fluvoxamine, and only 2 of the 29 fluvoxamine dropouts could be considered to represent significant events (1 case of hypertension, and 1 case of bradycardia--both pre-existing conditions).

A search of the entire database (including post-marketing reports) for serious events involving vital signs changes yielded only 4 cases, three of which most likely resulted from drug interactions (see biopharmaceutics section of this memo). There was 1 post-marketing report of significant bradycardia that normalized after fluvoxamine discontinuation.

ECG:

The Strata I OCD and depression pools were evaluated separately. For the OCD pool, fluvoxamine and placebo groups were compared on the basis of changes from baseline of possible clinical significance. There were no statistically significant differences between groups, and furthermore, all of the individual changes observed were felt to represent

benign changes. A similar analysis for the depression pool revealed no fluvoxamine/placebo differences overall, although 2 statistically significant differences were observed when specific changes were compared (a higher incidence of shortened PR interval and of T-wave flattening was observed for fluvoxamine compared to placebo). However, none of these changes was considered to be of clinical significance. Only 1 patient in the entire dataset was considered to have an important cardiac event, i.e., a fluvoxamine-treated patient with a history of CAD experienced an acute MI after 9 days of therapy.

Possible longerterm ECG changes were evaluated by comparing baseline to followup ECGs in patients participating in extensions of shorter-term studies for both the Strata I OCD and depression pools (no control groups). The only change observed was a mean decrease in HR of 2.6 BPM in the OCD pool (no similar change was observed in the depression pool).

A search of the Strata I/II database for dropouts for ECG changes identified 7 fluvoxamine patients (but essentially no difference in the overall rate of dropout compared to placebo). There was no pattern to these 7 cases. Three were clinically non-significant; 3 were unlikely related to fluvoxamine treatment; the most serious case (sinus arrest) occurred in a patient with a history of CAD.

A search of the entire clinical trials (Strata I/II/III) database for serious cardiac events revealed 8 cases of MI, 3 cases of cardiac arrhythmia, and 1 case of pulmonary edema. None were considered by Dr. Dubitsky to be reasonably linked causally to fluvoxamine use.

Withdrawal Phenomena/Abuse Potential: Although there were some reports from uncontrolled experience with fluvoxamine of what were thought to represent withdrawal symptoms, an attempt to identify newly emerging symptoms during taper and following withdrawal from placebo controlled trials did not reveal any drug/placebo differences in emerging symptoms. Thus, there was no indication of important withdrawal symptoms associated with the discontinuation of fluvoxamine. There were no systematic attempts to evaluate abuse potential.

Human Reproductive Data: There were 34 pregnant women exposed to fluvoxamine during the development program. The outcomes of these pregnancies were not suggestive of any particular teratogenic risk associated with fluvoxamine, but obviously, this experience is too limited to be a basis for any definitive statement.

Overdose Experience: The overdose experience with fluvoxamine consisted of 354 reports either from the development program

or from postmarketing reports. The outcome was fatal in 19 of these cases, however, only 2 of the cases were associated with the use of fluvoxamine alone. Frequently observed signs/symptoms associated with fluvoxamine overdose included drowsiness, vomiting, diarrhea, and dizziness.

Summary of Drug Interactions

Drug-Demographic: Drug-demographic interactions were explored for age, sex, and race. These analyses did not reveal any important differences, however, there was limited power to detect any but very substantial differences. PK studies suggested a decreased clearance for elderly compared to younger patients.

Drug-Disease: 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 fluvoxamine was found for hepatically impaired but not renally impaired patients.

Drug-Drug: (see Biopharm section)

Summary of Important Adverse Events Considered Drug-Related

Mania/Hypomania: It would not be unexpected to observe instances of mania/hypomania occurring in trials of an antidepressant, and approximately 1.1% of fluvoxamine patients in Strata I/II did experience this event. The comparable rates for placebo and active control were 0.8% and 1.4%, respectively. The rates of dropout for this event were more clearly distinguishable for fluvoxamine and active control (both 0.5%) from placebo (0.1%).

Seizures: Seizure rates in the Strata I/II database were as follows: fluvoxamine (0.2%); placebo (0.1%); active control (0.5%).

Liver Dysfunction: Exploration of the placebo controlled database (Strata I/OCD and depression pools) revealed only a suggestion for some minimal transaminase elevations in association with fluvoxamine use. As noted earlier, comparisons within Strata I pools on (1) median change from baseline and (2) incidence of potentially clinically change from baseline for SGPT and SGOT revealed no differences across treatment groups. However, an evaluation of percentiles for these data (using box plots) suggested that the more substantial elevations of LFTs were among fluvoxamine compared to placebo patients. Nevertheless, of the 7 fluvoxamine-exposed patients in the Strata I database who met criteria for potentially significant increases in either SGPT or SGOT, none had jaundice or liver failure and none was discontinued

specifically for the LFT increases. Of those with followup (5), 4 improved after stopping fluvoxamine and the 5th patient improved with continued fluvoxamine.

An exploration of the entire Strata I/II database for patients coded for liver dysfunction (COSTART terms: increased LFT, SGOT, or SGPT; or jaundice) revealed no difference between fluvoxamine and placebo. Only 1 of these patients (a fluvoxamine-treated patient) had jaundice, and this patient improved with dose reduction. The Strata I/II database was also explored for [illegible] uations for serum chemistry changes, revealing [illegible] ring rates of dropout for LFT increases: fluvoxam[illegible] Placebo (0.1%), and active control (0.7%). Of [illegible] amine patients stopping for LFT increase, only 2 [illegible] ant changes: 1 had hepatitis B; 1 had LFTs 7XULN and [illegible] d after stopping. None of these patients discontinu[illegible] LFT increases had jaundice.

There were two dropouts from Strata III for jaundice (no lab data available); 1 patient recovered and no followup was available on the 2nd patient. Six other patients with liver dysfunction in the Strata III database had other plausible explanations for the changes observed.

There were 15 spontaneous reports of hepatitis from the post-marketing reports database classified as serious. Dr. Dubitsky considered 5 of these to be possibly fluvoxamine-related (6 others were complicated by other drugs and/or alcohol and 4 others were judged to not be fluvoxamine-related. Jaundice was present in 3 of the 5 cases, and pruritis/abdominal pain in a 4th. All 5 patients recovered after discontinuation of fluvoxamine. There was also a literature report of a 60XULN LFT increase in association with a fluvoxamine overdose.

In summary, it would appear that fluvoxamine may be associated with infrequent instances of significant LFT increases, rarely associated with jaundice and/or other symptoms, and that this toxicity resolves following discontinuation.

Skin Reactions: While rashes occurred in 2-3% of fluvoxamine-exposed patients in Strata I placebo controlled trials, these rates were no different than the placebo rates. There were several significant rash cases in the development program, including: a case of urticaria and dyspnea; 3 cases of photosensitivity. In addition, there were 3 past-marketing reports of serious skin reactions: 2 cases of Stevens-Johnson syndrome; 1 case of toxic epidermal necrolysis. All patients recovered following discontinuation of fluvoxamine.

Hyponatremia: Rare cases of hyponatremia have been reported for many antidepressants, so it was not unexpected to find 3

reports for fluvoxamine as well. Only 1 of these cases occurred in the development program; there were 2 spontaneous post-marketing reports of hyponatremia. All patients recovered following discontinuation of fluvoxamine.

Movement Disorders: Between group comparisons on rates of akathisia, dystonia, EPS, and dyskinesia revealed that, although the rates for these events were low overall, the rates for fluvoxamine were statistically significantly greater for fluvoxamine than placebo, but not different than active control. There were few dropouts for these events, mostly for akathisia. In addition, there were several post-marketing reports of various EPS.

5.2.2 11-23-93 Safety Update

The most recent safety update (11-23-93) focused on serious events identified after the cutoff dates for the earlier submissions and up to a cutoff date of 10-22-93. The serious events reported in this update came from a variety of sources, including: Strata II, Strata III, additional post-marketing reports, Strata V (a residual category of studies with incomplete data), US depression studies supporting the recent for depression, other US investigational studies (panic disorder, OCD), and various completed and ongoing European studies.

There were 35 additional deaths reported from these various sources, none of which could be reasonably attributed to fluvoxamine. There were 366 non-fatal serious events reported from these sources. Dr. Dubitsky selected 77 of these as clinically significant and possibly drug-related to review in detail. After review, only 11 of these were considered to represent clinically important and possibly drug-related events. Four of these serious events represented cases of liver dysfunction, but none involved permanent liver damage. Five of these events represented cases of possible drug interaction, including 4 potential interactions that had already been noted in the earlier review. The fifth possible interaction involved the occurrence of seizures in association with the combined use of fluvoxamine and levopromazine, a phenothiazine not marketed in the US. One other report was a case of significant bradycardia, and the final case was an occurrence of Henoch-Schoenlein purpura. The labeling has been modified to incorporate any important new findings derived from this update.

5.2.3 Conclusion Regarding Safety Data for Fluvoxamine

In conclusion, the safety experience for patients/subjects exposed to fluvoxamine in the premarketing program revealed no adverse findings that would preclude its use in the treatment of OCD.

5.3 Clinical Sections of Labeling

I have substantially rewritten the clinical sections of the draft labeling that is included with the approvable letter. The explanations for the changes are provided in bracketed comments in the draft labeling.

6.0 WORLD LITERATURE

Dr. Dubitsky reviewed the published literature for fluvoxamine included in the original NDA submission and did not discover any previously unrecognized important safety concerns for this drug. The 11-23-93 amendment included a literature update (cutoff date Oct, 1993) that had identified 219 additional papers. We received a warrant from the sponsor that their review of these additional papers revealed no findings that would alter the conclusion that fluvoxamine is reasonably safe for clinical use. Dr. Dubitsky also reviewed the bibliography and 7 copies of papers provided. He agreed that no important new safety information was revealed from this literature.

7.0 FOREIGN REGULATORY ACTIONS

The 11-23-93 amendment included a regulatory status update. Fluvoxamine is marketed in 37 countries at present, mostly as an antidepressant. It is approved for the treatment of OCD in both Switzerland and Canada. It has not been withdrawn from any market.

8.0 PSYCHOPHARMACOLOGICAL DRUGS ADVISORY COMMITTEE (PDAC) MEETING

A meeting of the PDAC was held on 10-18-93 to discuss the safety and efficacy of fluvoxamine for the treatment of OCD. As noted above, the Committee voted in favor of both its efficacy (6 for, 0 against) and safety (6 for, 0 against).

9.0 DSI INSPECTIONS

Three inspections were requested, including 2 sites for study 5529 (Greist and Rasmussen) and 1 site from study 5534 (Kozak). The inspections of Greist and Kozak are completed, and both had VAI-2 designations (both for minor problems). We are still awaiting the inspection report for Rasmussen, however, what we have is sufficient to proceed with an approvable action.

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. As noted, I have made substantial changes to the clinical sections of the sponsor's draft labeling dated 10-27-93. Other sections have also been substantially modified.

10.2 Foreign Labeling

Dr. Dubitsky reviewed the foreign labeling included in the 11-23-93 amendment and discovered no important new safety findings that would necessitate any further modifications of our labeling proposal for this product.

10.3 Draft SBA

We have not drafted an SBA for fluvoxamine. In my view, the primary reviews are sufficient to serve as an alternative to an SBA. Nevertheless, we have included in the approvable package the sponsor's draft SBA (not modified by us); this document summarizes the sponsor's case for the approvability of fluvoxamine and their labeling proposal.

10.4 Approvable Letter

The approvable letter includes (1) draft labeling, (2) a request for an additional serious events safety update, (3) a request for an additional serious events world literature update, (4) a request for a regulatory status update, (5) an acknowledgement of the ongoing pediatric OCD study, (6) a request for a commitment to conduct a relapse prevention study, (7) a suggestion to do additional animal reproduction studies, (8) a request for clarification regarding the finding of adenocarcinomas in the rat carcinogenicity study, (9) a request to do additional studies to further clarify the important isoenzymes in the metabolism of fluvoxamine, (10) a request for clarification of the finding of decreased fluvoxamine concentrations with the combined use of fluvoxamine and alprazolam, and (11) dissolution specifications.

11.0 CONCLUSIONS AND RECOMMENDATIONS

I believe that Solvay has submitted sufficient data to support the conclusion that fluvoxamine is effective and acceptably safe in the treatment of OCD. I recommend that we issue the attached approvable letter with our labeling proposal and the above noted requests, in anticipation of final approval.

cc:
Orig NDA 20-243
HFD-120/Division File
HFD-120/TLaughren/PLeber/GDubitsky/PDavid
HFD-100/RTemple

DOC: MEMFLUVX.AE1

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: APR 19 1995

FROM: Director, Office of Drug Evaluation I, HFD-100

SUBJECT: NDA 20-243, Fluvoxamine

TO: Dr. Paul Leber, HFD-120

I had only one minor change in the letter. I think the request for long-term effectiveness data is reasonable and the information needed. What do you think of doing that study as a randomized dose-response withdrawal study, e.g., randomizing to placebo, 150, 250 mg/day, or something like that? It is good to see they are doing a peds study. It is, as you say, very critical that they define the metabolic drug-drug interactions of fluvoxamine.

Apart from a fair number of comments and questions on the text, I have one major question about labeling, a general one about drugs with multiple claims. I am not convinced that most ADR rates are truly different from one population to the next, although there is surely random movement. The depression plus OCD data base is much larger and gives, I presume, a more reliable rate estimate. Why not use it and mention separately any ADRs [e.g., asthenia, decreased libido, tremor, anxiety, insomnia, rhinitis, abnormal ejaculation, anorgasmia M.F.] that seemed more prominent in OCD. Perhaps those could be pulled out in a separate table. I'm very uncomfortable with the multiplication of tables.

Robert Temple

Robert Temple, M.D.

MINUTES OF CONFERENCE CALL
LUVOX® (FLUVOXAMINE MALEATE)

NDA #: 20-243
SPONSOR: Solvay
DATE/TIME: November 9, 1994; 2:00 - 2:20 PM
LOCATION: Conference Room 4023 WOC 2
ATTENDEES:

FDA; HFD-120
Dr. Tom Laughren
Dr. Greg Dubitsky
Mr. Paul David

Solvay:
Dr. Greg Perkins
Dr. Vince Hauser
Dr. Drew From
Dr. John Brennan
Dr. Mike Williams
Mr. Eric Phillip

MEETING

Dr. Laughren initiated the conference call by informing Solvay that the Division had previously met with Dr. Temple to discuss their application. In that meeting, Dr. Temple felt very strongly about Solvay committing to the following studies post approval, i.e., Phase 4 commitments:

1. To study the elimination half-life of fluvoxamine at steady state after multiple oral doses of 300 mg/day. This information may be obtained as part of a future clinical study, a de novo study, or through the literature. Solvay responded that this information is not available in the literature, however, they are willing to conduct such a study.

2. To conduct a clinical study to explore the possible effect of the combined use of fluvoxamine and terfenadine on parent terfenadine levels and/or QT intervals. The Agency would be willing to assist Solvay in designing a protocol to explore this interaction. Solvay agreed to conducting this study.

Solvay questioned whether other approved antidepressants that had similar mechanisms of action would be requested to revise their labeling to include the terfenadine contraindication. Dr. Laughren responded that the Agency would revise other antidepressant labeling that had inhibitory effects like Luvox. Likewise, if a study was adequately designed and the results demonstrated that no interaction was present, then this contraindication may possibly be removed.

Solvay formally confirmed acceptance of the labeling sent to them via fax on November 7, 1994. Additionally, they committed to completing any outstanding environmental assessment studies post approval.

Paul A. David, R.Ph.
Regulatory Management Officer

cc:
NDA 20-243
HFD-120/DIV FILE
HFD-120/PLeber/TLaughren
HFD-120/GDubitsky/PDavid
rd:11/09/94pd;rev:11/10/94tl
ft:11/10/94pd
Doc #FLUVOX/OCD/11-9-94.MM
MEETING MINUTES

MINUTES OF CONFERENCE CALL
LUVOX® (FLUVOXAMINE MALEATE)

NDA #: 20-243
SPONSOR: Solvay
DATE/TIME: November 4, 1994; 1:30 - 2:00 PM
LOCATION: Conference Room 4023 WOC 2
ATTENDEES:

FDA
HFD-120/Mr. Paul David
HFD-102/Ms. Nancy Sager

Solvay:
Mr. Don Ruggirello
Ms. Virginia Ackerman
Dr. Greg Perkins

BACKGROUND

The sponsor requested a meeting to discuss the environmental assessment deficiencies that were faxed to them on November 1, 1994.

DISCUSSION

Solvay questioned the need for additional testing to satisfactorily complete their EA package. Ms. Sager responded that the sponsor had only completed testing in microorganisms. Since there was no rapid environmental depletion mechanism of the drug, the sponsor must conduct testing in higher species, i.e., animal organisms.

Ms. Sager recommended that Solvay do a tier approach of the acute aquatic testing, i.e., initiate their testing with the daphnia magna. Based upon this data, the sponsor may need to conduct further testing in algae and fresh water fish.

The compound used should be fluvoxamine maleate, however the study report should state in term concentrations of fluvoxamine and not fluvoxamine maleate.

Ms. Sager reminded the sponsor that they should use the standard testing and reporting for the daphnia study which may be found in the EA Agency guidelines.

Ms. Sager then proceeded to review the sponsor's EA package to assist the sponsor in determining what is and is not appropriate for the FOI releasable section.

Ms. Sager stressed that the EA review would not be acceptable until this testing is completed and reviewed by the Agency. Solvay questioned whether this absence of data would impede the Agency from approving their NDA. I informed Solvay that this decision would be made at the office level.

The sponsor thanked the Agency for the meeting.

Paul A. David, R.Ph.
Regulatory Management Officer

cc:
NDA 20-243
HFD-120/DIV FILE
HFD-120/PLeber/TLaughren/PDavid
HFD-102/PVincent/NSager
HFD-005/MJones
rd:11/09/94pd;rev:11/09/94ns
ft:11/09/94pd
Doc #FLUVOX/OCD/11-4-94.MM
MEETING MINUTES

Co. Corres.

ORIGINAL

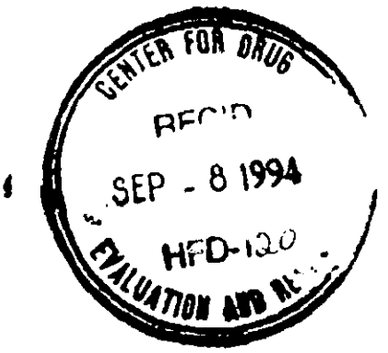
ORIG AMENDMENT

NEW CORRESP

SOLVAY PHARMACEUTICALS

September 7, 1994

W. Januez Rzeszotarski, Ph.D.
Division of Neuropharmacological
Drug Products
Food and Drug Administration
Woodmont Office Complex II
1451 Rockville Pike
Rockville, Maryland 20852



Dear Dr. Rzeszotarski:

RE: **LUVOX™ (Fluvoxamine Maleate Tablets)**
NDA 20-243
Product Labels

Reference is made to our pending new drug application for LUVOX™ (Fluvoxamine Maleate Tablets), NDA 20-243, for use in the treatment of obsessive and compulsive disorder. Reference is also made to the phone conversation on September 6, 1994 between you and Theresa Cheung, Solvay Pharmaceuticals, Inc., concerning the immediate container labels and shelf cartons to be used for the drug product.

Enclosed is a copy of each of the following labels and cartons in the final printed form:

STRENGTH	PACKAGE SIZE	LABEL/CARTON	CODE
50 mg	bottle of 100s	immediate container label	1E1253F13
	bottle of 1000s	immediate container label	1E1251F13
	blister of 100s	blister card of 10s	1E REV 1/94
		shelf carton	1E REV NOV 93
	blister of 7s (physician's sample)	blister card	1E REV 11/93
		shelf carton	1E REV 11/93

LV129153.250

Solvay Pharmaceuticals Inc
Corporate Offices 901 Sawyer Road □ Marietta, GA 30062 □ Telephone (404) 578 9000 □ Fax (404) 578 5597
Manufacturing 210 Main Street W □ Baudette, MN 56623 □ Telephone (218) 634-1866 □ Fax (218) 634-2785

STRENGTH	PACKAGE SIZE	LABEL/CARTON	CODE
100 mg	bottle of 100s	immediate container label	1E1260F13
	bottle of 100s (physician's sample)	immediate container label	1E1262F13
		shelf carton (5 bottles of 100s)	1E 1/94
	bottle of 1000s	immediate container label	1E1261F13
	blister of 100s	blister card of 10s	1E REV 1/94
		shelf carton	1E REV NOV 93
	blister of 4s (physician's sample)	blister card	1E REV 11/93
		shelf carton	1E REV 11/93

It is understood that twelve copies of each of the final printed labeling materials will be submitted to the Food and Drug Administration prior to approval of NDA 20-243.

If any additional information is needed, please contact either Mrs. Theresa Cheung or me at (404) 598-5887.

Yours truly,

Virginia O. Ackerman
Director, Regulatory Liaison

VOA/icl

Enclosures

LV129153.250

S
SOLVAY
SOLVAY
PHARMACEUTICALS

September 9, 1994

Paul Leber, M.D.,Director
Division of Neuropharmacological
Drug Products, HFD-120
Document Control Room 10B-20
Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20857

Dear Dr. Leber:

RE: LUVOX™ (Fluvoxamine Maleate) Tablets
NDA 20-243
Response To Approvable Letter

Reference is made to our pending New Drug Application 20-243 for LUVOX™ (Fluvoxamine Maleate) Tablets for the treatment of obsessive-compulsive. Further reference is made to the approvable letter dated August 30, 1994, from Robert Temple, M.D., Food and Drug Administration (FDA) requesting additional information for this NDA. A copy of this letter is included (Attachment I).

With this response, we are requesting meetings with the Agency to discuss labeling and the environmental assesement.

Specific requests from the approvable letter are listed below in bold print, with our response following:

CLINICAL

1. Labeling

Accompanying this letter (ATTACHMENT 2) is the Agency's proposal for the labeling of Luvox™. Our proposal is based on your labeling proposal submitted in an October 27, 1993 amendment. We believe it presents a fair summary of the information available on the benefits and risks of fluvoxamine. Please use the proposed text verbatim.

LV129154.252

Solvay Pharmaceuticals, Inc
Corporate Offices 901 Sawyer Road □ Marietta, GA 30062 □ Telephone (404) 578-9000 □ Fax (404) 578-5597
Manufacturing 210 Main Street W. □ Baudette, MN 56623 □ Telephone (218) 634-1866 □ Fax (218) 634-2765

CLINICAL (Continued)

We have proposed a number of changes to your draft labeling, and explanations for these changes are provided in the bracketed comments embedded within the proposed text. In certain instances, we have asked you to further modify labeling. Division staff would be happy to meet with you to discuss any disagreement you might have with any part of the proposed labeling format or content.

A copy of the requested modification to the labeling and diskette, plus additional changes that we are proposing are enclosed (Attachment II). Our comments for these changes are bracketed in the proposed text.

2. Safety Update

Our assessment of the safety of fluvoxamine in the treatment of OCD is based on our review of all safety information submitted up to and including your final safety update (11-23-93). This update focused on serious events with a cutoff date of 10-22-93. Please provide a final serious events update to include serious adverse events up to a more recent cutoff date. In addition, please provide a summary of any additional postmarketing data available since the 11-23-93 safety update, with a focus on serious events. This final safety update may be in the same general format as your November 23, 1993 safety update. Of particular importance, it should include a line listing of previously unreported deaths and other serious events associated with the use of fluvoxamine along with narrative summaries. The safety update should identify any previously unrecognized serious adverse events that appear to be causally related to the use of fluvoxamine.

Please refer to Attachment III for a listing of serious adverse events between October 22, 1993 and August 31, 1994. Please note that we are reporting a case study involving a rise in clozapine plasma levels in association with administration of LUVOX™ Tablets.

3. World Literature Update

Please provide a world literature update for fluvoxamine including information available subsequent to the literature update provided in your 11-23-93 amendment. This update should focus on reports of serious adverse events associated with the use of fluvoxamine and can be in the same general format as that utilized in your 11-23-93 literature update.

CLINICAL (Continued)

In Attachment IV, please find a world literature update covering the period since our November 23, 1993 update. No serious adverse events have been found. This update has been certified by our Medical Officer.

4. Foreign Regulatory Update

Please provide any new information on the regulatory status of fluvoxamine worldwide, i.e., information available subsequent to the regulatory status update provided in your 11-23-93 amendment.

There is no new significant information to report regarding the worldwide registration status of fluvoxamine.

Since the November 23, 1993 update, Fluvoxamine has been registered for the treatment of depression in three additional countries, i.e. Bahrain, Lebanon and Solvakia (formerly part of Czechoslovakia).

5. Long-Term Efficacy Data

One deficiency of your development program for fluvoxamine in the treatment of OCD was the absence of adequate relapse prevention data. It is not unreasonable to expect relapse prevention data for treatments of chronic conditions such as OCD, and the PDAC is also increasingly focused on this issue. In managing OCD, the clinician is faced with the question of what to do following response to acute treatment. While there were some data available from open and uncontrolled extensions from studies 5529 and 5534, these data were inadequate for analysis and they do not shed much useful light on this question. In the absence of adequate data bearing on this question, we have proposed in labeling an acknowledgement of the absence of data, along with a suggestion that it would not be unreasonable to continue responding patients beyond the acute treatment phase. However, prior to the final approval of this application, we ask that you commit to conducting, following the approval of this indication, an adequate and well-controlled relapse prevention trial for fluvoxamine in the maintenance treatment of OCD.

We commit to conducting such study. Our intention is to work closely with the Agency to develop an appropriate protocol.

CLINICAL (Continued)

6. Pediatric OCD Information

Another important deficiency in your development program for this indication was the absence of safety and efficacy data for children and adolescents. There were only a few adolescents and no children represented in the population of OCD patients that you studied. This is a problem for OCD because of the very early age of onset for this disorder (peak age of onset is 9 for males and 12 for females). Once fluvoxamine is approved for treating adults with OCD, it is likely that many children and adolescents with OCD will be treated with this drug as well. We are aware that you have underway a 10-week trial involving children and adolescents with OCD, and we encourage you to complete this trial in a timely manner so that the labeling can be updated following approval with information pertinent to the treatment of patients in these age groups.

Protocol RH.114.02.01 entitled "Fluvoxamine in the Treatment of Obsessive Compulsive Disorder: A Multi-Center, Placebo-Controlled Study in Outpatient Children and Adolescents" is nearing completion. When the report is available, we will submit it to this NDA as part of a labeling supplement.

PHARMACOLOGY

1. Pregnancy Category C

The segment III reproduction studies in rats revealed a decrease in pup weight and survival. Because it could not be determined whether or not all of these findings were related to effects of the drug on the developing fetus in utero or were secondary to postnatal drug effects on the dams and/or pups, we have labeled fluvoxamine pregnancy Category C. We would be happy to discuss with you approaches to studying this question. If such a study or studies clearly establish that the adverse effect on pup weight and survival is occurring as a result of postnatal effect rather than an in utero effect of drug on the fetus, the labeling may be changed from pregnancy Category C to pregnancy Category B.

We appreciate the FDA's offer to discuss the design of studies to address whether the pup effects were due to an in utero or postnatal effect. If definitive studies are possible, we are willing to conduct them.

PHARMACOLOGY (Continued)

2. Segment I and II Rat Studies

The segment I and II rat reproduction studies were conducted at doses which were too low to provide a valid assessment of the potential of fluvoxamine to produce adverse effects on these phases of reproduction in this species. We thus request that these studies be repeated postmarketing. Doses used in these studies should be based on rangefinding studies and/or other relevant data to insure adequate exposure.

We will repeat the Segment I and II rat studies. The protocols with the proposed doses will be forwarded to the FDA for approval and comment. However, if rangefinding and/or toxicokinetic studies indicate that the doses of the original studies were adequate, we will request that the FDA accept these studies.

MANUFACTURING AND CONTROLS

I. Methods Validation

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.

Solvay Pharmaceuticals, Inc. hereby commits to fully cooperate with the FDA in resolving any problems that may arise during the validation process of the analytical methods for the drug substance and drug product.

2. Establishment Inspections

Please note that the establishment inspections have not yet been completed. We cannot approve this application until satisfactory Establishment Inspection Reports have been received for all facilities involved in the manufacture and packaging of the bulk drug and the drug product.

We have confirmed that the Division has received inspection verification from Compliance for Baudette and Solvay Duphar (Weesp).

The need to fulfill the administrative requirements is fully recognized.

MANUFACTURING AND CONTROLS (Continued)

3. Nomenclature

The established name, fluvoxamine maleate, has not been adopted by the USAN Council we request that you submit this name to the council expeditiously.

The free base "fluvoxamine" has been adopted by the USAN Council. The information is currently provided on page 295 of the USAN and the USP Dictionary of Drug Names, 1994 Edition.

Solvay Pharmaceuticals, Inc. will immediately amend the above information to provide for the maleate salt.

4. Environmental Assessment

The response to this section will be submitted to Drs. Leber and Vincent under separate covers in the next several days.

BIOPHARMACEUTICS

1. Additional Metabolism Studies

On the basis of positive in vivo interaction studies and case reports suggestive of fluvoxamine interactions, it appears that fluvoxamine may inhibit several cytochrome P450 isozymes, i.e., IA2, IIC9, IIIA4, and possibly IID6. The preliminary in vitro data submitted October 29, 1993 support the in vivo findings regarding IIIA4 inhibition, but not for IID6 inhibition. Given the likelihood that fluvoxamine is a potent IIIA4 inhibitor, we have proposed a contraindication for the concomitant use of fluvoxamine and either terfenadine or astemizole because of the potentially very serious risks of such use.

There is a need for more studies to establish definitively the extent to which fluvoxamine may inhibit any of these isozymes. Consequently, we ask that you conduct, subsequent to approval, additional studies to clarify the metabolism of fluvoxamine. We would be happy to discuss with you the design of appropriate studies to achieve this goal.

BIOPHARMACEUTICS (Continued)

We commit to the conduct of additional studies to clarify the metabolism of fluvoxamine. One study (Protocol 114.1.11) to elucidate IID6 isozyme in extensive and poor metabolizers of dextromethorphan is underway.

Additionally, in association with Dr. David Greenblatt, we are conducting in-vitro studies on the metabolism of terfenadine, using human liver preparations. These studies are designed to determine the relative extent of inhibition of metabolism caused by the SSRIs including fluvoxamine, ketoconazole, and fluconazole. Ketoconazole is the most potent in vitro and in vivo inhibitor of CYPIIIA4 metabolism presently known. Fluconazole causes in vitro inhibition of terfenadine metabolism, but clinically coadministration of this drug with terfenadine does not result in any clinically significant cardiovascular adverse events or measurable plasma levels of terfenadine. Thus, the potency of in vitro inhibition of terfenadine metabolism by an SSRI relative to fluconazole will serve to indicate the likelihood of an in vivo interaction. The preliminary results indicate that the SSRIs are approximately 28- to 775-fold less potent than ketoconazole as inhibitors of terfenadine metabolism. Thus, when terfenadine and an SSRI are coadministered, it appears unlikely that terfenadine clearance will be greatly affected, leading to the well established cardiac dysfunction. The preliminary results of the terfenadine metabolism inhibition studies are enclosed (Attachment V).

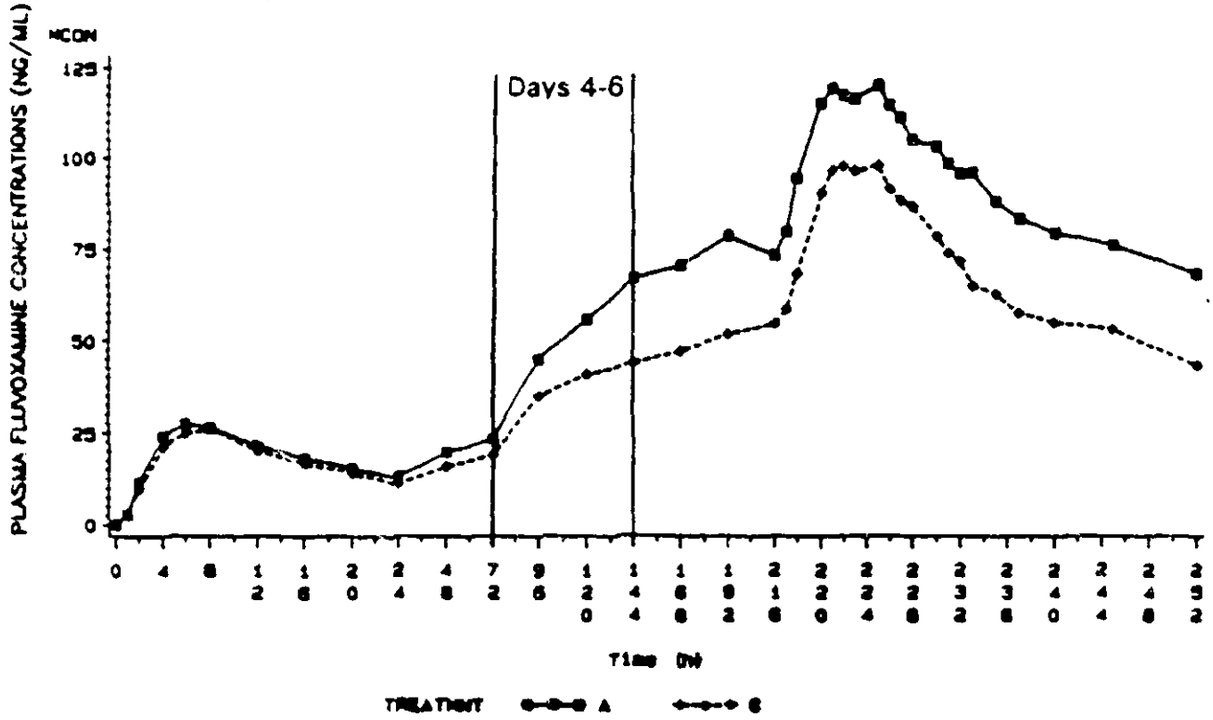
2. <u>Alprazolam/Fluvoxamine Interaction</u>

We note that in a study involving the coadministration of alprazolam 1 mg qid and fluvoxamine 100 mg qd, the mean fluvoxamine concentration was decreased by about 25% compared to fluvoxamine alone. Although a 25% decrease in fluvoxamine concentration may not represent a clinically important difference, this finding raises a question about a possibly clinically important effect on fluvoxamine concentration at higher doses of fluvoxamine given on a bid schedule, especially since fluvoxamine pharmacokinetics become nonlinear at higher doses. Please comment on this finding.

In the reference report, please refer to the graph of fluvoxamine plasma concentrations before and after coadministration of alprazolam (page 498 of NDA 20-243, May 21, 1993).

BIOPHARMACEUTICS (Continued)

Figure 4
Mean plasma concentrations of fluvoxamine following the administration of fluvoxamine alone (Treatment A: 50 mg/day on Days 1-3, 100 mg/day on Days 4-10); or fluvoxamine plus alprazolam (Treatment C: 50 mg/day on Days 1-3 and 100 mg/day on Days 4-10) to healthy male volunteers.



Fluvoxamine levels between the two parallel groups (Treatment A: fluvoxamine 50 mg/day on Days 1-3, 100 mg/day, Treatment C: fluvoxamine 50 mg/day on Days 1-3 and 100 mg/day on Days 4-10, plus alprazolam 4 mg/day on Days 7-10) begin to diverge over Days 4-6, even before alprazolam is initiated in Treatment C. This indicates that alprazolam is not the cause for the lower levels of fluvoxamine observed in Treatment group C. In fact, as indicated in the text of the report, this difference between the two groups may be at least partly due to lack of achievement of steady-state conditions with fluvoxamine.

BIOPHARMACEUTICS (Continued)

Considering the high variability in fluvoxamine plasma levels which we have observed in other pharmacokinetic studies, a 25% difference in levels between two parallel groups of subjects is not unexpected and may be considered clinically insignificant. For example, in Protocol RH.114.01.08 (young/elderly study), at the 100 mg/day dose, the mean AUC(0-24) at steady-state for twelve healthy male volunteers had a coefficient of variation of approximately 80% and individual values were in the range ng·hr/mL.

Furthermore, in Protocol RH.114.01.08, seven 100-mg fluvoxamine doses were administered and pre-dose plasma concentrations were determined prior to the 5th and 6th doses, and just prior to and at 24 hours after the 7th dose. No significant difference in fluvoxamine plasma concentration was observed in these trough levels in individual subjects indicating the achievement of steady-state conditions. Thus, no decline in minimum plasma concentrations of fluvoxamine was observed on repeated dosing in this study and would not be expected in the clinical situation.

In summary, the clinically insignificant difference in fluvoxamine plasma levels observed between the two treatment groups in the alprazolam interaction study is 1) not due to the effect of alprazolam and 2) not due to any change in of fluvoxamine clearance during repeated dosing.

Consequently, the observed differences are most likely due to the expected heterogeneity between the two treatment groups, based upon the high variability of fluvoxamine pharmacokinetics. Lack of achievement of steady-state conditions for fluvoxamine may have contributed to the observed differences as well.

BIOPHARMACEUTICS (Continued)

3. Dissolution Specification

We ask that you agree to the following recommendation by the Division of Biopharmaceutics for a dissolution method and specification for all tablet strengths:

Apparatus:	**USP Apparatus (Paddle)**
Paddle Speed:	**RPM**
Medium:	**ml purified water at**
Q:	**NLT % in minutes**

Provided in Attachment VI is the revised Finished Product Specifications and Test Methods for LUVOX™ Tablets, reflecting the adoption of the dissolution specifications, i.e., Q % in minutes, as recommended by the Division of Biopharmaceutics. With regard to the methodology parameters, they are currently provided for in NDA 20-243.

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-18. Please submit all proposed materials in draft or mock-up form, not final print. Also, please do not used form FD-2253 for this submission, this form is for routine use, not proposed materials.

The promotional advertising materials were previously submitted to Janet L. Rose, Director, Division of Drug Marketing, Advertising, and Communications, with a copy to Paul Leber, M.D., on August 25, 1994.

Please submit 12 copies of the final printed labeling.

Final printed labeling will be submitted post discussion with the Division.

Should you have any questions, please contact Don Ruggirello or me at (404) 578-5504.

Yours truly,

J. Greg Perkins, Ph.D.
Vice President, Regulatory Affairs

JGP/lsm

Attachments I-VI, Volumes 01-02

CC: Paul David, RMO

ORIGINAL

ORIG AMENDMENT

SOLVAY PHARMACEUTICALS

J. Greg Perkins, Ph.D.
Vice President, Regulatory Affairs

September 20, 1994

Paul Leber, M.D., Director
Division of Neuropharmacological
Drug Products, HFD-120
Document Control Room 10B-20
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

Dear Dr. Leber:

RE: LUVOX™ (Fluvoxamine Maleate) Tablets
NDA 20-243
Response to FDA

Reference is made to our pending New Drug Application for LUVOX™ (fluvoxamine maleate) Tablets for the treatment of obsessive compulsive disorder. Reference is also made to a letter from the Agency dated August 30, 1994, noting deficiencies in the environmental assessment for fluvoxamine maleate (Attachment I).

The following submission contains responses to comments received from the FDA with special emphasis on the fate of fluvoxamine maleate in the environment (Attachment II). Enclosed is a revised environmental assessment addressing all of the comments received from FDA (Attachment III).

As you know, this drug has undergone extensive biological testing and has been found to be safe and effective for its intended use. In accordance with FDA regulation 21 CFR 25, environmental testing was performed. In fact, specific toxicity tests were previously agreed upon with Dr. Philip Vincent of the FDA in a meeting on October 27, 1992.

Many of the comments noted in the above referenced letter from FDA centered upon the observation of a precipitate at high-end (basic) pHs. This precipitate is reasonably expected to be the fluvoxamine free base, which reached a solubility limit under the test conditions. These saturation conditions would not exist in the environment, however, even with worst-case assumptions regarding emissions. Moreover, the characteristics of the free base, shown both by the maleate testing data and chemical

structure, indicate that this form of the molecule would not behave in a significantly different manner from the maleate under environmental conditions. Additionally, the small amounts of this material that would enter the general environment would be so minimal that they could not be practicably monitored.

Should you require additional information, please contact Don Ruggirello or me at (404)578-5887.

Sincerely,

J. Greg Perkins, Ph.D.
Vice President
Regulatory Affairs

JGP/jlh

atts.

SOLVAY PHARMACEUTICALS

November 4, 1994

Paul Leber, M.D., Director
Division of Neuropharmacological
Drug Products (HFD-120)
Food and Drug Administration
Woodmont Office Complex II
1451 Rockville Pike
Rockville, Maryland 20852

Dear Dr. Leber:

RE: LUVOX™ (Fluvoxamine Maleate Tablets)
NDA 20-243
Product Labels

Reference is made to our pending new drug application for LUVOX™ (Fluvoxamine Maleate Tablets), NDA 20-243, for use in the treatment of obsessive and compulsive disorder. Reference is also made to the phone conversation on November 4, 1994 between Mr. Paul David of the Food and Drug Administration and Mrs. Theresa Cheung of Solvay Pharmaceuticals, Inc., concerning the immediate container labels and shelf cartons to be used for the sample packaging of the drug product. These labels and cartons have been reworked to include the manufacturing/marketing responsibility declaration for the firms that are named on the labeling materials.

Enclosed is a copy of each of the following corrected labels and cartons in the final printed form:

STRENGTH	PACKAGE SIZE	LABEL/CARTON	CODE
50 mg	blister of s (phvsician s sample)	shelf carton	1E REV 11/93

LV129153.308

Solvay Pharmaceuticals Inc
Corporate Offices: 901 Sawyer Road, Marietta, GA 30062 Telephone (404) 578-9000 Fax (404) 578-5597
Manufacturing: 210 Main Street W Baudette, MN 56623 Telephone (218) 634-1866 Fax (218) 634-2785

STRENGTH	PACKAGE SIZE	LABEL/CARTON	CODE
100 mg	bottle of 100s (physician's sample)	immediate container label	1E1262II4
		shelf carton (5 bottles of 100s)	1E 1/94
	blister of 4s (physician's sample)	shelf carton	1E REV 11/93

A copy of the shipping labels for transporting bulk LUVOX Tablets to PACO Pharmaceutical Services, New Jersey for blister packaging is also included.

It is understood that twelve copies of each of the final printed labeling materials will be submitted to the Food and Drug Administration prior to approval of NDA 20-243.

If any additional information is needed, please contact either Mrs. Theresa Cheung or me at (404) 598-5887.

Yours truly,

Virginia O. Ackerman

Virginia O. Ackerman
Director, Regulatory Liaison

VOA/icl

Enclosures

cc: Mr. Paul David (HFD-120) (cover letter only)
Dr. W. Januez Rzeszotarski (HFD-120) (complete copy)

SECTION 13. PATENT INFORMATION ON ANY PATENT WHICH CLAIMS THE DRUG

To the best of Solvay Pharmaceuticals' knowledge, there is only one patent which applies to the various drug forms and/or formulations of fluvoxamine maleate:

United States Patent No. 4,085,225
Issued: April 18, 1978
Expires: April 18, 1995

The patent copy which is attached indicates the assignee as U.S. Phillips Corporation of New York. This assignment was transferred to Duphar International Research B.V. on or about 1979. In October 1991, Duphar B.V. changed its corporate name to Solvay Duphar, which reflects its membership in the Solvay group of companies.

Solvay Pharmaceuticals (US) is a sister company to Solvay Duphar under the Solvay Group and is filing this original new drug application on fluvoxamine maleate tablets with their full knowledge and support.

4085225

THE UNITED STATES OF AMERICA

TO ALL TO WHOM THESE PRESENTS SHALL COME:

Whereas, THERE HAS BEEN PRESENTED TO THE

Commissioner of Patents and Trademarks

A PETITION PRAYING FOR THE GRANT OF LETTERS PATENT FOR AN ALLEGED NEW AND USEFUL INVENTION THE TITLE AND DESCRIPTION OF WHICH ARE CONTAINED IN THE SPECIFICATIONS OF WHICH A COPY IS HEREUNTO ANNEXED AND MADE A PART HEREOF, AND THE VARIOUS REQUIREMENTS OF LAW IN SUCH CASES MADE AND PROVIDED HAVE BEEN COMPLIED WITH, AND THE TITLE THERETO IS, FROM THE RECORDS OF THE PATENT AND TRADEMARK OFFICE IN THE CLAIMANT(S) INDICATED IN THE SAID COPY, AND WHEREAS, UPON DUE EXAMINATION MADE, THE SAID CLAIMANT(S) IS (ARE) ADJUDGED TO BE ENTITLED TO A PATENT UNDER THE LAW.

NOW, THEREFORE, THESE Letters Patent ARE TO GRANT UNTO THE SAID CLAIMANT(S) AND THE SUCCESSORS, HEIRS OR ASSIGNS OF THE SAID CLAIMANT(S) FOR THE TERM OF SEVENTEEN YEARS FROM THE DATE OF THIS GRANT, SUBJECT TO THE PAYMENT OF ISSUE FEES AS PROVIDED BY LAW, THE RIGHT TO EXCLUDE OTHERS FROM MAKING, USING OR SELLING THE SAID INVENTION THROUGHOUT THE UNITED STATES.

In testimony whereof *I have hereunto set my hand and caused the seal of the* **Patent and Trademark Office** *to be affixed at the City of Washington this eighteenth day of April in the year of our Lord one thousand nine hundred and seventy-eight and of the Independence of the United States of America the two hundred and second.*

Attest:

Attesting Officer

Acting Commissioner of Patents and Trademarks

02-000004

FORM PTO 317A
REV. 10-77

1 7931

UNITED STATES PATENT AND TRADEMARK OFFICE
CERTIFICATE OF CORRECTION

PATENT NO. 4,085,225

DATED April 18, 1978

INVENTOR(S) HENDRICUS BERNARDUS ANTONIUS WELLE ET AL

It is certified that error appears in the above-identified patent and that said Letters Patent are hereby corrected as shown below:

Col. 2, line 36, change "of" to --or--

Col. 6, line 31, change "179" to --1/2--

Signed and Sealed this

Eighth Day of May 1979

Attest:

Ruth C. Mason

RUTH C. MASON
Attesting Officer

Donald W. Banner

DONALD W. BANNER
Commissioner of Patents and Trademarks

United States Patent [19]

Welle et al.

[11] 4,085,225

[45] Apr. 18, 1978

[54] OXIME ETHERS HAVING ANTI-DEPRESSIVE ACTIVITY

[75] Inventors: Hendricus Bernardus Antonius Welle, Utrecht; Volkert Claassen, Weesp, both of Netherlands

[73] Assignee: U.S. Philips Corporation, New York, N.Y.

[21] Appl. No.: 668,461

[22] Filed: Mar. 19, 1976

[30] Foreign Application Priority Data

Mar. 20, 1975 Netherlands 7503310

[51] Int. Cl.[2] A61K 31/15; A61K 31/275; C07C 121/78; C07C 131/00

[52] U.S. Cl. ..... 424/304; 260/465 E; 260/501.17; 260/566 AE; 424/316; 424/327

[58] Field of Search ..... 260/465 E, 566 AE; 424/304, 327

[56] References Cited

U.S. PATENT DOCUMENTS

3,692,835 9/1972 Van Dijk et al. ..... 260/566 AE

Primary Examiner—Dolph H. Torrence

Attorney, Agent, or Firm—Frank R. Trifari; Norman N. Spain

[57] ABSTRACT

Novel 4'-trifluoromethylvalerophenone O-(2-aminoethyl)oxmes are found to exhibit a strong anti-depressive activity based on a strong serotone potentiation but with the absence of monoamino/oxidase inhibition and undesirable side effects.

8 Claims, No Drawings

OXIME ETHERS HAVING ANTI-DEPRESSIVE ACTIVITY

The invention relates to novel oxime ether compounds having anti-depressive activity. In British Patent Specification No. 1,205,665, a large group of compounds is described as having an anti-depressive, a sedative and/or an anti-convulsive activity. The anti-depressive activity of the known compounds according to this Patent Specification is based on monoamino oxidase (MAO) inhibition and/or on noradrenaline potentiation.

Compounds which inhibit monoamino oxidase are particularly difficult to administer. They often have serious side effects and they are often incompatible with other medicines and nutrients. As the regulations governing the use of medicines become more and more stringent only certain compounds which are substantially free from noxious side effects can be considered for administration to human beings.

It is the object of the invention to provide novel anti-depressive agents whose activity component is not based on MAO inhibition and which in addition are substantially free from side effects and whose action is primarily expressed in an elevation of mood of the treated patient and to a much smaller extent in an increase of the motor activity.

Prior biochemical investigations in depressive patients, Brit. J. Phychiatr. 113 1407 (1967); Nature 225 1259 (1970), and Arch. Gen. Psychiatr. 28 827 (1973) have lent support to the hypothesis that a decrease of the serotonergic processes in the brains is a factor in the pathogenesis of depressions.

However, investigations in other patients do not lend to this supposition, Arch. Gen. Psychiatr. 25 354 (1971). Therefore, a current opinion, which is gaining support, is that there are various "sub-types" classifications of patients whose depressions are caused by different deviations in the metabolism of biogenic amines. This may account for the fact why patients who fall into these different "sub-type" classifications of depressions react differently to the treatment with anti-depressive compounds (Drugs 4, 361, (1972)).

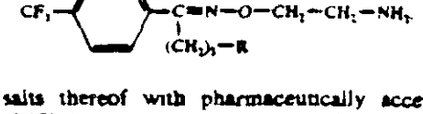
The now clinically used anti-depressive compounds influence to a different extent the re-uptake of amines in the neurons. desmethylimipramine and protriptyline have mainly a blocking effect on the cell membrane of noradrenergic neurons, while imipramine and amitriptyline in addition inhibit the re-uptake of serotonine by

serotonergic neurons (J. Pharm. Pharmacol. 20 150 (1968), J. Pharmacol. 4 135 (1968)).

There are a number of brain processes in which serotonine and noradrenaline have opposite activities (Ann. N.Y. Acad. Sci. 66 631 (1957); Adv. Pharmacol 6B 97 (1968); and Jouvet in Van Praag: Brain and Sleep 1974). In the medicinal treatment of depressive patients, the intensification of the function of one amine might result in a decrease of the function of the other amine.

As a means to elevate the mood of depressive patients, there exists, on the basis of the above, a significant need of pharmacy, for a compound whose activity mainly consists of blocking the cell membrane of the serotonergic neurons (Van Praag, Psyche aan banden, (1974), i.e. whose activity is mainly based on the potentiation of serotonine.

It was found that the novel compounds of formula I

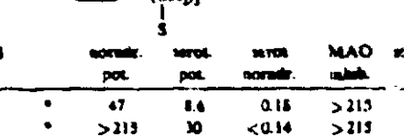


and salts thereof with pharmaceutically acceptable acids fulfil the imposed requirements. The compounds provide a very powerful serotonine potentiation which is associated with a weaker noradrenaline potentiation. The compounds do not have an activity component based on monoamine oxidase inhibition, are substantially free from side effects such as stomach ulceration and bronchoconstriction and have a very low toxicity.

In Formula I, R has the following meanings: a cyano group, a cyano methyl group, a methoxymethyl group or an ethoxymethyl group.

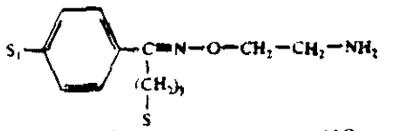
While it is surprising that a very strong serotonine potentiation was found for the novel compounds of the present invention when compared with known compounds from British Patent Specification No. 1,205,665 which known compounds only show an anti-depressive activity based on noradrenaline potentiation and/or on MAO inhibition, even more surprising is the selectivity by which the compounds according to the invention potentiate serotonine (expressed in the low ratios ED_{50} serotonine potentiation/ED_{50} noradrenaline potentiation (serot./noradr.)).

The compounds according to the invention were compared with the most closely structurally related known compounds. The results of this examination are recorded in the following table.



S_1	Compound S		noradr. pot.	serot. pot.	serot. noradr.	MAO inhib.	stomach ulcer.	bronch. constr.
CF_3	CN	*	47	8.6	0.18	>215	–	–
CF_3	CH_2CN	*	>215	30	<0.14	>215	–	–
CF_3	$(CH_2)OCH_3$	**	107	36	0.3	>215	–	–
CF_3	$(CH_2)OC_2H_5$	***	43	37	0.85	>215	–	–
CF_3	C_2H_5	*	?	32	?	>215	–	+
Cl	H	*	6.2	22	3.5	52	+	–
Cl	CH_3	*	5.6	12	2.1	>215	+	–

-continued



S_1	Compound S	noradr	serot. pot.	serot noradr	MAO inhib.	stomach ulcer.	broach. constr.
Cl	C_2H_5	* 19	14	74	>215	-	-

* HCl salt
** maleate 1:1
*** fumarate 1:1

In this table, the numbers ED_{50} denote values expressed in mg/kg; with the exception of the column serot./noradr. which states ratios of ED_{50} values. These ratios which are smaller to much smaller than 1 for the compounds according to the invention are indicative of the selectivity of the compounds. This is in strong contrast with the numbers which were found for the known compounds. It is to be noted that for the compound $S_1 = CF_3$, $S = C_2H_5$, no ED_{50} value for the noradrenaline potentiation could be measured. As a matter of fact, the results obtained with this substance vary so considerably that no estimation of the presumable ED_{50} value can even be given.

The second known compound ($S_1 = Cl$; $S = H$) has a significant MAO inhibition, while it holds for all the four known compounds that they give stomach ulceration and/or broncho-constriction.

The data recorded in the table were determined in the following tests.

The noradrenaline potentiation was determined in the tetrabenazine test. In this test, a quantity of the compound to be tested was administered orally to five male albino mice. After 45 minutes the animals were injected subcutaneously with 80 mg/kg of tetrabenzine. After another 45 minutes the degree of ptosis was determined and compared with the ptosis of animals which have received tetrabenazine alone. The ED_{50} was determined from the results.

The serotonine potentiation was determined in the 5-hydroxytryptophan test. For this purpose the compounds to be tested were administered orally in a series of dosages to isolated male albino mice (5 mice per dosage) 1 hour prior to intraperitoneal administration of 150 mg/kg of dl-5-hydroxytryptophan. 30 Minutes after this threshold dosage the mice were observed individually and the following parameters were scored: stereotypical shaking of the head, spreading of the hindlegs, tremor, tendency to flee, lordosis, clonic stamping with the frontlegs. The ED_{50} value was calculated from the results.

The monoamino oxidase (MAO) inhibiting effect was determined in experiments in which a quantity of the compound to be tested was administered orally to five male albino mice. One hour later the animals were injected subcutaneously with tryptamine hydrochloride in a quantity of 250 mg/kg. This quantity did not cause mortality in animals which did not receive the compound to be tested, but did cause morality in animals to which an active substance has been administered. Eighteen hours after the administration of tryptamine hydrochloride it was determined how many treated animals had died. The ED_{50} was determined from the results.

By means of the method by Metyšová, Arzneimittelforschung 13 - 1039 (1963) it was determined whether the oral administration of 200 mg of a compound to be tested causes stomach ulceration.

By means of the method by Konzett-Rössler, Arch. Exp. Path. Pharmakol 195 71 (1940) it was investigated whether a compound to be tested causes broncho-constriction after intravenous administration of 3 mg. In this method reduction of the breathing function as a result of broncho-constriction is expressed in a smaller volume of air taken in.

On the basis of their properties the compounds of formula I and their salts are particularly suitable for use in the treatment of depressive patients, in particular to elevate their mood.

This applies in particular to 5-methoxy-4'-trifluoromethylvalerophenone O-(2-aminoethyl) oxime and salts thereof with pharmaceutically acceptable acids, such as the maleate 1:1.

This compound was tested clinically in a number of very heavily depressive patients which had previously been treated unsuccessfully with commercially available anti-depressive agents. The patients reacted particularly well to the compounds according to the invention, while a significantly strong elevation of mood occurred.

The quantity, the frequency and route by which the substances according to the invention are administered may vary for each individual patient and also in accordance with the nature and the severity of the disturbances to be treated. In general, adults will receive a daily dose of from 25-500 mg orally. As a rule, a daily oral dosage of 50 to 200 mg will suffice.

The compounds are preferably used in the form of pills, tablets, coated tablets, capsules, powders, injection liquids, and the like. The compounds may be processed to such compositions according to methods which are known per se.

The invention therefore also relates to compositions having a compound of formula I or a salt thereof as the active constituent with a pharmaceutically acceptable acid and to methods to prepare said compositions, for example, by mixing the active compound with or dissolving it in solid or liquid pharmaceutical carrier materials.

As examples of pharmaceutically acceptable acids with which compounds of formula I can form salts may be mentioned: inorganic acids, for example hydrochloric acid, sulphuric acid, nitric acid and organic acids, such as citric acid, fumaric acid, tartaric acid, benzoic acid, maleic acid and the like.

The compounds of formula I and their salts may be prepared according to methods which are known for the preparation of this type of compounds and according to methods analogous thereto.

EXAMPLE 1

5-Methoxy-4'-trifluoromethylvalerophenone O-(2-aminoethyl) oxime maleate (1:1).

20.4 Mmol (5.3 g) of 5-methoxy-4'-trifluoromethylvalerophenone (melting point 43°–44° C), 20.5 mmol (3.1 g) of 2-aminooxyethylaminedihydrochloride and 10 ml of pyridine were refluxed for 15 hours in 20 ml of absolute ethanol. After evaporating the pyridine and the ethanol in vacuo, the residue was dissolved in water. This solution was washed with petroleum ether and 10 ml of 50% sodium hydroxide solution were then added. Then three extractions with 40 ml of ether were carried out. The ether extract was washed successively with 20 ml of 5% sodium bicarbonate solution and 20 ml of water. After drying on sodium sulphate, the ether layer was evaporated in vacuo. Toluene was then evaporated another three times (to remove the pyridine) and the oil thus obtained was dissolved in 15 ml of absolute ethanol. An equimolar quantity of maleic acid was added to said solution and the solution was then heated until a clear solution was obtained. The ethanol was then removed in vacuo and the residue was crystallized from 10 ml of acetonitrile at +5° C. After sucking off and washing with cold acetonitrile, it was dried in air. The melting point of the resulting title compound was 120°–121.5° C.

EXAMPLE 2

5-Ethoxy-4'-trifluoromethylvalerophenone O-(2-aminoethyl) oxime fumarate (1:1).

The title compound having a melting point of 150°–150.5° C was obtained in an identical manner from 5-ethoxy-4'-trifluoromethylvalerophenone with the difference that fumaric acid was added to the solution in ethanol.

EXAMPLE 3

4-Cyano-4'-trifluoromethylbutyrophenone O-(2-aminoethyl) oxime hydrochloride.

5.6 Mmol (1.35 g) of 4-cyano-4'-trifluoromethylbutyrophenone, 5.6 mmol (0.84 g) of 2 aminooxyethylamine dihydrochloride and 0.8 ml of pyridine were refluxed in 20 ml of absolute ethanol for 2.5 hours. The processing was equal to that of example 1. The resulting free base was dissolved in absolute ethanol and an equivalent quantity of 2N alcoholic hydrochloric acid was added. The ethanol was then removed in vacuo and the residue was crystallized twice from ethanol/ether (1:5). The melting point of the resulting title compound was 136°–136.5° C.

EXAMPLE 4

5-Cyano-4'-trifluoromethylvalerophenone O-(2-aminoethyl) oxime hydrochloride.

The title compound having a melting point of 142°–143.5° C was obtained in an identical manner from 5-cyano-4'-trifluoromethylvalerophenone (31°–32° C).

EXAMPLE 5

4-Cyano-4'-trifluoromethylbutyrophenone O-(2-aminoethyl) oxime hydrochloride.

8.0 Mmol (4.3 g) of 4-cyano-4'-trifluoromethylbutyrophenone O-(2-tritylaminoethyl) oxime (melting point 87°–88° C) were dissolved in 40 ml of 90% acetic acid. After standing at room temperature for three days, this reaction mixture was evaporated to dryness in vacuo after which the residue was dissolved in 50 ml of ether. The resulting solution was extracted with 40 ml of 0.2N hydrochloric acid and this extract was extracted with 50 and 25 ml of methylene chloride, respectively, after rendering alkaline with 10 ml of 2N sodium hydroxide solution. The resulting solution was dried (sodium sulphate) and evaporated in vacuo. The residue was dissolved in 80 ml of absolute ethanol and acidified with an equivalent quantity of 2N alcoholic hydrochloric acid. After evaporating the ethanol, two crystallizations were carried out from ethanol/ether (1:5). Melting point 136°–136.5° C.

EXAMPLE 6

5-Methoxy-4'-trifluoromethylvalerophenone O-(2-aminoethyl) oxime maleate (1:1).

5.0 Mmol of 5-methoxy-4'-trifluoromethylvalerophenone oxime (melting point 41.5°–42.5° C), 5.2 mmol (0.60 g) of 2-chloro-ethyl-amine-hydrochloride and 0.7 g of KOH powder were added in this sequence and while stirring at 10° C to 12.5 ml of dimethylformamide (DMF). After stirring at room temperature for 2 days, DMF was removed in vacuo, the residue was brought in water and then 2N hydrochloric acid was added until pH = 3. The remaining oxime was removed by means of ether, after which 15 ml of 2N sodium hydroxide solution were added. Three extractions with ether were then carried out. The collected ether layers were washed with a 5% sodium bicarbonate solution and dried on sodium sulphate. After removing the ether in vacuo, the residue was dissolved in absolute ethanol to which an equimolar quantity of maleic acid was added. There was heated until a clear solution was obtained, after which the ethanol was removed in vacuo. The residue was crystallized from acetonitrile. The resulting title compound had a melting point of 120°–121.5° C.

EXAMPLE 7

5-Methoxy-4'-trifluoromethylvalerophenone O-(2-aminoethyl) oxime maleate (1:1)

a. 26 Mmol (1.15 g) of ethylene oxide were led into a suspension of 15.5 mmol (4.3 g) of 5-methoxy-4'-trifluoromethylvalerophenone-oxime (melting point 41.5°–43.5° C) in 25 ml of absolute ethanol in which first 0.03 g or Li had been dissolved, while stirring at 55° C and by means of a flow of nitrogen. Then stirring was continued for another hour at 60° C. After the addition of 0.3 ml of acetic acid, the ethanol was distilled off in vacuo and the residue was purified chromatographically over silica gel with CH_2Cl_2 as an eluent. After evaporating the solvent, the O-(2-hydroxy-ethyl) oxime was obtained as an oil.

b. 2.23 Ml of triethylamine were added to a solution of 11 mmol (3.6 g) hereof in 60 ml of methylene chloride while stirring at −5° C to 0° C and 12 mmol (0.9 ml) of mesylchloride were then added dropwise in approximately 20 minutes. Stirring was continued at 0° C for another 30 minutes, the mixture was then washed with successively ice water (4x), with a 5% sodium bicarbonate solution of 0° C (1x) and with a saturated NaCl solution of 0° C (2x). After drying on sodium sulphate at 5° C, the CH_2Cl_2 was distilled off in vacuo at a bath temperature of 40 to 60° C. The O-(2-mesyloxy-ethyl) oxime was obtained in this manner.

A mixture of 8 mmol (3.2 g) hereof in 30 ml of methanol which contained 233 mmol (4.0 g) of NH_3 was kept at 100° C in an autoclave for 10 hours. After cooling the methanol was removed in vacuo, the residue was stirred with 50 ml of 2% sodium hydroxide solution and extracted with ether. The ether layer was washed with 5% sodium bicarbonate solution. After drying on sodium sulphate and distilling off the ether in vacuo, it was dissolved in absolute ethanol to which an equimolar quantity of maleic acid was added. The ethanol was evaporated in vacuo and the residue taken up in acetonitrile from which the title compound crystallized.

EXAMPLE 8

5-Ethoxy-4'-trifluoromethylvalerophenone O-(2-aminoethyl) oxime fumarate (1:1)

7 Mmol (2.2 g) of 5-ethoxy-4'-trifluoromethylvalerophenone-ethylene-ketal and 7 mmol (1.0 g) of 2-aminooxyethylamine dihydrochloride were refluxed in 10 ml of methanol for 4 hours. After evaporating the methanol in vacuo, the residue was dissolved in water and washed two times with ether. 3 Ml of 50% sodium hydroxide solution were then added and three extractions with CH_2Cl_2 were carried out. This extract was washed with 5% sodium bicarbonate solution (1x) and water (1x). The solution was then dried on sodium sulphate and the CH_2Cl_2 was distilled off in vacuo. The residue was taken up in absolute ethanol and acidified with an equimolar quantity of fumaric acid. The title compound crystallized from the solution. Melting point 150°-150.5° C.

EXAMPLE 9

5-Cyano-4'-trifluoromethylvalerophenone O-(2-aminoethyl) oxime hydrochloride.

10 Mmol (4.3 g) of 5-chloro-4'-trifluoromethylvalerophenone O-(2-aminoethyl) oxime maleate (1:1) (melting point 121.5°-122.5° C) were dissolved in 50 ml of water. 5 Ml of 50% sodium hydroxide solution at 0° C were added. Three extractions with 25 ml of CH_2Cl_2 were then carried out and this extract was washed with 5% sodium bicarbonate solution (1x) and water (1x). The solution was then dried on sodium sulphate and the CH_2Cl_2 was distilled off in vacuo. The residue was dissolved in 10 ml of dimethylsulfoxide (DMSO) and 25 mmol (1.2 g) of sodium cyanide were then added. The suspension was heated at a temperature of 50° to 70° C for 3 hours and then cooled to room temperature. Then there was diluted with 100 ml of 0.5 N sodium hydroxide solution and three extractions with 40 ml of ether were carried out. The ether extract was washed with water (1x), dried on sodium sulphate and evaporated in vacuo. The residue was purified chromatographically over silica gel with ethanol/ammonia (95:5) as an eluent. After evaporating the solvents, the residue was dissolved in absolute ethanol and acidified with ethanolic hydrochloric acid. After crystallization from ethanol/ether (1:3) the title compound having a melting point of 142°-143.5° C was obtained.

EXAMPLE 10

5-Ethoxy-4'-trifluoromethylvalerophenone O-(2-aminoethyl)oxime fumarate (1:1)

12 Mmol (5.1 g) of 5-chloro-4'-trifluoromethylvalerophenone O-(2-aminoethyl) oxime maleate (1:1) (melting point 121.5°-122.5° C) were added to a solution of 240 mgat. (5.5 g) of sodium in 100 ml of absolute ethanol. The mixture was heated at 70° C for 8 hours followed by neutralization at 0° C with alcoholic hydrochloric acid and the sodium chloride was filtered off. The alcohol was distilled off in vacuo and the residue was dissolved in water. 5 Ml of 50% sodium hydroxide solution were added to this solution and three extractions with 40 ml of ether were then carried out. The ether extract was washed with 5% sodium bicarbonate solution (1x) and with water (1x), followed by drying on sodium sulphate. The ether was distilled off in vacuo and the residue was dissolved in absolute ethanol. The solution was acidified with an equimolar quantity of fumaric acid. The title compound crystallized from the solution. Melting point 105°-105.5° C.

EXAMPLE 11

5-Ethoxy-4'-trifluoromethylvalerophenone O-(2-aminoethyl) oxime fumarate (1:1)

24.7 Mmol (1.00 ml) of methanol and 3 ml of tetrahydrofuran (THF) were added to 7.8 mmol (0.3 g) of $LiAlH_4$ in 10 ml of THF while stirring and cooling in ice water for 3 minutes. A solution of 1.15 mmol of 5-ethoxy-4'-trifluoromethylvalerophenone O-(cyanomethyl) oxime was then added while stirring and cooling for ten minutes. After stirring the reaction mixture at 5° C for another 3 hours it was decomposed with 1.0 ml of water. The formed hydroxides were sucked off, washed with chloroform and the filtrate was evaporated to dryness in vacuo. The resulting base was dissolved in absolute ethanol and an equimolar quantity of fumaric acid was added. The mixture was heated until a clear solution was obtained. The solvent was removed, the residue was taken up in ethanol/acetonitrile 1:1. The title compound crystallized. Melting point 150°-150.5° C.

EXAMPLE 12

TABLET

50 mg of 5-methoxy-4'-trifluoromethylvalerophenone O-(2-aminoethyl) oxime maleate (1:1).
335 mg of lactose
60 mg of potato starch
25 mg of talc
5 mg of magnesium stearate
5 mg of gelatine

EXAMPLE 13

SUPPOSITORY

50 mg of 5-methoxy-4'-trifluoromethylvalerophenone O-(2-aminoethyl) oxime maleate (1:1)
1500 mg of suppository mass.

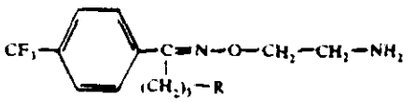
EXAMPLE 14

INJECTION LIQUID

25 g of 5-methoxy-4'-trifluoromethylvalerophenone O-(2-aminoethyl)oxime maleate (1:1).
1.80 g of methyl p-hydroxybenzoate
0.20 g of propyl o-hydroxybenzoate
9.0 g of sodium chloride
4.0 g of poly(oxyethylene)$_{20}$ sorbitan monooleate
water to 1000 ml.

What is claimed is:

1. Oxime ether compounds of the formula



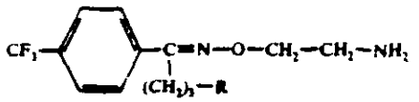
(I)

and salts thereof with pharmaceutically acceptable acids, in which formula R is a cyano group, a cyanomethyl group, a methoxymethyl group or an ethoxymethyl group.

2. The 5-Methoxy-4'-trifluoromethylvalerophenone O-(2-aminoethyl) oxime and salts thereof with pharmaceutically acceptable acids of claim 1.

3. The 5-Ethoxy-4'-trifluoromethylvalerophenone O-(2-aminoethyl) oxime and salts thereof with pharmaceutically acceptable acids of claim 1.

4. An oxime compound of the formula:



wherein R is cyano or cyanomethyl.

5. The 4-Cyano-4'-trifluoromethylbutyrophenone O-(2-aminoethyl) oxime and salts thereof with pharmaceutically acceptable acids of claim 4.

6. The 5-Cyano-4'-trifluoromethylvalerophenone O-(2-aminoethyl) oxime and salts thereof with pharmaceutically acceptable acids of claim 4.

7. An antidepressive composition comprising a compound of claim 1 in an antidepressively effective amount and a pharmaceutically acceptable carrier therefore.

8. A method of treating patients suffering from depression comprising administering to said patients a composition of claim 7 in an antidepressively effective amount.

* * * * *

SECTION 14. A PATENT CERTIFICATION WITH RESPECT TO ANY PATENT WHICH CLAIMS THE DRUG

December 13, 1991

Solvay Pharmaceuticals, Inc., hereby certifies that, as of this date and to the best of its knowledge, there are no other patents which claim the use of fluvoxamine maleate other than that cited in Section 13.

END

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