CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

19-839/S-045

20-990/S-011

Trade Name: Zoloft Tablets and Oral Concentrate

Generic Name: sertraline hydrochloride

Sponsor: Pfizer, Inc.

Approval Date: February 7, 2003

Indications: Provides for the treatment of social anxiety disorder as a new indication.

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Reviews / Information Included in this NDA Review.

CENTER FOR DRUG EVALUATION AND RESEARCH

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APPROVAL LETTER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 19-839/S-045 & 20-990/S-011

Pfizer, Inc.
Attention: Alan Dunbar
Director, Worldwide Regulatory Strategy
235 East 42nd Street 150/7/100
New York, NY 10017

Dear Mr. Dunbar:

Please refer to your supplemental new drug application dated January 18, 2002, received January 22, 2002, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Zoloft® (sertraline hydrochloride) Tablets and Oral Concentrate.

We acknowledge receipt of your amendments dated December 11, 2002 (revised draft labeling).

Your submission of December 11, 2002, constituted a complete response to our November 19, 2002, action letter.

This supplemental new drug application provides for the use of Zoloft® (sertraline hydrochloride) Tablets and Oral Concentrate for the treatment of social anxiety disorder as a new indication.

We also refer to a January 24, 2003, telephone conversation between you and Ms. Anna Marie H. Weikel of this Division, during which it was agreed that the term '————— would be deleted from the heading for Social Anxiety Disorder in the 'Clinical Trials' section as indicated in the enclosed labeling.

We have completed the review of this supplemental application, as amended, and have concluded that adequate information has been presented to demonstrate that the drug product is safe and effective for use as recommended in the enclosed labeling text dated December 11, 2002, with the agreed upon change. Accordingly, the supplemental application is approved effective on the date of this letter.

The final printed labeling (FPL) must be identical to the enclosed labeling.

Please submit the copies of final printed labeling (FPL) electronically according to the guidance for industry titled *Providing Regulatory Submissions in Electronic Format - NDA* (January 1999). Alternatively, you may submit 20 paper copies of the FPL as soon as it is available but no more than 30 days after it is printed. Please individually mount ten of the copies on heavy-weight paper or similar material. For administrative purposes, this submission should be designated "FPL for approved supplement NDA 19-839/S-045 & 20-990/S-011." Approval of this submission by FDA is not required before the labeling is used.

NDA 19-839/S-045

FDA's Pediatric Rule [at 21 CFR 314.55/21 CFR 601.27] was challenged in court. On October 17, 2002, the court ruled that FDA did not have the authority to issue the Pediatric Rule and has barred FDA from enforcing it. Although the government decided not to pursue an appeal in the courts, it will work with Congress in an effort to enact legislation requiring pharmaceutical manufacturers to conduct appropriate pediatric clinical trials. In addition, third party interveners have decided to appeal the court's decision striking down the rule. Therefore, we encourage you to submit a pediatric plan that describes development of your product in the pediatric population where it may be used. Please be aware that whether or not this pediatric plan and subsequent submission of pediatric data will be required depends upon passage of legislation or the success of the third party appeal. In any event, we hope you will decide to submit a pediatric plan and conduct the appropriate pediatric studies to provide important information on the safe and effective use of this drug in the relevant pediatric populations.

In addition, please submit three copies of the introductory promotional materials that you propose to use for this product. All proposed materials should be submitted in draft or mock-up form, not final print. Please submit one copy to this Division and two copies of both the promotional materials and the package insert directly to:

Division of Drug Marketing, Advertising, and Communications, HFD-42
Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20857

If you should have any questions, please call Ms. Anna Marie H. Weikel, R.Ph., Senior Regulatory Project Manager, at (301) 594-5535.

Sincerely,

{See appended electronic signature page}

Russell Katz, M.D.
Director
Division of Neuropharmacological Drug Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

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NDA 19-839/S-045

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This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Russell Katz
2/7/03 03:55:55 PM

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

19-839/S-045

20-990/S-011

APPROVED LABELING

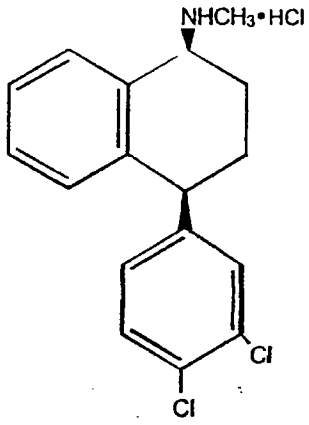
**[FDA Approved Labeling for Zoloft® for the Treatment of Social Anxiety Disorder
Attachment to FDA Approval Letter for NDA 19-839/S-045]**

69-4721-00-4.2

ZOLOFT®
(sertraline hydrochloride)
Tablets and Oral Concentrate

DESCRIPTION

ZOLOFT® (sertraline hydrochloride) is a selective serotonin reuptake inhibitor (SSRI) for oral administration. It has a molecular weight of 342.7. Sertraline hydrochloride has the following chemical name: (1S-cis)-4-(3,4-dichlorophenyl)-1,2,3,4-tetrahydro-N-methyl-1-naphthalenamine hydrochloride. The empirical formula $C_{17}H_{17}NCl_2 \cdot HCl$ is represented by the following structural formula:



Sertraline hydrochloride is a white crystalline powder that is slightly soluble in water and isopropyl alcohol, and sparingly soluble in ethanol.

ZOLOFT is supplied for oral administration as scored tablets containing sertraline hydrochloride equivalent to 25, 50 and 100 mg of sertraline and the following inactive ingredients: dibasic calcium phosphate dihydrate, D & C Yellow #10 aluminum lake (in 25 mg tablet), FD & C Blue #1 aluminum lake (in 25 mg tablet), FD & C Red #40 aluminum lake (in 25 mg tablet), FD & C Blue #2 aluminum lake (in 50 mg tablet), hydroxypropyl cellulose, hydroxypropyl methylcellulose, magnesium stearate, microcrystalline cellulose, polyethylene glycol, polysorbate 80, sodium starch glycolate, synthetic yellow iron oxide (in 100 mg tablet), and titanium dioxide.

ZOLOFT oral concentrate is available in a multidose 60 mL bottle. Each mL of solution contains sertraline hydrochloride equivalent to 20 mg of sertraline. The solution contains the following inactive ingredients: glycerin, alcohol (12%), menthol, butylated hydroxytoluene (BHT). The oral concentrate must be diluted prior to administration (see PRECAUTIONS, Information for Patients and DOSAGE AND ADMINISTRATION).

CLINICAL PHARMACOLOGY

Pharmacodynamics

The mechanism of action of sertraline is presumed to be linked to its inhibition of CNS neuronal uptake of serotonin (5HT). Studies at clinically relevant doses in man have demonstrated that sertraline blocks the uptake of serotonin into human platelets. *In vitro* studies in animals also suggest that sertraline is a potent and selective inhibitor of neuronal serotonin reuptake and has only very weak effects on norepinephrine and dopamine neuronal reuptake. *In vitro* studies have shown that sertraline has no significant affinity for adrenergic ($alpha_1$, $alpha_2$, beta), cholinergic, GABA, dopaminergic, histaminergic, serotonergic ($5HT_{1A}$, $5HT_{1B}$, $5HT_2$), or benzodiazepine receptors; antagonism of such receptors has been hypothesized to be associated with various anticholinergic, sedative, and cardiovascular effects for other psychotropic drugs. The chronic administration of sertraline was found in animals to downregulate brain norepinephrine receptors, as has been observed with other drugs effective in the treatment of major depressive disorder. Sertraline does not inhibit monoamine oxidase.

Pharmacokinetics

Systemic Bioavailability--In man, following oral once-daily dosing over the range of 50 to 200 mg for 14 days, mean peak plasma concentrations (Cmax) of sertraline occurred between 4.5 to 8.4 hours post-dosing. The average terminal elimination half-life of plasma sertraline is about 26 hours. Based on this pharmacokinetic parameter, steady-state sertraline plasma levels should be achieved after approximately one week of once-daily dosing. Linear dose-proportional pharmacokinetics were demonstrated in a single dose study in which the Cmax and area under the plasma concentration time curve (AUC) of sertraline were proportional to dose over a range of 50 to 200 mg. Consistent with the terminal elimination half-life, there is an approximately two-fold accumulation, compared to a single dose, of sertraline with repeated dosing over a 50 to 200 mg dose range. The single dose bioavailability of sertraline tablets is approximately equal to an equivalent dose of solution.

In a relative bioavailability study comparing the pharmacokinetics of 100 mg sertraline as the oral solution to a 100 mg sertraline tablet in 16 healthy adults, the solution to tablet ratio of geometric mean AUC and Cmax values were 114.8% and 120.6%, respectively. 90% confidence intervals (CI) were within the range of 80-125% with the exception of the upper 90% CI limit for Cmax which was 126.5%.

The effects of food on the bioavailability of the sertraline tablet and oral concentrate were studied in subjects administered a single dose with and without food. For the tablet, AUC was slightly increased when drug was administered with food but the Cmax was 25% greater, while the time to reach peak plasma concentration (Tmax) decreased from 8 hours post-dosing to 5.5 hours. For the oral concentrate, Tmax was slightly prolonged from 5.9 hours to 7.0 hours with food.

Metabolism–Sertraline undergoes extensive first pass metabolism. The principal initial pathway of metabolism for sertraline is N-demethylation. N-desmethylsertraline has a plasma terminal elimination half-life of 62 to 104 hours. Both *in vitro* biochemical and *in vivo* pharmacological testing have shown N-desmethylsertraline to be substantially less active than sertraline. Both sertraline and N-desmethylsertraline undergo oxidative deamination and subsequent reduction, hydroxylation, and glucuronide conjugation. In a study of radiolabeled sertraline involving two healthy male subjects, sertraline accounted for less than 5% of the plasma radioactivity. About 40-45% of the administered radioactivity was recovered in urine in 9 days. Unchanged sertraline was not detectable in the urine. For the same period, about 40-45% of the administered radioactivity was accounted for in feces, including 12-14% unchanged sertraline.

Desmethylsertraline exhibits time-related, dose dependent increases in AUC (0-24 hour), Cmax and Cmin, with about a 5-9 fold increase in these pharmacokinetic parameters between day 1 and day 14.

Protein Binding–*In vitro* protein binding studies performed with radiolabeled ^{3}H-sertraline showed that sertraline is highly bound to serum proteins (98%) in the range of 20 to 500 ng/mL. However, at up to 300 and 200 ng/mL concentrations, respectively, sertraline and N-desmethylsertraline did not alter the plasma protein binding of two other highly protein bound drugs, viz., warfarin and propranolol (see PRECAUTIONS).

Pediatric Pharmacokinetics–Sertraline pharmacokinetics were evaluated in a group of 61 pediatric patients (29 aged 6-12 years, 32 aged 13-17 years) with a DSM-III-R diagnosis of major depressive disorder or obsessive-compulsive disorder. Patients included both males (N=28) and females (N=33). During 42 days of chronic sertraline dosing, sertraline was titrated up to 200 mg/day and maintained at that dose for a minimum of 11 days. On the final day of sertraline 200 mg/day, the 6-12 year old group exhibited a mean sertraline AUC (0-24 hr) of 3107 ng-hr/mL, mean Cmax of 165 ng/mL, and mean half-life of 26.2 hr. The 13-17 year old group exhibited a mean sertraline AUC (0-24 hr) of 2296 ng-hr/mL, mean Cmax of 123 ng/mL, and mean half-life of 27.8 hr. Higher plasma levels in the 6-12 year old group were largely attributable to patients with lower body weights. No gender associated differences were observed. By comparison, a group of 22 separately studied adults between 18 and 45 years of age (11 male, 11 female) received 30 days of 200 mg/day sertraline and exhibited a

mean sertraline AUC (0-24 hr) of 2570 ng-hr/mL, mean Cmax of 142 ng/mL, and mean half-life of 27.2 hr. Relative to the adults, both the 6-12 year olds and the 13-17 year olds showed about 22% lower AUC (0-24 hr) and Cmax values when plasma concentration was adjusted for weight. These data suggest that pediatric patients metabolize sertraline with slightly greater efficiency than adults. Nevertheless, lower doses may be advisable for pediatric patients given their lower body weights, especially in very young patients, in order to avoid excessive plasma levels (see DOSAGE AND ADMINISTRATION).

Age–Sertraline plasma clearance in a group of 16 (8 male, 8 female) elderly patients treated for 14 days at a dose of 100 mg/day was approximately 40% lower than in a similarly studied group of younger (25 to 32 y.o.) individuals. Steady-state, therefore, should be achieved after 2 to 3 weeks in older patients. The same study showed a decreased clearance of desmethylsertraline in older males, but not in older females.

Liver Disease–As might be predicted from its primary site of metabolism, liver impairment can affect the elimination of sertraline. In patients with chronic mild liver impairment (N=10, 8 patients with Child-Pugh scores of 5-6 and 2 patients with Child-Pugh scores of 7-8) who received 50 mg sertraline per day maintained for 21 days, sertraline clearance was reduced, resulting in approximately 3-fold greater exposure compared to age-matched volunteers with no hepatic impairment (N=10). The exposure to desmethylsertraline was approximately 2-fold greater compared to age-matched volunteers with no hepatic impairment. There were no significant differences in plasma protein binding observed between the two groups. The effects of sertraline in patients with moderate and severe hepatic impairment have not been studied. The results suggest that the use of sertraline in patients with liver disease must be approached with caution. If sertraline is administered to patients with liver impairment, a lower or less frequent dose should be used (see PRECAUTIONS and DOSAGE AND ADMINISTRATION).

Renal Disease–Sertraline is extensively metabolized and excretion of unchanged drug in urine is a minor route of elimination. In volunteers with mild to moderate (CLcr=30-60 mL/min), moderate to severe (CLcr=10-29 mL/min) or severe (receiving hemodialysis) renal impairment (N=10 each group), the pharmacokinetics and protein binding of 200 mg sertraline per day maintained for 21 days were not altered compared to age-matched volunteers (N=12) with no renal impairment. Thus sertraline multiple dose pharmacokinetics appear to be unaffected by renal impairment (see PRECAUTIONS).

Clinical Trials

Major Depressive Disorder–The efficacy of ZOLOFT as a treatment for major depressive disorder was established in two placebo-controlled studies in adult outpatients meeting DSM-III criteria for major depressive disorder. Study 1 was an 8-week study with flexible dosing of ZOLOFT in a range of 50 to 200 mg/day; the mean dose for completers was 145 mg/day. Study 2 was a 6-week fixed-dose study, including ZOLOFT doses of 50, 100, and 200 mg/day. Overall, these studies demonstrated ZOLOFT to be superior to placebo on the Hamilton Depression Rating Scale and the Clinical Global Impression Severity and Improvement scales. Study 2 was not readily interpretable regarding a dose response relationship for effectiveness.

Study 3 involved depressed outpatients who had responded by the end of an initial 8-week open treatment phase on ZOLOFT 50-200 mg/day. These patients (N=295) were randomized to continuation for 44 weeks on double-blind ZOLOFT 50-200 mg/day or placebo. A statistically significantly lower relapse rate was observed for patients taking ZOLOFT compared to those on placebo. The mean dose for completers was 70 mg/day.

Analyses for gender effects on outcome did not suggest any differential responsiveness on the basis of sex.

Obsessive-Compulsive Disorder (OCD)–The effectiveness of ZOLOFT in the treatment of OCD was demonstrated in three multicenter placebo-controlled studies of adult outpatients (Studies 1-3). Patients in all studies had moderate to severe OCD (DSM-III or DSM-III-R) with mean baseline ratings on the Yale–Brown Obsessive-Compulsive Scale (YBOCS) total score ranging from 23 to 25.

Study 1 was an 8-week study with flexible dosing of ZOLOFT in a range of 50 to 200 mg/day; the mean dose for completers was 186 mg/day. Patients receiving ZOLOFT experienced a mean reduction of approximately 4 points on the YBOCS total score which was significantly greater than the mean reduction of 2 points in placebo-treated patients.

Study 2 was a 12-week fixed-dose study, including ZOLOFT doses of 50, 100, and 200 mg/day. Patients receiving ZOLOFT doses of 50 and 200 mg/day experienced mean reductions of approximately 6 points on the YBOCS total score which were significantly greater than the approximately 3 point reduction in placebo-treated patients.

Study 3 was a 12-week study with flexible dosing of ZOLOFT in a range of 50 to 200 mg/day; the mean dose for completers was 185 mg/day. Patients receiving ZOLOFT experienced a mean reduction of approximately 7 points on the YBOCS total score which was significantly greater than the mean reduction of approximately 4 points in placebo-treated patients.

Analyses for age and gender effects on outcome did not suggest any differential responsiveness on the basis of age or sex.

The effectiveness of ZOLOFT for the treatment of OCD was also demonstrated in a 12-week, multicenter, placebo-controlled, parallel group study in a pediatric outpatient population (children and adolescents, ages 6-17). Patients receiving ZOLOFT in this study were initiated at doses of either 25 mg/day (children, ages 6-12) or 50 mg/day (adolescents, ages 13-17), and then titrated over the next four weeks to a maximum dose of 200 mg/day, as tolerated. The mean dose for completers was 178 mg/day. Dosing was once a day in the morning or evening. Patients in this study had moderate to severe OCD (DSM-III-R) with mean baseline ratings on the Children's Yale-Brown Obsessive-Compulsive Scale (CYBOCS) total score of 22. Patients receiving sertraline experienced a mean reduction of approximately 7 points on the CYBOCS total score which was significantly greater than the 3 point reduction for placebo patients. Analyses for age and gender effects on outcome did not suggest any differential responsiveness on the basis of age or sex.

In a longer-term study, patients meeting DSM-III-R criteria for OCD who had responded during a 52-week single-blind trial on ZOLOFT 50-200 mg/day (n=224) were randomized to continuation of ZOLOFT or to substitution of placebo for up to 28 weeks of observation for discontinuation due to relapse or insufficient clinical response. Response during the single-blind phase was defined as a decrease in the YBOCS score of ≥ 25% compared to baseline and a CGI-I of 1 (very much improved), 2 (much improved) or 3 (minimally improved). Relapse during the double-blind phase was defined as the following conditions being met (on three consecutive visits for 1 and 2, and for visit 3 for condition 3): (1) YBOCS score increased by ≥ 5 points, to a minimum of 20, relative to baseline; (2) CGI-I increased by ≥ one point; and (3) worsening of the patient's condition in the investigator's judgment, to justify alternative treatment. Insufficient clinical response indicated a worsening of the patient's condition that resulted in study discontinuation, as assessed by the investigator. Patients receiving continued ZOLOFT treatment experienced a significantly lower rate of discontinuation due to relapse or insufficient clinical response over the subsequent 28 weeks compared to those receiving placebo. This pattern was demonstrated in male and female subjects.

Panic Disorder–The effectiveness of ZOLOFT in the treatment of panic disorder was demonstrated in three double-blind, placebo-controlled studies (Studies 1-3) of adult outpatients who had a primary diagnosis of panic disorder (DSM-III-R), with or without agoraphobia.

Studies 1 and 2 were 10-week flexible dose studies. ZOLOFT was initiated at 25 mg/day for the first week, and then patients were dosed in a range of 50-200 mg/day on the basis of clinical response and toleration. The mean ZOLOFT doses for completers to 10 weeks were 131 mg/day and 144 mg/day, respectively, for Studies 1 and 2. In these studies, ZOLOFT was shown to be significantly more effective than placebo on change from baseline in panic attack frequency and on the Clinical Global Impression Severity of Illness and Global Improvement scores. The difference between ZOLOFT and placebo in reduction from baseline in the number of full panic attacks was approximately 2 panic attacks per week in both studies.

Study 3 was a 12-week fixed-dose study, including ZOLOFT doses of 50, 100, and 200 mg/day. Patients receiving ZOLOFT experienced a significantly greater reduction in panic attack frequency than

patients receiving placebo. Study 3 was not readily interpretable regarding a dose response relationship for effectiveness.

Subgroup analyses did not indicate that there were any differences in treatment outcomes as a function of age, race, or gender.

In a longer-term study, patients meeting DSM-III-R criteria for Panic Disorder who had responded during a 52-week open trial on ZOLOFT 50-200 mg/day (n=183) were randomized to continuation of ZOLOFT or to substitution of placebo for up to 28 weeks of observation for discontinuation due to relapse or insufficient clinical response. Response during the open phase was defined as a CGI-I score of 1(very much improved) or 2 (much improved). Relapse during the double-blind phase was defined as the following conditions being met on three consecutive visits: (1) CGI-I $\geq$ 3; (2) meets DSM-III-R criteria for Panic Disorder; (3) number of panic attacks greater than at baseline. Insufficient clinical response indicated a worsening of the patient's condition that resulted in study discontinuation, as assessed by the investigator. Patients receiving continued ZOLOFT treatment experienced a significantly lower rate of discontinuation due to relapse or insufficient clinical response over the subsequent 28 weeks compared to those receiving placebo. This pattern was demonstrated in male and female subjects.

Posttraumatic Stress Disorder (PTSD)–The effectiveness of ZOLOFT in the treatment of PTSD was established in two multicenter placebo-controlled studies (Studies 1-2) of adult outpatients who met DSM-III-R criteria for PTSD. The mean duration of PTSD for these patients was 12 years (Studies 1 and 2 combined) and 44% of patients (169 of the 385 patients treated) had secondary depressive disorder.

Studies 1 and 2 were 12-week flexible dose studies. ZOLOFT was initiated at 25 mg/day for the first week, and patients were then dosed in the range of 50-200 mg/day on the basis of clinical response and toleration. The mean ZOLOFT dose for completers was 146 mg/day and 151 mg/day, respectively for Studies 1 and 2. Study outcome was assessed by the Clinician-Administered PTSD Scale Part 2 (CAPS) which is a multi-item instrument that measures the three PTSD diagnostic symptom clusters of reexperiencing/intrusion, avoidance/numbing, and hyperarousal as well as the patient-rated Impact of Event Scale (IES) which measures intrusion and avoidance symptoms. ZOLOFT was shown to be significantly more effective than placebo on change from baseline to endpoint on the CAPS, IES and on the Clinical Global Impressions (CGI) Severity of Illness and Global Improvement scores. In two additional placebo-controlled PTSD trials, the difference in response to treatment between patients receiving ZOLOFT and patients receiving placebo was not statistically significant. One of these additional studies was conducted in patients similar to those recruited for Studies 1 and 2, while the second additional study was conducted in predominantly male veterans.

As PTSD is a more common disorder in women than men, the majority (76%) of patients in these trials were women (152 and 139 women on sertraline and placebo versus 39 and 55 men on sertraline and placebo; Studies 1 and 2 combined). Post hoc exploratory analyses revealed a significant difference between ZOLOFT and placebo on the CAPS, IES and CGI in women, regardless of baseline diagnosis

of comorbid major depressive disorder, but essentially no effect in the relatively smaller number of men in these studies. The clinical significance of this apparent gender interaction is unknown at this time. There was insufficient information to determine the effect of race or age on outcome.

In a longer-term study, patients meeting DSM-III-R criteria for PTSD who had responded during a 24-week open trial on ZOLOFT 50-200 mg/day (n=96) were randomized to continuation of ZOLOFT or to substitution of placebo for up to 28 weeks of observation for relapse. Response during the open phase was defined as a CGI-I of 1 (very much improved) or 2 (much improved), and a decrease in the CAPS-2 score of > 30% compared to baseline. Relapse during the double-blind phase was defined as the following conditions being met on two consecutive visits: (1) CGI-I ≥ 3; (2) CAPS-2 score increased by ≥ 30% and by ≥ 15 points relative to baseline; and (3) worsening of the patient's condition in the investigator's judgment. Patients receiving continued ZOLOFT treatment experienced significantly lower relapse rates over the subsequent 28 weeks compared to those receiving placebo. This pattern was demonstrated in male and female subjects.

Premenstrual Dysphoric Disorder (PMDD) – The effectiveness of ZOLOFT for the treatment of PMDD was established in two double-blind, parallel group, placebo-controlled flexible dose trials (Studies 1 and 2) conducted over 3 menstrual cycles. Patients in Study 1 met DSM-III-R criteria for Late Luteal Phase Dysphoric Disorder (LLPDD), the clinical entity now referred to as Premenstrual Dysphoric Disorder (PMDD) in DSM-IV. Patients in Study 2 met DSM-IV criteria for PMDD. Study 1 utilized daily dosing throughout the study, while Study 2 utilized luteal phase dosing for the 2 weeks prior to the onset of menses. The mean duration of PMDD symptoms for these patients was approximately 10.5 years in both studies. Patients on oral contraceptives were excluded from these trials; therefore, the efficacy of sertraline in combination with oral contraceptives for the treatment of PMDD is unknown.

Efficacy was assessed with the Daily Record of Severity of Problems (DRSP), a patient-rated instrument that mirrors the diagnostic criteria for PMDD as identified in the DSM-IV, and includes assessments for mood, physical symptoms, and other symptoms. Other efficacy assessments included the Hamilton Depression Rating Scale (HAMD-17), and the Clinical Global Impression Severity of Illness (CGI-S) and Improvement (CGI-I) scores.

In Study 1, involving n=251 randomized patients, ZOLOFT treatment was initiated at 50 mg/day and administered daily throughout the menstrual cycle. In subsequent cycles, patients were dosed in the range of 50-150 mg/day on the basis of clinical response and toleration. The mean dose for completers was 102 mg/day. ZOLOFT administered daily throughout the menstrual cycle was significantly more effective than placebo on change from baseline to endpoint on the DRSP total score, the HAMD-17 total score, and the CGI-S score, as well as the CGI-I score at endpoint.

In Study 2, involving n=281 randomized patients, ZOLOFT treatment was initiated at 50 mg/day in the late luteal phase (last 2 weeks) of each menstrual cycle and then discontinued at the onset of menses. In subsequent cycles, patients were dosed in the range of 50-100 mg/day in the luteal phase of each cycle, on the basis of clinical response and toleration. Patients who were titrated to 100 mg/day received 50

mg/day for the first 3 days of the cycle, then 100 mg/day for the remainder of the cycle. The mean ZOLOFT dose for completers was 74 mg/day. ZOLOFT administered in the late luteal phase of the menstrual cycle was significantly more effective than placebo on change from baseline to endpoint on the DRSP total score and the CGI-S score, as well as the CGI-I score at endpoint.

There was insufficient information to determine the effect of race or age on outcome in these studies.

Social Anxiety Disorder– The effectiveness of ZOLOFT in the treatment of social anxiety disorder (also known as social phobia) was established in two multicenter placebo-controlled studies (Study 1 and 2) of adult outpatients who met DSM-IV criteria for social anxiety disorder.

Study 1 was a 12-week, multicenter, flexible dose study comparing ZOLOFT (50-200 mg/day) to placebo, in which ZOLOFT was initiated at 25 mg/day for the first week. Study outcome was assessed by (a) the Liebowitz Social Anxiety Scale (LSAS), a 24-item clinician administered instrument that measures fear, anxiety and avoidance of social and performance situations, and by (b) the proportion of responders as defined by the Clinical Global Impression of Improvement (CGI-I) criterion of CGI-I ≤ 2 (very much or much improved). ZOLOFT was statistically significantly more effective than placebo as measured by the LSAS and the percentage of responders.

Study 2 was a 20-week, multicenter, flexible dose study that compared ZOLOFT (50-200 mg/day) to placebo. Study outcome was assessed by the (a) Duke Brief Social Phobia Scale (BSPS), a multi-item clinician-rated instrument that measures fear, avoidance and physiologic response to social or performance situations, (b) the Marks Fear Questionnaire Social Phobia Subscale (FQ-SPS), a 5-item patient-rated instrument that measures change in the severity of phobic avoidance and distress, and (c) the CGI-I responder criterion of ≤ 2. ZOLOFT was shown to be statistically significantly more effective than placebo as measured by the BSPS total score and fear, avoidance and physiologic factor scores, as well as the FQ-SPS total score, and to have significantly more responders than placebo as defined by the CGI-I.

Subgroup analyses did not suggest differences in treatment outcome on the basis of gender. There was insufficient information to determine the effect of race or age on outcome.

In a longer-term study, patients meeting DSM-IV criteria for social anxiety disorder who had responded while assigned to ZOLOFT (CGI-I of 1 or 2) during a 20-week placebo-controlled trial on ZOLOFT 50-200 mg/day were randomized to continuation of ZOLOFT or to substitution of placebo for up to 24 weeks of observation for relapse. Relapse was defined as ≥ 2 point increase in the Clinical Global Impression – Severity of Illness (CGI-S) score compared to baseline or study discontinuation due to lack of efficacy. Patients receiving ZOLOFT continuation treatment experienced a statistically

significantly lower relapse rate over this 24-week study than patients randomized to placebo substitution.

INDICATIONS AND USAGE

Major Depressive Disorder–ZOLOFT® (sertraline hydrochloride) is indicated for the treatment of major depressive disorder.

The efficacy of ZOLOFT in the treatment of a major depressive episode was established in six to eight week controlled trials of outpatients whose diagnoses corresponded most closely to the DSM-III category of major depressive disorder (see Clinical Trials under CLINICAL PHARMACOLOGY).

A major depressive episode implies a prominent and relatively persistent depressed or dysphoric mood that usually interferes with daily functioning (nearly every day for at least 2 weeks); it should include at least 4 of the following 8 symptoms: change in appetite, change in sleep, psychomotor agitation or retardation, loss of interest in usual activities or decrease in sexual drive, increased fatigue, feelings of guilt or worthlessness, slowed thinking or impaired concentration, and a suicide attempt or suicidal ideation.

The antidepressant action of ZOLOFT in hospitalized depressed patients has not been adequately studied.

The efficacy of ZOLOFT in maintaining an antidepressant response for up to 44 weeks following 8 weeks of open-label acute treatment (52 weeks total) was demonstrated in a placebo-controlled trial. The usefulness of the drug in patients receiving ZOLOFT for extended periods should be reevaluated periodically (see Clinical Trials under CLINICAL PHARMACOLOGY).

Obsessive-Compulsive Disorder–ZOLOFT is indicated for the treatment of obsessions and compulsions in patients with obsessive-compulsive disorder (OCD), as defined in the DSM-III-R; i.e., the obsessions or compulsions cause marked distress, are time-consuming, or significantly interfere with social or occupational functioning.

The efficacy of ZOLOFT was established in 12-week trials with obsessive-compulsive outpatients having diagnoses of obsessive-compulsive disorder as defined according to DSM-III or DSM-III-R criteria (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 efficacy of ZOLOFT in maintaining a response, in patients with OCD who responded during a 52-week treatment phase while taking ZOLOFT and were then observed for relapse during a period of up to 28 weeks, was demonstrated in a placebo-controlled trial (see Clinical Trials under CLINICAL

PHARMACOLOGY). Nevertheless, the physician who elects to use ZOLOFT for extended periods should periodically re-evaluate the long-term usefulness of the drug for the individual patient (see DOSAGE AND ADMINISTRATION).

Panic Disorder–ZOLOFT is indicated for the treatment of panic disorder, with or without agoraphobia, as defined in DSM-IV. Panic disorder is characterized by the occurrence of unexpected panic attacks and associated concern about having additional attacks, worry about the implications or consequences of the attacks, and/or a significant change in behavior related to the attacks.

The efficacy of ZOLOFT was established in three 10-12 week trials in panic disorder patients whose diagnoses corresponded to the DSM-III-R category of panic disorder (see Clinical Trials under CLINICAL PHARMACOLOGY).

Panic disorder (DSM-IV) is characterized by recurrent unexpected panic attacks, i.e., a discrete period of intense fear or discomfort in which four (or more) of the following symptoms develop abruptly and reach a peak within 10 minutes: (1) palpitations, pounding heart, or accelerated heart rate; (2) sweating; (3) trembling or shaking; (4) sensations of shortness of breath or smothering; (5) feeling of choking; (6) chest pain or discomfort; (7) nausea or abdominal distress; (8) feeling dizzy, unsteady, lightheaded, or faint; (9) derealization (feelings of unreality) or depersonalization (being detached from oneself); (10) fear of losing control; (11) fear of dying; (12) paresthesias (numbness or tingling sensations); (13) chills or hot flushes.

The efficacy of ZOLOFT in maintaining a response, in patients with panic disorder who responded during a 52-week treatment phase while taking ZOLOFT and were then observed for relapse during a period of up to 28 weeks, was demonstrated in a placebo-controlled trial (see Clinical Trials under CLINICAL PHARMACOLOGY). Nevertheless, the physician who elects to use ZOLOFT for extended periods should periodically re-evaluate the long-term usefulness of the drug for the individual patient (see DOSAGE AND ADMINISTRATION).

Posttraumatic Stress Disorder (PTSD)–ZOLOFT (sertraline hydrochloride) is indicated for the treatment of posttraumatic stress disorder.

The efficacy of ZOLOFT in the treatment of PTSD was established in two 12-week placebo-controlled trials of outpatients whose diagnosis met criteria for the DSM-III-R category of PTSD (see Clinical Trials under CLINICAL PHARMACOLOGY).

PTSD, as defined by DSM-III-R/IV, requires exposure to a traumatic event that involved actual or threatened death or serious injury, or threat to the physical integrity of self or others, and a response which involves intense fear, helplessness, or horror. Symptoms that occur as a result of exposure to the traumatic event include reexperiencing of the event in the form of intrusive thoughts, flashbacks or dreams, and intense psychological distress and physiological reactivity on exposure to cues to the event; avoidance of situations reminiscent of the traumatic event, inability to recall details of the event, and/or numbing of general responsiveness manifested as diminished interest in significant activities, estrangement

from others, restricted range of affect, or sense of foreshortened future; and symptoms of autonomic arousal including hypervigilance, exaggerated startle response, sleep disturbance, impaired concentration, and irritability or outbursts of anger. A PTSD diagnosis requires that the symptoms are present for at least a month and that they cause clinically significant distress or impairment in social, occupational, or other important areas of functioning.

The efficacy of ZOLOFT in maintaining a response in patients with PTSD for up to 28 weeks following 24 weeks of open-label treatment was demonstrated in a placebo-controlled trial. Nevertheless, the physician who elects to use ZOLOFT for extended periods should periodically re-evaluate the long-term usefulness of the drug for the individual patient (see DOSAGE AND ADMINISTRATION).

Premenstrual Dysphoric Disorder (PMDD) – ZOLOFT is indicated for the treatment of premenstrual dysphoric disorder (PMDD).

The efficacy of ZOLOFT in the treatment of PMDD was established in 2 placebo-controlled trials of female outpatients treated for 3 menstrual cycles who met criteria for the DSM-III-R/IV category of PMDD (see Clinical Trials under CLINICAL PHARMACOLOGY).

The essential features of PMDD include markedly depressed mood, anxiety or tension, affective lability, and persistent anger or irritability. Other features include decreased interest in activities, difficulty concentrating, lack of energy, change in appetite or sleep, and feeling out of control. Physical symptoms associated with PMDD include breast tenderness, headache, joint and muscle pain, bloating and weight gain. These symptoms occur regularly during the luteal phase and remit within a few days following onset of menses; the disturbance markedly interferes with work or school or with usual social activities and relationships with others. In making the diagnosis, care should be taken to rule out other cyclical mood disorders that may be exacerbated by treatment with an antidepressant.

The effectiveness of ZOLOFT in long-term use, that is, for more than 3 menstrual cycles, has not been systematically evaluated in controlled trials. Therefore, the physician who elects to use ZOLOFT for extended periods should periodically re-evaluate the long-term usefulness of the drug for the individual patient (see DOSAGE AND ADMINISTRATION).

Social Anxiety Disorder – ZOLOFT (sertraline hydrochloride) is indicated for the treatment of social anxiety disorder, also known as social phobia.

The efficacy of ZOLOFT in the treatment of social anxiety disorder was established in two placebo-controlled trials of outpatients with a diagnosis of social anxiety disorder as defined by DSM-IV criteria (see Clinical Trials under CLINICAL PHARMACOLOGY).

Social anxiety disorder, as defined by DSM-IV, is characterized by marked and persistent fear of social or performance situations involving exposure to unfamiliar people or possible scrutiny by others and by fears of acting in a humiliating or embarrassing way. Exposure to the feared social situation almost always provokes anxiety and feared social or

performance situations are avoided or else are endured with intense anxiety or distress. In addition, patients recognize that the fear is excessive or unreasonable and the avoidance and anticipatory anxiety of the feared situation is associated with functional impairment or marked distress.

The efficacy of ZOLOFT in maintaining a response in patients with social anxiety disorder for up to 24 weeks following 20 weeks of ZOLOFT treatment was demonstrated in a placebo-controlled trial. Physicians who prescribe ZOLOFT for extended periods should periodically re-evaluate the long-term usefulness of the drug for the individual patient (see Clinical Trials under CLINICAL PHARMACOLOGY).

CONTRAINDICATIONS

All Dosage Forms of ZOLOFT:
Concomitant use in patients taking monoamine oxidase inhibitors (MAOIs) is contraindicated (see WARNINGS). Concomitant use in patients taking pimozide is contraindicated (see PRECAUTIONS).

ZOLOFT is contraindicated in patients with a hypersensitivity to sertraline or any of the inactive ingredients in ZOLOFT.

Oral Concentrate:
ZOLOFT oral concentrate is contraindicated with ANTABUSE (disulfiram) due to the alcohol content of the concentrate.

WARNINGS

Cases of serious sometimes fatal reactions have been reported in patients receiving ZOLOFT® (sertraline hydrochloride), a selective serotonin reuptake inhibitor (SSRI), in combination with a monoamine oxidase inhibitor (MAOI). Symptoms of a drug interaction between an SSRI and an MAOI include: hyperthermia, rigidity, myoclonus, autonomic instability with possible rapid fluctuations of vital signs, mental status changes that include confusion, irritability, and extreme agitation progressing to delirium and coma. These reactions have also been reported in patients who have recently discontinued an SSRI and have been started on an MAOI. Some cases presented with features resembling neuroleptic malignant syndrome. Therefore, ZOLOFT should not be used in combination with an MAOI, or within 14 days of discontinuing treatment with an MAOI. Similarly, at least 14 days should be allowed after stopping ZOLOFT before starting an MAOI.

PRECAUTIONS

General

Activation of Mania/Hypomania–During premarketing testing, hypomania or mania occurred in approximately 0.4% of ZOLOFT® (sertraline hydrochloride) treated patients.

Weight Loss–Significant weight loss may be an undesirable result of treatment with sertraline for some patients, but on average, patients in controlled trials had minimal, 1 to 2 pound weight loss, versus smaller changes on placebo. Only rarely have sertraline patients been discontinued for weight loss.

Seizure–ZOLOFT has not been evaluated in patients with a seizure disorder. These patients were excluded from clinical studies during the product's premarket testing. No seizures were observed among approximately 3000 patients treated with ZOLOFT in the development program for major depressive disorder. However, 4 patients out of approximately 1800 (220<18 years of age) exposed during the development program for obsessive-compulsive disorder experienced seizures, representing a crude incidence of 0.2%. Three of these patients were adolescents, two with a seizure disorder and one with a family history of seizure disorder, none of whom were receiving anticonvulsant medication. Accordingly, ZOLOFT should be introduced with care in patients with a seizure disorder.

Suicide–The possibility of a suicide attempt is inherent in major depressive disorder and may persist until significant remission occurs. Close supervision of high risk patients should accompany initial drug therapy. Prescriptions for ZOLOFT should be written for the smallest quantity of tablets consistent with good patient management, in order to reduce the risk of overdose.

Because of the well-established comorbidity between OCD, panic disorder, PTSD, PMDD or social anxiety disorder and major depressive disorder, the same precautions observed when treating patients with major depressive disorder should be observed when treating patients with OCD, panic disorder, PTSD, PMDD or social anxiety disorder.

Weak Uricosuric Effect–ZOLOFT® (sertraline hydrochloride) is associated with a mean decrease in serum uric acid of approximately 7%. The clinical significance of this weak uricosuric effect is unknown.

Use in Patients with Concomitant Illness–Clinical experience with ZOLOFT in patients with certain concomitant systemic illness is limited. Caution is advisable in using ZOLOFT in patients with diseases or conditions that could affect metabolism or hemodynamic responses.

ZOLOFT has not been evaluated or used to any appreciable extent in patients with a recent history of myocardial infarction or unstable heart disease. Patients with these diagnoses were excluded from clinical studies during the product's premarket testing. However, the electrocardiograms of 774 patients who received ZOLOFT in double-blind trials were evaluated and the data indicate that ZOLOFT is not associated with the development of significant ECG abnormalities.

ZOLOFT is extensively metabolized by the liver. In patients with chronic mild liver impairment, sertraline clearance was reduced, resulting in increased AUC, Cmax and elimination half-life. The

effects of sertraline in patients with moderate and severe hepatic impairment have not been studied. The use of sertraline in patients with liver disease must be approached with caution. If sertraline is administered to patients with liver impairment, a lower or less frequent dose should be used (see CLINICAL PHARMACOLOGY and DOSAGE AND ADMINISTRATION).

Since ZOLOFT is extensively metabolized, excretion of unchanged drug in urine is a minor route of elimination. A clinical study comparing sertraline pharmacokinetics in healthy volunteers to that in patients with renal impairment ranging from mild to severe (requiring dialysis) indicated that the pharmacokinetics and protein binding are unaffected by renal disease. Based on the pharmacokinetic results, there is no need for dosage adjustment in patients with renal impairment (see CLINICAL PHARMACOLOGY).

Interference with Cognitive and Motor Performance–In controlled studies, ZOLOFT did not cause sedation and did not interfere with psychomotor performance. (See **Information for Patients.**)

Hyponatremia–Several cases of hyponatremia have been reported and appeared to be reversible when ZOLOFT was discontinued. Some cases were possibly due to the syndrome of inappropriate antidiuretic hormone secretion. The majority of these occurrences have been in elderly individuals, some in patients taking diuretics or who were otherwise volume depleted.

Platelet Function–There have been rare reports of altered platelet function and/or abnormal results from laboratory studies in patients taking ZOLOFT. While there have been reports of abnormal bleeding or purpura in several patients taking ZOLOFT, it is unclear whether ZOLOFT had a causative role.

Information for Patients

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

Patients should be told that although ZOLOFT has not been shown to impair the ability of normal subjects to perform tasks requiring complex motor and mental skills in laboratory experiments, drugs that act upon the central nervous system may affect some individuals adversely. Therefore, patients should be told that until they learn how they respond to ZOLOFT they should be careful doing activities when they need to be alert, such as driving a car or operating machinery.

Patients should be told that although ZOLOFT has not been shown in experiments with normal subjects to increase the mental and motor skill impairments caused by alcohol, the concomitant use of ZOLOFT and alcohol is not advised.

Patients should be told that while no adverse interaction of ZOLOFT with over-the-counter (OTC) drug products is known to occur, the potential for interaction exists. Thus, the use of any OTC product should be initiated cautiously according to the directions of use given for the OTC product.

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

Patients should be advised to notify their physician if they are breast feeding an infant.

ZOLOFT oral concentrate is contraindicated with ANTABUSE (disulfiram) due to the alcohol content of the concentrate.

ZOLOFT Oral Concentrate contains 20 mg/mL of sertraline (as the hydrochloride) as the active ingredient and 12% alcohol. ZOLOFT Oral Concentrate must be diluted before use. Just before taking, use the dropper provided to remove the required amount of ZOLOFT Oral Concentrate and mix with 4 oz (1/2 cup) of water, ginger ale, lemon/lime soda, lemonade or orange juice ONLY. Do not mix ZOLOFT Oral Concentrate with anything other than the liquids listed. The dose should be taken immediately after mixing. Do not mix in advance. At times, a slight haze may appear after mixing; this is normal. Note that caution should be exercised for persons with latex sensitivity, as the dropper dispenser contains dry natural rubber.

Laboratory Tests
None.

Drug Interactions
Potential Effects of Coadministration of Drugs Highly Bound to Plasma Proteins–Because sertraline is tightly bound to plasma protein, the administration of ZOLOFT® (sertraline hydrochloride) to a patient taking another drug which is tightly bound to protein (e.g., warfarin, digitoxin) may cause a shift in plasma concentrations potentially resulting in an adverse effect. Conversely, adverse effects may result from displacement of protein bound ZOLOFT by other tightly bound drugs.

In a study comparing prothrombin time AUC (0-120 hr) following dosing with warfarin (0.75 mg/kg) before and after 21 days of dosing with either ZOLOFT (50-200 mg/day) or placebo, there was a mean increase in prothrombin time of 8% relative to baseline for ZOLOFT compared to a 1% decrease for placebo ($p<0.02$). The normalization of prothrombin time for the ZOLOFT group was delayed compared to the placebo group. The clinical significance of this change is unknown. Accordingly, prothrombin time should be carefully monitored when ZOLOFT therapy is initiated or stopped.

Cimetidine–In a study assessing disposition of ZOLOFT (100 mg) on the second of 8 days of cimetidine administration (800 mg daily), there were significant increases in ZOLOFT mean AUC (50%), Cmax (24%) and half-life (26%) compared to the placebo group. The clinical significance of these changes is unknown.

CNS Active Drugs–In a study comparing the disposition of intravenously administered diazepam before and after 21 days of dosing with either ZOLOFT (50 to 200 mg/day escalating dose) or placebo, there was a 32% decrease relative to baseline in diazepam clearance for the ZOLOFT group compared to a 19% decrease relative to baseline for the placebo group ($p<0.03$). There was a 23%

increase in Tmax for desmethyldiazepam in the ZOLOFT group compared to a 20% decrease in the placebo group ($p<0.03$). The clinical significance of these changes is unknown.

In a placebo-controlled trial in normal volunteers, the administration of two doses of ZOLOFT did not significantly alter steady-state lithium levels or the renal clearance of lithium.

Nonetheless, at this time, it is recommended that plasma lithium levels be monitored following initiation of ZOLOFT therapy with appropriate adjustments to the lithium dose.

In a controlled study of a single dose (2 mg) of pimozide, 200 mg sertraline (q.d.) co-administration to steady state was associated with a mean increase in pimozide AUC and Cmax of about 40%, but was not associated with any changes in EKG. Since the highest recommended pimozide dose (10 mg) has not been evaluated in combination with sertraline, the effect on QT interval and PK parameters at doses higher than 2 mg at this time are not known. While the mechanism of this interaction is unknown, due to the narrow therapeutic index of pimozide and due to the interaction noted at a low dose of pimozide, concomitant administration of ZOLOFT and pimozide should be contraindicated (see CONTRAINDICATIONS).

The risk of using ZOLOFT in combination with other CNS active drugs has not been systematically evaluated. Consequently, caution is advised if the concomitant administration of ZOLOFT and such drugs is required.

There is limited controlled experience regarding the optimal timing of switching from other drugs effective in the treatment of major depressive disorder, obsessive-compulsive disorder, panic disorder, posttraumatic stress disorder, premenstrual dysphoric disorder and social anxiety disorder to ZOLOFT. Care and prudent medical judgment should be exercised when switching, particularly from long-acting agents. The duration of an appropriate washout period which should intervene before switching from one selective serotonin reuptake inhibitor (SSRI) to another has not been established.

Monoamine Oxidase Inhibitors–See CONTRAINDICATIONS and WARNINGS.

Drugs Metabolized by P450 3A4–In three separate *in vivo* interaction studies, sertraline was co-administered with cytochrome P450 3A4 substrates, terfenadine, carbamazepine, or cisapride under steady-state conditions. The results of these studies indicated that sertraline did not increase plasma concentrations of terfenadine, carbamazepine, or cisapride. These data indicate that sertraline's extent of inhibition of P450 3A4 activity is not likely to be of clinical significance. Results of the interaction study with cisapride indicate that sertraline 200 mg (q.d.) induces the metabolism of cisapride (cisapride AUC and Cmax were reduced by about 35%).

Drugs Metabolized by P450 2D6–Many drugs effective in the treatment of major depressive disorder, e.g., the SSRIs, including sertraline, and most tricyclic antidepressant drugs effective in the treatment of major depressive disorder inhibit the biochemical activity of the drug metabolizing isozyme cytochrome P450 2D6 (debrisoquin hydroxylase), and, thus, may increase the plasma concentrations of

co-administered drugs that are metabolized by P450 2D6. The drugs for which this potential interaction is of greatest concern are those metabolized primarily by 2D6 and which have a narrow therapeutic index, e.g., the tricyclic antidepressant drugs effective in the treatment of major depressive disorder and the Type 1C antiarrhythmics propafenone and flecainide. The extent to which this interaction is an important clinical problem depends on the extent of the inhibition of P450 2D6 by the antidepressant and the therapeutic index of the co-administered drug. There is variability among the drugs effective in the treatment of major depressive disorder in the extent of clinically important 2D6 inhibition, and in fact sertraline at lower doses has a less prominent inhibitory effect on 2D6 than some others in the class. Nevertheless, even sertraline has the potential for clinically important 2D6 inhibition. Consequently, concomitant use of a drug metabolized by P450 2D6 with ZOLOFT may require lower doses than usually prescribed for the other drug. Furthermore, whenever ZOLOFT is withdrawn from co-therapy, an increased dose of the co-administered drug may be required (see Tricyclic Antidepressant Drugs Effective in the Treatment of Major Depressive Disorder under PRECAUTIONS).

Sumatriptan–There have been rare postmarketing reports describing patients with weakness, hyperreflexia, and incoordination following the use of a selective serotonin reuptake inhibitor (SSRI) and sumatriptan. If concomitant treatment with sumatriptan and an SSRI (e.g., citalopram, fluoxetine, fluvoxamine, paroxetine, sertraline) is clinically warranted, appropriate observation of the patient is advised.

Tricyclic Antidepressant Drugs Effective in the Treatment of Major Depressive Disorder (TCAs)–The extent to which SSRI–TCA interactions may pose clinical problems will depend on the degree of inhibition and the pharmacokinetics of the SSRI involved. Nevertheless, caution is indicated in the co-administration of TCAs with ZOLOFT, because sertraline may inhibit TCA metabolism. Plasma TCA concentrations may need to be monitored, and the dose of TCA may need to be reduced, if a TCA is co-administered with ZOLOFT (see Drugs Metabolized by P450 2D6 under PRECAUTIONS).

Hypoglycemic Drugs–In a placebo-controlled trial in normal volunteers, administration of ZOLOFT for 22 days (including 200 mg/day for the final 13 days) caused a statistically significant 16% decrease from baseline in the clearance of tolbutamide following an intravenous 1000 mg dose. ZOLOFT administration did not noticeably change either the plasma protein binding or the apparent volume of distribution of tolbutamide, suggesting that the decreased clearance was due to a change in the metabolism of the drug. The clinical significance of this decrease in tolbutamide clearance is unknown.

Atenolol–ZOLOFT (100 mg) when administered to 10 healthy male subjects had no effect on the beta-adrenergic blocking ability of atenolol.

Digoxin–In a placebo-controlled trial in normal volunteers, administration of ZOLOFT for 17 days (including 200 mg/day for the last 10 days) did not change serum digoxin levels or digoxin renal clearance.

Microsomal Enzyme Induction–Preclinical studies have shown ZOLOFT to induce hepatic microsomal enzymes. In clinical studies, ZOLOFT was shown to induce hepatic enzymes minimally as determined by a small (5%) but statistically significant decrease in antipyrine half-life following administration of 200 mg/day for 21 days. This small change in antipyrine half-life reflects a clinically insignificant change in hepatic metabolism.

Electroconvulsive Therapy–There are no clinical studies establishing the risks or benefits of the combined use of electroconvulsive therapy (ECT) and ZOLOFT.

Alcohol–Although ZOLOFT did not potentiate the cognitive and psychomotor effects of alcohol in experiments with normal subjects, the concomitant use of ZOLOFT and alcohol is not recommended.

Carcinogenesis–Lifetime carcinogenicity studies were carried out in CD-1 mice and Long-Evans rats at doses up to 40 mg/kg/day. These doses correspond to 1 times (mice) and 2 times (rats) the maximum recommended human dose (MRHD) on a mg/m^2 basis. There was a dose-related increase of liver adenomas in male mice receiving sertraline at 10-40 mg/kg (0.25-1.0 times the MRHD on a mg/m^2 basis). No increase was seen in female mice or in rats of either sex receiving the same treatments, nor was there an increase in hepatocellular carcinomas. Liver adenomas have a variable rate of spontaneous occurrence in the CD-1 mouse and are of unknown significance to humans. There was an increase in follicular adenomas of the thyroid in female rats receiving sertraline at 40 mg/kg (2 times the MRHD on a mg/m^2 basis); this was not accompanied by thyroid hyperplasia. While there was an increase in uterine adenocarcinomas in rats receiving sertraline at 10-40 mg/kg (0.5-2.0 times the MRHD on a mg/m^2 basis) compared to placebo controls, this effect was not clearly drug related.

Mutagenesis–Sertraline had no genotoxic effects, with or without metabolic activation, based on the following assays: bacterial mutation assay; mouse lymphoma mutation assay; and tests for cytogenetic aberrations *in vivo* in mouse bone marrow and *in vitro* in human lymphocytes.

Impairment of Fertility–A decrease in fertility was seen in one of two rat studies at a dose of 80 mg/kg (4 times the maximum recommended human dose on a mg/m^2 basis).

Pregnancy–Pregnancy Category C–Reproduction studies have been performed in rats and rabbits at doses up to 80 mg/kg/day and 40 mg/kg/day, respectively. These doses correspond to approximately 4 times the maximum recommended human dose (MRHD) on a mg/m^2 basis. There was no evidence of teratogenicity at any dose level. When pregnant rats and rabbits were given sertraline during the period of organogenesis, delayed ossification was observed in fetuses at doses of 10 mg/kg (0.5 times the MRHD on a mg/m^2 basis) in rats and 40 mg/kg (4 times the MRHD on a mg/m^2 basis) in rabbits. When female rats received sertraline during the last third of gestation and throughout lactation, there was an increase in the number of stillborn pups and in the number of pups dying during the first 4 days after birth. Pup body weights were also decreased during the first four days after birth. These effects occurred at a dose of 20 mg/kg (1 times the MRHD on a mg/m^2 basis). The no effect dose for rat pup mortality was 10 mg/kg (0.5 times the MRHD on a mg/m^2 basis). The decrease in pup survival was shown to be due to *in utero* exposure to sertraline. The clinical significance of these effects is unknown.

There are no adequate and well-controlled studies in pregnant women. ZOLOFT® (sertraline hydrochloride) should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Labor and Delivery–The effect of ZOLOFT on labor and delivery in humans is unknown.

Nursing Mothers–It is not known whether, and if so in what amount, sertraline or its metabolites are excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when ZOLOFT is administered to a nursing woman.

Pediatric Use–The efficacy of ZOLOFT for the treatment of obsessive-compulsive disorder was demonstrated in a 12-week, multicenter, placebo-controlled study with 187 outpatients ages 6-17 (see Clinical Trials under CLINICAL PHARMACOLOGY). The efficacy of ZOLOFT in pediatric patients with major depressive disorder, panic disorder, PTSD, PMDD or social anxiety disorder has not been systematically evaluated.

The safety of ZOLOFT use in children and adolescents, ages 6-18, was evaluated in a 12-week, multicenter, placebo-controlled study with 187 outpatients, ages 6-17, and in a flexible dose, 52 week open extension study of 137 patients, ages 6-18, who had completed the initial 12-week, double-blind, placebo-controlled study. ZOLOFT was administered at doses of either 25 mg/day (children, ages 6-12) or 50 mg/day (adolescents, ages 13-18) and then titrated in weekly 25 mg/day or 50 mg/day increments, respectively, to a maximum dose of 200 mg/day based upon clinical response. The mean dose for completers was 157 mg/day. In the acute 12 week pediatric study and in the 52 week study, ZOLOFT had an adverse event profile generally similar to that observed in adults.

Sertraline pharmacokinetics were evaluated in 61 pediatric patients between 6 and 18 years of age with major depressive disorder and/or OCD and revealed similar drug exposures to those of adults when plasma concentration was adjusted for weight (see Pharmacokinetics under CLINICAL PHARMACOLOGY).

More than 250 patients with major depressive disorder and/or OCD between 6 and 18 years of age have received ZOLOFT in clinical trials. The adverse event profile observed in these patients was generally similar to that observed in adult studies with ZOLOFT (see ADVERSE REACTIONS). As with other SSRIs, decreased appetite and weight loss have been observed in association with the use of ZOLOFT. Consequently, regular monitoring of weight and growth is recommended if treatment of a child with an SSRI is to be continued long term. Safety and effectiveness in pediatric patients below the age of 6 have not been established.

The risks, if any, that may be associated with the use of ZOLOFT beyond 1 year in children and adolescents with OCD have not been systematically assessed. The prescriber should be mindful that the evidence relied upon to conclude that sertraline is safe for use in children and adolescents derives from clinical studies that were 12 to 52 weeks in duration and from the extrapolation of experience gained with adult patients. In particular, there are no studies that directly evaluate the effects of long-term

sertraline use on the growth, development, and maturation of children and adolescents. Although there is no affirmative finding to suggest that sertraline possesses a capacity to adversely affect growth, development or maturation, the absence of such findings is not compelling evidence of the absence of the potential of sertraline to have adverse effects in chronic use.

Geriatric Use–U.S. geriatric clinical studies of ZOLOFT in major depressive disorder included 663 ZOLOFT-treated subjects ≥ 65 years of age, of those, 180 were ≥ 75 years of age. No overall differences in the pattern of adverse reactions were observed in the geriatric clinical trial subjects relative to those reported in younger subjects (see ADVERSE REACTIONS), and other reported experience has not identified differences in safety patterns between the elderly and younger subjects. As with all medications, greater sensitivity of some older individuals cannot be ruled out. There were 947 subjects in placebo-controlled geriatric clinical studies of ZOLOFT in major depressive disorder. No overall differences in the pattern of efficacy were observed in the geriatric clinical trial subjects relative to those reported in younger subjects.

Other Adverse Events in Geriatric Patients. In 354 geriatric subjects treated with ZOLOFT in placebo-controlled trials, the overall profile of adverse events was generally similar to that shown in Tables 1 and 2. Urinary tract infection was the only adverse event not appearing in Tables 1 and 2 and reported at an incidence of at least 2% and at a rate greater than placebo in placebo-controlled trials.

As with other SSRIs, ZOLOFT has been associated with cases of clinically significant hyponatremia in elderly patients (see Hyponatremia under PRECAUTIONS).

ADVERSE REACTIONS

During its premarketing assessment, multiple doses of ZOLOFT were administered to over 4000 adult subjects as of February 26, 1998. The conditions and duration of exposure to ZOLOFT varied greatly, and included (in overlapping categories) clinical pharmacology studies, open and double-blind studies, uncontrolled and controlled studies, inpatient and outpatient studies, fixed-dose and titration studies, and studies for multiple indications, including major depressive disorder, OCD, panic disorder, PTSD, PMDD and social anxiety disorder.

Untoward events associated with this exposure were recorded by clinical investigators using terminology of their own choosing. Consequently, it is not possible to provide a meaningful estimate of the proportion of individuals experiencing adverse events without first grouping similar types of untoward events into a smaller number of standardized event categories.

In the tabulations that follow, a World Health Organization dictionary of terminology has been used to classify reported adverse events. The frequencies presented, therefore, represent the proportion of the over 4000 adult individuals exposed to multiple doses of ZOLOFT who experienced a treatment-emergent adverse event of the type cited on at least one occasion while receiving ZOLOFT. An event was considered treatment-emergent if it occurred for the first time or worsened while receiving

therapy following baseline evaluation. It is important to emphasize that events reported during therapy were not necessarily caused by it.

The prescriber should be aware that the figures in the tables and tabulations cannot be used to predict the incidence of side effects in the course of usual medical practice where patient characteristics and other factors differ from those that prevailed in 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 nondrug factors to the side effect incidence rate in the population studied.

Incidence in Placebo-Controlled Trials–Table 1 enumerates the most common treatment-emergent adverse events associated with the use of ZOLOFT (incidence of at least 5% for ZOLOFT and at least twice that for placebo within at least one of the indications) for the treatment of adult patients with major depressive disorder/other*, OCD, panic disorder, PTSD, PMDD and social anxiety disorder in placebo-controlled clinical trials. Most patients in major depressive disorder/other*, OCD, panic disorder, PTSD and social anxiety disorder studies received doses of 50 to 200 mg/day. Patients in the PMDD study with daily dosing throughout the menstrual cycle received doses of 50 to 150 mg/day, and in the PMDD study with dosing during the luteal phase of the menstrual cycle received doses of 50 to 100 mg/day. Table 2 enumerates treatment-emergent adverse events that occurred in 2% or more of adult patients treated with ZOLOFT and with incidence greater than placebo who participated in controlled clinical trials comparing ZOLOFT with placebo in the treatment of major depressive disorder/other*, OCD, panic disorder, PTSD, PMDD and social anxiety disorder. Table 2 provides combined data for the pool of studies that are provided separately by indication in Table 1.

TABLE 1
MOST COMMON TREATMENT-EMERGENT ADVERSE EVENTS: INCIDENCE IN PLACEBO-CONTROLLED CLINICAL TRIALS

	Percentage of Patients Reporting Event							
	Major Depressive Disorder/Other*		OCD		Panic Disorder		PTSD	
Body System/Adverse Event	ZOLOFT (N=861)	Placebo (N=853)	ZOLOFT (N=533)	Placebo (N=373)	ZOLOFT (N=430)	Placebo (N=275)	ZOLOFT (N=374)	Placebo (N=376)
Autonomic Nervous System Disorders								
Ejaculation Failure[1]	7	<1	17	2	19	1	11	1
Mouth Dry	16	9	14	9	15	10	11	6
Sweating Increased	8	3	6	1	5	1	4	2
Centr. & Periph. Nerv. System Disorders								
Somnolence	13	6	15	8	15	9	13	9
Tremor	11	3	8	1	5	1	5	1
Dizziness	12	7	17	9	10	10	8	5
General								
Fatigue	11	8	14	10	11	6	10	5
Pain	1	2	3	1	3	3	4	6
Malaise	<1	1	1	1	7	14	10	10
Gastrointestinal Disorders								
Abdominal Pain	2	2	5	5	6	7	6	5
Anorexia	3	2	11	2	7	2	8	2
Constipation	8	6	6	4	7	3	3	3
Diarrhea/Loose Stools	18	9	24	10	20	9	24	15
Dyspepsia	6	3	10	4	10	8	6	6
Nausea	26	12	30	11	29	18	21	11
Psychiatric Disorders								
Agitation	6	4	6	3	6	2	5	5
Insomnia	16	9	28	12	25	18	20	11
Libido Decreased	1	<1	11	2	7	1	7	2
	PMDD Daily Dosing		PMDD Luteal Phase Dosing[2]		Social Anxiety Disorder			
Body System/Adverse Event	ZOLOFT (N=121)	Placebo (N=122)	ZOLOFT (N=136)	Placebo (N=127)	ZOLOFT (N=344)	Placebo (N=268)		
Autonomic Nervous System Disorders								
Ejaculation Failure[1]	N/A	N/A	N/A	N/A	14	-		
Mouth Dry	6	3	10	3	12	4		
Sweating Increased	6	<1	3	0	11	2		
Centr. & Periph. Nerv. System Disorders								
Somnolence	7	<1	2	0	9	6		
Tremor	2	0	<1	<1	9	3		
Dizziness	6	3	7	5	14	6		
General								
Fatigue	16	7	10	<1	12	6		
Pain	6	<1	3	2	1	3		
Malaise	9	5	7	5	8	3		
Gastrointestinal Disorders								
Abdominal Pain	7	<1	3	3	5	5		
Anorexia	3	2	5	0	6	3		
Constipation	2	3	1	2	5	3		
Diarrhea/Loose Stools	13	3	13	7	21	8		
Dyspepsia	7	2	7	3	13	5		

Nausea	23	9	13	3	22	8		
Psychiatric Disorders								
Agitation	2	<1	1	0	4	2		
Insomnia	17	11	12	10	25	10		
Libido Decreased	11	2	4	2	9	3		

[1]Primarily ejaculatory delay. Denominator used was for male patients only (N=271 ZOLOFT major depressive disorder/other*; N=271 placebo major depressive disorder/other*; N=296 ZOLOFT OCD; N=219 placebo OCD; N=216 ZOLOFT panic disorder; N=134 placebo panic disorder; N=130 ZOLOFT PTSD; N=149 placebo PTSD; No male patients in PMDD studies; N=205 ZOLOFT social anxiety disorder; N=153 placebo social anxiety disorder).
*Major depressive disorder and other premarketing controlled trials.
[2]The luteal phase and daily dosing PMDD trials were not designed for making direct comparisons between the two dosing regimens. Therefore, a comparison between the two dosing regimens of the PMDD trials of incidence rates shown in Table 1 should be avoided.

TABLE 2
TREATMENT-EMERGENT ADVERSE EVENTS:
INCIDENCE IN PLACEBO-CONTROLLED CLINICAL TRIALS
Percentage of Patients Reporting Event
Major Depressive Disorder/Other*, OCD, Panic Disorder, PTSD, PMDD and Social Anxiety Disorder combined

Body System/Adverse Event**	ZOLOFT (N=2799)	Placebo (N=2394)
Autonomic Nervous System Disorders		
Ejaculation Failure[1]	14	1
Mouth Dry	14	8
Sweating Increased	7	2
Centr. & Periph. Nerv. System Disorders		
Somnolence	13	7
Dizziness	12	7
Headache	25	23
Paresthesia	2	1
Tremor	8	2
Disorders of Skin and Appendages		
Rash	3	2
Gastrointestinal Disorders		
Anorexia	6	2
Constipation	6	4
Diarrhea/Loose Stools	20	10
Dyspepsia	8	4
Nausea	25	11
Vomiting	4	2
General		
Fatigue	12	7
Psychiatric Disorders		
Agitation	5	3
Anxiety	4	3
Insomnia	21	11
Libido Decreased	6	2
Nervousness	5	4
Special Senses		
Vision Abnormal	3	2

[1]Primarily ejaculatory delay. Denominator used was for male patients only (N=1118 ZOLOFT; N=926 placebo).

*Major depressive disorder and other premarketing controlled trials.
**Included are events reported by at least 2% of patients taking ZOLOFT except the following events, which had an incidence on placebo greater than or equal to ZOLOFT: abdominal pain, back pain, flatulence, malaise, pain, pharyngitis, respiratory disorder, upper respiratory tract infection.

Associated with Discontinuation in Placebo-Controlled Clinical Trials

Table 3 lists the adverse events associated with discontinuation of ZOLOFT® (sertraline hydrochloride) treatment (incidence at least twice that for placebo and at least 1% for ZOLOFT in clinical trials) in major depressive disorder/other*, OCD, panic disorder, PTSD, PMDD and social anxiety disorder.

TABLE 3
MOST COMMON ADVERSE EVENTS ASSOCIATED WITH DISCONTINUATION IN PLACEBO-CONTROLLED CLINICAL TRIALS

Adverse Event	Major Depressive Disorder/Other*, OCD, Panic Disorder, PTSD, PMDD and Social Anxiety Disorder combined (N=2799)	Major Depressive Disorder/ Other* (N=861)	OCD (N=533)	Panic Disorder (N=430)	PTSD (N=374)	PMDD Daily Dosing (N=121)	PMDD Luteal Phase Dosing (N=136)	Social Anxiety Disorder (N=344)
Abdominal Pain	–	–	–	–	–	–	–	1%
Agitation	–	1%	–	2%	–	–	–	–
Anxiety	–	–	–	–	–	–	–	2%
Diarrhea/ Loose Stools	2%	2%	2%	1%	–	2%	–	–
Dizziness	–	–	1%	–	–	–	–	–
Dry Mouth	–	1%	–	–	–	–	–	–
Dyspepsia	–	–	–	1%	–	–	–	–
Ejaculation Failure[1]	1%	1%	1%	2%	–	N/A	N/A	2%
Fatigue	–	–	–	–	–	–	–	2%
Headache	1%	2%	–	–	1%	–	–	2%
Hot Flushes	–	–	–	–	–	–	1%	–
Insomnia	2%	1%	3%	2%	–	–	1%	3%
Nausea	3%	4%	3%	3%	2%	2%	1%	2%
Nervousness	–	–	–	–	–	2%	–	
Palpitation	–	–	–	–	–	–	1%	–
Somnolence	1%	1%	2%	2%	–	–	–	–
Tremor	–	2%	–	–	–	–	–	–

[1]Primarily ejaculatory delay. Denominator used was for male patients only (N=271 major depressive disorder/other*; N=296 OCD; N=216 panic disorder; N=130 PTSD; No male patients in PMDD studies; N=205 social anxiety disorder).
*Major depressive disorder and other premarketing controlled trials.

Male and Female Sexual Dysfunction with SSRIs
Although changes in sexual desire, sexual performance and sexual satisfaction often occur as manifestations of a psychiatric disorder, they may also be a consequence of pharmacologic treatment. In particular, some evidence suggests that selective serotonin reuptake inhibitors (SSRIs) can cause such untoward sexual experiences. Reliable estimates of the incidence and severity of untoward experiences involving sexual desire, performance and satisfaction are difficult to obtain, however, in part because patients and physicians may be reluctant to discuss them. Accordingly, estimates of the incidence of untoward sexual experience and performance cited in product labeling, are likely to underestimate their actual incidence.

Table 4 below displays the incidence of sexual side effects reported by at least 2% of patients taking ZOLOFT in placebo-controlled trials.

TABLE 4

Adverse Event	ZOLOFT	Placebo
Ejaculation failure* (primarily delayed ejaculation)	14%	1%
Decreased libido**	6%	1%

*Denominator used was for male patients only (N=1118 ZOLOFT; N=926 placebo)
**Denominator used was for male and female patients (N=2799 ZOLOFT; N=2394 placebo)

There are no adequate and well-controlled studies examining sexual dysfunction with sertraline treatment.

Priapism has been reported with all SSRIs.

While it is difficult to know the precise risk of sexual dysfunction associated with the use of SSRIs, physicians should routinely inquire about such possible side effects.

Other Adverse Events in Pediatric Patients–In approximately N=250 pediatric patients treated with ZOLOFT, the overall profile of adverse events was generally similar to that seen in adult studies, as shown in Tables 1 and 2. However, the following adverse events, not appearing in Tables 1 and 2, were reported at an incidence of at least 2% and occurred at a rate of at least twice the placebo rate in a controlled trial (N=187): hyperkinesia, twitching, fever, malaise, purpura, weight decrease, concentration impaired, manic reaction, emotional lability, thinking abnormal, and epistaxis.

Other Events Observed During the Premarketing Evaluation of ZOLOFT® (sertraline hydrochloride)–Following is a list of treatment-emergent adverse events reported during premarketing assessment of ZOLOFT in clinical trials (over 4000 adult subjects) except those already listed in the previous tables or elsewhere in labeling.

In the tabulations that follow, a World Health Organization dictionary of terminology has been used to classify reported adverse events. The frequencies presented, therefore, represent the proportion of the over 4000 adult individuals exposed to multiple doses of ZOLOFT who experienced an event of the type cited on at least one occasion while receiving ZOLOFT. All events are included except those already listed in the previous tables or elsewhere in labeling and those reported in terms so general as to be uninformative and those for which a causal relationship to ZOLOFT treatment seemed remote. It is important to emphasize that although the events reported occurred during treatment with ZOLOFT, they were not necessarily caused by it.

Events are further categorized by body system and listed in order of decreasing frequency according to the following definitions: frequent adverse events are those occurring on one or more occasions in at least 1/100 patients; infrequent adverse events are those occurring in 1/100 to 1/1000 patients; rare events are those occurring in fewer than 1/1000 patients. Events of major clinical importance are also described in the PRECAUTIONS section.

Autonomic Nervous System Disorders–*Frequent:* impotence; *Infrequent:* flushing, increased saliva, cold clammy skin, mydriasis; *Rare:* pallor, glaucoma, priapism, vasodilation.

Body as a Whole–General Disorders–*Rare:* allergic reaction, allergy.

Cardiovascular–*Frequent:* palpitations, chest pain; *Infrequent:* hypertension, tachycardia, postural dizziness, postural hypotension, periorbital edema, peripheral edema, hypotension, peripheral ischemia, syncope, edema, dependent edema; *Rare:* precordial chest pain, substernal chest pain, aggravated hypertension, myocardial infarction, cerebrovascular disorder.

Central and Peripheral Nervous System Disorders–*Frequent:* hypertonia, hypoesthesia; *Infrequent:* twitching, confusion, hyperkinesia, vertigo, ataxia, migraine, abnormal coordination, hyperesthesia, leg cramps, abnormal gait, nystagmus, hypokinesia; *Rare:* dysphonia, coma, dyskinesia, hypotonia, ptosis, choreoathetosis, hyporeflexia.

Disorders of Skin and Appendages–*Infrequent:* pruritus, acne, urticaria, alopecia, dry skin, erythematous rash, photosensitivity reaction, maculopapular rash; *Rare:* follicular rash, eczema, dermatitis, contact dermatitis, bullous eruption, hypertrichosis, skin discoloration, pustular rash.

Endocrine Disorders–*Rare:* exophthalmos, gynecomastia.

Gastrointestinal Disorders–*Frequent:* appetite increased; *Infrequent:* dysphagia, tooth caries aggravated, eructation, esophagitis, gastroenteritis; *Rare:* melena, glossitis, gum hyperplasia, hiccup, stomatitis, tenesmus, colitis, diverticulitis, fecal incontinence, gastritis, rectum hemorrhage, hemorrhagic peptic ulcer, proctitis, ulcerative stomatitis, tongue edema, tongue ulceration.

General–*Frequent:* back pain, asthenia, malaise, weight increase; *Infrequent:* fever, rigors, generalized edema; *Rare:* face edema, aphthous stomatitis.

Hearing and Vestibular Disorders–*Rare:* hyperacusis, labyrinthine disorder.

Hematopoietic and Lymphatic–*Rare:* anemia, anterior chamber eye hemorrhage.

Liver and Biliary System Disorders–*Rare:* abnormal hepatic function.

Metabolic and Nutritional Disorders–*Infrequent:* thirst; *Rare:* hypoglycemia, hypoglycemia reaction.

Musculoskeletal System Disorders–*Frequent:* myalgia; *Infrequent:* arthralgia, dystonia, arthrosis, muscle cramps, muscle weakness.

Psychiatric Disorders–*Frequent:* yawning, other male sexual dysfunction, other female sexual dysfunction; *Infrequent:* depression, amnesia, paroniria, teeth-grinding, emotional lability, apathy, abnormal dreams, euphoria, paranoid reaction, hallucination, aggressive reaction, aggravated depression, delusions; *Rare:* withdrawal syndrome, suicide ideation, libido increased, somnambulism, illusion.

Reproductive–*Infrequent:* menstrual disorder, dysmenorrhea, intermenstrual bleeding, vaginal hemorrhage, amenorrhea, leukorrhea; *Rare:* female breast pain, menorrhagia, balanoposthitis, breast enlargement, atrophic vaginitis, acute female mastitis.

Respiratory System Disorders–*Frequent:* rhinitis; *Infrequent:* coughing, dyspnea, upper respiratory tract infection, epistaxis, bronchospasm, sinusitis; *Rare:* hyperventilation, bradypnea, stridor, apnea, bronchitis, hemoptysis, hypoventilation, laryngismus, laryngitis.

Special Senses–*Frequent:* tinnitus; *Infrequent:* conjunctivitis, earache, eye pain, abnormal accommodation; *Rare:* xerophthalmia, photophobia, diplopia, abnormal lacrimation, scotoma, visual field defect.

Urinary System Disorders–*Infrequent:* micturition frequency, polyuria, urinary retention, dysuria, nocturia, urinary incontinence; *Rare:* cystitis, oliguria, pyelonephritis, hematuria, renal pain, strangury.

Laboratory Tests–In man, asymptomatic elevations in serum transaminases (SGOT [or AST] and SGPT [or ALT]) have been reported infrequently (approximately 0.8%) in association with ZOLOFT® (sertraline hydrochloride) administration. These hepatic enzyme elevations usually occurred within the first 1 to 9 weeks of drug treatment and promptly diminished upon drug discontinuation.

ZOLOFT therapy was associated with small mean increases in total cholesterol (approximately 3%) and triglycerides (approximately 5%), and a small mean decrease in serum uric acid (approximately 7%) of no apparent clinical importance.

The safety profile observed with ZOLOFT treatment in patients with major depressive disorder, OCD, panic disorder, PTSD, PMDD and social anxiety disorder is similar.

Other Events Observed During the Postmarketing Evaluation of ZOLOFT–Reports of adverse events temporally associated with ZOLOFT that have been received since market introduction, that are not listed above and that may have no causal relationship with the drug, include the following: acute renal failure, anaphylactoid reaction, angioedema, blindness, optic neuritis, cataract, increased coagulation times, bradycardia, AV block, atrial arrhythmias, QT-interval prolongation, ventricular tachycardia (including torsade de pointes-type arrhythmias), hypothyroidism, agranulocytosis, aplastic anemia and pancytopenia, leukopenia, thrombocytopenia, lupus-like syndrome, serum sickness, hyperglycemia, , galactorrhea, hyperprolactinemia, neuroleptic malignant syndrome-like events, extrapyramidal symptoms, oculogyric crisis, serotonin syndrome, psychosis, pulmonary hypertension, severe skin reactions, which potentially can be fatal, such as Stevens-Johnson syndrome, vasculitis, photosensitivity and other severe cutaneous disorders, rare reports of pancreatitis, and liver events—clinical features (which in the majority of cases appeared to be reversible with discontinuation of ZOLOFT) occurring in one or more patients include: elevated enzymes, increased bilirubin, hepatomegaly, hepatitis, jaundice, abdominal pain, vomiting, liver failure and death.

DRUG ABUSE AND DEPENDENCE

Controlled Substance Class–ZOLOFT® (sertraline hydrochloride) is not a controlled substance.

Physical and Psychological Dependence–In a placebo-controlled, double-blind, randomized study of the comparative abuse liability of ZOLOFT, alprazolam, and d-amphetamine in humans, ZOLOFT did not produce the positive subjective effects indicative of abuse potential, such as euphoria or drug liking, that were observed with the other two drugs. Premarketing clinical experience with ZOLOFT did not reveal any tendency for a withdrawal syndrome or any drug-seeking behavior. In animal studies ZOLOFT does not demonstrate stimulant or barbiturate-like (depressant) abuse potential. As with any CNS active drug, however, physicians should carefully evaluate patients for history of drug abuse and follow such patients closely, observing them for signs of ZOLOFT misuse or abuse (e.g., development of tolerance, incrementation of dose, drug-seeking behavior).

OVERDOSAGE

Human Experience– Of 1,027 cases of overdose involving sertraline hydrochloride worldwide, alone or with other drugs, there were 72 deaths (circa 1999).

Among 634 overdoses in which sertraline hydrochloride was the only drug ingested, 8 resulted in fatal outcome, 75 completely recovered, and 27 patients experienced sequelae after overdosage to include

alopecia, decreased libido, diarrhea, ejaculation disorder, fatigue, insomnia, somnolence and serotonin syndrome. The remaining 524 cases had an unknown outcome. The most common signs and symptoms associated with non-fatal sertraline hydrochloride overdosage were somnolence, vomiting, tachycardia, nausea, dizziness, agitation and tremor.

The largest known ingestion was 13.5 grams in a patient who took sertraline hydrochloride alone and subsequently recovered. However, another patient who took 2.5 grams of sertraline hydrochloride alone experienced a fatal outcome.

Other important adverse events reported with sertraline hydrochloride overdose (single or multiple drugs) include bradycardia, bundle branch block, coma, convulsions, delirium, hallucinations, hypertension, hypotension, manic reaction, pancreatitis, QT-interval prolongation, serotonin syndrome, stupor and syncope.

Overdose Management–Treatment should consist of those general measures employed in the management of overdosage with any antidepressant.

Ensure an adequate airway, oxygenation and ventilation. Monitor cardiac rhythm and vital signs. General supportive and symptomatic measures are also recommended. Induction of emesis is not recommended. Gastric lavage with a large-bore orogastric tube with appropriate airway protection, if needed, may be indicated if performed soon after ingestion, or in symptomatic patients.

Activated charcoal should be administered. Due to large volume of distribution of this drug, forced diuresis, dialysis, hemoperfusion and exchange transfusion are unlikely to be of benefit. No specific antidotes for sertraline are known.

In managing overdosage, consider the possibility of multiple drug involvement. The physician should consider contacting a poison control center on the treatment of any overdose. Telephone numbers for certified poison control centers are listed in the *Physicians' Desk Reference*® (PDR®).

DOSAGE AND ADMINISTRATION

Initial Treatment

Dosage for Adults

Major Depressive Disorder and Obsessive-Compulsive Disorder–ZOLOFT treatment should be administered at a dose of 50 mg once daily.

Panic Disorder, Posttraumatic Stress Disorder and Social Anxiety Disorder–ZOLOFT treatment should be initiated with a dose of 25 mg once daily. After one week, the dose should be increased to 50 mg once daily.

While a relationship between dose and effect has not been established for major depressive disorder, OCD, panic disorder, PTSD or social anxiety disorder, patients were

dosed in a range of 50-200 mg/day in the clinical trials demonstrating the effectiveness of ZOLOFT for the treatment of these indications. Consequently, a dose of 50 mg, administered once daily, is recommended as the initial therapeutic dose. Patients not responding to a 50 mg dose may benefit from dose increases up to a maximum of 200 mg/day. Given the 24 hour elimination half-life of ZOLOFT, dose changes should not occur at intervals of less than 1 week.

Premenstrual Dysphoric Disorder–ZOLOFT treatment should be initiated with a dose of 50 mg/day, either daily throughout the menstrual cycle or limited to the luteal phase of the menstrual cycle, depending on physician assessment.

While a relationship between dose and effect has not been established for PMDD, patients were dosed in the range of 50-150 mg/day with dose increases at the onset of each new menstrual cycle (see Clinical Trials under CLINICAL PHARMACOLOGY). Patients not responding to a 50 mg/day dose may benefit from dose increases (at 50 mg increments/menstrual cycle) up to 150 mg/day when dosing daily throughout the menstrual cycle, or 100 mg/day when dosing during the luteal phase of the menstrual cycle. If a 100 mg/day dose has been established with luteal phase dosing, a 50 mg/day titration step for three days should be utilized at the beginning of each luteal phase dosing period.

ZOLOFT should be administered once daily, either in the morning or evening.

Dosage for Pediatric Population (Children and Adolescents)
Obsessive-Compulsive Disorder–ZOLOFT treatment should be initiated with a dose of 25 mg once daily in children (ages 6-12) and at a dose of 50 mg once daily in adolescents (ages 13-17).

While a relationship between dose and effect has not been established for OCD, patients were dosed in a range of 25-200 mg/day in the clinical trials demonstrating the effectiveness of ZOLOFT for pediatric patients (6-17 years) with OCD. Patients not responding to an initial dose of 25 or 50 mg/day may benefit from dose increases up to a maximum of 200 mg/day. For children with OCD, their generally lower body weights compared to adults should be taken into consideration in advancing the dose, in order to avoid excess dosing. Given the 24 hour elimination half-life of ZOLOFT, dose changes should not occur at intervals of less than 1 week.

ZOLOFT should be administered once daily, either in the morning or evening.

Dosage for Hepatically Impaired Patients
The use of sertraline in patients with liver disease should be approached with caution. The effects of sertraline in patients with moderate and severe hepatic impairment have not been studied. If sertraline is administered to patients with liver impairment, a lower or less frequent dose should be used (see CLINICAL PHARMACOLOGY and PRECAUTIONS).

Maintenance/Continuation/Extended Treatment

Major Depressive Disorder–It is generally agreed that acute episodes of major depressive disorder require several months or longer of sustained pharmacologic therapy beyond response to the acute episode. Systematic evaluation of ZOLOFT has demonstrated that its antidepressant efficacy is maintained for periods of up to 44 weeks following 8 weeks of initial treatment at a dose of 50-200 mg/day (mean dose of 70 mg/day) (see Clinical Trials under CLINICAL PHARMACOLOGY). It is not known whether the dose of ZOLOFT needed for maintenance treatment is identical to the dose needed to achieve an initial response. Patients should be periodically reassessed to determine the need for maintenance treatment.

Posttraumatic Stress Disorder–It is generally agreed that PTSD requires several months or longer of sustained pharmacological therapy beyond response to initial treatment. Systematic evaluation of ZOLOFT has demonstrated that its efficacy in PTSD is maintained for periods of up to 28 weeks following 24 weeks of treatment at a dose of 50-200 mg/day (see Clinical Trials under CLINICAL PHARMACOLOGY). It is not known whether the dose of ZOLOFT needed for maintenance treatment is identical to the dose needed to achieve an initial response. Patients should be periodically reassessed to determine the need for maintenance treatment.

Social Anxiety Disorder–Social anxiety disorder is a chronic condition that may require several months or longer of sustained pharmacological therapy beyond response to initial treatment. Systematic evaluation of ZOLOFT has demonstrated that its efficacy in social anxiety disorder is maintained for periods of up to 24 weeks following 20 weeks of treatment at a dose of 50-200 mg/day (see Clinical Trials under CLINICAL PHARMACOLOGY). Dosage adjustments should be made to maintain patients on the lowest effective dose and patients should be periodically reassessed to determine the need for long-term treatment.

Obsessive-Compulsive Disorder and Panic Disorder–It is generally agreed that OCD and Panic Disorder require several months or longer of sustained pharmacological therapy beyond response to initial treatment. Systematic evaluation of continuing ZOLOFT for periods of up to 28 weeks in patients with OCD and Panic Disorder who have responded while taking ZOLOFT during initial treatment phases of 24 to 52 weeks of treatment at a dose range of 50-200 mg/day has demonstrated a benefit of such maintenance treatment (see Clinical Trials under CLINICAL PHARMACOLOGY). It is not known whether the dose of ZOLOFT needed for maintenance treatment is identical to the dose needed to achieve an initial response. Nevertheless, patients should be periodically reassessed to determine the need for maintenance treatment.

Premenstrual Dysphoric Disorder–The effectiveness of ZOLOFT in long-term use, that is, for more than 3 menstrual cycles, has not been systematically evaluated in controlled trials. However, as women commonly report that symptoms worsen with age until relieved by the onset of menopause, it is reasonable to consider continuation of a responding patient. Dosage adjustments, which may include changes between dosage regimens (e.g., daily throughout the menstrual cycle versus during the luteal

phase of the menstrual cycle), may be needed to maintain the patient on the lowest effective dosage and patients should be periodically reassessed to determine the need for continued treatment.

Switching Patients to or from a Monoamine Oxidase Inhibitor--At least 14 days should elapse between discontinuation of an MAOI and initiation of therapy with ZOLOFT. In addition, at least 14 days should be allowed after stopping ZOLOFT before starting an MAOI (see CONTRAINDICATIONS and WARNINGS).

ZOLOFT Oral Concentrate

ZOLOFT Oral Concentrate contains 20 mg/mL of sertraline (as the hydrochloride) as the active ingredient and 12% alcohol. ZOLOFT Oral Concentrate must be diluted before use. Just before taking, use the dropper provided to remove the required amount of ZOLOFT Oral Concentrate and mix with 4 oz (1/2 cup) of water, ginger ale, lemon/lime soda, lemonade or orange juice ONLY. Do not mix ZOLOFT Oral Concentrate with anything other than the liquids listed. The dose should be taken immediately after mixing. Do not mix in advance. At times, a slight haze may appear after mixing; this is normal. Note that caution should be exercised for patients with latex sensitivity, as the dropper dispenser contains dry natural rubber.

ZOLOFT Oral Concentrate is contraindicated with ANTABUSE (disulfiram) due to the alcohol content of the concentrate.

HOW SUPPLIED

ZOLOFT® (sertraline hydrochloride) capsular-shaped scored tablets, containing sertraline hydrochloride equivalent to 25, 50 and 100 mg of sertraline, are packaged in bottles.

ZOLOFT® 25 mg Tablets: light green film coated tablets engraved on one side with ZOLOFT and on the other side scored and engraved with 25 mg.

NDC 0049-4960-50	Bottles of 50

ZOLOFT® 50 mg Tablets: light blue film coated tablets engraved on one side with ZOLOFT and on the other side scored and engraved with 50 mg.

NDC 0049-4900-66	Bottles of 100
NDC 0049-4900-73	Bottles of 500
NDC 0049-4900-94	Bottles of 5000
NDC 0049-4900-41	Unit Dose Packages of 100

ZOLOFT® 100 mg Tablets: light yellow film coated tablets engraved on one side with ZOLOFT and on the other side scored and engraved with 100 mg.

NDC 0049-4910-66	Bottles of 100
NDC 0049-4910-73	Bottles of 500
NDC 0049-4910-94	Bottles of 5000
NDC 0049-4910-41	Unit Dose Packages of 100

Store at 25°C (77°F); excursions permitted to 15° - 30°C (59° - 86°F)[see USP Controlled Room Temperature].

ZOLOFT® Oral Concentrate: ZOLOFT Oral Concentrate is a clear, colorless solution with a menthol scent containing sertraline hydrochloride equivalent to 20 mg of sertraline per mL and 12% alcohol. It is supplied as a 60 mL bottle with an accompanying calibrated dropper.

NDC 0049-4940-23	Bottles of 60 mL

Store at 25°C (77°F); excursions permitted to 15° - 30°C (59° - 86°F) [see USP Controlled Room Temperature].

Rx only

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

19-839/S-045

20-990/S-011

APPROVABLE LETTER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 19-839/S-045
NDA 20-990/S-011

Pfizer Inc.
Attention: Alan Dunbar
Regulatory Affairs Department
235 East 42nd Street
New York, NY 10017-5755

Dear Mr. Dunbar:

Please refer to your supplemental new drug applications dated January 18, 2002, received January 22, 2002, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Zoloft® (sertraline hydrochloride) Tablets and Oral Concentrate.

We acknowledge receipt of your submissions dated March 25, June 4, June 25, August 15 and October 28, 2002.

These supplemental new drug applications provide for the use of Zoloft® Tablets and Oral Concentrate for social anxiety disorder.

We have completed the review of these applications, as submitted with the draft labeling, and they are approvable. Before these application may be approved, however, it will be necessary for you to address the following:

Clinical Issues

Please provide documentation for the change in the analysis plan for the longer-term trial.

Labeling Issues

Accompanying this letter as an attachment is our proposal for the labeling of Zoloft® Tablets and oral concentrate for the social anxiety disorder indication. Please submit revised draft labeling identical in content to the enclosed labeling (text for the package insert) along with labeling changes due to recent approvals for premenstrual dysphoric disorder, relapse prevention of obsessive compulsive disorder and panic disorder, and the pimozide drug interaction language. Explanations for our proposed changes are provided in the bracketed comments embedded within the proposed text. We are willing to discuss these proposed changes in more detail through a teleconference if you wish.

Safety Update

Under 21 CFR 314.50(d)(vi)(b), we request that you provide a final safety update for Zoloft® for social anxiety disorder.

Regulatory Status Update

Please provide any new information on the worldwide regulatory status of Zoloft® for social anxiety disorder, including the status of all actions either taken or pending before foreign regulatory authorities.

World Literature Update

Prior to the approval of Zoloft® for social anxiety disorder, we will require an updated report on the world archival literature pertaining to the safety of this product for this indication.

In addition, all previous revisions as reflected in the most recently approved labeling must be included. To facilitate review of your submission, please provide a highlighted or marked-up copy that shows the changes that are being made.

If additional information relating to the safety or effectiveness of this drug becomes available, revision of the labeling may be required.

Within 10 days after the date of this letter, you are required to amend the supplemental applications, notify us of your intent to file an amendment, or follow one of your other options under 21 CFR 314.110. In the absence of any such action FDA may proceed to withdraw the applications. Any amendment should respond to all the deficiencies listed. We will not process a partial reply as a major amendment nor will the review clock be reactivated until all deficiencies have been addressed.

Under 21 CFR 314.102(d) of the new drug regulations, you may request an informal meeting or telephone conference with this division to discuss what further steps need to be taken before the application may be approved.

This product may be considered to be misbranded under the Federal Food, Drug, and Cosmetic Act if it is marketed with these changes prior to approval of this supplemental application.

If you should have any questions, please call Ms. Anna Marie H. Weikel, R.Ph., Regulatory Affairs Manager, at (301) 594-5535.

Sincerely,

{See appended electronic signature page}

Russell Katz, M.D.
Director
Division of Neuropharmacological Drug Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

Enclosure

31 Page(s) Withheld

_____ § 552(b)(4) Trade Secret / Confidential

✓ § 552(b)(4) Draft Labeling

_____ § 552(b)(5) Deliberative Process

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

19-839/S-045

20-990/S-011

MEDICAL REVIEW

Supplemental NDA 19,839-(SEI-045/SEI-011):

Sertraline in the Treatment of Social Phobia

Sponsor:	Pfizer Pharmaceuticals Group
Drug:	Sertraline (ZOLOFT)
Material Submitted:	Response to Approvable Letter
Correspondence Date:	December 11, 2002
Date Received:	December 12, 2002
Drug Category:	Antidepressant; SSRI
Forms available for indication:	Sertraline HCl Tablets & Oral Concentrate
Related IND:	20,990

I. Background & Summary

The sponsor has responded to the approvable letter dated November 18, 2002, regarding the supplemental NDA for the use of sertraline in treatment of Social Phobia. The Division requested responses and information pertaining to: 1) suggested changes in labeling; 2) a safety profile update; and 3) a Worldwide literature update. The sponsor has also submitted a Worldwide regulatory status update. In summary, the sponsor has responded fully and adequately, incorporating in labeling the Division's recommendations. Together, the safety update and the Worldwide literature update do not indicate that there are any new or unexpected safety concerns associated with the use of sertraline in patients with Social Phobia.

II. Specific Items

A. Labeling Changes

The sponsor has accepted and included all of the Division's recommendations for changes in labeling. Relevant sections of the final label include: Clinical Trials, PRECAUTIONS, Adverse Events (tables), and Drug Metabolism. The changes reflect the data from the trials which have been submitted to the Division.

B. Safety Update

The final safety update for this sNDA includes data obtained for the period, October 17, 2001 through November 19, 2002. The Pfizer clinical trials database was reviewed using the search terms: social phobia and social anxiety disorder. There are no new Pfizer-sponsored studies to report that have not already been included in the original sNDA submission. No clinical studies on the use of sertraline in social anxiety disorder have been completed since October 16, 2001. There are no ongoing studies of Zoloft in Social Anxiety Disorder.

Deaths and Serious Adverse Events

Pfizer's early alert safety database was reviewed for cases reported from sources other than clinical trials (registries, spontaneous reports, literature and solicited reports). No reports of deaths (occurring during the clinical use of sertraline in Social Anxiety Disorder) have been filed into the safety database. A total of 2 serious adverse events have been reported. In one case, a 12-year-old male experienced a seizure after having taken sertraline 50mg/day for approximately 2 months. The patient had no history of seizure disorder and was reported to have had a normal EEG and CT scan after the seizure. Sertraline was discontinued, and no further seizures were reported. Case A213684 involved a newborn male with congenital malformations (agenesis of the left fifth finger, atrophic left thumb, and deformity of the musculature of the left forearm). His mother had taken sertraline (dose unknown) for approximately 18 months before discontinuing treatment 4 ½ months prior to delivery. Information provided for these two cases was limited.

C. Worldwide Literature Update

The sponsor conducted a review of the Worldwide literature from October 17, 2001 through November 19, 2002 on the use and safety of sertraline in the treatment of social anxiety disorder, using five commercial databases: Medline, Embase, PsycINFO, Biosis Previews and SciSearch. The search terms included the following: sertraline, Zoloft, social, phobia, social phobia, anxiety,social anxiety, social anxiety disorder, anxiety disorder. Original articles, review articles, case reports, letters, and book chapters were reviewed to identify publications that contain original

data pertaining to the safety of sertraline for Social Anxiety Disorder. The search identified no publications that met these criteria. Therefore, there has been no published original data on the safety of sertraline for social anxiety disorder since the literature search of October 16, 2001, which was reported in the Zoloft social anxiety disorder sNDA submission of January 18, 2002.

D. Worldwide Regulatory Status Update

The sponsor provided information about the Worldwide Regulatory Status of sertraline for Social Anxiety Disorder as of November 19, 2002. This information was not available at the time of the sNDA filing. Since November 29, 2001, sertraline has been approved for Social Anxiety Disorder in 16 countries (Brazil, Bulgaria, Costa Rica, El Salvador, Estonia, Guatemala, Guyana, Haiti, Honduras, Latvia, Mexico, New Zealand, Nicaragua, Panama, Romania, and Thailand). In some Central American countries, regulatory authority approval is based upon study publication rather than submission filing, thereby accounting for earlier dates of submission and approval.

The following is a complete list of countries in which the Sertraline & Social Anxiety Disorder Submission is under review: [redacted]

[redacted] On November 18, 2002, the pertinent regulatory authority in [redacted] submitted queries to Pfizer about the submission. As of November 19, 2002, no applications filed worldwide for Social Anxiety Disorder (Social Phobia) have been rejected (not approved) by the regulatory authority.

III. Recommendations & Conclusions

The sponsor has responded fully and appropriately to the approvable letter. I recommend that the Division take an approval action on this supplemental NDA.

Robert L. Levin, M.D., January 17, 2003
Medical Reviewer,
FDA, CDER, ODE1, DNDP, HFD 120

cc: HFD 120
T Laughren
P Andreason
AM Homonnay-Weikel

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/s/

Robert Levin
1/17/03 03:54:33 PM
MEDICAL OFFICER

Thomas Laughren
1/22/03 08:55:30 AM
MEDICAL OFFICER
I agree that this supplement can now be approved; see memo to file for more detailed comments.--TPL

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Review and Evaluation of Clinical Data

SNDA 19,839-(SEI-045)

Sertraline in the Treatment of Social Phobia

SPONSOR:	PFIZER
Drug:	Sertraline (ZOLOFT)
Material Submitted:	Supplemental NDA; Electronic Documents
Correspondence Date:	December 7, 2001
Date Received:	December 10, 2001
Drug Category:	SSRI
Forms available for proposed study:	Sertraline HCl Tablets & Oral Concentrate
Related IND:	20,990

Robert Levin, M.D.
Medical Reviewer
Division of Neuropharmacological Drug Products
HFD-120
October 23, 2002

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Executive Summary

I. Recommendations

I recommend that the Division take an approvable action for supplemental NDA 19,839/SEI-045. The sponsor seeks claims indicating sertraline for the acute and maintenance treatment of Generalized Social Phobia.

II. Summary of Clinical Findings

A. Brief Overview of Submission

Safety and efficacy data from 3 trials of sertraline in Social Phobia were reviewed. These included 2 trials of sertraline in acute treatment of Social Phobia (Studies R- 0601 and Study STL-NY-94-004) and one trial (STL-NY-94-004) of sertraline in maintenance treatment (relapse prevention) of Social Phobia. Safety data were also reviewed from a third acute treatment trial (Study STL-NY-94-003) of sertraline in Social Phobia. This was a Phase IV study designed and conducted for publication purposes. The study has been included in the application as additional information pertaining to the safety and efficacy of sertraline in the treatment of Social Phobia; it is not considered by the sponsor as supportive of the indication claim. As such, the results were submitted as an abbreviated report.

B. Efficacy Findings

1. Efficacy in Acute Treatment of Social Phobia

Data from two controlled clinical trials demonstrated the efficacy of sertraline (50-200 mg daily) in improving the symptoms of social phobia. In the first study (R-0601), sertraline was statistically significantly superior to placebo with respect to both primary efficacy measures: (1) percentage of responders defined by a Clinical Global Impression of Improvement (CGI-I) < 2, and (2) the Liebowitz Social Anxiety Scale (LSAS) total score. The higher percentage of treatment responders, (defined as subjects with a CGI-I rating of 1 or 2), in the sertraline treatment group (46.8%) versus the placebo group (25.5%) was statistically significant ($p = 0.001$) from the end of Week 6 through the end of the study. The greater degree of improvement in sertraline-treated subjects' LSAS total scores (-31.3/1.87%) compared to that in placebo-treated subjects (-21.4/1.90%) was statistically significant ($p = 0.001$) from Week 8 through the end of the study. The results provide evidence that sertraline had a significant treatment effect on core features of social phobia, which include fear and avoidance of social and performance situations.

In the second study (STL-NY-94-004), sertraline was statistically significantly superior to placebo on all primary efficacy measures, including percentage of responders (defined by a CGI-I < 2), the Duke Brief Social Phobia Scale (BSPS) total and factor scores, BSPS fear, avoidance, and physiologic factor scores, and the Marks Fear Questionnaire Social Phobia (FQ-SPS) total score. At endpoint in Study STL-NY-94-004, there were statistically significant differences between treatment groups in favor of sertraline for all primary efficacy parameters:1) percentage of treatment responders (53% versus 29%; $p = 0.001$); 2) change in Duke BSPS total score (-16.44 versus –8.56; $p = 0.001$); 3) changes

in BSPS fear (-6.61 versus –3.07; p = 0.001), 4) avoidance (-6.65 versus –3.40; p = 0.001); and 5) physiologic factor (-3.16 versus –2.09; p = 0.016) subscale scores; and 4) Marks Fear Questionnaire Social Phobia Subscale (FQ-SPS) total score. These findings also provide evidence that sertraline-treated subjects, (compared to placebo-treated subjects), experienced significantly greater improvements in core features of social phobia: fear and avoidance of social and performance situations, anxiety or distress upon exposure to such situations, and interference with functioning in vocational and social situations. The combined analysis of these two acute treatment trials demonstrates an almost two-fold increase in subjects' response rate to sertraline compared with placebo, and it indicates that the superior efficacy of sertraline began as early as Week 8 and lasted until Week 20, the final visit week of Study STL-NY-94-004.

2. Efficacy in Maintenance Treatment of Social Phobia

Results of Study STL-NY-94-004C provide evidence that sertraline was effective in the long-term (up to 44 weeks) treatment of Social Phobia, as demonstrated by a significantly lower rate of relapse in subjects treated with sertraline compared with subjects treated with placebo. The continuation study demonstrated that the tapering and discontinuation of sertraline, following 20 weeks of successful, double-blind treatment with sertraline, resulted in a significantly greater chance of relapsing during an additional 24-week double-blind period of placebo treatment than did continuation of sertraline treatment. In Study 004C, for the rates of subjects experiencing relapse, there was a significantly smaller proportion of subjects who relapsed in the sertraline/sertraline group (1/25; 4%) than in the sertraline/placebo group (9/25; 36%) [p = 0.005].

Relapse was defined by having either: a) a CGI-S score $\geq$ 2 points higher than at baseline or b) discontinuation from the study due to lack of efficacy. The majority of subjects (9/10; 90%) met relapse criteria as a result of discontinuing from the study due to lack of efficacy. One subject in the sertraline/placebo group met relapse criteria on the basis of having a 2-point increase in CGI-S. For rates of subjects with CGI-S score $\geq$ 2 points higher than at baseline, there was no significant difference at any time point between the sertraline/sertraline and sertraline/placebo or between the sertraline/sertraline and placebo/placebo groups. For rates of subjects who discontinued due to lack of efficacy, there were significantly fewer sertraline/sertraline (1/25; 4%) than sertraline/placebo (8/25; 32%) subjects who discontinued due to a lack of efficacy at the end of Weeks 8, 12, 16, 20, and 24.

Time to Relapse

Survival analysis demonstrated that there was a statistically significantly longer time to relapse for subjects in the sertraline/sertraline group as compared to the sertraline/placebo group (log-rank test p = 0.001)

Potential Effect of SSRI Discontinuation Syndrome in Study 004C

Analysis of the timing of "relapses" among placebo-treated subjects suggests that the subjects experienced a recurrence of anxiety disorder as opposed to SSRI discontinuation syndrome. However, it must be noted that narrative descriptions of events for these subjects was not available for the current review.

3. Subgroup Analysis
Subgroup analyses did not suggest differences in treatment outcome on the basis of gender. There was insufficient information to determine the effect of race or age on outcome.

Safety Findings
Safety results of 3 acute treatment trials and 1 maintenance treatment trial of sertraline in Social Phobia support the conclusion that sertraline, in doses between 50-200 mg/day, is reasonably safe and well tolerated by subjects with Social Phobia, for up to 44 weeks. No significant medical concerns or adverse events were identified in subjects with Social Phobia that had not been identified in safety profiles of sertraline in the treatment of subjects with Major Depression, Obsessive-Compulsive Disorder, Panic Disorder, and Post-Traumatic Stress Disorder. The adverse events that occurred in the Social Phobia studies had been reported in the current Zoloft product label. There were no deaths reported in studies, and there were no serious adverse events or adverse events associated with study discontinuation which were unexpected or drug-related and unlabeled.

In studies 601 and 004, adverse events that occurred in at least 5% of sertraline-treated subjects and with a rate at least twice that seen in placebo-treated subjects were insomnia, nausea, diarrhea, dizziness, dyspepsia, libido decreased (male), ejaculation disorder, dry mouth, fatigue, increased sweating, tremor, influenza-like symptoms, and anorexia.
In the maintenance treatment study, (in which some subjects were treated with sertraline continuously for up to 44 weeks), the adverse event profile was similar to that observed in the acute, controlled studies. The adverse events that occurred in at least 5% of sertraline/sertraline-treated subjects and at a rate at least two times that in any other group were influenza-like symptoms, dizziness, headache, insomnia, dyspepsia, upper respiratory tract infection, abdominal pain, nausea, dysmenorrhea, coughing, and rash. With the exception of decreased libido, which occurred in 13% of sertraline-treated males compared with 2% of sertraline-treated females, there did not appear to be any clinically significant differences in the safety profile of sertraline on the basis of gender. Because the subject population was predominantly white and less than 65 years of age, data were not analyzed according to race or age.

In studies 601, 004, 004C, 003, sertraline had no clinically important effect on vital signs or body weight. No subjects discontinued due to clinically significant changes in vital signs or body weight. In Study 601, there were no clinically significant changes in electrocardiograms and no unusual or unexpected laboratory test results. No subject discontinued due to a laboratory test or ECG abnormality.

D. Dosage and Administration

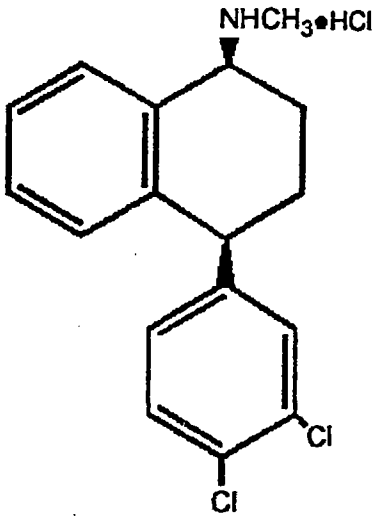
The sponsor states that treatment with sertraline should be initiated with a dose of 25 mg once daily. After one week, the dose should be increased to 50 mg once daily. While a relationship between dose and effect has not been established for Social Phobia, patients were dosed in a range of 50-200 mg/day in the clinical trials demonstrating the effectiveness of sertraline for the treatment of this condition. Thus, a dose of 50 mg, administered once daily, is recommended as the initial therapeutic dose. Patients who do not respond to a 50 mg dose may benefit from dose increases up to a maximum of 200 mg/day. Given the 24-hour elimination half-life of sertraline, dose changes should not occur at intervals of less than 1 week. Sertraline should be administered once daily, either in the morning or evening.

Clinical Review

I. Introduction and Background

A. Drug Established and Proposed Trade Name, Drug Class, Sponsor's Proposed Indication(s), Dose, Regimens, Age Group

ZOLOFT® (sertraline hydrochloride) is a selective serotonin reuptake inhibitor (SSRI) for oral administration. It has a molecular weight of 342.7. Sertraline hydrochloride has the following chemical name: (1S-cis)-4-(3,4-dichlorophenyl)-1,2,3,4-tetrahydro-N-methyl-1-naphthalenamine hydrochloride. The empirical formula C17H17NCl2·HCl is represented by the following structural formula:



Proposed Indications:

1. _____

2. _____

Dosage and Administration

The sponsor states that treatment with sertraline should be initiated with a dose of 25 mg once daily. After one week, the dose should be increased to 50 mg once daily. While a relationship between dose and effect has not been established for Social Phobia, patients were dosed in a range of 50-200 mg/day in the clinical trials demonstrating the effectiveness of sertraline for the treatment of this condition. Thus, a dose of 50 mg, administered once daily, is recommended as the initial therapeutic dose. Patients who do not respond to a 50 mg dose may benefit from dose increases up to a maximum of 200 mg/day. Given the 24-hour elimination half-life of sertraline, dose changes should not

occur at intervals of less than 1 week. Sertraline should be administered once daily, either in the morning or evening.

B. State of Armamentarium for the Proposed Indication

Paroxetine has been approved in the U.S. to treat Social Phobia. Paroxetine and other compounds, including moclobemide and citalopram, have been approved in various other countries for the treatment of Social Phobia.

C. Important Milestones in Product Development

On December 30, 1991, sertraline was approved for the treatment of Major Depression. Supplemental NDAs for the use of sertraline in the treatment of Obsessive-Compulsive Disorder (OCD), Panic Disorder, and Post-Traumatic Stress Disorder (PTSD) were approved on October 25, 1996, July 8, 1997 and December 7, 1999, respectively. Sertraline's use in pediatric OCD was approved on October 10, 1997. A liquid oral concentrate (LOC) formulation was approved on December 7, 1999. The Social Phobia studies were conducted from August 29, 1996 through February 27, 1998.

D. Division Interactions with the Sponsor

During the June 8, 1999 pre-SNDA meeting, the sponsor presented its sertraline and Social Phobia program. Two placebo-controlled, multi-center studies were described in support of registration for the social phobia indication claim. Study STL-NY-94-004 was conducted in Canada, and Study STL-N/S-95-003 was conducted in Norway and Sweden. It was agreed that the submission of studies utilizing differing primary outcome measures in Social Phobia constituted an acceptable registration package. Two other studies were introduced: 1) Study R-0601, a placebo-controlled, multi-center study to be conducted in the US, and 2) Study STL-NY-94-004C, a completed relapse prevention study which was an extension of STL-NY-94-004C. The Division suggested that the sponsor carefully evaluate the study conduct and data management of the non-U.S. studies (004 and 003) relative to FDA regulatory compliance standards.

On November 8, 2001, a teleconference was held with the sponsor to discuss the contents of a briefing document, (submitted to the Division on October 26, 2001), that described the Sertraline & Social Phobia filing package. The studies providing primary support for registration of the Social Phobia indication claim were stated to be Studies R-601 and 004. Study 004C would be submitted in support of relapse prevention. Based on the Division's guidance from the June 8, 1999 meeting, the sponsor decided that Study STL-N/S-95-003 would not be submitted as a pivotal trial. The briefing document provided bioequivalence information regarding the research capsule used in studies 004 and 004C, and it documented the sponsor's intention to market the current commercial tablet for the Social Phobia indication. The Division agreed that the filing package, as described in the briefing document, was acceptable and requested that Pfizer provide the original bioequivalence study report results (Studies 006, 008 and 009) as part of the submission. The bioequivalence study reports were provided and reviewed.

E. Brief Description of the Submission

The current submission includes safety and efficacy data from: a) two double-blind, placebo-controlled clinical trials (R-0601 and STL-NY-94-004) of sertraline in the acute treatment of Social Phobia (Social Anxiety Disorder), and b) one placebo-controlled, randomized withdrawal study (STL-NY-94-004C), which investigated relapse prevention in Social Phobia subjects who had responded to sertraline and completed the acute, double-blind, placebo-controlled trial, STL-NY-94-004. Safety data from a third acute treatment trial in Social Phobia (STL-N/S-003) have been submitted as well.

II. Clinical Pharmacokinetics and Pharmacodynamics of Sertraline

No new pharmacokinetic/pharmacodynamic data was provided in this submission. For details regarding clinical PK and PD profiles of sertraline, please refer to other reviews of NDAs and SNDAs 19,839.

III. Description of Clinical Data and Sources

A. Overall Data

1. Safety and efficacy data from 3 trials of sertraline in Social Phobia were reviewed. These included 2 trials of sertraline in acute treatment of Social Phobia (Studies R-0601 and Study STL-NY-94-004) and one trial (STL-NY-94-004) of sertraline in maintenance treatment (relapse prevention) of Social Phobia.

2. Safety data were also reviewed from a third trial (Study STL-NY-94-003) of sertraline in acute treatment of Social Phobia. This was a Phase IV study designed and conducted for publication purposes. The study has been included in this application as additional information pertaining to the safety and efficacy of sertraline in the treatment of social phobia and is not considered supportive to the indication claim. As such, the results were submitted as an abbreviated report. Although efficacy data from Study 003 have not been formally submitted or reviewed, the results of the study have been published and will be summarized in this review.

B. Tables Listing the Clinical Trials Reviewed

1. Review of Efficacy and Safety: 2 Trials in Acute Treatment of Social Phobia

Protocol #	Study Design	Sertraline Dosage (qd)	Safety Evaluable N Sertraline/Placebo	Primary Efficacy Measures
R-0601 Multicenter 20 US sites	Randomized Double-blind Placebo-controlled Parallel group Flexible-dose 12 weeks double-blind treatment 1 week single-blind placebo run-in Up to 2 weeks taper period	25 mg/day for first week of double-blind treatment 50-200 mg/day thereafter AM or PM dosing (at same time every day)	209/199	CGI-I, LSAS
STL-NY-94-004 Multicenter 10 Canadian sites	Randomized Double-blind Placebo-controlled Parallel group Flexible dosing 20 weeks double-blind treatment 1 week single-blind placebo run-in	50 mg/day during Weeks 1-4 50-200 mg/day thereafter AM or PM dosing (at same time every day)	135/69	CGI-I, BSPS, FQ-SPS

2. Review of Efficacy and Safety: 1 Trial in Relapse Prevention of Social Phobia

Protocol #	Study Design	Sertraline Dosage (qd)	Safety Evaluable N	Primary Efficacy Measures
STL-NY-94-004C Multicenter 10 Canadian sites	Randomized Double-blind Placebo-controlled Parallel group Relapse prevention extension of STL-NY-94-004 24 weeks double-blind treatment	The dosage level attained at the end of STL-NY-94-004 (50-200 mg/day) was maintained in the absence of limiting adverse events. PM dosing (may switch to AM dosing)	Sertraline/Sertraline 25 Sertraline/Placebo 25 Placebo/Placebo 15	CGI-I, CGI-S, BSPS, FQ-SPS

3. Review of Safety Only: Phase IV, Study STL-N/S-95-003 Acute Treatment of Social Phobia

Protocol #	Study Design	Sertraline Dosage (qd)	Safety Evaluable N Sertraline/Placebo	Primary Efficacy Measures
STL-N/S-95-003 Multicenter 47 Norwegian/Swedish sites	Randomized Double-blind Placebo-controlled Parallel-group Flexible-dose	50 mg/day during Weeks 1-4 50-150 mg/day thereafter PM dosing (may switch to AM) dosing)	196/191	CGI-I, SPS

C. Post-marketing Experience

Sertraline has not been marketed in any country for the treatment of Social Phobia, and there are currently no applications outside the U.S pending for this indication. As of November 2001, sertraline has beenapproved in 92 countries for the treatment of depression, 75 countries for the treatment of OCD(66 countries for pediatric OCD), 59 countries for the treatment of panic disorder, 49 countriesfor the treatment of PTSD, 12 countries for the treatment of depression with anxiety, and one country for the treatment of pre-menstrual dysphoric disorder.

D. Worldwide Literature Review

A review of the worldwide literature through October 16, 2001 on the use of sertraline in the treatment of Social Phobia was conducted using five commercial databases: Medline, Embase, PsycINFO, Biosis Previews and SciSearch. The search included the following terms: sertraline, Zoloft, social, phobia, social phobia, anxiety, social anxiety, social anxiety disorder, anxiety disorder. Original articles, review articles, case reports, letters, and book chapters were reviewed to identify publications that contain original data on sertraline treatment of social phobia. The search identified 13 articles and letters that met these criteria. The articles were published during the period of 1993 through October 16, 2001. In summary, the review of the worldwide literature for the use of sertraline in social phobia did not reveal any new or unexpected safety concerns that would be unique to patients with Social Phobia. The table below summarizes the published studies.

Table. Summary of Published Studies on Sertraline in Social Phobia

Study Type	Number of Studies	Number of Subjects	Sertraline Dose	Duration of Treatment
Placebo-controlled	4	12-385	50-200 mg	10-24 weeks
Open-label	5	11-22	25-200mg	4-12 weeks
Case reports	4	1-2	50-200 mg	12-52+

IV. Clinical Review Methods

A. How the Review was Conducted

The safety and efficacy analyses were conducted by reviewing the sources of information described in sections **V.A.** and **V.B.** Results of the analyses were compared with those conducted by the sponsor. The reviewer consulted with reviewers from other disciplines, including Biometrics, Biopharmaceutics, and the Division of Scientific Investigations.

B. Overview of Materials Consulted in Review

Please refer to Sections **V.A.** and **V.B.**

C. Overview of Methods Used to Evaluate Data Quality and Integrity

Methods used included detailed review of all data submitted in the supplemental NDA and consultation with disciplines mentioned above.

D. Were Trials Conducted in Accordance with Accepted Ethical Standards?

The sponsor documents that protocols STL-NY-94-004 and STL-NY-94-004C were conducted in Canada in conformity with Canadian laws and regulations and the 1989 Declaration of Helsinki, and accordingly, were filed with the Canadian Health Protection Branch. Study R-601 was conducted in the U.S. in accordance with U.S. regulations and the 1989 Declaration of Helsinki. The investigators provided written documentation that the study protocol, protocol amendments, and informed consent form were approved by all appropriate Institutional Review Boards. In addition, any advertisements used to recruit patients were reviewed and approved in their final form by the IRB. All printed information was also approved by the IRB. A list of the IRBs is provided in the submission.

Subject Information and Informed Consent Documentation

Written, informed consent was obtained before any study-related procedures were initiated and/or performed. Consent was documented on the Informed Consent Form (ICF) by the subject's dated signature and the dated signature of the investigator who conducted the informed consent discussion. The sponsor provided a sample ICF. The final ICF was approved by the sponsor and IRBs and contained all the elements contained in the sponsor's sample form, in plain language readily understood by subjects. The investigator retained the original, signed and dated ICF; a copy was given to the subject.

E. Evaluation of Financial Disclosure

The sponsor has provided documentation of financial disclosure. There are no discernable indications of conflict of interest that would impact the integrity of the outcomes of the studies.

V. Integrated Review of Efficacy

A. Brief Statement of Conclusions

Efficacy in Acute Treatment of Social Phobia

Data from two controlled clinical trials demonstrated the efficacy of sertraline (50-200 mg daily) in improving the symptoms of social phobia. In the first study (R-0601), sertraline was statistically significantly superior to placebo with respect to both primary efficacy measures: (1) percentage of responders defined by a Clinical Global Impression of Improvement (CGI-I) < 2, and (2) the Liebowitz Social Anxiety Scale (LSAS) total score. The higher percentage of treatment responders, (defined as subjects with a CGI-I rating of 1 or 2), in the sertraline treatment group (46.8%) versus the placebo group (25.5%) was statistically significant ($p = 0.001$) from the end of Week 6 through the end of the study. The greater degree of improvement in sertraline-treated subjects' LSAS total scores (-31.3/1.87%) compared to that in placebo-treated subjects (-21.4/1.90%) was statistically significant ($p = 0.001$) from Week 8 through the end of the study. The results provide evidence that sertraline had a significant treatment effect on core features of social phobia, which include fear and avoidance of social and performance situations.

In the second study (STL-NY-94-004), sertraline was statistically significantly superior to placebo on all primary efficacy measures, including percentage of responders (defined by a CGI-I < 2), the Duke Brief Social Phobia Scale (BSPS) total and factor scores, BSPS fear, avoidance, and physiologic factor scores, and the Marks Fear Questionnaire Social Phobia (FQ-SPS) total score. At endpoint in Study STL-NY-94-004, there were statistically significant differences between treatment groups in favor of sertraline for all primary efficacy parameters:1) percentage of treatment responders (53% versus 29%; $p = 0.001$); 2) change in Duke BSPS total score (-16.44 versus –8.56; $p = 0.001$); 3) changes in BSPS fear (-6.61 versus –3.07; $p = 0.001$), 4) avoidance (-6.65 versus –3.40; $p = 0.001$); and 5) physiologic factor (-3.16 versus –2.09; $p = 0.016$) subscale scores; and 4) Marks Fear Questionnaire Social Phobia Subscale (FQ-SPS) total score. These findings also provide evidence that sertraline-treated subjects, (compared to placebo-treated subjects), experienced significantly greater improvements in core features of social phobia: fear and avoidance of social and performance situations, anxiety or distress upon exposure to such situations, and interference with functioning in vocational and social situations. The combined analysis of these two acute treatment trials demonstrates an almost two-fold increase in subjects' response rate to sertraline compared with placebo, and it indicates that the superior efficacy of sertraline began as early as Week 8 and lasted until Week 20, the final visit week of Study STL-NY-94-004.

Efficacy in Maintenance Treatment of Social Phobia
Results of Study STL-NY-94-004C provide evidence that sertraline was effective in the long-term (up to 44 weeks) treatment of Social Phobia, as demonstrated by a significantly lower rate of relapse in subjects treated with sertraline compared with subjects treated with placebo. The continuation study demonstrated that the tapering and discontinuation of sertraline, following 20 weeks of successful, double-blind treatment with sertraline, resulted in a significantly greater chance of relapsing during an additional 24-week double-blind period of placebo treatment than did continuation of sertraline treatment. In Study 004C, for the rates of subjects experiencing relapse, there was a significantly smaller proportion of subjects who relapsed in the sertraline/sertraline group (1/25; 4%) than in the sertraline/placebo group (9/25; 36%) [p = 0.005].

Relapse was defined by having either: a) a CGI-S score $\geq$ 2 points higher than at baseline or b) discontinuation from the study due to lack of efficacy. The majority of subjects (9/10; 90%) met relapse criteria as a result of discontinuing from the study due to lack of efficacy. One subject in the sertraline/placebo group met relapse criteria on the basis of having a 2-point increase in CGI-S. For rates of subjects with CGI-S score $\geq$ 2 points higher than at baseline, there was no significant difference at any time point between the sertraline/sertraline and sertraline/placebo or between the sertraline/sertraline and placebo/placebo groups. For rates of subjects who discontinued due to lack of efficacy, there were significantly fewer sertraline/sertraline (1/25; 4%) than sertraline/placebo (8/25; 32%) subjects who discontinued due to a lack of efficacy at the end of Weeks 8, 12, 16, 20, and 24

Time to Relapse
Survival analysis demonstrated that there was a statistically significantly longer time to relapse for subjects in the sertraline/sertraline group as compared to the sertraline/placebo group (log-rank test p = 0.001)

Potential Effect of SSRI Discontinuation Syndrome
Analysis of the timing of "relapses" among placebo-treated subjects suggests that the subjects experienced a recurrence of anxiety disorder as opposed to SSRI discontinuation syndrome. However, it must be noted that narrative descriptions of events for these subjects was not available for the current review.

Subgroup Analysis
Subgroup analyses in all studies reviewed did not suggest differences in treatment outcome on the basis of gender. There was insufficient information to determine the effect of race or age on outcome.

B. General Approach to Review of the Efficacy of the Drug
Efficacy data from the 2 pivotal acute treatment trials and the single relapse prevention study were reviewed in detail. The analysis results obtained by the clinical and biometrics reviewers were compared with the sponsor's efficacy analyses

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C. Detailed Review of Trials by Indication

1-Investigators and Sites
Refer to Appendix A for full listings of investigators and study sites.

Study R-0601:

2-Objectives
The primary objective of this study was to compare the efficacy (including the potential effects on social anxiety and phobic avoidance), safety, and tolerability of sertraline versus placebo in adults with generalized social phobia. A secondary objective was to determine the effect of sertraline treatment on quality of life in subjects with generalized social phobia.

3-Study Population: (Refer to Appendix B for complete Inclusion & Exclusion Criteria). A primary diagnosis of DSM-IV-defined generalized social phobia with a duration of illness $\geq$ 2 years was required for study inclusion. In addition, to ensure that subjects' social phobia was at least moderate-to-severe, a baseline Liebowitz Social Anxiety Scale (LSAS) total score of $\geq$ 68 was required. Male and non-pregnant female outpatients at least 18 years of age were eligible for study inclusion. Subjects were ineligible to participate in the study if, within the six months prior to the study, they were diagnosed with body dysmorphic disorder, major depressive disorder, dysthymia, panic disorder, post-traumatic stress disorder, eating disorder, or substance abuse or substance dependence. To exclude placebo responders, after completing a one-week single-blind run-in period, subjects who had a CGI-I score of 1 (very much improved) or 2 (much improved) were ineligible to continue in the study.

4-Design of the Study
This was a randomized, double-blind, placebo-controlled, parallel group, flexible-dose, multicenter study that consisted of (a) a screening visit, (b) a one-week single-blind placebo run-in period, (c) a 12-week double-blind treatment period during which subjects received either sertraline or placebo, and (d) a taper period of up to two weeks. Subjects returned to the study site at the end of Weeks 1, 2, 3, 4, 6, 8, and 12 for efficacy and safety assessments. In addition, subjects who were tapered from study drug were assessed for adverse events at the post-taper visit (Week 14).

Treatment Phase

During the single-blind placebo run-in period, all subjects took one placebo tablet daily for one week. At the end of the single-blind placebo period, eligible subjects were randomized to double-blind treatment and received either 25 mg/day sertraline or matching placebo for one week. At the end of the first week of double-blind treatment, the dose was increased to 50 mg/day, and all subjects received either 50 mg/day sertraline or matching placebo until the end of Study Week 3. Subjects who had an inadequate response to treatment (based on clinical judgment) and were free of dose-limiting adverse events at the end of Week 3 could have the dose increased to a maximum dose of 100 mg/day (2 X 50 mg). Subjects who had an inadequate response to treatment and who were free of dose-limiting adverse events at the end of Study Week 5 could have the dose increased to a maximum dose of 150 mg/day (3 X 50 mg). As there were no protocol-specified visits scheduled at the end of Week 5, clinical evaluations to determine a subject's response to treatment had to be scheduled at the discretion of the investigator. At the end of Study Week 6, subjects who demonstrated an inadequate response to treatment and were free of dose-limiting adverse events could have the dose increased to 200 mg/day, the maximum dose allowed for the remainder of the study. Subjects who were receiving less than 200 mg/day at the end of Week 6 could have the dose increased to the next higher dose (to a maximum of 200 mg/day) at the end of Weeks 8, 9, 10, or 11. As there were no protocol-specified visits scheduled at the end of Weeks 9, 10, or 11, clinical evaluations that occurred between Weeks 8 and 12 had to be scheduled at the discretion of the investigator. If intolerable side effects occurred at any time during the study, the dose could be reduced to a lower dose level in 50 mg decrements per week to a minimum dose of 50 mg/day sertraline or matching placebo. If the dose was decreased, one attempt to titrate the dose upward could be made within one week. Subjects who could not tolerate a dose of 50 mg/day sertraline were to be discontinued from the study.

Taper & Discontinuation Phase

After receiving 12 weeks of double-blind study medication, (or fewer weeks in the event of early withdrawal), subjects receiving more than 50 mg/day were tapered from study drug at a rate not exceeding 50 mg every four days. No drug taper or post-taper study visit was required for subjects at the 50 mg/day dose level.

Rationale for Dosage & Duration of Treatment

The 50-200 mg/day dose range was selected for use in this trial, because this dose range of sertraline had been approved for use in the treatment of other anxiety disorders. The 12-week duration was selected because, in controlled trials of sertraline in other anxiety disorders, 12 weeks was of sufficient duration to demonstrate a difference in the treatment effect of sertraline versus placebo. In addition, a duration of 12 weeks allows for sufficient time to flexibly titrate the dose from 50 mg/day to the maximum dose of 200 mg/day.

5- Primary and Secondary Efficacy Measures

The primary efficacy measures were: 1) percentage of treatment responders, defined as subjects with a CGI-I score of 1 or 2 at endpoint, and 2) Leibowitz Social Anxiety Scale (LSAS) total score at endpoint.

The secondary efficacy parameters were: 1) LSAS subscale scores; 2) Duke Brief Social Phobia Scale (BSPS) total and subscale scores; 3) Clinical Global Impression of Severity (CGI-S) and Improvement (CGI-I) Scale scores; 4) Hamilton Anxiety Scale (HAM-A) scores; 5)17-Item Hamilton Depression Scale (17-Item HAM-D) scores; 6) Quality of Life Enjoyment and Satisfaction Questionnaire (Q-LES-Q) scores; 7) Sheehan Disability Inventory (SDI) scores; and 8) Endicott Work Productivity Index.

6-Subject Disposition in 601

Sertraline Protocol: R-0601
Discontinuations from Study - All Randomized Subjects

NUMBER (%) OF SUBJECTS	Sertraline 211		Placebo 204	
DISCONTINUATIONS				
Related to Study Drug	17	(8.1)	13	(6.4)
Insufficient Clinical Response	5	(2.4)	9	(4.4)
Adverse Event(s)	12	(5.7)	4	(2.0)
Laboratory Abnormality	0		0	
Special Safety Test(s)	0		0	
Subject Died	0		0	
Not Related to Study Drug	42	(19.9)	50	(24.5)
Adverse Event(s)	4	(1.9)	2	(1.0)
Laboratory Abnormality	0		0	
Special Safety Test(s)	0		0	
Protocol Violation	2	(0.9)	3	(1.5)
Subject Died	0		0	
Lost to follow-up	17	(8.1)	10	(4.9)
Did not meet entrance criteria	1	(0.5)	0	
Withdrew consent	11	(5.2)	17	(8.3)
Other	7	(3.3)	18	(8.8)
TOTAL	59	(28.0)	63	(30.9)

In Study 601, 2.4% of the sertraline treatment group and 4.4% of the placebo treatment group discontinued due to insufficient clinical response. Discontinuations due to adverse events occurred in 7.6% of the sertraline group and 3.0% of the placebo group.

7-Baseline Demographics and Severity of Illness

a) Table. Baseline Demographic Characteristics of Subjects in Studies 601

Sertraline Protocol: R-0601
Summary of Demographic Characteristics - All Randomized Subjects (Page 1 of 2)

	Sertraline			Placebo			
	Male	Female	Total	Male	Female	Total	P-value (a)
NUMBER OF SUBJECTS	127	84	211	120	84	204	
Age (years):							
18-44	105	64	169	96	70	166	
45-64	22	19	41	24	12	36	
>= 65	0	1	1	0	2	2	
Mean	36.1	33.5	35.1	35.9	33.8	35.0	0.935
SD	10.03	11.39	10.64	9.89	11.47	10.60	
Range	(18.0, 60.0)	(18.0, 65.0)	(18.0, 65.0)	(18.0, 62.0)	(18.0, 67.0)	(18.0, 67.0)	
N	127	84	211	120	84	204	
Race:							
White	86	55	141	93	63	156	0.009
Black	14	13	27	10	13	23	
Asian	2	4	6	4	3	7	
Hispanic	18	10	28	10	1	11	
Other	7	2	9	3	4	7	
Weight (kg)							
Mean	84.4	70.7		86.6	66.0		0.495
SD	15.36	18.74		16.41	15.85		
Range	(57.0, 131.4)	(44.5, 142.3)		(56.8, 158.6)	(39.7, 129.1)		
N	127	81		117	84		

There were no statistically significant differences between treatment groups in gender, race, age, or height. The majority of subjects were white (72%). The percentages of African American, Asian, Latino, and other subjects were 12%, 3%, 9%, and 4%, respectively.

b) Table. Baseline Severity of Illness of Subjects in Studies 601

Sertraline Protocol: R-0601
Liebowitz Social Anxiety Scale (LSAS) Total Score - Intent-to-Treat Subjects (Page 1 of 3)

				P-value (a)			Treatment Difference	
VISIT NAME	STATISTICS	Sertraline	Placebo	Treatment	Baseline	Center	Estimate	S.E.
Baseline	N	205	196					
	Mean	91.3	93.9					
	Std. Dev.	15.89	16.05					
	Min, Max	68.0, 137.0	68.0, 144.0					
	LS mean	90.8	93.2	0.118		0.001	-2.4	1.53
	S.E. LS mean	1.13	1.13					
Week 1	N	204	195					
	Mean	86.0	89.1					
	Std. Dev. (mean)	20.18	18.74					
	Min, Max	30.0, 131.0	43.0, 144.0					
	Mean change from baseline	-5.4	-4.8					
	LS mean change	-5.3	-4.6	0.542	0.868	0.048	-0.7	1.13
	S.E. LS mean (change)	0.82	0.84					
Week 2	N	195	186					
	Mean	82.7	84.7					
	Std. Dev. (mean)	20.36	19.99					
	Min, Max	36.0, 135.0	38.0, 138.0					
	Mean change from baseline	-8.4	-9.1					
	LS mean change	-8.4	-9.0	0.654	0.211	0.013	0.6	1.37
	S.E. LS mean (change)	0.99	1.01					

At baseline, there was no statistically significant difference between treatment groups in Liebowitz Social Anxiety Scale scores.

8-Efficacy Results

Table. Primary Efficacy Results in Study 601

Primary Efficacy Parameters	Sertraline (N=205) N (%)	Placebo (N=196) N (%)	P-value
Treatment responders [1] (%) at Endpoint	96.0 (46.8)	50.0 (25.5)	0.001
LSAS Total Score			
Baseline (SE) [2]	90.8 (1.11)	93.2 (1.13)	0.118
Endpoint (SD) [3]	60.3 (28.13)	72.2 (27.75)	
Change from baseline (SE) [2]	-31.3 (1.87)	-21.4 (1.90)	0.001

[1] Defined as subjects with a CGI-I rating of 1 or 2. [2] Values are least square adjusted mean scores or changes from baseline to endpoint and standard errors. [3] Values are mean scores and standard deviations.

Primary Efficacy Measure Results

The higher percentage of treatment responders, (defined as subjects with a CGI-I rating of 1 or 2), in the sertraline treatment group (46.8%) versus the placebo group (25.5%) was statistically significant ($p = 0.001$) from the end of Week 6 through the end of the study. The greater degree of improvement in sertraline-treated subjects' LSAS total scores (-31.3/1.87%) compared to that in placebo-treated subjects (-21.4/1.90%) was statistically significant ($p = 0.001$) from Week 8 through the end of the study.

Secondary Efficacy Measure Results

Secondary efficacy analyses demonstrated that at endpoint, sertraline-treated subjects had statistically significantly improved scores on both the LSAS fear/anxiety factor ($p = 0.001$) and the LSAS avoidance factor ($p = 0.001$) compared with placebo-treated subjects. Additionally, sertraline-treated subjects' fear/anxiety and avoidance of 21 of the 24 common social and performance situations included on the LSAS were statistically significantly diminished ($p \leq 0.038$) in comparison with placebo-treated subjects. Statistically significantly greater improvement in sertraline-treated subjects compared with placebo-treated subjects was also demonstrated in secondary analyses of the CGI-I ($p = 0.001$) and CGI-S ($p = 0.004$) scores, the BSPS total score ($p = 0.001$), and the BSPS fear ($p = 0.001$) and avoidance ($p = 0.001$) factor scores. There was no difference between groups in the BSPS physiologic factor scores. Sertraline-treated subjects also had significantly greater improvement in HAM-A and HAM-D total scores compared with placebo-treated subjects, although in both groups, baseline scores for these two parameters were low. Between-group comparisons of the Q-LES-Q total scores ($p = 0.001$), 11 of the 16 Q-LES-Q item scores ($p \leq 0.05$), and all three SDI item scores ($p \leq 0.04$) indicated that sertraline-treated subjects experienced statistically significantly enhanced satisfaction with their overall quality of life compared with placebo-treated subjects, and specifically in regard to their mood, work, social and family relationships,

leisure time activities, ability to function in daily life, economic status, and living and household situations. There was no statistically significant difference between groups at endpoint in the EWPI total score, a measure of work productivity.

Study STL-NY-94-004

2-Objectives
The objective of this study was to evaluate the efficacy (including effects on social phobic avoidance and anxiety), safety, tolerability, and the effects on quality of life of sertraline in outpatients with generalized social phobia as defined by DSM-IV, with or without concurrent mild secondary depression, compared with a parallel outpatient population receiving placebo.

3-Study Population
A primary diagnosis of DSM-IV-defined generalized social phobia with a duration of illness $\geq$ 1 year was required for study inclusion. Subjects could also have a concurrent episode of Major Depression if: 1) the diagnosis was secondary to the Social Phobia; 2) the Social Phobia began at least 5 years prior to the current episode of depression; and 3) the current episode of depression was mild (MADRS score $\leq$ 19). Male and non-pregnant female outpatients from 18 to 60 years of age were eligible for study inclusion Subjects were excluded if within six months prior to screening they met DSM-IV criteria for panic disorder, agoraphobia, obsessive-compulsive disorder, eating disorders, body dysmorphic disorder, or alcohol or substance abuse. At baseline, after completing the one-week single-blind placebo run-in period, subjects were required to have a CGI-S score of $\geq$ 4 in order to continue in the study

4-Study Design
This was a randomized, placebo-controlled (2:1 sertraline: placebo), double-blind, parallel
group, flexible-dose, multicenter (10 Canadian sites) study that consisted of (a) a screening visit, (b) a washout period (if necessary), (c) a 1-week single-blind placebo run-in period, and (d) a 20-week double-blind treatment period during which subjects received either sertraline or placebo. Subjects returned to the study site at the end of Weeks 1, 2, 4, 7, 10, 13, 16, and 20 for efficacy and safety assessments. The primary outcome measures were the CGI-I, the Marks Fear Questionnaire- Social Phobia Subscale (FQ-SPS) and the Duke Brief Social Phobia Scale (BSPS).

Treatment Phase
The dose-titration schedule differed slightly from that in Study R-0601. During the single-blind placebo run-in period, all subjects took a single placebo capsule daily for one week. At the end of the placebo period, eligible subjects were randomized in a 2:1 ratio to receive either 50 mg/day sertraline or matching placebo until the end of Week 4. Subjects with an inadequate response to treatment (defined as a CGI-I rating of 3) at the Week 4 visit had their dose increased to 100 mg/day (2 x 50 mg) sertraline or matching placebo, and were maintained on that dose until the end of Week 7. Subjects with an inadequate

response to treatment at the Week 7 visit had their dose increased to 150 mg/day (3 x 50 mg) sertraline or matching placebo and were maintained on that dose until the end of Week 10. Subjects with an inadequate response to treatment at the Week 10 visit had their dose increased to 200 mg/day (4 x 50 mg) sertraline or matching placebo and were to be maintained on that dose until the end of the study. Thus, increases in dose to the next dose level were to occur only at the end of Weeks 4, 7, and 10. Following Week 10, no further increases in dose were permitted. Subjects who achieved a satisfactory clinical response at any dose level were to be maintained on that dose until the end of the study (Week 20). If a subject experienced intolerable adverse events at any time during the study, the dose could be reduced to the next lowest dose level (in 50 mg decrements). Subjects who could not tolerate the 50 mg dose were discontinued from the study.

Rationale for Dosage & Duration of Treatment

The 50-200 mg/day dose range was selected for use in this trial because this dose range of sertraline has been approved for use in the treatment of other anxiety disorders. A study length of 20 weeks and a relatively slow titration were selected because they were considered optimal to allow those subjects who may have required titration to a higher dose adequate time at that dose to respond to treatment. This would then provide the greatest opportunity for subjects to complete the study as responders and, therefore, be eligible to enter the 24-week continuation study.

5-Primary Efficacy Measures

The primary efficacy measures were:

1) Percentage of treatment responders at endpoint, defined as subjects with a CGI score of 1 or 2 at endpoint;
2) Change in Duke Brief Social Phobia Scale (BSPS) total score
3-5) Change in BSPS fear, avoidance and physiologic factor scores at endpoint
6) Change in Marks Fear Questionnaire Social Phobia Scale (FQ-SPS) score at endpoint.

Secondary efficacy measures were not specified.

6-Disposition of Subjects in Study 004

Number (%) of Subjects	SERTRALINE 135		PLACEBO 69	
Discontinuations				
Related to Study Drug	19	(14.1)	5	(7.2)
Adverse event	15	(11.1)	1	(1.4)
Lack of efficacy	4	(3.0)	4	(5.8)
Not Related to Study Drug	12	(8.9)	10	(14.5)
Adverse event	1	(0.7)	0	
Others	4	(3.0)	3	(4.3)
Other	3	(2.2)	3	(4.3)
Protocol violation	1	(0.7)	0	
Subject defaulted	7	(5.2)	7	(10.1)
Lost to follow-up	2	(1.5)	0	
Withdrawn consent	5	(3.7)	7	(10.1)
Total	31	(23.0)	15	(21.7)

Discontinuations due to adverse events occurred in 11.8% of the sertraline treatment group and 1.4% of the placebo treatment group.

7-Baseline Demographics and Severity of Illness in Study 004

Baseline Demographics

There were no statistically significant differences between treatment groups in any of the variables analyzed: age, gender, race, weight, and height. The study population was 56% male and 44% female; 93% of the population was white.

Baseline Severity of Illness- Duke Brief Social Phobia Scale (BSPS)

SERTRALINE Protocol STL-NY-94-004
BSPS Total Score by Week -- Intent-to-Treat Subjects

VISIT WEEK		SERTRALINE N	MEAN	+/-	SD/SE	PLACEBO N	MEAN	+/-	SD/SE	TREATMENT EFFECT P-VALUE(d)
BASELINE	RAW RESULT (a)	134	47.43	+/-	9.39	69	45.75	+/-	8.98	
	ADJUSTED RESULT (b)		47.26	+/-	0.79		45.65	+/-	1.10	0.229

The difference in severity of illness between the treatment groups was not statistically significant.

8-Primary Efficacy Results in Study 004

Primary Efficacy Measure Results

At endpoint in Study STL-NY-94-004, there were statistically significant differences between treatment groups in favor of sertraline for all primary efficacy parameters: 1) percentage of treatment responders (53% versus 29%; p = 0.001); 2) change in Duke BSPS total score (-16.44 versus –8.56; p = 0.001); 3) changes in BSPS fear (-6.61 versus –3.07; p = 0.001), 4) avoidance (-6.65 versus –3.40; p = 0.001); and 5) physiologic factor (-3.16 versus –2.09; p = 0.016) subscale scores; and 4) Marks Fear Questionnaire Social Phobia Subscale (FQ-SPS) total score.

Primary Efficacy Parameters	Sertraline (N=134)	Placebo (N=69)	p-value[2]
Treatment Responders[1] (%) at Endpoint	71.0 (53.0)	20 (29.0)	0.001
Duke BSPS Total Score[2]			
Baseline	47.26 (0.79)	45.65(1.10)	
Change from baseline	-16.44 (1.22)	-8.56 (1.71)	0.001
Duke BSPS Fear Factor Score[2]			
Baseline	19.62 (0.32)	19.13 (0.45)	
Change from baseline	-6.61 (0.51)	-3.07 (0.71)	0.001
Duke BSPS Avoidance Factor Score[2]			
Baseline	19.60 (0.35)	19.57 (0.49)	
Change from baseline	-6.65 (0.54)	-3.40 (0.75)	0.001
Duke BSPS Physiologic Factor Score[2]			
Baseline	8.04 (0.29)	6.95 (0.40)	
Change from baseline	-3.16 (0.26)	-2.09 (0.36)	0.016
FQ-SPS Total Score[2]			
Baseline	23.14 (0.59)	21.63 (0.82)	
Change from baseline	-7.84 (0.68)	-2.60 (0.94)	0.001

[1]Defined as subjects with a CGI-I of 1 or 2. [2]Values are least square adjusted mean scores or least square adjusted mean changes from baseline to endpoint and standard errors. [2]All baseline scores were comparable different between groups except the BSPS physiologic factor score (p = 0.027).

The greater improvement seen in sertraline treated subjects was statistically significant from Week 10 through the end of the study for the BSPS total scores, FQ-SPS total scores, and BSPS avoidance factor score. There were statistically significant differences between treatment groups from Weeks 7 and 16 through the end of the study, respectively, for the BSPS fear and physiologic factor scores. Analyses of primary efficacy data showed that compared with placebo-treated subjects, sertraline-treated subjects had statistically significantly lower scores at endpoint for all seven BSPS fear items, all seven BSPS avoidance items, one of the four BSPS physiologic items, and all five FQ-SPS items.

Secondary Efficacy Measure Results
Statistically significant differences in secondary efficacy measures were observed at endpoint in sertraline-treated subjects compared with placebo-treated subjects for all parameters derived from the social phobia scales (CGI-Liebowitz, SPAI, SADS, FNE) and clinical global impressions scales (CGI-I, CGI-S, Physician and Subject Global Impression of Efficacy) used in this study. Significantly greater improvement in MADRS scores was seen in sertraline-treated subjects compared with placebo-treated subjects, although at baseline, scores were low in both groups. Scores on the CAS, which measures anxiety not specifically provoked by social or performance situations, and the BDI were also low at baseline in both groups, and no between-group difference was observed in CAS or BDI scores at endpoint. Several aspects of quality of life were significantly enhanced in sertraline-treated subjects, as shown by statistically significantly lower scores at endpoint in the sertraline treatment group compared with the placebo treatment group on the SDI work and social life/leisure activities subscales; the SF-36 social functioning and mental health subscales; and the SAS-SR social/leisure and parental subscales. There was no difference between treatment groups in the change from baseline to endpoint in the EuroQol score; SDI family life/home responsibilities factor score; the SF-36 physical functioning, role functioning (physical), bodily pain, general health, vitality, and role functioning (emotional) factor scores; or the SAS-SR work, housework, student, extended family, marital, or family unit factor scores. Primary efficacy results for ITT subjects are summarized below.

<u>Study STL-NY-94-004C</u>

2-Objectives
The objective of the study was to determine whether the efficacy of sertraline, (established in a 20 week acute clinical efficacy study, STL-NY-94-004), could be maintained over an additional 24 weeks. The study evaluated whether subjects with Social Phobia manifesting a response (CGI-I $\leq$ 2) to 20 weeks of sertraline therapy would relapse when switched to placebo for an additional 24 weeks. Relapse was defined as either: a) an increase of at least 2 points in the CGI-S score or b) discontinuation from the study due of lack of efficacy of double-blind treatment.

3-Study Population
Subjects with a diagnosis of Social Phobia who completed the 20-week study STL-NY-94-004 and were responders, (defined as having a CGI-I score of 1 or 2), were eligible for inclusion in the continuation study. The population included subjects who had been treated with either sertraline or placebo. Subjects who received sertraline in Study STL-NY-94-004 were re-randomized, (in a 1:1 ratio), either to continue on sertaline or to receive placebo during the 24-week treatment period of study STL-NY-94-004C. Subjects who received placebo in Study STL-NY-94-004 continued to receive placebo in Study STL-NY-94-004C.

Secondary Efficacy Measures

The secondary efficacy parameters included: BSPS fear, avoidance, and physiologic factor scores; CGI; Liebowitz Scale; Social Phobia and Anxiety Inventory (SPAI); Social Avoidance and Distress Scale; (SADS), Fear of Negative Evaluation (FNE); clinical global impression rating scales: Physician and Subject Global Impression of Efficacy; Montgomery Asberg Depression Rating Scale (MADRS); Clinical Anxiety Scale (CAS); Beck Depression Inventory (BDI); and quality of life/functioning rating scales: Sheehan Disability Inventory (SDI), MOS 36-Item Short-Form Health Survey (SF-36), European Quality of Life Scale (EuroQol), 54-Item Social Adjustment Scale (SAS-SR).

6- Subject Disposition in Study STL-NY-94-004C

Of the 65 subjects randomized to treatment in the maintenance phase, all were included in the ITT population for efficacy and safety analyses. In the sertraline/sertraline group, 3/25 (12%) subjects discontinued from the study. In the sertraline/placebo group, 15/25 (60%) subjects discontinued from the study. In the placebo/placebo group, 9/15 (60%) subjects discontinued. In the sertraline group, 4% of subjects discontinued due to lack of efficacy; in the placebo group, 32% of subjects discontinued due to lack of efficacy. In the sertraline group, 0% of subjects discontinued due to adverse events, whereas 20% of subjects in the placebo group discontinued due to adverse events. (Refer to the table below for details.

Table. Discontinuations in Study 004C

Sertraline Protocol STL-NY-94-004C
Discontinuations from Study - All Randomized Subjects

	SERTRALINE/SERTRALINE		SERTRALINE/PLACEBO		PLACEBO/PLACEBO	
Number of Subjects	25		25		15	
Discontinuations						
Related to Study Drug	1	(4.0)	12	(48.0)	5	(33.3)
Adverse event	0		4	(16.0)	1	(6.7)
Lack of efficacy	1	(4.0)	8	(32.0)	4	(26.7)
Not Related to Study Drug	2	(8.0)	3	(12.0)	4	(26.7)
Adverse event	0		1	(4.0)	0	
Others	1	(4.0)	1	(4.0)	2	(13.3)
Other	1	(4.0)	0		1	(6.7)
Protocol violation	0		1	(4.0)	1	(6.7)
Subject defaulted	1	(4.0)	1	(4.0)	2	(13.3)
Lost to follow-up	0		0		1	(6.7)
Withdrawn consent	1	(4.0)	1	(4.0)	1	(6.7)
Total	3	(12.0)	15	(60.0)	9	(60.0)

7-Baseline Demographics and Severity of Illness in Study 004C

Baseline Demographic Characteristics in Study STL-NY-94-004C

At baseline in Study 004C, there were no statistically significant differences among treatment groups for any of the demographic variables analyzed (gender, age, race, weight, or height); although); although 94% of subjects were white. The subject population in Study 004C was similar to that of Study 004 with respect to gender and age. The three treatment groups were comparable with respect to demographic characteristics. Sixty percent (15/25) of sertraline/sertraline-treated subjects compared with 68% (17/25) of sertraline/placebo-treated subjects and 47% (7/15) of placebo/placebo-treated subjects were male; 100% of sertraline/sertraline-treated subjects compared with 84% (21/25) of sertraline/placebo-treated subjects and 100% of placebo/placebo-treated subjects were white. The mean age in the sertraline/sertraline, sertraline/placebo, and placebo/placebo treatment groups was 37 years, 36 years, and 36 years, respectively.

- **Baseline severity of Illness in Study 004C**

Measure	Sertraline/Seraline Group	Sertraline/Placebo Group	Placebo/Placebo Group	S/S vs. S/P P-Value	S/S vs. P/P P-Value
BSPS	17.64 +/- 1.79	18.72 +/- 1.79	27.27 +/- 2.32	0.672	0.002 *
CGI-S	2.40 +/- 0.20	2.52 +/- 0.20	3.07 +/- 0.26	0.671	0.044 *

The primary efficacy analysis involved only comparisons between the sertraline/sertraline group and the sertraline/placebo groups. These 2 groups had similar severity of illness at baseline of 004C, as measured by BSPS and CGI-S.

8-Efficacy Results in Study 004C

Primary Efficacy Parameter	Statistic	Sert/Sert (N = 25)	Sert/Pbo (N = 25)	Pbo/Pbo (N = 15)	p-Value	
					Sert/Sert vs. Sert/Pbo	Sert/Sert vs. Pbo/Pbo
Treatment Relapse[a]	No. Subjects (%), Week 24 Cumulative Count	1 (4.0%)	9 (36.0%)	4 (26.7%)	0.005	0.038
CGI-S Score[b]	Baseline	2.40 (0.20)	2.52 (0.20)	3.07 (0.26)	0.671	0.044
	Change from Baseline to Endpoint	-0.19 (0.23)	0.48 (0.22)	0.51 (0.30)	0.040	0.069
Treatment Responders[c]	No. Subjects (%) at Endpoint	5 (20.0%)	6 (24.0%)	2 (13.3%)	0.735	0.596
CGI-I Score[b,d]	Baseline	1.40 (0.10)	1.36 (0.10)	1.60 (0.13)	0.777	0.223
	Endpoint	3.52 (0.32)	4.00 (0.32)	4.00 (0.41)	0.292	0.361
BSPS Total Score[b]	Baseline	17.64 (1.79)	18.72 (1.79)	27.27 (2.32)	0.672	0.002
	Change from Baseline to Endpoint	-2.04 (1.76)	3.25 (1.74)	-0.21 (2.39)	0.035	0.552
FQ-SPS Total Score[b]	Baseline	8.72 (0.99)	9.04 (1.01)	13.80 (1.27)	0.820	0.002
	Change from Baseline to Endpoint	-1.07 (1.08)	2.16 (1.10)	1.39 (1.47)	0.038	0.195

Sert = Sertraline; Pbo = placebo.

[a] Treatment relapse defined by a CGI-S score ≥2 points higher than at baseline or discontinuation due to lack of efficacy.

[b] Values given are least square adjusted mean score or least square adjusted mean change and standard error.

[c] Treatment response defined by CGI-I score of 1 or 2.

[d] The baseline CGI-I value is the Week 20 value for Study STL-NY-94-004 and the CGI-I value at endpoint is relative to that baseline.

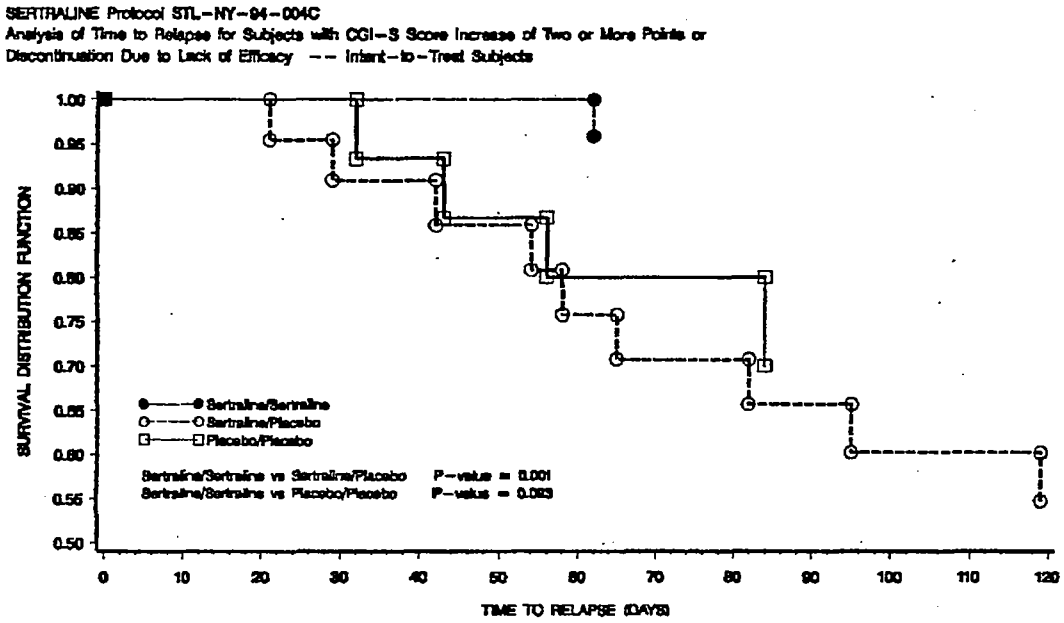
Primary Efficacy Results of Study 004C: Analysis of Relapse Rates
For rate of relapse, there was a significantly smaller proportion of subjects who relapsed in the sertraline/sertraline group (1/25; 4%) than in the sertraline/placebo group (9/25 36%) [p = 0.005]. Thus, the odds ratio was 9. Treatment relapse was defined as having either: a) a CGI-S score $\geq$ 2 points higher than at baseline or b) discontinuation from the study due to lack of efficacy. The majority of relapsed subjects (9/10; 90%) from all groups met relapse criteria on the basis of having discontinued from the study due to lack of efficacy. One subject in the sertraline/placebo group relapsed due to having a 2-point increase in CGI-S. For rates of subjects with CGI-S score $\geq$ 2 points higher than at baseline, there was no significant difference at any time point between the sertraline/sertraline and sertraline/placebo or sertraline/sertraline and placebo/placebo groups. For rates of subjects who discontinued due to lack of efficacy, there were significantly fewer sertraline/sertraline (1/25; 4%) than sertraline/placebo (8/25; 32%) subjects who discontinued due to a lack of efficacy at the end of Weeks 8, 12, 16, 20, and 24. There were also significantly fewer sertraline/sertraline than placebo/placebo subjects who discontinued due to a lack of efficacy at the end of Weeks 8, 16, 20, and 24. There was no statistically significant difference at endpoint or at any visit in the rate of treatment responders between the sertraline/sertraline and sertraline/placebo groups, and there was no statistically significant difference at endpoint in the adjusted mean CGI-I scores between the sertraline/sertraline and sertraline/placebo groups.

Secondary Efficacy Measure Results
There were statistically significant differences in the sertraline/sertraline group compared to the sertraline/placebo group for the following social anxiety ratings: 1) fear and avoidance factors of BSPS; 2) CGI-Liebowitz severity of illness total; 3) social phobia factor score of SPAI; and 4) SPAI total score. Improvement in mood was indicated by a statistically significantly lower MADRS score in the sertraline/sertraline group than in the sertraline/placebo group. Improvement in quality of life/functioning was suggested by statistically significant differences between the sertraline/sertraline and the sertraline/placebo groups in several factor scores of the SF-36 (role functioning-physical, general health, and vitality), and the SAS-SR (total score and extended family.

Analysis of Time to Relapse
Kaplan-Meier estimations were used in the analysis of time to relapse, which was not considered a primary efficacy parameter. A Kaplan-Meier estimation of the probability of relapse over time, in subjects who either a) had a CGI-S score $\geq$ 2 points higher during treatment than at baseline or b) discontinued due to lack of efficacy, showed a statistically significantly longer time to relapse for subjects in the sertraline/sertraline group as compared to the sertraline/placebo group (log-rank test p = 0.001) and in the sertraline/sertraline group as compared to the placebo/placebo group (log-rank test p = 0.023). A Kaplan-Meier estimation in subjects who had a CGI-S score $\geq$ 2 point higher during treatment than at baseline showed a statistically significantly longer time to relapse for subjects in the sertraline/sertraline group than the sertraline/placebo group (log-rank test p = 0.031). A Kaplan-Meier estimation of the probability of relapse over

time in subjects who discontinued due to a lack of efficacy showed a statistically significantly longer time to relapse for subjects in the sertraline/sertraline group than in the sertraline/placebo group (log-rank test p = 0.002) and in the sertraline/sertraline group as compared to the placebo/placebo group (log-rank test p = 0.019).

Table. Analysis of Time to Relapse in Study 004C



Study STL-N/S-95-003

2-Objectives

The objectives of the study were as follows: (1) To compare the efficacy of sertraline (with and without exposure therapy) with placebo (with and without exposure therapy) on social phobic anxiety and avoidance, (2) To compare the safety and tolerability profiles of sertraline with placebo, (3) To compare the efficacy of sertraline (with and without exposure therapy) with placebo (with and without exposure therapy) on quality of life, and (4) To examine the predictive power of personality factors with respect to treatment response.

3-Study Population

Key criteria for inclusion of subjects were: males and females, aged 18-65 years, inclusive; DSM-IV Axis I diagnosis of primary, generalized social phobia, present for at least 1 year prior to study entry; Montgomery-Asberg Depression Rating Scale

(MADRS) Baseline score < 20; and Clinical Global Impressions-Liebowitz (CGI-L) Overall Severity Baseline score ≥ 4 (at least moderately ill).

4-Design of Study 003

This was a 24-week, double-blind, randomized, placebo-controlled, flexible dose comparison of the efficacy, safety, and tolerability of sertraline (50-150 mg/day) and placebo with & without exposure therapy in the treatment of Generalized Social Phobia. The study conducted at 47 sites in Norway and Sweden. It consisted of a screening visit, a washout phase (if necessary), a 1-week single-blind placebo period, and randomization to a flexible dose (50mg-150mg) 24-week treatment period, followed by a dose reduction and drug discontinuation period for up to 4 weeks for those taking >50mg/day at the final visit. Following the Baseline visit, subjects returned for study visits at the end of Weeks 1, 2, 3, 4, 6, 8, 10, 12, 16, and 24. In addition, a follow-up contact was initiated 6 months after the 24-week treatment period to assess the long-term consequences of the study intervention.

Treatment & Taper and Discontinuation Phases

All subjects received 50 mg/day study drug during Weeks 1-4. Subsequently, subjects with an inadequate clinical response and who were free of dose-limiting side effects could have the dose increased in 50 mg increments at the end of Weeks 4, 8, and 12, to a maximum dose of 150 mg/day. (Subjects with a Liebowitz Clinical Global Impressions change measures score of > 3 at the end of Week 4, or of >1 at the end of Weeks 8 or 12 were considered to have had an inadequate clinical response). If a subject experienced intolerable side effects, the dose could be titrated downward in 50 mg decrements to a minimum of 50 mg/day. Subjects who completed 24 weeks of double-blind treatment and who were receiving more than 50 mg/day at Week 24 were tapered off study drug in 50 mg decrements every 14 days. This was a Phase IV study designed and conducted for publication purposes.

5-Primary Efficacy Measures: CGI-Lebowitz Severity total scores

6-Subject Disposition

	SERTRALINE 196		PLACEBO 191	
Number (%) of Subjects				
Discontinuations*				
Related to Study Drug	38	(19.3)	43	(22.5)
Adverse Event	17	(8.6)	10	(5.2)
Lack of Efficacy	21	(10.7)	33	(17.2)
Not Related to Study Drug	29	(14.7)	27	(14.1)
Adverse Event	7	(3.5)	5	(2.6)
Protocol Violations	13	(6.6)	8	(4.1)
Others	9	(4.5)	14	(7.3)

For both treatment groups in study 003, the most common reasons for study discontinuation were lack of efficacy (10.7% for the sertraline group and 17.2% for the placebo group) and adverse events (12.1% and 7.8% for the sertraline and placebo groups, respectively).

7-Baseline Demographics and Severity of Illness
There was no significant difference between treatment groups in baseline CGI-Liebowitz Severity total scores.

D. Efficacy Conclusions

Sertraline in Acute Treatment of Social Phobia
In study 601, the higher rate of treatment responders, (defined as subjects with a CGI-I rating of 1 or 2), in the sertraline treatment group, compared with the placebo group, was statistically significant from the end of Week 6 through the end of the study. The greater degree of reduction in sertraline-treated subjects' LSAS total scores compared to that in placebo-treated subjects was statistically significant from Week 8 through the end of the study. Similarly, at endpoint in Study STL-NY-94-004, there were statistically significant differences between treatment groups in favor of sertraline for all primary efficacy parameters: 1) percentage of treatment responders; 2) Duke Brief Social Phobia Scale (BSPS) total score; 3) BSPS fear,avoidance, and physiologic factor subscale scores; and 4) Marks Fear Questionnaire Social Phobia Subscale (FQ-SPS) total scorse.
The greater improvement seen in sertraline-treated subjects was statistically significant from Week 10 through the end of the study for the BSPS total scores, FQ-SPS total scores, and BSPS avoidance factor score. There were statistically significant differences between treatment groups from Weeks 7 and 16 through the end of the study, respectively, for the BSPS fear and physiologic factor scores. Analyses of primary efficacy data showed that, compared with placebo-treated subjects, sertraline-treated subjects had statistically significantly lower scores at endpoint for all seven BSPS fear items, all seven BSPS avoidance items, one of the four BSPS physiologic items, and all five FQ-SPS items.

Efficacy of Sertraline in Maintenance Treatment of Social Phobia
Results of Study STL-NY-94-004C provide evidence that sertraline was effective in the long-term (up to 44 weeks) treatment of Social Phobia, as demonstrated by a significantly lower rate of relapse in subjects treated with sertraline compared with subjects treated with placebo. The continuation study demonstrated that the tapering and discontinuation of sertraline, following 20 weeks of successful, double-blind treatment with sertraline, resulted in a significantly greater chance of relapsing during an additional 24-week double-blind period of placebo treatment than did continuation of sertraline treatment.
In Study 004C, for the rates of subjects experiencing relapse, there was a significantly smaller proportion of subjects who relapsed in the sertraline/sertraline group (1/25; 4%) than in the sertraline/placebo group (9/25; 36%) [$p = 0.005$]. Relapse was defined by having either: a) a CGI-S score ≥ 2 points higher than at baseline or b) discontinuation from the study due to lack of efficacy. The majority of subjects (9/10; 90%) met relapse criteria as a result of discontinuing from the study due to lack of efficacy. One subject in

the sertraline/placebo group met relapse criteria on the basis of having a 2-point increase in CGI-S. For rates of subjects with CGI-S score $\geq$ 2 points higher than at baseline, there was no significant difference at any time point between the sertraline/sertraline and sertraline/placebo or between the sertraline/sertraline and placebo/placebo groups. For rates of subjects who discontinued due to lack of efficacy, there were significantly fewer sertraline/sertraline (1/25; 4%) than sertraline/placebo (8/25; 32%) subjects who discontinued due to a lack of efficacy at the end of Weeks 8, 12, 16, 20, and 24.

Time to Relapse
Survival analysis demonstrated that there was a statistically significantly longer time to relapse for subjects in the sertraline/sertraline group as compared to the sertraline/placebo group (log-rank test p = 0.001)

Potential Effect of SSRI Discontinuation Syndrome
Analysis of the timing of "relapses" among placebo-treated subjects suggest that the subjects experienced an exacerbation of anxiety disorder as opposed to SSRI discontinuation syndrome. However, it must be noted that narrative descriptions of events for these subjects was not available for the current review.

Subgroup Analysis
Subgroup analyses did not suggest differences in treatment outcome on the basis of gender. There was insufficient information to determine the effect of race or age on outcome.

VI. Integrated Review of Safety

A. Safety Conclusions

Safety results of 3 acute treatment trials and 1 maintenance treatment trial of sertraline in Social Phobia support the conclusion that sertraline, in doses between 50-200 mg/day, is reasonably safe and well tolerated by subjects with Social Phobia, for up to 44 weeks. No significant medical concerns or adverse events were identified in subjects with Social Phobia that had not been identified in safety profiles of sertraline in the treatment of subjects with Major Depression, Obsessive-Compulsive Disorder, Panic Disorder, and Post-Traumatic Stress Disorder. The adverse events that occurred in the Social Phobia studies had been reported in the current Zoloft product label. There were no deaths reported in studies, and there were no serious adverse events or adverse events associated with study discontinuation which were unexpected or drug-related and unlabeled.

In studies 601 and 004, adverse events that occurred in at least 5% of sertraline-treated subjects and with a rate at least twice that seen in placebo-treated subjects were insomnia, nausea, diarrhea, dizziness, dyspepsia, libido decreased (male), ejaculation disorder, dry mouth, fatigue, increased sweating, tremor, influenza-like symptoms, and anorexia.
In the maintenance treatment study, (in which some subjects were treated with sertraline continuously for up to 44 weeks), the adverse event profile was similar to that observed in the acute, controlled studies. The adverse events that occurred in at least 5% of

sertraline/sertraline-treated subjects and at a rate at least two times that in any other group were influenza-like symptoms, dizziness, headache, insomnia, dyspepsia, upper respiratory tract infection, abdominal pain, nausea, dysmenorrhea, coughing, and rash. With the exception of decreased libido, which occurred in 13% of sertraline-treated males compared with 2% of sertraline-treated females, there did not appear to be any clinically significant differences in the safety profile of sertraline on the basis of gender. Because the subject population was predominantly white and less than 65 years of age, data were not analyzed according to race or age.

In studies 601, 004, 004C, 003, sertraline had no clinically important effect on vital signs or body weight. No subjects discontinued due to clinically significant changes in vital signs or body weight. In Study 601, there were no clinically significant changes in electrocardiograms and no unusual or unexpected laboratory test results. No subject discontinued due to a laboratory test or ECG abnormality.

B. Description of Patient Exposure

In the 3 acute treatment trials of sertraline in Social Phobia, a total of 540 subjects received at least one dose of sertraline. The duration of the studies ranged from 14-24 weeks, including a tapering period in Study 601. In study 601, the mean daily dose during weeks 9-12 was 173.3 mg. The median duration of sertraline treatment was 95 days. During Study 004, 135 subjects were treated with sertraline for up to 181 days. The median duration of therapy was 139 days. All subjects began treatment with 50 mg/day for weeks 1-4. Thereafter, dosing was flexible up to 200 mg/day. The mean daily dose of sertraline during weeks 17-20 was 159.3 mg. For Study 003, 196 subjects were treated with sertraline for a median duration of 180 days. The mean daily dose at week 24 was 113.5 mg. In Study 004C, 25 subjects from Study 004 were treated with sertraline for an additional 24 weeks. All 25 subjects completed a total of 44 weeks (308 days) of treatment with sertraline. The mean daily dose at endpoint for subjects in the sertraline/sertraline treatment group was 139.4 mg.

C. Overview of Trials Reviewed

For the safety review, studies 601, 004, 004C, and 003. The acute treatment studies include 601, 004, and 003. Study 004C was a maintenance treatment study. For details about the design and method of safety analysis, please refer to sections **V.C-4** and **VI.D.**

D. Safety Parameters Assessed in the Studies

For Study 601, The safety evaluation was based on the following parameters: discontinuations, adverse events, clinical laboratory tests, ECGs, and vital sign and body weight measurements) which was collected throughout the 14-week double-blind treatment period, including the taper period. For Study 004, the safety evaluation was based on these parameters: discontinuations, adverse events, serious adverse events, vital signs, and body weight measurements collected throughout the 20-week double-blind treatment period for subjects in this study. In this study, ECGs were not obtained, and laboratory data were collected at baseline only. As in Study 004, the safety evaluation in Study 004C was based on discontinuations from study, adverse events, serious adverse events, vital signs, and body weight measurements.

E. Adequacy of Safety Testing

Generally, the methods used to monitor safety in these trials were adequate. Study 601 was well designed for monitoring potential treatment-emergent ECG and laboratory test abnormalities. In studies 004 and 004C, safety monitoring would have been improved if ECG and laboratory testing had been done both at baseline and endpoint.

F. Summary of Critical Safety Findings and Limitations of Data

F-1 Deaths in Controlled Trials

No deaths from studies R-0601 and 004 were reported. There were no deaths reported in Studies STL-NY-94-004C and STL-N/S-95003.

F-2 Serious Adverse Events

Definition of Serious Adverse Event

In Study 601, a serious adverse event was defined as any event that: a) resulted in death, b) was life-threatening, c) resulted in inpatient hospitalization or prolongation of an existing hospitalization, d) resulted in a persistent or significant disability/incapacity, e) resulted in a congenital anomaly/birth defect, or f) were considered to be serious by the investigator. Any event meeting this definition that occurred during the study through the last follow-up visit required by the protocol or up to 30 days after the last dose of study drug, whichever came later, was to be reported regardless of causality. In addition, any serious adverse event that occurred at any other time after the completion of the study had to be reported promptly if a causal relationship to the study drug was suspected.

Serious Adverse Events in Studies 601 and 004

There were a total of 3 reported serious adverse events reported in these 2 studies. None of the SAEs were unexpected or drug-related and unlabeled. Refer to Table C-1 in Appendix C.

004C: Study STL-NY-94-004C

No serious adverse events were reported in this study.

Study STL-N/S-95-003003

There were 20 serious adverse events reported. None of these were unexpected or drug-related and unlabeled. Details are included in table form in **Appendix C.**

F-3 Discontinuations Due to Adverse Events

Acute Treatment Studies 004 & 601

In the sertraline treatment group, 9% (31/344) of subjects discontinued, due adverse events (total of 83 AE), and 3% (7/268) of placebo-treated subjects discontinued due adverse events (total of 9 AE). The adverse events that led to the discontinuation of ≥ 1% of sertraline-treated subjects and with an incidence of two times that in placebo-treated subjects are displayed in table below. The most common were: insomnia 9,

nausea 7, nervousness 5, headache 5, anxiety 5, fatigue 5%, abdominal pain 4%, and decreased libido 2% and ejaculation 2% in males. Refer to Table C-5 in **Appendix C.**

Study 003 Discontinuations Due to Adverse Events
There were 39 subjects who discontinued to due to adverse events. None of these were unexpected or drug-related and unlabelled. For details, refer to the table in Appendix C.

Study 004C Discontinuations Due to Adverse Events
During the maintenance treatment, 6 subjects who discontinued due to adverse events. These included 5 subjects who were randomized to placebo treatment after receiving treatment with 150 mg sertraline for 20 weeks in Study 004. In 4 of these cases, the events and the timing of events appear to be consistent with SSRI discontinuation syndrome. Details are described in Table C-4 in **Appendix C.**

F-4 Adverse Events

Most Common Treatment-Emergent Adverse Events
Occurring in ≥ 5% of Sertraline Subjects and with a Rate ≥ 2X Placebo in Social Phobia Trials **004 & 601**

Adverse Events	Number (%) of Subjects	
	Sertraline N=344	Placebo N=268
Total no. subjects with ≥1 TEAE	309 (90)	205 (77)
Subjects with [1]:		
Insomnia	87 (25)	28 (10)
Nausea	76 (22)	22 (8)
Diarrhea	60 (17)	16 (6)
Dizziness	47 (14)	16 (6)
Dyspepsia	46 (13)	14 (5)
Libido decreased – male [2]	27 (13)	5 (3)
Ejaculation disorder [2]	25 (12)	0 (0)
Mouth dry	42 (12)	10 (4)
Fatigue	41 (12)	16 (6)
Sweating increased	38 (11)	4 (2)
Tremor	31 (9)	7 (3)
Influenza-like symptoms	29 (8)	7 (3)
Anorexia	20 (6)	7 (3)

In Studies 601 and 004, 90% (309/344) of sertraline-treated subjects had a total of 1,229 treatment emergent adverse events, and 77% (205/268) of placebo-treated subjects had a total of 566 treatment emergent adverse event. The most common AEs with a rate > 5% and > twice the rate of the placebo group were: insomnia (25%), nausea (22%), diarrhea (17%), dizziness (14%), dyspepsia (13%), libido decreased-male (13%), ejaculation

disorder (12%), dry mouth (12%), fatigue (12%), sweating increased (11%), tremor (9%), influena-like symptoms (8%), and anorexia (6%).

Incidence of Treatment Emergent Adverse Events by Gender

The treatment emergent adverse events that occurred in at least 5% of female or male sertraline-treated subjects and with an incidence at least twice that in female or male placebo-treated subjects, respectively, are displayed in the table below.

Panel 5. Treatment Emergent Adverse Events (All Causalities) Occurring in ≥5% of Sertraline Subjects of Either Gender and with an Incidence ≥2X Placebo

Adverse Events	Number (%) Females		Number (%) Males	
	Sert N=139	Pbo N=115	Sert N=205	Pbo N=153
Subjects with [1]:				
Insomnia	38 (27)	15 (13)	49 (24)	13 (9)
Nausea	38 (27)	13 (11)	38 (19)	9 (6)
Diarrhea	22 (16)	11 (10)	38 (19)	5 (3)
Dizziness	20 (14)	9 (8)	27 (13)	7 (5)
Dyspepsia	19 (14)	9 (8)	27 (13)	5 (3)
Tremor	19 (14)	4 (4)	12 (6)	3 (2)
Influenza-like symptoms	19 (14)	5 (4)	10 (5)	2 (1)
Mouth dry	17 (12)	2 (2)	25 (12)	8 (5)
Fatigue	17 (12)	9 (8)	24 (12)	7 (5)
Sweating increased	16 (12)	2 (2)	22 (11)	2 (1)
Pharyngitis	13 (9)	5 (4)	8 (4)	4 (3)
Anorexia	10 (7)	4 (4)	10 (5)	3 (2)
Anxiety	8 (6)	2 (2)	7 (3)	2 (1)
Nervousness	7 (5)	4 (4)	14 (7)	5 (3)
Stools loose	6 (4)	3 (3)	11 (5)	4 (3)
Libido decreased	3 (2)	4 (4)	27 (13)	5 (3)
Ejaculation disorder	N/A	N/A	25 (12)	0 (0)

Of the treatment emergent adverse events that occurred in at ≥ 5% of sertraline-treated subjects of either gender and at a rate ≥ 2 times that in the placebo-treated subjects, nearly all occurred at rates that were similar between females and males. The exceptions included libido decreased, which occurred more frequently in sertraline-treated males (13%) than sertraline-treated females (2%). In addition, both tremor and influenza-like symptoms occurred somewhat more frequently in sertraline-treated females than sertraline-treated males.

Adverse Events in Study STL-94-004C

Panel 8.1.2.2 Most Frequent Treatment Emergent Adverse Events (Occurring in ≥5% of Sertraline Subjects and with an Incidence of 2X Comparator Subjects)

Number and Percentage of Subjects with TEAEs [1,2]	Sertraline/Sertraline (N=25) N (%)	Sertraline/Placebo (N=25) N (%)	Placebo/Placebo (N=15) N (%)
No. (%) of subjects with ≥ 1 TEAE	24 (96)	18 (72)	10 (67)
No. (%) of subjects with:			
Influenza-like symptoms	9 (36)	3 (12)	2 (13)
Dizziness	6 (24)	4 (16)	1 (7)
Headache	5 (20)	1 (4)	4 (27)
Insomnia	5 (20)	1 (4)	2 (13)
Dyspepsia	5 (20)	0 (0)	0 (0)
Upper respiratory tract infection	4 (16)	2 (8)	1 (7)
Abdominal pain	3 (12)	1 (4)	1 (7)
Nausea	3 (12)	2 (8)	0 (0)
Dysmenorrhea	1 (10)	0 (0)	0 (0)
Coughing	2 (8)	0 (0)	0 (0)
Rash	2 (8)	0 (0)	0 (0)

As depicted in the table above, rates of several AE were considerably higher in the sertraline/sertraline group than in the sertraline/placebo group: Influenza-like symptoms, dizziness, headache, insomnia, dyspepsia, abdominal pain, URI, nausea, dysmenorrhea, cough, and rash. None of these are unexpected or drug-related and unlabeled.

F-5 Laboratory Findings

In Study 601 and 003, clinical laboratory test data were collected both at baseline and post-baseline. In Study 004, laboratory tests were performed at screening only and were not summarized in the sponsor's safety summary. In Study 601 and 003, the following clinical laboratory tests were performed at screening and at Week 12 (or at the final visit for subjects who discontinued early): blood chemistries (including electrolytes, BUN, creatinine, liver function tests (total bilirubin, SGOT, SGPT, alkaline phosphatase, total protein, albumin); thyroid function tests (T3, T4, TSH); complete blood count (including hemoglobin, hematocrit, WBC with differential, and platelet count); and urinalysis (glucose, protein, blood, and microscopic). Potential subjects who at screening had significant laboratory abnormalities in the investigator's opinion and, specifically potential subjects with abnormal LFTs, were excluded from the study. Laboratory test data were summarized by presenting the number and percentage of subjects in each treatment group with clinically significant laboratory abnormalities as well as the mean change from baseline to last observation in laboratory test results.

The incidence of clinically significant laboratory tests was similar between treatment groups, and there were no unusual or unexpected clinical laboratory test results reported for any subject in Study 601. In addition, there were no clinically significant mean changes from baseline to endpoint for any laboratory test parameter No subject discontinued due to an abnormal clinical laboratory parameter.

In Study 003, there was a very low incidence of clinically significant liver function and renal function test abnormalities in both treatment groups (1% sertraline, 2% placebo) and no clinically important change from baseline to endpoint in laboratory values

F-6 Electrocardiography

Electrocardiograms were obtained in Study 601 only. A standard 12-lead ECG with lead II rhythm strip was performed during the screening visit and at the end of Week 12 or during the last visit for subjects who prematurely discontinued treatment. Of the safety-evaluable subjects for whom an ECG was obtained at endpoint (169 sertraline, 162 placebo), all subjects either had ECGs that were within the normal limits or had abnormalities that, in the opinion of the investigator, were either clinically insignificant or were stable and consistent with the subject's past medical history. No subject discontinued due to an ECG abnormality.

F-7 Weights and Vital Signs

Diastolic blood pressure, systolic blood pressure, heart rate, and body weight were collected in Study 601 (at Weeks 1, 2, 3, 4, 6, 8, and 12 [or the final visit for subjects who discontinued early]), Study 004 (at Weeks 7 and 20 [or the final visit for subjects who discontinued early]), and Study 004C (at Weeks 12 and 24 [or the final visit for subjects who discontinued early]). Data were summarized by presenting the number and percentage of subjects in each treatment group with clinically significant vital sign abnormalities or body weight changes, as well as the group mean changes from baseline to last observation in vital sign or body weight measurements. Data from Studies 601 and 004 were pooled and summarized in the ISS.

In Studies 601 and 004, the incidence of changes in vital signs or body weight that met the protocol-specified criteria for clinical significance were similar in the two treatment groups, and none of the changes recorded for any subject in either group was clinically significant. In addition, there were no clinically significant changes from baseline to endpoint in vital signs or body weight in either treatment group, and no subject discontinued due to a vital sign or body weight abnormality.

G. Safety Conclusions

Safety results of 3 acute treatment trials and 1 maintenance treatment trial of sertraline in Social Phobia support the conclusion that sertraline, in doses between 50-200 mg/day, is reasonably safe and well tolerated by subjects with Social Phobia, for up to 44 weeks . No significant medical concerns or adverse events were identified in subjects with Social Phobia that had not been identified in safety profiles of sertraline in the treatment of subjects with Major Depression, Obsessive-Compulsive Disorder, Panic Disorder, and Post-Traumatic Stress Disorder. The adverse events that occurred in the Social Phobia studies had been reported in the current Zoloft product label. There were no deaths reported in studies, and there were no serious adverse events or adverse events associated with study discontinuation which were unexpected or drug-related and unlabeled.

In studies 601 and 004, adverse events that occurred in at least 5% of sertraline-treated subjects and with a rate at least twice that seen in placebo-treated subjects were insomnia, nausea, diarrhea, dizziness, dyspepsia, libido decreased (male), ejaculation disorder, dry mouth, fatigue, increased sweating, tremor, influenza-like symptoms, and anorexia.
In the maintenance treatment study, (in which some subjects were treated with sertraline continuously for up to 44 weeks), the adverse event profile was similar to that observed in the acute, controlled studies. The adverse events that occurred in at least 5% of sertraline/sertraline-treated subjects and at a rate at least two times that in any other group were influenza-like symptoms, dizziness, headache, insomnia, dyspepsia, upper respiratory tract infection, abdominal pain, nausea, dysmenorrhea, coughing, and rash.
With the exception of decreased libido, which occurred in 13% of sertraline-treated males compared with 2% of sertraline-treated females, there did not appear to be any clinically significant differences in the safety profile of sertraline on the basis of gender. Because the subject population was predominantly white and less than 65 years of age, data were not analyzed according to race or age.

In studies 601, 004, 004C, 003, sertraline had no clinically important effect on vital signs or body weight. No subjects discontinued due to clinically significant changes in vital signs or body weight. In Study 601, there were no clinically significant changes in electrocardiograms and no unusual or unexpected laboratory test results. No subject discontinued due to a laboratory test or ECG abnormality.

VII. Use in Special Populations

A. Women

1. Pregnancy–Pregnancy Category C–
There are no adequate and well-controlled studies in pregnant women. ZOLOFT® (sertraline hydrochloride) should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

2. Labor and Delivery–The effect of ZOLOFT on labor and delivery in humans is unknown.

3. Nursing Mothers–It is not known whether, and if so in what amount, sertraline or its metabolites are excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when ZOLOFT is administered to a nursing woman.

B. Pediatric Use
The efficacy of ZOLOFT in pediatric patients with social phobia has not been systematically evaluated. However, the safety of ZOLOFT use in children and adolescents, ages 6-18, was evaluated in a 12-week, multicenter, placebo-controlled study with 187 outpatients, ages 6-17, and in a flexible dose, 52 week open extension study of

137 patients, ages 6-18, who had completed the initial 12-week, double-blind, placebo-controlled study. ZOLOFT was administered at doses of either 25 mg/day (children, ages 6-12) or 50 mg/day (adolescents, ages 13-18) and then titrated in weekly 25 mg/day or 50 mg/day increments, respectively, to a maximum dose of 200 mg/day based upon clinical response. The mean dose for completers was 157 mg/day. In the acute 12 week pediatric study and in the 52 week study, ZOLOFT had an adverse event profile generally similar to that observed in adults.

Sertraline pharmacokinetics were evaluated in 61 pediatric patients between 6 and 18 years of age with major depressive disorder and/or OCD and revealed similar drug exposures to those of adults when plasma concentration was adjusted for weight. More than 250 patients with major depressive disorder and/or OCD between 6 and 18 years of age have received ZOLOFT in clinical trials. The adverse event profile observed in these patients was generally similar to that observed in adult studies with ZOLOFT. As with other SSRIs, decreased appetite and weight loss have been observed in association with the use of ZOLOFT. Consequently, regular monitoring of weight and growth is recommended if treatment of a child with an SSRI is to be continued long term. Safety and effectiveness in pediatric patients below the age of 6 have not been established. The risks, if any, that may be associated with the use of ZOLOFT beyond 1 year in children and adolescents with OCD have not been systematically assessed. The prescriber should be mindful that the evidence relied upon to conclude that sertraline is safe for use in children and adolescents derives from clinical studies that were 12 to 52 weeks in duration and from the extrapolation of experience gained with adult patients. In particular, there are no studies that directly evaluate the effects of long-term sertraline use on the growth, development, and maturation of children and adolescents. Although there are no affirmative finding to suggest that sertraline has the capacity to adversely affect growth, development or maturation, the absence of such findings is not compelling evidence of the absence of the potential of sertraline to have adverse effects in chronic use.

C. Geriatric Use–U.S. geriatric clinical studies of ZOLOFT in major depressive disorder included 663 ZOLOFT-treated subjects ³ 65 years of age, of those, 180 were ³ 75 years of age. No overall differences in the pattern of adverse reactions were observed in the geriatric clinical trial subjects relative to those reported in younger subjects (see ADVERSE REACTIONS), and other reported experience has not identified differences in safety patterns between the elderly and younger subjects. As with all medications, greater sensitivity of some older individuals cannot be ruled out. There were 947 subjects in placebo-controlled geriatric clinical studies of ZOLOFT in major depressive disorder. No overall differences in the pattern of efficacy were observed in the geriatric clinical trial subjects relative to those reported in younger subjects. Other Adverse Events in Geriatric Patients. In 354 geriatric subjects treated with ZOLOFT in placebo-controlled trials, the overall profile of adverse events was generally similar to that shown in Tables 1 and 2. Urinary tract infection was the only adverse event not appearing in Tables 1 and 2 and reported at an incidence of at least 2% and at a rate greater than placebo in placebo-controlled trials. As with other SSRIs, ZOLOFT has been

associated with cases of clinically significant hyponatremia in elderly patients (see Hyponatremia under PRECAUTIONS).

VIII. Labeling, Dosing, Regimen, and Administration Issues
A. Labeling

Proposed labeling in the CLINICAL TRIALS and INDICATIONS AND USAGE sections is appropriate for the acute treatment and maintenance treatment of Social Phobia. Proposed labeling clearly reflects the design, conduct, results, and analyses of the 2 acute treatment trials and the maintenance treatment trial. Regarding maintenance treatment, the sponsor proposes the following language in labeling: "The efficacy of ZOLOFT in maintaining a response in patients with [redacted] for up to 24 weeks following 20 weeks of ZOLOFT treatment was demonstrated in a placebo-controlled trial." In proposed labeling, the sponsor also states that: "Physicians who prescribe ZOLOFT for extended periods should periodically re-evaluate the long-term usefulness of the drug for the individual patient." Language in other sections of proposed labeling are appropriate.

Subgroup analyses did not suggest differences in treatment outcome on the basis of gender. There was insufficient information to determine the effect of race or age on outcome.

IX. Recommendations and Conclusions

I recommend that the Division take an approvable action for supplemental NDA 19,839/SEI-045. The sponsor seeks claims indicating sertraline for [redacted].

Data from two controlled clinical trials demonstrated the efficacy of sertraline in improving the symptoms of social phobia. Treatment with sertraline was statistically significantly superior to placebo with respect to a number of primary efficacy measures that reflect the core features of Social Phobia. The results of the studies suggest that treatment with sertraline results in a significant clinical benefit in patients with Social Phobia. Furthermore, results of Study 004C provide evidence that sertraline was effective in the long-term (up to 44 weeks) treatment of Social Phobia, as demonstrated by a significantly lower rate of relapse in subjects treated with sertraline compared with subjects treated with placebo. The continuation study demonstrated that the tapering and discontinuation of sertraline, following 20 weeks of successful, double-blind treatment with sertraline, resulted in a significantly greater chance of relapsing during an additional 24-week double-blind period of placebo treatment than did continuation of sertraline treatment. Analysis of the timing of relapses among placebo-treated subjects suggests that the subjects experienced a recurrence of anxiety disorder as opposed to SSRI discontinuation syndrome.

Subgroup analyses of the studies did not suggest differences in treatment outcome on the basis of gender. There was insufficient information to determine the effect of race or age on outcome due to small numbers of non-white and elderly subjects studied.

Safety results of 3 acute treatment trials and 1 maintenance treatment trial of sertraline in Social Phobia support the conclusion that sertraline, in doses between 50-200 mg/day, is reasonably safe and well tolerated by subjects with Social Phobia, for up to 44 weeks. No significant medical concerns or adverse events were identified in subjects with Social Phobia that had not been identified in safety profiles of sertraline in the treatment of subjects with Major Depression, Obsessive-Compulsive Disorder, Panic Disorder, and Post-Traumatic Stress Disorder. The adverse events that occurred in the Social Phobia studies had been reported in the current Zoloft product label. There were no deaths reported in studies, and there were no serious adverse events or adverse events associated with study discontinuation which were unexpected or drug-related and unlabeled.

Robert L. Levin, M.D., October 24, 2002
Medical Reviewer
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X. Appendix

A. Investigators & Study Sites

1. Study R-0601:

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United States	98-S-7001	Jeffrey Apter, MD, Princeton Biomedical Research, Princeton, NJ
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Studies STL-NY-94-004 & STL-NY-94-004C:

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	362, 390	Elliot Goldner, MD, FRCP(C), St. Paul's Hospital, Vancouver, British Columbia
	363	David G. Johnston, MD, FRCP(C), Peter Lougheed Hospital Centre, Calgary, Alberta, and Calgary General Hospital, Calgary, Alberta
	365, 366, 367	Pratap R. Chokka, MD, FRCP(C), Grey Nuns Hospital, Edmonton, Alberta
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Study STL-N/S-95-003

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Appendix B: Subject Inclusion and Exclusion Criteria

1. Study R-0601

Inclusion Criteria

1. Male and female subjects aged 18 and over.
2. Subjects with a primary diagnosis of social phobia of at least two years' duration. Social phobia was diagnosed using the Structured Clinical Interview for DSM-IV (SCID).
3. In addition to meeting DSM-IV criteria for social phobia, subjects were required to exhibit fear and/or avoidance of at least four social situations. At least two of these were required to involve interpersonal interactions.
4. Hamilton Depression Rating Scale score (17-item) of $\leq$ 14 at screening. Item no. 1 was required to be < 2.
5. Liebowitz Social Anxiety Scale score of ³68 at baseline.
6. Subjects were required to provide witnessed, written informed consent before entering the study. The investigator was responsible for obtaining informed consent and documenting this on the case report form.
7. Screening laboratory values were required to be within normal limits, or abnormalities were to be clinically insignificant.
8. Females of childbearing potential were required to have a negative serum b-HCG pregnancy test result and to be practicing an effective form of contraception. Acceptable methods were hormonal, double-barrier with spermicide, or IUD. Complete abstinence could be considered on a case-by-case basis, but first this had to be discussed with the designated Pfizer medical monitor.

Exclusion Criteria

1. Subjects who did not meet the DSM-IV criteria for generalized social phobia as their primary diagnosis.
2. Subjects who scored more than minimally improved on the Clinical Global Impression of Improvement Scale (CGI-I) after the one-week single-blind placebo run-in at the baseline visit (a CGI-I score of <3 were to be excluded).
3. Subjects who met DSM-IV criteria for substance abuse or substance dependence within the six months prior to this study.
4. Subjects who were judged to be a serious suicidal or homicidal risk.
5. Subjects with body dysmorphic disorder, major depressive disorder, dysthymia, panic disorder, post-traumatic stress disorder, or eating disorder within the six months prior to screening or a current or past diagnosis of schizophrenia, psychotic disorder, bipolar affective disorder, or obsessive-compulsive disorder.
6. Subjects with a primary diagnosis of generalized anxiety disorder.
7. Subjects who were receiving specific behavior or supportive therapy for social phobia or other anxiety disorder at screening and subjects who were contemplating beginning a course of psychotherapy and/or behavioral therapy during the study. Subjects in psychotherapy (unrelated to the treatment of social phobia or other anxiety disorder) for at least three months prior to enrollment could be entered provided their therapy remained unrelated to the treatment of social phobia or other anxiety disorder and provided there was no change in the type of therapy or frequency of therapy sessions during the study.

8. Subjects with a history of seizure disorder, excluding febrile seizures of childhood.
9. Subjects with any serious or uncontrolled medical illness or condition that precluded sertraline use.
10. Subjects who, in the judgment of the investigator, might require hospitalization for any reason during the course of the study.
11. Subjects who had electroconvulsive therapy within the six months prior to the study.
12. Subjects who had a major life event in the three months prior to the study that in the judgment of the investigator could influence their current condition.
13. Women who were pregnant, nursing, lactating, or not using a clinically acceptable (effective) method of birth control. If a subject became pregnant during the study, she was to be discontinued immediately and followed appropriately (at a minimum, until the outcome of the pregnancy was determined).
14. Subjects who required concomitant therapy with any psychotropic drug or with any drug with a psychotropic component (except zolpidem for insomnia). (See Appendix A of the protocol, which is provided in Section 11, Item 1 of this report, for a comprehensive list of prohibited concomitant medications.)
15. Subjects who were being treated with medications other than those permitted by the protocol at the end of the placebo run-in period. (See Appendix A of the protocol, which is provided in Section 11, Item 1 of this report, for a comprehensive list of prohibited concomitant medications.)
16. Subjects who had taken a monoamine oxidase inhibitor (MAOI) within the two weeks prior to randomization (subjects were instructed not to take an MAOI until three weeks after they had stopped taking study drug) and fluoxetine HCl within the five weeks prior to randomization.
17. Subjects who had taken any psychotropic agents or b-blockers within the 14 days prior to randomization.
18. Subjects who received depot neuroleptics within the six months prior to the study.
19. Subjects who had taken an investigational drug or had participated in a clinical trial within the six months prior to the study.
20. Subjects previously shown to be intolerant to sertraline.
21. Subjects who had failed to respond to an adequate trial of sertraline (defined as a minimum of 50 mg for at least four weeks) for any disorder.
22. Subjects who had failed an adequate trial of drug treatment for social phobia. Adequate treatment was defined as at least four weeks of treatment with 20 mg paroxetine or the equivalent.
23. Subjects who, in the judgment of the investigator, could not tolerate a trial of sertraline.
24. Subjects with clinically significant laboratory or electrocardiogram findings (liver function tests >2 times the upper limit of normal were considered significant).
25. Subjects who could require general anesthetics during the course of the study.
26. Subjects who were planning to be blood donors during the course of the study. Subjects were instructed not to donate blood until four weeks after completing the trial.
27. Subjects whose urine screen was positive for benzodiazepines or illicit substances at screening.
28. Subjects who were illiterate or were unable to read or write English or who were judged by the investigator to be unable or unlikely to follow the study protocol.

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2. Study STL-NY-94-004

Inclusion Criteria

1. Male and female outpatients between the ages of 18 to 60 years inclusive.
2. Subjects who, using the operationalized criteria of the SCID met, for at least the previous year, the DSM-IV criteria for an Axis I diagnosis of primary, social phobia. Subjects with an additional diagnosis Avoidant Personality were permitted to participate in the study. Subjects with a diagnosis of comorbid DSM-IV Major Depressive Episode were permitted to participate in the study provided that the diagnosis was secondary to social phobia, baseline MADRS £19, and the onset of social phobia predated the onset of the current episode of depression by five or more years.
3. Subjects who provided witnessed, written informed consent, in a manner consistent with nationally approved standards before entering the study. The investigator was responsible for obtaining informed consent, having first offered the subject an information sheet and an explanation of it. Informed consent was documented by the investigator on the case report form.
4. Subjects with a CGI-S score ³4 at baseline.
5. Females of childbearing potential who had a negative pregnancy test and practiced successful contraception for at least 3 months before entry into the study.

Exclusion Criteria:

1. Women who were pregnant, lactating, or who were of childbearing potential and not using reliable contraception, or who intended to become pregnant during the study or within one month of completing the study.
2. Subjects with any primary Axis I psychiatric diagnosis other than social phobia (ie, social phobia was the major problem).
3. Subjects who received therapeutic doses of clomipramine, an SSRI or MAOI and/or anti-anxiety medications for 3 or more weeks in the 3 months before screening.
4. Subjects who within the previous 6 months fulfilled the criteria for DSM-IV Panic Disorder, Agoraphobia, Obsessive-Compulsive Disorder, eating disorders, Body Dysmorphic Disorder, Alcohol Abuse, or Substance Abuse, or subjects who had a lifetime history of Bipolar Disorder Type 1.
5. Subjects with a MADRS total score >19 at baseline.
6. Subjects who, in the investigator's opinion, represented a significant suicide risk.
7. Subjects who within 6 months before screening had a seizure disorder or organic brain disease, anorexia nervosa, bulimia nervosa or purgative abuse, and subjects who had abused or been dependent on any drug, including alcohol, within 6 months before screening.
8. Subjects who had treatment with depot neuroleptic drugs in the 7 months before screening, or antidepressants within five half-lives of the drug concerned before study entry, or low-dose benzodiazepines (£20 mg/day of diazepam or equivalent) within 2 weeks of study entry, or high-dose benzodiazepines (>20 mg/day of diazepam or equivalent) within 4 weeks of study entry, or cognitive behavior therapy specific for social phobia within 4 weeks of study entry.
9. Subjects receiving psychotropics of any kind, beta blockers, reserpine, methyldopa, guanethidine, or clonidine, or any serotonergic drugs including fenfluramine, buspirone, sumatriptan, ondansetron, or granisetron.

10. Subjects with contraindications to sertraline as found in the local product document.
11. Subjects with the following medical conditions: severe allergies (in particular to sertraline or lactose), multiple adverse drug reactions, or epilepsy. Subjects who had suffered severe infections or a major surgical operation within 2 months of entering double-blind therapy.
12. Subjects who previously received sertraline.
13. Subjects who participated in clinical trials within 12 months prior to entry in this study or were scheduled to do so concurrently with this study.
14. Subjects who wanted to donate blood or blood products while participating in the study or within 4 weeks after the study.
15. Subjects considered to have had poor motivation for treatment, or with other emotional or social problems likely to invalidate informed consent or limit ability to comply with protocol requirements, including the admonition against alcohol abuse during the study.
16. Subjects who might require general anesthetics during the study.
17. Subjects who, in the investigator's opinion, would require treatment during the study with additional psychotropic drugs (except zopiclone or chloral hydrate as hypnotic), electroconvulsive therapy, behavior therapy, or intensive psychotherapy.
18. Subjects who at baseline had a total CGI-S score that improved ³2 points from screening.
19. Subjects who at baseline had a urinary screen positive for benzodiazepines.
20. Subjects who had a major life event within 3 months prior to the study which, in the judgment of the investigator, influenced their current condition.

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3. Study STL-NY-94-004C:

Inclusion Criteria

1. Participants in Study STL-NY-94-004 who were responders (CGI-I score of 1 or 2) and completed 20 weeks of double-blind therapy.
2. Subjects provided witnessed, written informed consent, in a manner consistent with nationally approved standards before entering the study. The investigator was responsible for obtaining informed consent, having first offered the subject an information sheet and an explanation of it. Informed consent was documented by the investigator on the case report form.
3. Females of childbearing potential who had a negative pregnancy test and practiced successful contraception at study entry and during the study.

Exclusion Criteria

1. Women who were pregnant, lactating, of childbearing potential and not using reliable contraception, or who intended to become pregnant during the study or within 1 month after completing the study.
2. Subjects who were scheduled to participate in other clinical studies.
3. Subjects considered to have poor motivation for treatment, or with other emotional or intellectual problems that were likely to invalidate informed consent, or limit the ability of the subject to comply with the protocol requirements.

Appendix C: Tables of Safety Assessments

Table C-1. Serious Adverse Events (SAE) in Studies R-0601 & STL-94-004

Study	SAE	Study Action	Outcome
R-0601	Asthma exacerbation, Pneumonia, Atelectasis	Continued study treatment (sertraline)	Hospitalization; Resolved
STL-94-004	Bipolar II d/o exacerbation, psychosis, paranoia (Day 41)	Study treatment discontinued (sertraline)	Hospitalization; Resolved
STL-94-004	Spontaneous abortion 2 ½ months post-study; pregnancy diagnosed at final visit	Post-treatment event (sertraline treatment was completed)	Resolved

Table C-1. Serious Adverse Events in Study STL-N/S-95-003

Serious Adverse Event	Study Action	Treatment and Outcome
Bilateral Parotitis	Continued (sertraline)	Hospitalization
Accidental fall, head injury, no LOC	Continued (sertraline)	Observation; resolved
Suicide attempt (clomipramine & paroxetine	Dicontinued from study (sertraline)	Hospitalization; resolved
Acutely herniated intervertebral disc	Dicontinued from study (sertraline)	Surgery
Convulsive syncope	Continued (sertraline)	Resolved
Spontaneous abortion	Dicontinued from study (sertraline)	Hospitalized
Alcohol intoxication	Continued (sertraline)	Resolved
Attempted Suicide; oxazepam andflunitrazepam	Continued (sertraline)	Hospitalized; resolved
Accidental trauma to the right eye	Continued (sertraline)	Surgery
syncope	Continued (sertraline)	Hospitalized; resolved
Thyroid cyst	Discontinued (placebo)	Surgery
Pneumonia, fever, dyspnea	Continued (placebo)	Hospitalization
Recurrent paroxysmal supraventricular tachycardia	Completed study before AE	
Acute abdominal pain	Dicontinued from study	Hospitalized; resolved
Hodgkins lymphoma	Completed study before AE	Hospitalized; chemotherapy
Synovectomy; Rheumatoid Arthritis	Completed study before AE	Surgery
Erysipelas	Continued study treatment	Hospitalized; resolved
Pressure neuropathy	Completed study before AE	Hospatilized; partially resolved
Fall, lower extremity fracture	Continued (placebo)	Resolved

Table C-3. Discontinuations Due to Adverse Events in Study 003

Adverse Events by Subject Discontinued from the Study
Relapse of alcohol abuse as well as depression, insomnia, and anxiety.
Severe chest pain, severe dyspnea, mild altered bowel habit, mild nausea, and mild fatigue
Severe headache, severe fatigue, and severe abnormal thinking
Severe palpitations, severe hypoesthesia, severe dyspnea, moderate dizziness, and moderate nausea
Severe aggravated depression, moderate nausea, moderate vomiting, and agitation
Severe depression
Severe anxiety, mild drug abuse (alcohol and benzodiazepines)
Mild fatigue and mild paresthesia
Mild anxiety
Moderate vertigo, noderate depression, moderate insomnia, moderate nausea, moderate chest pain
Moderate dyspnea, moderate dizziness, moderate abnormal thinking
Moderate headache, moderate dizziness, mild nausea, moderate nausea, mild dizziness
Mild rash, mild nausea, mild headache, moderate hallucinations, moderate anxiety, mild anxiety
Moderate anxiety
Severe abdominal pain
Severe increased sweating, moderate dizziness, severe constipation
Severe abnormal thinking, severe dizziness, moderate abnormal vision
Severe anxiety
Severe hypertonia, severe speech disorder, severe back pain
Severe dysphagia
Severe anxiety, moderate apathy, severe malaise, moderate vertigo
Severe tinnitus,upper respiratory tract infection
Severe acute back pain, underwent surgery for herniated disc.
Severe paranoia, severe constipation, moderate diarrhea, moderate headache
Severe agitation
Severe abdominal pain
Mild abnormal serum T4 level, mild hypothyroidism
Moderate nausea
Thyroid cyst of moderate severity, removal of the cyst and started on thyroxine
Moderate abnormal dreaming
Severe abdominal pain, severe nausea, severe vomiting, moderate gastroenteritis
Severe labyrinthitis (Meniere's Disease), mild to moderate nausea
Severe anxiety and moderate gastroenteritis
Intermittent mild to moderate decrease in libido
Suicide attempt by taking an overdose of clomipramine and paroxetine
Severe hallucinations
Pregnancy. Subject experienced a spontaneous abortion.
Severe abdominal pain and severe nausea
Mild diarrhea, moderate headache, moderate nausea, moderate agitation, moderate anxiety

Table C-4. Discontinuations due Adverse Events in Study 004

Treatment Group	Adverse Events	Day of Onset of AE	Day of Discontinuation
Sertraiine/placebo 150 mg	Dizziness, nausea, fatigue, anorexia, insomnia depression	2-11	30
Sertraline/placebo 150 mg	Severe sweating, confusion, abdominal pain, diarrhea	10	12
Sertraline/placebo 150 mg	Moderate dizziness	3	7
Sertraline/placebo 150 mg	Dizziness, anxiety, nervousness	4	26
Sertraline/placebo 150 mg	Mild allergy	5	14
Placebo/placebo	Severe anxiety, moderate agitation	42	55

Table C-5. Discontinuations to AE in Study 004C

Panel 4. Treatment Emergent Adverse Events (All Causalities) [1] Associated with Discontinuation in ≥1% of Sertraline Subjects and with an Incidence ≥2X Placebo

Adverse Events	Number (%) of Subjects	
	Sertraline N=344	Placebo N=268
Total no. subjects who discontinued due to ≥1 TEAE	31 (9)	7 (3)
Subjects who discontinued due to:		
Insomnia	9 (3)	1 (<1)
Nausea	7 (2)	0 (0)
Nervousness	5 (2)	2 (1)
Headache	5 (2)	1 (<1)
Anxiety	5 (2)	1 (<1)
Fatigue	5 (2)	0 (0)
Abdominal pain	4 (1)	1 (<1)
Libido decreased – male [2]	2 (1)	0 (0)
Ejaculation disorder [2]	2 (1)	0 (0)

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Robert Levin
10/24/02 05:54:28 PM
MEDICAL OFFICER

Thomas Laughren
10/25/02 07:34:48 AM
MEDICAL OFFICER
I agree that this supplement is approvable; see memo to file for more detailed comments.--TPL

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

19-839/S-045

20-990/S-011

STATISTICAL REVIEW(S)

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

STATISTICAL REVIEW AND EVALUATION

Medical Division: Neuropharm Drug Products (HFD-120)
Biometrics Division: Division of Biometrics I (HFD-710)

NDA NUMBER:	19-839
DRUG NAME:	Zoloft (Sertraline HCl)
INDICATION:	Social phobia
SPONSOR:	Pfizer
STATISTICAL REVIEWER:	Fanhui Kong, Ph.D. (HFD-710)
DATE OF DOCUMENT:	1/29/2002

DISTRIBUTION:

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Statistical Review and Evaluation

1. Executive Summary

This submission consists of three Phase III, randomized, double-blind, multi-center studies comparing the effectiveness of sertraline with placebo in adults with generalized social phobia. The two studies (R-0601, STL-NY-94-004) were double-blind, multi-center, flexible dose comparisons of sertraline (50-200 mg/day) and placebo conducted at U.S. and Canada centers respectively. The third study (STL-NY-94-004C) was designed as a relapse prevention extension of study 004 and was conducted at the same 10 Canadian sites as study 004.

Study R-0601 was a multicenter, randomized, double-blind, placebo-controlled study of sertraline for acute treatment of DSM-IV generalized social phobia in outpatients. A total of 415 patients were randomized and 401 were in the intent-to-treat population.

Study STL-NY-94-004 was a twenty-week, prospective, randomized, multicenter, group, double-blind, dose titration comparison of the safety, efficacy, and tolerability of sertraline (50-200 mg/day) and placebo in the treatment of DSM-IV generalized social phobia in outpatients. A total of 204 patients were randomized and 203 were in the intent-to-treat population.

STL-NY-94-004C was a twenty-four Week, Continuation Study STL-NY-94-004 of sertraline (50-200 mg/day) or Placebo in the Treatment of DSM-IV Generalized Social Phobia in outpatients. A total of 65 patients were randomized and 65 were in the intent-to-treat population.

In this submission there are two primary endpoints for Study R0601, there are 6 primary endpoints for Studies STL-NY-94-004 and STL-NY-94-004C. Studies R-601 and STL-NY-94-004 were positive with p-values below 0.05 in all the primary outcomes in LOCF analyses. Study STL-NY-94-004 was positive in 4 of the 6 primary endpoints in LOCF analyses.

2. Introduction

The studies in the current NDA submission were conducted from 1996 to 2001. At that time it was not required to specify a single primary endpoint. This is the main reason for the multiple primary endpoints in each study.

The current submission NDA 19-839 for Zoloft (Sertraline HCl) consists of three phase-III studies to compare the efficacy and safety of sertraline with that of placebo for treating patients with generalized social phobia..

> **Study R-0601** was a multicenter, randomized, double-blind, placebo-controlled study of sertraline for acute treatment of DSM-IV generalized social phobia in

outpatients. A total of 415 patients were randomized and 401 were in the intent-to-treat population.

Study STL-NY-94-004 was a twenty-week, prospective, randomized, multicenter, group, double-blind, dose titration comparison of the safety, efficacy, and tolerability of sertraline (50-200 mg/day) and placebo in the treatment of DSM-IV generalized social phobia in outpatients. A total of 204 patients were randomized and 203 were in the intent-to-treat population.

Study STL-NY-94-004C was a twenty-four Week, Continuation Study STL-NY-94-004 of sertraline (50-200 mg/day) or Placebo in the Treatment of DSM-IV Generalized Social Phobia in outpatients. A total of 65 patients were randomized and 65 were in the intent-to-treat population.

The protocols of these studies were started around 1995 or 1996, so these studies all have multiple primary endpoints. In both LOCF and OC analyses, Study R-601 and Study NY-94-004 are positive in all primary endpoints and the studies support the conclusion that sertraline is more effective than placebo in improving clinical conditions of the patients with DSM-IV-defined social phobia.

However, the reviewer is concerned with the validity of the significant test regarding primary endpoint of the number of relapses in Study NY-94-004C. The sponsor changed the definition of this endpoint just one week before the opening of blindness. No official records of such a change has been provided. Consequently, the p-value of significant test between Sertraline/Sertraline and Sertraline/Placebo group changed from 0.085 to 0.005. At the same time, the normality assumption on primary endpoints CGI-S and FQ-SPS do not hold. The Wilcoxon nonparametric test does not support sponsor's positive conclusions. As a result, among the six primary endpoints proposed by the sponsor, only BSPS Total Score is positive with a p-value of 0.035.

3 Study R-0601

The study period is between January 13, 2000 and May 15, 2001. The final protocol was signed off on May 3, 2000. The statistical analysis plan (SAP) for the study was finalized and approved by the sponsor on July 27, 2000. Most of the amendment items were related to the operational procedures and safety report. One statistically related item is that the power was increased from 80% to 85%, therefore the sample size increased from 160 per arm to 180 per arm.

3.1 Study Objectives

The primary objective of this study was to compare the efficacy (including the potential effects on social anxiety and phobic avoidance), safety, and tolerability of sertraline versus placebo in adults with generalized social phobia. A secondary objective was to determine the effect of sertraline treatment on quality of life in subjects with generalized social phobia.

3.2 Study Design

This was a randomized, multicenter, double-blind, parallel group, placebo-controlled, flexible-dose study that consisted of (a) a screening visit, (b) a one-week single-blind placebo run-in period, (c) a 12-week double-blind treatment period during which subjects received either sertraline or placebo, and (d) a taper period of up to two weeks for subjects receiving more than 50 mg/day at Week 12. Subjects returned to the study site at the end of Weeks 1, 2, 3, 4, 6, 8, and 12 for efficacy and safety assessments. In addition, subjects who were tapered off study drug were assessed for adverse events only at the post-taper visit (Week 14).

It was estimated that a sample size of 180 subjects in each treatment group in the intent-to-treat (ITT) analysis would provide at least 85% power for a two-sided test, at a significance level of $\alpha = 0.05$, to detect (1) a 20% difference in the rate of response (CGI-I = 1 or 2 at endpoint), and (2) a 10 point difference in the change from baseline to endpoint in the LSAS (standard deviation of change = 30).

Assuming that approximately 10% of randomized subjects would be excluded from the ITT analysis, a total of 400 subjects were to be randomized. The sponsor pointed out that when the protocol was amended, 03 May 2000, the power was increased from 80% to 85%, which required that the sample size be increased from 160 to 180 subjects in each treatment group in the ITT analysis.

3.3 Efficacy Measures

The primary efficacy measures were the percentage of treatment responders (defined as subjects with a Clinical Global Impression of Improvement [CGI-I] rating of 1 or 2) and the Liebowitz Social Anxiety Scale (LSAS) total score.

The secondary efficacy measures were Duke Brief Social Phobia Scale (BSPS), Clinical Global Impression of Severity (CGI-S) and Improvement (CGI-I), Hamilton Anxiety (HAM-A) Scale, 17-Item Hamilton Depression (17-Item HAM-D) Scale, Quality of Life Enjoyment and Satisfaction Questionnaire (Q-LES-Q), Sheehan Disability Inventory (SDI) and Endicott Work Productivity Index (EWPI).

3.4 Statistical Analysis Plan

Primary and secondary measures were analyzed for the intent-to-treat (ITT) population which was defined as all enrolled subjects who took at least one dose of study drug medication and who had a baseline and at least one post-baseline efficacy assessment. In addition, primary efficacy measures only were analyzed for the efficacy-evaluable population which were defined as ITT subjects who had no major protocol violations, received at least 80% of the protocol-specified study drug dosage for at least two weeks, and had at least one primary efficacy assessment while on study drug or within 72 hours after the last dose.

Endpoint was defined as the last post-baseline observation during the 12-week double-blind treatment period (before taper period) carried forward (LOCF) for each subject. Statistical tests for efficacy measures were two-sided and performed at the 0.05 level of significance. Tests of interaction were performed at the 0.1 significance level.

For both primary and secondary efficacy measures, treatment responders for binary and ordinal in each treatment group at endpoint were compared using a Cochran-Mantel-Haenszel (CMH) test with center as strata. The adjusted mean changes from baseline to endpoint of the total score of continuous measures in each treatment group were compared using analysis of covariance (ANCOVA) models with baseline score, treatment, and center as covariates. The adjusted mean baseline total scores of the continuous variables were compared using an analysis of variance (ANOVA) model with treatment and center in the model.

3.5 Study Population

The study population consists of male or non-pregnant female outpatients at least 18 years of age with a primary diagnosis of DSM-IV-defined generalized social phobia with duration of illness for at least two years. The subjects had a baseline Liebowitz Social Anxiety Scale (LSAS) total score of ≥ 68 and a HAM-D (17-Item) total score of ≤ 14, with a score of <2 on the "depressed mood" item of the scale. Within the six months prior to the study, they were not diagnosed with body dysmorphic disorder, major depressive disorder, dysthymia, panic disorder, post-traumatic stress disorder, eating disorder, or met DSM-IV criteria for substance abuse or substance dependence. Both treatment groups included a slightly higher proportion of males (60% sertraline, 59% placebo) than females, and a higher proportion of whites (67% sertraline, 76% placebo) than non-whites. Subjects in both groups had a mean age of approximately 35 years. The mean age of symptom onset was 13.4 years in the sertraline treatment group and 13.0 years in the placebo treatment group.

There were 20 investigative sites that randomized patients into the study. Of the 520 subjects screened, 415 subjects (211 sertraline, 204 placebo) were randomized and of whom 408 (209 sertraline, 199 placebo) subjects received treatment. Of those who received treatment, 401 subjects (205 [98%] sertraline, 196 [99%] placebo) were included in the ITT analysis. The four sertraline-treated subjects and three placebo-treated subjects were excluded from the ITT analysis because they did not have a baseline and at least one post-baseline efficacy assessment.

For patient disposition (Table 3.5.1), sertraline group has protocol completed rate (72%) as compared to placebo (69%). The primary reasons for early discontinuation in were "Adverse effects", "Lost to Follow-Up" and "Withdrew concent". Sertraline group has a higher rate of "Adverse effects" while the placebo group has higher rate of "Insufficient Clinical Response". The sertraline group has a higher rate of " Lost to Follow up" while the placebo group has a higher rate of "Withdraw Consent".

Protocol derivation is moderate. The related violation includes that some subjects were not seen at the clinic for medical evaluation at the appointed time points, but were evaluated by the investigators over the telephone.

Table 3.5.1 Reasons for Discontinuations from Study - All Randomized Subjects

	Sertraline		Placebo	
Primary Reason for Discontinuation	(n=211) n	(%)	(n=204) n	(%)
Related to Study Drug	17	(8.1)	13	(6.4)
Insuff. Clinical Response	5	(2.4)	9	(4.4)
Adverse Event(s)	12	(5.7)	4	(2.0)
Laboratory Abnormality	0		0	
Special Safety Test(s)	0		0	
Subject Died	0		0	
Not Related to Study Drug	42	(19.9)	50	(24.5)
Adverse Event(s)	4	(1.9)	2	(1.0)
Laboratory Abnormality	0		0	
Special Safety Test(s)	0		0	
Protocol Violation	2	(0.9)	3	(1.5)
Subject Died	0		0	
Lost to follow-up	17	(8.1)	10	(4.9)
Did not meet entrance criteria	1	(0.5)	0	
Withdrew consent	11	(5.2)	17	(8.3)
Other	7	(3.3)	18	(8.8)
TOTAL	59	(28.0)	63	(30.9)

Baseline patient characteristics including age, race, height, weight and duration of illness appeared to be comparable across treatment groups, except for race (p=0.009). The number of years of duration of social phobia and the age of symptom onset were also comparable across treatment groups. Results were similar for the efficacy-evaluable population. There were no statistically significant differences between treatment groups for any of the parameters.

Baseline severity of illness based on both primary efficacy measures (CGI-score, LASA total score) and secondary efficacy measures (BSPS score, HAM-A score, HAM-D score, Q-LES-Q score, EWPI score) appeared to be comparable across treatment groups. The baseline HAM-A score and Q-LES-Q score appear to be close to significance level indicating there are some imbalance between the treatment and placebo groups.

Treatment compliance is not of a great concern according to the sponsor's report. Within the ITT population (205 sertraline, 196 placebo), there were a total of 12 (6%) sertraline-treated subjects and 9 (5%) placebo-treated subjects who received less than 80% or more

than 120% of the protocol-specified, double-blind study drug dosage over the course of the study. For one (0.5%) additional placebo-treated subject, the percent compliance could not be determined because unused medication was not returned.

Other protocol violation includes: (1) Some raters did not have an MS, MD, or PhD degree as specified by the protocol. (2) Not all subjects were rated by the same raters or physicians at every visit. (3) Some subjects were not seen at the clinic for a medical evaluation at these time points, but were evaluated by the investigator over the telephone. However, the sponsor declared that none of these protocol deviations was thought to have altered the safety or efficacy conclusions presented in the study report.

Table 3.5.2 Baseline Characteristics – All Randomized Patients

VARIABLE	Sertraline (n=211)			Placebo (n=204)			p-value (a)
	Male	Female	Total	Male	Female	Total	
AGE							
N	105	64	211	120	84	204	
Mean	36.1	33.5	35.1	35.9	33.8	35.0	0.935
Std	10.0	11.4	10.6	9.9	11.5	10.6	
Range	18.0-60.0	18.0-65.0	18.0-65.0	18.0-62.0	18.0-67.0	18.0-67.0	
RACE			211			204	0.009
White	86	55	141	93	63	156	
Black	14	13	27	10	13	23	
Asian	2	4	6	4	3	7	
Hispanic	18	10	28	10	1	11	
Other	7	2	9	3	4	7	
WEIGHT (kg)							
N	127	81	117	84			
Mean	84.4	70.7	86.6	66.0			0.495
Std	15.4	18.7	16.4	15.9			
Range	57.0-131.4	44.5-142.3	56.8-158.6	39.7-129.1			
HEIGHT(cm)							
N	127	84	120	83			
Mean	176.9	164.9	177.7	165.2			0.637
Std	8.5	6.1	7.9	6.8			
Range	152.4-195.6	154.9-177.8	154.9-200.7	147.3-180.3			
DURATION OF ILLNESS							
N			211			204	
Mean			20.8			21.5	
Range			2.0-55.0			3.0-59.0	

(a) p-value for the continuous variables was from ANOVA model with investigator and treatment in the model; p-value for the categorical variable was from Fisher's exact test.

Table 3.5.3 Baseline Efficacy Score - Baseline severity of Illness in Intent-to-Treat Population

Efficacy Parameters at Baseline	Sertraline (N=205) N (%)	Placebo (N=196) N (%)	P-value
CGI-Score			
Mean (SE) (a)	4.8 (0.04)	4.8 (0.05)	0.607
N	205	196	
LSAS Total Score			
Mean (SE)	90.8 (1.11)	93.2 (1.13)	0.118
N	205	196	
BSPS Total Score			
Mean (SE)	48.1 (0.64)	48.4 (0.66)	0.769
N	187	177	
HAM-A Total Score			
Mean (SE)	10.9 (0.36)	9.9 (0.37)	0.054
N	187	177	
HAM-D Total Score			
Mean (SE)	6.5 (0.24)	6.4 (0.24)	0.762
N	170	165	
Q-LES-Q Total Score			
Mean (SE)	68.9 (0.80)	71.0 (0.83)	0.059
N	184	174	
EWPI Total Score			
Mean (SE)	32.7 (1.33)	30.3 (1.38)	0.195
N	144	133	

(a) These are the least square adjusted means and standard errors. (b) The p-values are derived based on the least square adjusted means and standard errors.

3.6 Sponsor's Efficacy Results

3.6.1 Primary Efficacy Results

In the primary efficacy analysis, the sponsor showed that there were statistically significant differences between treatment groups in favor of sertraline with respect to both primary efficacy parameters at endpoint (percentage of treatment responders and the adjusted mean change from baseline in the LSAS total score).

At the endpoint (defined as the last post-baseline observation during the 12-week double-blind treatment period (before taper period) carried forward) of the ITT population, there were statistically significantly more ($p = 0.001$) treatment responders in the sertraline

treatment group (47%) than in the placebo treatment group (26%). (Treatment responders were defined as subjects with a CGI-I rating of 1 or 2 at endpoint.) Statistically significant greater adjusted mean decreases from baseline were observed in the sertraline treatment group compared with the placebo treatment group in the LSAS total score (sertraline: -31.3, placebo: -21.4, p = 0.001). Similar results were obtained for the efficacy-evaluable population.

Table 3.6.1 Primary Efficacy Measure at Endpoint—ITT LOCF Population

Primary Efficacy Parameters	Sertraline (N=205) N (%)	Placebo (N=196) N (%)	P-value
Treatment responders [1] (%) at Endpoint	96.0 (46.8)	50.0 (25.5)	0.001
LSAS Total Score			
Baseline (SE) 2	90.8 (1.11)	93.2 (1.13)	0.118
Endpoint (SD) [3]	60.3 (28.13)	72.2 (27.75)	
Change from baseline (SE) 2	-31.3 (1.87)	-21.4 (1.90)	0.001

[1] Defined as subjects with a CGI-I rating of 1 or 2. [2] Values given are least square adjusted mean scores or least square adjusted mean changes from baseline to endpoint and standard errors. [3] Values given are mean scores at endpoint and standard deviations.

Table 3.6.2 Primary Efficacy Measure at Endpoint—ITT OC Population at Week 12

Primary Efficacy Parameters	Sertraline (N=153) N (%)	Placebo (N=146) N (%)	P-value
Treatment responders [1] (%) at Endpoint	55.6	29.5	0.001
LSAS Total Score			
Endpoint (SD) [3]	56.9 (27.34)	70.2 (28.94)	
Change from baseline (SE) 2	-35.0 (2.28)	-24.2 (2.34)	0.001

[1] Defined as subjects with a CGI-I rating of 1 or 2. [2] Values given are least square adjusted mean scores or least square adjusted mean changes from baseline to endpoint and standard errors. [3] Values given are mean scores at endpoint and standard deviations.

3.6.2 Secondary Efficacy Results

Statistically significant improvement in sertraline-treated subjects compared with placebo-treated subjects was also demonstrated in secondary analyses of the CGI-I and CGI-S scores and the BSPS total score. Sertraline-treated subjects also demonstrated significantly greater improvement in HAM-A and HAM-D total scores compared with placebo-treated subjects. Between-group comparisons of outcome on the Q-LES-Q total scores and all three SDI item scores indicated that sertraline-treated subjects experienced statistically significantly enhanced satisfaction with their overall quality of life and perceived functioning compared with placebo-treated subjects. There was no difference between groups in EWPI total scores, a measure of work productivity.

Table 3.6.2 Secondary Efficacy Measure at Endpoint - Intent-to-Treat Population

Secondary Efficacy Parameters At Endpoint	Sertraline (N=205) N (%)	Placebo (N=196) N (%)	P-value
BSPS Total Score			
Mean at endpoint (SD)	32.6 (14.53)	37.8 (14.51)	
Mean change from baseline (SE)	-15.6 (1.05)	-10.8 (1.09)	0.001
N	187	177	
HAM-A Total Score			
Mean at endpoint (SD)	7.4 (5.02)	8.1 (5.33)	
Mean change from baseline (SE)	-2.5 (0.34)	-1.5 (0.35)	0.041
N	187	177	
HAM-D Total Score			
Mean at endpoint (SD)	5.3 (3.85)	6.0 (4.05)	
Mean change from baseline (SE)	-1.1 (0.28)	-0.4 (0.29)	0.042
N	170	165	
Q-LES-Q Total Score			
Mean at endpoint (SD)	74.9 (11.43)	72.5 (11.10)	
Mean change from baseline (SE)	5.2 (0.73)	1.6 (0.76)	0.001
N	184	174	
EWPI Total Score			
Mean at endpoint (SD)	26.6 (15.07)	27.9 (15.65)	
Mean change from baseline (SE)	-4.8 (1.11)	-2.3 (1.15)	0.10
N	144	133	

(a) These are the least square adjusted means and standard errors. (b) The p-values are derived based on the least square adjusted means and standard errors.

3.7 Reviewer's Analysis

The reviewer duplicated the sponsor's analyses according to the protocol.

The normality assumption failed for primary endpoint LASA Total score. The reviewer performed the Wilcoxon nonparametric test on the change from baseline as well as the percentage change from baseline, i.e., the change of LSAS from baseline divided by baseline. These tests give p-value .0001. The Shapiro-Wilk test on ratio failed on testing the normality of the endpoints but the result of the Wilcoxon test indicates the robustness. Because the normality failed, medians of the change from baseline at week 12 are calculated, which are –21.7 for Sertraline, and -15 for placebo, respectively.

The information of each investigator is presented in the following table to check whether the significance result is mainly contributed by one investigator. In the following table, NSertraline and NPlacebo are the number of patients in Sertraline and Placebo groups, respectively. T is TTEST statistic performed on the difference of the mean changes from baseline for unequal variances between two treatment groups.

Table 3.7.1 T Statistic by Investigator

Obs	Invest	NSertraline	NPlacebo	t-Value
01	01	8	7	-0.13
02	02	5	6	1.32
03	03	7	8	-0.85
04	04	14	11	0.51
05	05	16	17	-1.93
06	06	8	6	-0.40
07	08	6	7	1.33
08	09	10	9	0.30
09	10	18	16	-2.02
10	11	19	18	-1.33
11	12	16	16	-3.31
12	13	7	7	1.42
13	14	10	10	-0.57
14	16	15	13	-0.42
15	17	12	14	-1.65
16	18	8	7	-0.70
17	19	8	6	-0.63
18	20	11	11	1.69
19	21	7	7	-1.48

Most of the clinic centers show that the Sertraline reduces the total LSAS scores compared to the placebo. Center 12 seems to have especially high significance level. After removing this center, Wilcoxon test gives a p-value of 0.031 and t-test gives p-value of 0.013 for the significance test of the treatment effect of Sertraline. So the treatment effect is quite stable.

The following table gives the treatment difference by sex. DIFF is the mean change from baseline to week 12 on the LSAS Total. SERDIFF is the difference between DIFF of Sertraline and Placebo.

Table 3.7.2 Treatment Effect by Sex

Sex	Therapy	Patient	DIFF	SERDIFF	t-Value
Male	Sertraline	126	-25.24	-5.49	-1.72
	Placebo	116	-19.75		
Female	Sertraline	79	-24.48	-14.57	-1.83
	Placebo	80	-17.48		

The above table shows that Sertraline has treatment effect in both male and female groups.

4 Study NY-94-004

The study period is between March 22, 1996 and October 23, 1997. The statistical analysis plan (SAP) for the study was finalized on October 20, 1997. The blindness was broken on May 25, 1998. Two amendments were made on October 10, 1995 and March 21, 1996 prior to the enrollment of the first subject in this study.

4.1 Study Objectives

This study was to evaluate the efficacy (including effects on social phobic avoidance and anxiety), safety, tolerability, and the effects on quality of life of sertraline in outpatients with generalized social phobia as defined DSM-IV compared with outpatients receiving placebo.

4.2 Study Design

This was a randomized (2:1 sertraline:placebo), multicenter, double-blind, parallel group, placebo-controlled, flexible-dose study that consisted of (a) a screening visit, (b) a washout period, (c) a one-week single-blind placebo run-in period, (d) a 20-week double-blind treatment period during which subjects received either sertraline or placebo. Subjects returned to the study site at the end of Weeks 1, 2, 4, 7, 10, 13, 16, and 20 for efficacy and safety assessments.

Sample size of 180 subjects (120 sertraline and 60 placebo subjects) was estimated using Duke BSPS (estimated difference between groups of 5 with a SD of 8), CGI-I responder rates (estimated at 55% sertraline versus 20-25% placebo), and the FQ-SPS (estimated difference between groups of 4 with a SD of 7.5) and assuming a 20% drop-out rate in this 20-week study and another 10% in the 24-week continuation study (STL-NY-94-004C). The calculations were based on a ratio of 2:1 sertraline to placebo enrollment, an alpha level of 0.05, and a power of 80%.

4.3 Efficacy Measures

The primary efficacy endpoints were the percentage of treatment responders (defined as subjects with a CGI-I rating of 1 or 2); Duke Brief Social Phobia Scale (BSPS) total score; BSPS fear, avoidance, and physiologic factor scores; and the Marks Fear Questionnaire Social Phobia Subscale (FQ-SPS) total score.

The secondary efficacy endpoints included social phobia rating scales (CGI-Liebowitz Scale, Social Phobia and Anxiety Inventory [SPAI], Social Avoidance and Distress Scale [SADS], Fear of Negative Evaluation [FNE]); clinical global impressions rating scales (Clinical Global Impression of Severity [CGI-S] and Improvement [CGI-I], Physician and Subject Global Impression of Efficacy); mood and anxiety disorder rating scales (Montgomery Asberg Depression Rating Scale [MADRS], Clinical Anxiety Scale [CAS], Beck Depression Inventory [BDI]); and quality of life rating scales (Sheehan Disability

Inventory [SDI], MOS 36-Item Short-Form Health Survey [SF-36], European Quality of Life Scale [EuroQol], 54-Item Social Adjustment Scale [SAS-SR]).

4.4 Statistical Analysis Plan

Primary and secondary measures were analyzed for the intent-to-treat (ITT) population which was defined as all enrolled subjects who took at least one dose of double-blind study medication and who had a baseline and at least one post-baseline efficacy assessment. In addition, primary efficacy measures were analyzed for the efficacy-evaluable population which included all ITT subjects who completed at least seven weeks of double-blind treatment.

Endpoint was defined as the last post-baseline observation during the 20-week double-blind treatment period (before taper period) carried forward (LOCF) for each subject. Statistical tests for efficacy measures were two-sided and performed at the 0.05 level of significance. Tests of interaction were performed at the 0.1 significance level.

The percentages of treatment responders for binary primary measure in each treatment group at endpoint were compared using a Cochran-Mantel-Haenszel (CMH) test with center as strata. Treatment-by-center interactions were tested at endpoint only using logistic regression with treatment, center, and treatment-by-center interaction terms. The adjusted mean changes in each treatment group in all other primary efficacy parameters (BSPS and FQ-SPS total scores, and the BSPS factor scores) at endpoint were compared using analysis of covariance (ANCOVA) models with baseline, treatment, and center terms in the model. The adjusted mean baseline scores for these parameters were compared using an analysis of variance (ANOVA) model with treatment and center in the model. Treatment-by-center interactions were tested at endpoint only using an ANCOVA model with treatment, center, treatment-by-center interaction, and baseline terms in the model. For these primary efficacy parameters, increasingly negative changes from baseline connote greater improvement.

The same strategies were used for analyzing the secondary endpoints. Note that although the efficacy parameters CGI-S, CGI-I, CGI-Liebowitz change measures, and the Physician and Subject Global Impression of Efficacy were collected on an ordinal scale, they were analyzed as continuous measures.

In the preparation of this report, some important changes were made to the final SAP dated October 20, 1997: (1) The CGI-I was added as a secondary efficacy measure. (2) The efficacy-evaluable subjects were not required to not have committed any major protocol violations because major protocol violations were not defined prior to the breaking of the blind. (3) Although defined as a secondary efficacy parameter, the clinical global impression – overall tolerability was analyzed as a safety parameter. In addition, although not specified in the SAP dated October 20, 1997, secondary analyses of the individual BSPS fear, avoidance, and physiologic items were performed.

4.5 Study Population

The population consists of male or non-pregnant female outpatients from 18 to 60 years of age with at least one year of DSM-IV-defined social phobia and with or without concurrent mild secondary depression at 10 investigational sites in Canada.

Both groups included a slightly higher proportion of males (59% and 51% of sertraline- and placebo-treated subjects, respectively) than females, and subjects in both groups were primarily white (92% and 96% of sertraline- and placebo-treated subjects, respectively) and had a mean age of approximately 36 years. In the sertraline treatment group, 49 (36%) subjects compared with 17 (25%) placebo-treated subjects had had previous episodes of major depression.

One hundred eighty subjects were planned in the protocol (120 sertraline, 60 placebo). However, 204 subjects (135 sertraline, 69 placebo) were randomized to treatment. Of these, 158 subjects (104 [77%] sertraline, 54 [78%] placebo) completed the study. The ITT population included 203 subjects (134 [99%] sertraline, 69 [100%] placebo) and the efficacy-evaluable population included 179 subjects (115 [85%] sertraline, 64 [93%] placebo).

Of the 204 randomized subjects, 31 (23%) sertraline-treated subjects and 15 (22%) placebo-treated subjects discontinued from the study. The most common reason for discontinuation from the study are having adverse events for sertraline group (16 [12%] sertraline versus 1 [1%] for placebo) and withdrawal of consent for placebo group (5 [4%] for sertraline versus 7[10%] for placebo) (Table 4.5.1).

Table 4.5.1 Reasons for Discontinuations from Study - All Randomized Subjects

	Sertraline		Placebo	
Primary Reason for Discontinuation	(n=135) n	(%)	(n=69) n	(%)
Related to Study Drug	19	(14.1)	5	(7.2)
Adverse Event(s)	15	(11.1)	1	(1.4)
Lack of efficacy	4	(3.0)	4	(5.8)
Not Related to Study Drug	12	(8.9)	10	(14.5)
Adverse Event(s)	1	(0.7)	0	
Others	4	(3.0)	3	(4.3)
Other	3	(2.2)	3	(4.3)
Protocol Violation	1	(0.7)	0	
Subject Defaulted	7	(5.2)	7	(10.1)
Lost to follow-up	2	(1.5)	0	
Withdrew consent	5	(3.7)	7	(10.1)
TOTAL	31	(23.0)	15	(21.7)

Baseline patient demographic characteristics including sex, age, race, weight, height and duration since the first diagnosis for all randomized subjects appeared to be comparable across treatment groups. Demographic characteristics were similar across treatment groups within the efficacy-evaluable population.

Baseline severity of illness based on primary efficacy measures (Duke BSPS Total Score, Fear Score, Avoidance Score, FQ-SPS Total Score) appeared to be comparable across treatment groups. The baseline Duke BSPS Physiologic Score was significance there appeared to be some imbalance between the treatment and placebo groups.

Protocol was deviated when subject became pregnant, entered into the study without satisfying the criteria or received prohibited concomitant medicine. A total of 24 [18%] subjects in sertraline treatment group and 6 [9%] subjects in placebo group violated the protocol in these manners. Other ways of violating protocol included breaking the blind for medical management of the subjects and deviating from the titration criteria. However, the sponsor declared that none of these protocol deviations was thought to have altered the safety or efficacy conclusions presented in the study report.

Table 4.5.2 Baseline Characteristics – All Randomized Patients

Number of Subjects	SERTRALINE			PLACEBO			P-Value*
	Male 79	Female 56	Total 135	Male 35	Female 34	Total 69	0.329
Age (years):							
Mean	36.3	34.8	35.7	36.6	34.6	35.6	0.972
SD	9.1	9.6	9.3	8.9	8.8	8.8	
Range	19-56	19-55	19-56	21-54	20-54	20-54	
Race:							0.370
WHITE	73	51	124	33	33	66	
BLACK	0	3	3	0	0	0	
ASIAN	2	2	4	1	1	2	
HISPANIC	3	0	3	0	0	0	
OTHER	1	0	1	1	0	1	
Weight (kg):							
Mean	79.6	65.6		78.8	62.6		0.203
SD	12.3	16.0		13.2	9.5		
Range	55-116	44-114		55-113	48-90		
N	76	53		35	33		
Height (cm):							
Mean	176.8	163.3		177.4	163.5		0.696
SD	6.8	8.0		7.3	5.7		
Range	160-199	135-175		165-199	152-175		
N	78	56		35	34		
Duration since first Diagnosis (yrs)							
Mean			1.7			1.7	
Range			0.0-27.1			0.0-26.0	
N			135			69	

* P-values for race and sex were determined using Cochran-Mantel-Haenszel with center as strata. P-values for age, weight and height were determined using Analysis of Variance with effects for treatment and centers.

Table 4.5.3 Baseline Primary Efficacy Score - Baseline severity of Illness in Intent-to-Treat Population

Efficacy Parameters at Baseline	Sertraline (N=134) N (%)	Placebo (N=69) N (%)	P-value (b)
Duke BSPS Total Score Mean (SE) (a) N	47.26 (0.79) 134	45.65 (1.10) 69	0.229
Duke BSPS Fear Factor Score Mean (SE) N	19.62 (0.32) 134	19.13 (0.45) 69	0.367
Duke BSPS Avoidance Factor Score Mean (SE) N	19.60 (0.35) 134	19.57 (0.49) 69	0.962
Duke BSPS Physiologic Factor Score Mean (SE) N	8.04 (0.29) 134	6.95 (0.40) 69	0.027
FQ-SPS Total Score Mean (SE) N	23.14 (0.59) 134	21.63 (0.82) 69	0.131

(a) Least square mean and standard error are provided in this row from ANOVA including treatment and center terms. (b) P-values from ANOVA model including treatment and center.

4.6 Sponsor's Efficacy Results

4.6.1 Primary Efficacy Results

For the ITT population, there were statistically significant differences between treatment groups with respect to all primary efficacy parameters at endpoint, with the sertraline treatment group showing greater improvement than the placebo treatment group for each parameter. Statistically significant differences in favor of sertraline were also observed in the analysis of all primary efficacy parameters for the efficacy-evaluable population.

At endpoint in the ITT population, there were statistically significantly more ($p = 0.001$) treatment responders in the sertraline treatment group (53%) than in the placebo treatment group (29%). (Treatment responders were defined subjects with a CGI-I rating of 1 or 2 at endpoint.)

At endpoint, statistically significantly greater adjusted mean decreases from baseline were observed in the sertraline treatment group compared with the placebo treatment group in the BSPS total score (sertraline: -16.44, placebo: -8.56; $p = 0.001$), as well as in

the BSPS fear (sertraline: -6.61, placebo: -3.07; p = 0.001), avoidance (sertraline: -6.65, placebo: -3.40; p = 0.001), and physiologic (sertraline: -3.16, placebo: -2.09; p = 0.016) factor scores (Tables 4.6.1). A statistically significantly greater adjusted mean decrease from baseline (p = 0.001) in the FQ-SPS total score was observed in the sertraline treatment group compared with the placebo treatment group (sertraline: -7.84, placebo: -2.60). The results were similar for efficacy-evaluable population.

In addition, a statistically significant treatment-by-center interaction was observed (p = 0.054) for the change from baseline to endpoint FQ-SPS total score, ITT population. Review of these least squares means by center indicates treatment group differences consistently favored sertraline but in varying magnitude except in one center.

Table 4.6.1 Primary Efficacy Measure at Endpoint—ITT LOCF Population

Primary Efficacy Parameters	Sertraline (N=134)	Placebo (N=69)	p-value
Treatment Responders[1] (%) at Endpoint	71.0 (53.0)	20 (29.0)	0.001
Duke BSPS Total Score[2]			
Baseline	47.26 (0.79)	45.65(1.10)	
Endpoint	30.42 (1.22)	38.30 (1.71)	
Change from baseline	-16.44 (1.22)	-8.56 (1.71)	0.001
Duke BSPS Fear Factor Score[2]			
Baseline	19.62 (0.32)	19.13 (0.45)	
Endpoint	12.95 (0.51)	16.48 (0.71)	
Change from baseline	-6.61 (0.51)	-3.07 (0.71)	0.001
Duke BSPS Avoidance Factor Score[2]			
Baseline	19.60 (0.35)	19.57 (0.49)	
Endpoint	13.03 (0.54)	16.28 (0.75)	
Change from baseline[2]	-6.65 (0.54)	-3.40 (0.75)	0.001
Duke BSPS Physiologic Factor Score			
Baseline	8.04 (0.29)	6.95 (0.40)	
Endpoint	4.47 (0.26)	5.54 (0.36)	
Change from baseline[2]	-3.16 (0.26)	-2.09 (0.36)	0.016
FQ-SPS Total Score			
Baseline	23.14 (0.59)	21.63 (0.82)	
Endpoint	14.76 (0.68)	20.00 (0.94)	
Change from baseline	-7.84 (0.68)	-2.60 (0.94)	0.001

[1] Defined as subjects with a CGI-I rating of 1 or 2. [2] Values given are least square adjusted mean scores or least square adjusted mean changes from baseline to endpoint and standard errors.

Table 4.6.2 Primary Efficacy Measure at Endpoint—ITT OC Population At Week 20

Primary Efficacy Parameters	Sertraline (N=105)	Placebo (N=54)	p-value
Treatment Responders[1] (%) at Endpoint	63.8	37.0	0.004
Duke BSPS Total Score[2]			
Endpoint	27.74 (1.43)	36.35 (1.99)	
Change from baseline	-19.53 (1.43)	-10.92 (1.99)	0.001
Duke BSPS Fear Factor Score[2]			
Endpoint	11.89 (0.60)	15.76 (0.83)	
Change from baseline	-7.8 (0.60)	-3.93 (0.83)	0.001
Duke BSPS Avoidance Factor Score[2]			
Endpoint	11.80 (0.63)	15.35 (0.86)	
Change from baseline[2]	-7.99 (0.63)	-4.45 (0.86)	0.001
Duke BSPS Physiologic Factor Score			
Endpoint	4.06 (0.30)	5.30 (0.42)	
Change from baseline[2]	-3.72 (0.30)	-2.48 (0.42)	0.18
FQ-SPS Total Score	N=104	N=55	
Endpoint	13.34 (0.78)	19.14 (1.07)	
Change from baseline	-8.96 (0.78)	-3.16 (1.07)	0.001

[1] Defined as subjects with a CGI-I rating of 1 or 2. [2] Values given are least square adjusted mean scores or least square adjusted mean changes from baseline to endpoint and standard errors.

4.6.2 Secondary Efficacy Results

Statistically significantly greater improvement in sertraline-treated subjects compared with placebo-treated subjects was also demonstrated in analyses of all secondary efficacy parameters derived from the social phobia scales (CGI-Liebowitz, SPAI, SADS, FNE) and clinical global impression scales (CGI-S, CGI-I, Physician and Subject Global Impression of Efficacy) used in this study. Sertraline-treated subjects experienced greater improvement in MADRS scores compared with placebo-treated subjects (although in both groups baseline MADRS scores were low), and greater improvement in several aspects of quality of life, including social functioning and work as well as social and leisure activities. On both the CAS, which measures anxiety that does not specifically involve social interactions, and the BDI, baseline scores in both treatment groups were low, and at endpoint there was no between-group difference. There were no differences between groups with respect to physical functioning, physical health, or social functioning that specifically involved family members or relatives.

4.7 Reviewer's Analysis

The reviewer confirmed the sponsor's analyses according to the protocol.

The normality assumption holds for the FQ-SPS total score. For all the BSPS scores including this assumption fails for treatment groups and holds for placebo group. For these BSPS scores, the reviewer performed the Wilcoxon nonparametric test on the

change from baseline as well as the percentage change from baseline, i.e. their change at week 20 from baseline divided by baseline. The p-values of these tests are given in Table 4.7.1. The Shapiro-Wilk test on these endpoints failed but the result of the Wilcoxon test indicates the robustness. Because the normality failed, medians of the change as well as percentage change from baseline at week 20 are calculated, which are also given in Table 4.7.1.

Table 4.7.1 Nonparametric Test of Primary Endpoints at Week 20 — ITT LOCF Population.

Parameter	Median		P-Value*
	Sertraline	Placebo	
Duke BSPS Total Score			
Change from baseline	-13.0	-7.0	0.0004
Percentage change from baseline	-0.31	-0.14	0.0005
Duke BSPS Fear Factor Score			
Change from baseline	-5.50	-3.0	0.0002
Percentage change from baseline	-0.28	-0.13	0.0002
Duke BSPS Avoidance Factor Score			
Change from baseline	-5.0	-2.0	0.0021
Percentage change from baseline	-0.26	-0.13	0.0021
Duke BSPS Physiological Factor Score			
Change from baseline	-3.0	-2.0	0.0082
Percentage change from baseline	-0.375	-0.25	0.0103

p-values are derived using Wilcoxon nonparametric test.

Because there are multiple primary endpoints, we only choose one primary endpoint Duke BSPS Total Score and check whether the significance result of this endpoint is mainly caused by only a few investigators. The number of subjects on each treatment arm and the t-value for the treatment difference for each investigator are presented in Table 4.7.2. In this table, NSertraline and NPlacebo represent the number of patients in Sertraline and Placebo groups, respectively. T-Value is T-test statistic performed on the difference of the mean changes from baseline for unequal variances between two treatment groups.

Table 4.7.2 T-Statistic by Investigator for Duke BSPS Total Score Only

Obs	Invest	NSertraline	NPlacebo	t-Value
01	337	10	3	0.04
02	338	3	2	-2.96
03	342	15	6	-1.83
04	343	5	1	-0.56
05	344	12	4	0.48*
06	345	5	5	0.12
07	354	2	1	0.49*
08	362	15	8	-1.61
09	363	14	8	-2.67
10	364	5	6	-4.66
11	365	5	1	-0.96*
12	366	5	1	1.42*
13	367	2	4	-5.60
14	373	6	2	-1.43
15	374	4	2	1.04
16	385	1	2	-5.77*
17	386	11	7	-2.25
18	387	12	5	-1.07

* T-values are calculated using equal variance formula given only one observation in one of the two groups.

Most of the clinic centers show that the Sertraline reduces the total BSPS scores compared to the placebo. Centers 364 and 367 seem to have especially high significance level. After removing these centers, Wilcoxon test gives a p-value of 0.0071 and t-test gives p-value of 0.0011 for the significance test of the treatment effect of Sertraline. So the treatment effect is quite stable.

The following table gives the treatment difference by sex for primary endpoints: Treatment response, mean changes from baseline for four Duke BSPS scores and mean change from baseline for FQ-SPS total score at Week 20.

Subgroup analyses by the reviewer for male and female subgroups indicate that the treatment effects of both subgroups have the same direction yet the male group has a higher significance level. The results for LOCF analysis are depicted in Table 4.7.3.

Table 4.7.3 Primary Endpoints for Sex at Week 20 — ITT LOCF Population.

Parameter	Sertraline		Placebo		t-Value*	
	Male	Female	Male	Female	Male	Female
Treatment Responders at Endpoint	44 (79)*	27 (55)*	8 (39)*	12 (34)*	10.45#	1.60#
Duke BSPS Total Score Mean change from baseline	-18.0 (79)	-14.8 (55)	-5.6 (35)	-10.3 (34)	-4.51	-1.48
Duke BSPS Fear Factor Score Mean change from baseline	-7.3 (79)	-5.9 (55)	-2.0 (35)	-4.0 (34)	-4.42	-1.54
Duke BSPS Avoidance Factor Score Mean change from baseline	-7.4 (79)	-5.4 (55)	-2.3 (35)	-4.2 (34)	-4.25	-0.89
Duke BSPS Physiological Factor Score Mean change from baseline	-3.3 (79)	-3.5 (55)	-1.3 (35)	-2.1 (34)	-3.42	-1.88
FQ-SPS Total Score Mean change from baseline	-8.3 (79)	-7.4 (55)	-1.8 (35)	-2.6 (34)	-4.27	-2.84

* Number of treatment response. # Chi-square value for the test the significance between two treatment group, Chi-square value of 10.45 corresponds to p-value of 0.0012 and Chi-square value of 1.61 corresponds to p-value of 0.2050.

5 Study NY-94-004C

The study period is between April 29, 1996 and February 27, 1998. Without the support of any official document, the sponsor claims that the final change on the statistical analysis plan (SAP) was made on September 7, 1999. The blindness was broken on September 7, 1999. Two protocol amendments were made on October 10, 1995 and March 21, 1996 prior to the enrollment of the first subject in this study.

5.1 Study Objectives

The study investigates whether the efficacy of sertraline established in the initial 20 week acute clinical efficacy study NY-94-004 is maintained over an additional 24 weeks. The study, therefore, will also investigate whether patients with Social Phobia manifesting a response (CGI-I ≤ 2) to 20 weeks of sertraline therapy will relapse when switched to placebo for the subsequent 24 weeks.

5.2 Study Design

This was a 24-week extension study of a 20-week clinical trial NY-94-004 that evaluated the safety and relapse prevention with treatment of sertraline versus placebo in outpatients with DSM-IV-defined social phobia, with or without concurrent secondary mild depression. The study consisted of (a) the baseline visit and (b) a double-blind treatment phase.

(a) *Baseline visit.* To be eligible to participate in the present study, subjects were required to have completed 20 weeks of double-blind treatment in the acute study, to have demonstrated a treatment response (defined as a CGI-I score of 1 or 2) at the Week 20 visit. The Week 20 visit in the acute study was the baseline visit in this study. Eligible

subjects who had received sertraline in the acute study were re-randomized to treatment with either sertraline or placebo in a 1:1 ratio in the present study. Eligible subjects who had received placebo in the acute study continued to receive placebo in this study. These three treatment groups are identified in this report as sertraline/sertraline, sertraline/placebo, and placebo/placebo.

(b) *Double-blind treatment period (24 weeks).* Subjects were assigned to the same dose level (50, 100, 150, or 200 mg/day) that they were receiving at the end of the acute, the 20-week study. They were to be maintained at this dose, providing they did not have any dose-limiting adverse events that necessitated dosage reduction. If intolerable adverse events occurred at any time during the study, the dose could be reduced to the next lower dose level. However, any subject who could not tolerate 50 mg/day of double-blind medication was to be discontinued. After initial distribution of study drug at baseline, subjects were to return to the study site at the end of Weeks 4, 8, 12, 16, 20, and 24 for efficacy and safety assessment.

A total of 50 subjects who had received sertraline in the acute study were re-randomized to treatment with either sertraline or placebo in the present study, and 15 subjects who had received placebo in the acute study continued to receive placebo in the present study.

Protocol Amendment:

Two amendments were made to the protocol, and were approved internally at Pfizer on 10 October 1995 and 21 March 1996, respectively, prior to the enrollment of the first subject in the study.

- In the 1995 amendment, FQ-SPS was added as a primary efficacy parameter, FNE was changed to a secondary parameter, the weeks for use of MADRS were added, and the flowchart was changed to include details on FQ-SPS, MADRS, and weight.

- In the 1996 amendment, the study flow chart was changed to show that CGI-I was to be done at all visits as stated in the protocol text.

5.3 Efficacy Measures

The primary efficacy parameters were treatment relapse, defined as a Clinical Global Impression of Severity (CGI-S) score at least 2 points higher at any time during this study than the CGI-S score at baseline (the Week 20 visit of Study NY-94-004) or discontinuation because of lack of efficacy. The other primary efficacy parameters were the CGI-S score, CGI-I including the determination of treatment responders (defined as subjects with a CGI-I rating of 1 or 2), as well as the Duke Brief Social Phobia Scale (BSPS) overall total score, and the Marks Fear Questionnaire social phobia factor (FQ-SPS) score.

The secondary efficacy include social phobia rating scales: the BSPS fear, avoidance, and physiologic factor scores, CGI-Liebowitz Scale, Social Phobia and Anxiety Inventory

(SPAI), Social Avoidance and Distress Scale (SADS), Fear of Negative Evaluation (FNE); clinical global impression rating scales: Physician and Subject Global Impression of Efficacy: mood and anxiety rating scales: Montgomery Asberg Depression Rating Scale (MADRS), Clinical Anxiety Scale (CAS), Beck Depression Inventory (BDI); and quality of life/functioning rating scales: Sheehan Disability Inventory (SDI), MOS 36-Item Short-Form Health Survey (SF-36), European Quality of Life Scale (EuroQol), 54-Item Social Adjustment Scale (SAS-SR).

5.4 Statistical Analysis Plan

Primary and secondary parameters were analyzed for the intent-to-treat (ITT) population. Endpoint was defined as the last post-baseline observation carried forward (LOCF) for each subject. For primary efficacy variables, comparisons were made for the sertraline/sertraline vs. sertraline/placebo and sertraline/sertraline vs. placebo/placebo groups. The Cochran-Mantel-Haenszel (CMH) method was used to compare relapse rates. For continuous efficacy variables, if no baseline value was collected or assessment was a value relative to baseline (CGI-I), a General Linear Model (GLM) of analysis of variance (ANOVA) was used; if there were baseline data, analysis of covariance (ANCOVA) was used with the baseline value as the covariate. The main effects in GLM models were treatment group and baseline if available.

The protocol was approved internally at Pfizer on 4 August 1995, with amendments on 10 October 1995 and 21 March 1996. The SAP for the study was finalized on 7 September 1999. The blind was broken on 7 September 1999 to permit an analysis conducted 18 January 2000 for publication purpose.

Changes from Protocol to SAP

The protocol defined relapse as an increase of CGI-S score by 2 or more points from baseline. The SAP defined relapse as an increase of CGI-S score by 2 or more points from baseline or discontinuation from the study because of lack of efficacy. The change in the SAP was made on August 22, 1999 prior to finalization. The change was motivated by the use of an operational definition of relapse in a study of discontinuation of clonazepam in the treatment of social phobia. The protocol defined three analysis populations: safety, intent-to-treat, and efficacy-evaluable. (The efficacy-evaluable population was defined as all intent-to-treat subjects without protocol violations with a minimum of 4 weeks of double-blind treatment and efficacy evaluations.) However, because of a smaller than anticipated number of subjects in this study (not estimated in the protocol), the analysis of efficacy was limited to the intent-to-treat group as stated in the SAP.

Changes Following Approval of SAP

The SAP used categories of primary and secondary efficacy parameters, predictors, and quality of life/functioning parameters. The protocol did not define predictors as a separate

category. (The SAP defined the following as predictors: total score from the CAS, total score from MADRS, total score from BDI, and total score and agoraphobia factor score of SPAI.) In addition, the secondary efficacy parameters, predictors, and quality of life/functioning parameters were analyzed according to the same methodology. Therefore, the predictors and quality of life/functioning parameters are considered part of the secondary efficacy parameters. The secondary efficacy rating scales are categorized in this report according to whether they are social phobia rating scales, clinical global impression rating scales, mood or anxiety rating scales, or quality of life/functioning rating scales. Two additional efficacy analyses not specified in the SAP were performed: a treatment-by-sex interaction analysis at the p=0.1 level of statistical significance for change from baseline to endpoint in CGI-S score, BSPS total score, and total score for the social phobia factors of the Marks Fear Questionnaire and change from baseline to endpoint in BSPS and FQ-SPS individual item scores were analyzed by ANCOVA. These analyses were considered secondary analyses.

5.5 Study Population

The study is a continuation of study NY-94-004, so the study subjects will be the same as in the previous study, so as the investigational sites.

Baseline patient demographic characteristics including sex, age, race, weight, height for all randomized subjects appeared to be comparable across treatment groups. As shown in Table 5.5.2, the study population included slightly more males than females in the sertraline/sertraline (60%) and sertraline/placebo (68%) groups and slightly less in the placebo/placebo group (47%). Subjects were primarily white: 100% in both the sertraline/sertraline and placebo/placebo groups and 84% in the sertraline/placebo group. The mean age, mean weight and mean height were compatible in three groups. Social phobia was diagnosed a mean of 1.3, 0.3 and 1.2 years prior to study enrollment in study NY-94-004 in the sertraline/sertraline, sertraline/placebo and placebo/placebo group respectively.

Of the 65 subjects randomized to treatment, a total of 3 sertraline/sertraline subjects (12%), 15 sertraline/placebo subjects (60%), and 9 placebo/placebo subjects (60%) discontinued from the study. The most frequent reason for discontinuation was lack of efficacy with 1 (4%) in the sertraline/sertraline group, 8 (32%) in the sertraline/placebo group, and 4 (27%) in the placebo/placebo group (Table 5.5.1). No sertraline/sertraline subjects, 5 (20%) of the sertraline/placebo subjects, and 1 (7%) of the placebo/placebo subjects discontinued due to adverse events.

Table 5.5.1 Discontinuations from Study - All Randomized Subjects

	Sert/Sert		Sert/Placebo		Placebo/Placebo	
Number of Subjects	25		25		15	
Discontinuations						
Related to Study Drug	1	(4.0)	12	(48.0)	5	(33.3)
Adverse event	0		4	(16.0)	1	(6.7)
Lack of efficacy	1	(4.0)	8	(32.0)	4	(26.7)
Not Related to Study Drug	2	(8.0)	3	(12.0)	4	(26.7)
Adverse event	0		1	(4.0)	0	
Others	1	(4.0)	1	(4.0)	2	(13.3)
Other	1	(4.0)	0		1	(6.7)
Protocol violation	0		1	(4.0)	1	(6.7)
Subject defaulted	1	(4.0)	1	(4.0)	2	(13.3)
Lost to follow-up	0		0		1	(6.7)
Withdrawn consent	1	(4.0)	1	(4.0)	1	(6.7)
Total	3	(12.0)	15	(60.0)	9	(60.0)

Baseline severity of illness based on primary efficacy measures (CGI-S score and CGI-I score, Duke BSPS Total Score, FQ-SPS Total Score) appeared to be comparable across treatment groups.

Protocol deviations were categorized as becoming pregnant, being entered into the study despite having failed to satisfy the study entry criteria, and receiving a prohibited concomitant medication. According to these criteria, 8% (2/25) in the sertraline/sertraline group, 4% (1/25) in the sertraline/placebo group, and none in the placebo/placebo group deviated from the protocol. However, the sponsor declared that none of these protocol deviations was thought to have altered the safety or efficacy conclusions presented in the study report.

Table 5.5.2 Baseline Characteristics – All Randomized Patients

	Sert/Sert		Sert/Placebo		Placebo/Placebo	
Number of Subjects	Male 15	Female 10	Male 17	Female 8	Male 7	Female 8
Age (years):						
Mean	34.1	40.8	35.1	36.3	37.3	34.5
SD	8.7	5.8	5.3	8.3	11.7	11.6
Range	23-56	32-49	22-43	20-45	22-55	20-55
Race:						
WHITE	15	10	14	7	7	8
ASIAN	0	0	0	1	0	0
HISPANIC	0	0	3	0	0	0
Weight (kg):						
Mean	79.0	63.4	80.8	68.5	77.6	63.4
SD	14.0	9.9	9.4	19.2	13.4	8.9
Range	60-110	54-78	56-94	44-109	54-93	48-78
N	15	10	17	8	7	8
Height (cm):						
Mean	176.8	162.4	176.4	165.9	178.7	165.5
SD	6.1	7.9	8.2	6.4	7.1	6.8
Range	168-188	151-172	166-196	152-174	167-190	155-173
N	15	9	17	8	7	8

Table 5.5.3 Baseline Primary Efficacy Score - Baseline severity of Illness in Intent-to-Treat Population

Primary Endpoint	Sert/Sert (N = 25)	Sert/Pbo (N = 25)	Pbo/Pbo (N = 15)	p-Value	
				Sert/Sert vs. Sert/Pbo	Sert/Sert vs. Pbo/Pbo
CGI-S Score	2.40 (0.20)	2.52 (0.20)	3.07 (0.26)	0.671	0.044
CGI-I Score	1.40 (0.10)	1.36 (0.10)	1.60 (0.13)	0.777	0.223
BSPS Total Score	17.64 (1.79)	18.72 (1.79)	27.27 (2.32)	0.672	0.002
FQ-SPS Total Score	8.72 (0.99)	9.04 (1.01)	13.80 (1.27)	0.820	0.002

(a) Least square mean and standard error are provided in this row from ANOVA including treatment and center terms. (b) P-values from ANOVA model including treatment and center.

5.6 Sponsor's Efficacy Results

5.6.1 Primary Efficacy Results

For the ITT population, statistically significant differences in favor of the sertraline/sertraline treatment group over the sertraline/placebo treatment group were observed in the analysis of treatment relapse, CGI-S score, BSPS total score, and the FQ-SPS total score. There was no statistically significant difference at endpoint in the rate of treatment responders and in the adjusted mean CGI-I scores between the sertraline/sertraline and sertraline/placebo groups.

At endpoint in the ITT population, treatment relapse had occurred in 1 (4%) and 9 (36%) of sertraline/sertraline and sertraline/placebo groups, respectively (Treatment relapse was defined by a CGI-S score 2 points higher than at baseline or discontinuation due to lack of efficacy.). Most subjects who were classified as meeting relapse criteria as the result of discontinuation due to lack of efficacy. There was a significant difference ($p = 0.040$) in adjusted mean change from baseline of CGI-S score between the sertraline/sertraline group (-0.19) and the sertraline/placebo group (0.48). There was no significant difference in CGI-I score either between the sertraline/sertraline and sertraline/placebo groups or between the sertraline/sertraline and placebo/placebo groups. There was a statistically significant difference ($p = 0.035$) in adjusted mean change of BSPS score in the sertraline/sertraline group (-2.04) compared to the sertraline/placebo group (3.25). There was also a significantly greater improvement ($p = 0.038$) in adjusted mean change of FQ-SPS score in the sertraline/sertraline treatment group (-1.07) than in the sertraline/placebo treatment group (2.16).

There were 15 males and 10 females in the sertraline/sertraline group, 17 males and 8 females in the sertraline/placebo group, and 7 males and 8 females in the placebo/placebo group. There was a statistically significant difference overall between the sertraline/sertraline and sertraline/placebo groups for the results of the treatment-by-sex interaction analysis (not considered a primary efficacy measure), in each of the CGI-S scores ($p = 0.006$), BSPS total score ($p = 0.004$), and total score for FQ-SPS ($p = 0.002$). There was also a significant difference between sertraline/sertraline and sertraline/placebo female subjects, but not between male subjects, for each of the three parameters ($p = 0.003$, $p = 0.003$, and $p = 0.001$, respectively).

5.6.2 Analysis of Time to Relapse

A Kaplan-Meier estimation of the probability of relapse over time, in subjects who either had a CGI-S score 2 points higher during treatment than at baseline or discontinued due to lack of efficacy, showed a statistically significantly longer time to relapse for subjects in the sertraline/sertraline group as compared to the sertraline/placebo group (log-rank test $p = 0.001$).

Table 5.6.1 Primary Efficacy Measure at Endpoint—ITT LOCF Population

Primary Endpoint	Statistic	Sert/Sert (N = 25)	Sert/Pbo (N = 25)	Pbo/Pbo (N = 15)	p-Value	
					Sert/Sert vs. Sert/Pbo	Sert/Sert vs. Pbo/Pbo
Treatment Relapse[a]	No. Subjects (%), Week 24 Cumulative Count	1 (4.0%)	9 (36.0%)	4 (26.7%)	0.005	0.038
CGI-S Score[b]	Baseline	2.40 (0.20)	2.52 (0.20)	3.07 (0.26)	0.671	0.044
	Change from Baseline to Endpoint	-0.19 (0.23)	0.48 (0.22)	0.51 (0.30)	0.040	0.069
Treatment Responders[c]	No. Subjects (%) at Endpoint	5 (20.0%)	6 (24.0%)	2 (13.3%)	0.735	0.596
CGI-I Score[b,d]	Baseline	1.40 (0.10)	1.36 (0.10)	1.60 (0.13)	0.777	0.223
	Endpoint	3.52 (0.32)	4.00 (0.32)	4.00 (0.41)	0.292	0.361
BSPS Total Score[b]	Baseline	17.64 (1.79)	18.72 (1.79)	27.27 (2.32)	0.672	0.002
	Change from Baseline to Endpoint	-2.04 (1.76)	3.25 (1.74)	-0.21 (2.39)	0.035	0.552
FQ-SPS Total Score[b]	Baseline	8.72 (0.99)	9.04 (1.01)	13.80 (1.27)	0.820	0.002
	Change from Baseline to Endpoint	-1.07 (1.08)	2.16 (1.10)	1.39 (1.47)	0.038	0.195

a Treatment relapse defined by a CGI-S score ³2 points higher than at baseline or discontinuation due to lack of efficacy.
b Values given are least square adjusted mean score or least square adjusted mean change and standard error.
c Treatment response defined by CGI-I score of 1 or 2.
d The baseline CGI-I value is the Week 20 value for Study STL-NY-94-004 and the CGI-I value at endpoint is relative to that baseline.

5.6.2 Secondary Efficacy Results

A statistically significantly greater improvement was shown in the sertraline/sertraline group than in the sertraline/placebo group on mean decreases from baseline BSPS fear factor score ($p = 0.033$) and BSPS avoidance factor score ($p = 0.005$). No such significant difference was seen on BSPS physiologic score.

Comparing the sertraline/sertraline to the sertraline/placebo, statistically significant improvement on FQ-SPS was shown for eating and drinking with other people ($p = 0.006$) and speaking or acting to an audience ($p = 0.046$); statistically significant improvement was also shown on the adjusted mean decreases from baseline to endpoint on the CGI-Liebowitz severity of illness ($p = 0.032$), the social phobia subscale of SPAI ($p = 0.013$) and the SPAI total score ($p = 0.006$). No such significant differences of change from baseline to endpoint were shown for the CGI-Liebowitz change of illness total, SADS, or FNE. No such significant difference for either the Physician or Subject Global Impression of Efficacy score was shown.

There was a statistically significant difference favoring the sertraline/sertraline group over the sertraline/placebo group for MADRS ($p = 0.018$) while the clinical significance

of the difference is uncertain. No statistically significant difference was shown between the sertraline/sertraline and sertraline/placebo group for CAS and BDI scores.

For Quality of Life scores, sertraline/sertraline group significantly improved the sertraline/placebo group for the SF-36 scores on role functioning-physical ($p = 0.017$), general health ($p = 0.044$), and vitality ($p = 0.040$) factor. Sertraline/sertraline group also significantly improved the sertraline/placebo group for the total SAS-SR score ($p = 0.013$) and extended family SAS-SR factor score ($p = 0.034$). No such significant improvement was shown for the SDI scores, the SF-36 reported health transition score or the EuroQol score.

5.7 Reviewer's Analysis

The reviewer confirmed the sponsor's analyses according to the protocol.

The reviewer is seriously concern with the change of definition of the primary endpoint Treatment Relapse at the end of the study. In the protocol and its following amendments finished by March 11, 1996, the Treatment Relapse of patients was defined as "their CGI-S score increases by two or more points from their CGI-S score at Week 20 visit". However, on August 22, 1999, as claimed by the sponsor in this submission, which is one week before the breaking of blindness on September 9, 1999, the definition of this critical primary endpoint was changed to "an increase of CDI-S score by 2 or more points from baseline *or discontinuation from the study because of lack of efficacy*". There is no detailed description or any document showing how this decision was made. In fact, according to the sponsor, the finalization of SAP was on September 9, 1999, the day of breaking of blindness. This SAP was not submitted to us. Such a change totally changed the conclusion of the study. Using the original definition, the Sertraline/Sertraline group has 1 Treatment Relapse and the Sertraline/Placebo group has 5 Treatment Relapses and the CMH test gives a p-value of 0.085. Using the new definition however, the Treatment Relapse of Sertraline/Placebo increases to 9 while the Treatment Relapse in the Sertraline/Sertraline group is still 1, so the CMH test gives a p-value of 0.005.

This reviewer hasn't found any documents related to the change of the definition of the primary endpoint Treatment Relapse in this submission, so we cannot make the judgement regarding such a process. The sponsor should provide official documents to show detailed decision-making procedure, that may include the original documents of the time of a possible internal meeting, the personnel that attended the meeting, and meeting minutes. The sponsor should also provide copies of SAP pre and post the meeting.

In the original protocol and its amendments, no plans of analysis of "time to relapse" were made. The sponsor declared to have the information for each patient who withdrew before the end of the study in Section 13, but such information was not found in the submission.

The normality assumption for CGI-S score does not hold by the Shapiro-Wilk test. The Wilcoxon nonparametric test was performed on the change from baseline as well as the

percentage change from baseline, i.e. the change of the endpoint value from the baseline divided by baseline. Similarly, the normality assumption of FQ-SPS total score is not valid in the Sert/Placebo group. The p-values of the nonparametric tests are given in Table 5.7.2. The significant tests using Wilcoxon statistic on CGI-S score do not show statistical significant difference, therefore our results do not support the conclusion of the sponsor on these two endpoints. Given that the normality failed, medians of the change from baseline at Week 24 are calculated, which are also given in Table 5.7.2.

The normality assumption holds for BSPS Total score so no nonparametric analysis is made for this endpoint. Since CGI-I score is not statistically significant in the significant test between sertraline/sertraline and sertraline/placebo, the nonparametric test is not performed.

Table 5.7.1 Normality Test for the Primary Endpoints at Week 24 — ITT Population.

Parameter	P-Value*	
	Sert/Sert	Sert/Placebo
CGI-S Score		
Change from baseline	0.001	0.034
FQ-SPS Total Score		
Change from baseline	0.78	0.0024

p-values are derived using Shapiro-Wilk test.

Table 5.7.2 Nonparametric Test of Primary Endpoints at Week 24 — ITT Population.

Parameter	Median		P-Value*
	Sertraline	Placebo	
CGI-S Score			
Change from baseline	0.0	0.0	0.1324
Percentage change from baseline	0.0	0.0	0.1765
FQ-SPS Total Score			
Change from baseline	0.0	0.0	0.1591
Percentage change from baseline	0.0	0.0	0.5951

p-values are derived using Wilcoxon nonparametric test.

Although there are multiple primary endpoints, we only choose one endpoint CSI-S Score and check how much the results is influenced by single investigators. The number of subjects on each treatment arm and the t-value for the treatment difference for each investigator are presented in Table 5.7.2. In this table, Nsert/Nsert and Nsert/NPlbo represent the number of patients in Sertraline/Sertraline and Sertraline/Placebo groups, respectively. T-Value is TTEST statistic performed on the difference of the mean changes from baseline for unequal variances between two treatment groups.

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Statistical Summary

DATE:	**March 19, 2002 (45 day filing meeting)**
NDA NO.:	**19-839**
DRUG NAME:	**Zoloft (Sertraline HCl)**
SPONSOR:	**Pfizer**
INDICATION:	**Social Phobia**
DOSES STUDIED:	**Sertraline 50-200 mg/day, flexible dosing**
STUDY:	**R-0601, STL-NY-94-004, STL-NY-94-004C. STL-NY-95-003**

Tables of Controlled Clinical Studies:

1. Controlled Acute Treatment Studies

Protocol #	Study Design	Sertraline Dosage (qd)	Safety Evaluable N Sertraline/Placebo	Primary Efficacy Measures
R-0601 Multicenter 20 US sites	Randomized Double-blind Placebo-controlled Parallel group Flexible-dose 12 weeks double-blind treatment 1 week single-blind placebo run-in Up to 2 weeks taper period	25 mg/day for first week of double-blind treatment 50-200 mg/day thereafter PM dosing (may switch to AM dosing)	209/199	CGI-I, LSAS
STL-NY-94-004 Multicenter 10 Canadian sites	Randomized Double-blind Placebo-controlled Parallel group Flexible dosing 20 weeks double-blind treatment 1 week single-blind placebo run-in	50 mg/day during Weeks 1-4 50-200 mg/day thereafter PM dosing (may switch to AM dosing)	135/69	CGI-I, BSPS, FQ-SPS

2. Controlled Long-Term Relapse Prevention Study

Protocol #	Study Design	Sertraline Dosage (qd)	Safety Evaluable N	Primary Efficacy Measures
STL-NY-94-004C Multicenter 10 Canadian sites	Randomized Double-blind Placebo-controlled Parallel group Relapse prevention extension of STL-NY-94-004 24 weeks double-blind treatment	The dosage level attained at the end of STL-NY-94-004 (50-200 mg/day) was maintained in the absence of limiting adverse events. PM dosing (may switch to AM dosing)	Sertraline/Sertraline 25 Sertraline/Placebo 25 Placebo/Placebo 15	CGI-I, CGI-S, BSPS, FQ-SPS

3. Controlled Other Studies

Protocol #	Study Design	Sertraline Dosage (qd)	Safety Evaluable N Sertraline/Placebo	Primary Efficacy Measures
STL-N/S-95-003 Multicenter 47 Norwegian/Swedish sites	Randomized Double-blind Placebo-controlled Parallel-group Flexible-dose	50 mg/day during Weeks 1-4 50-150 mg/day thereafter PM dosing (may switch to AM dosing)	196/191	CGI-I, SPS

R-0601: Primary Efficacy Parameters at Endpoint—Intent-to-Treat Population

Primary Efficacy Parameters	Sertraline (N=205) N (%)	Placebo (N=196) N (%)	P-value
Treatment responders [1] (%) at Endpoint	96.0 (46.8)	50.0 (25.5)	0.001
LSAS Total Score			
Baseline (SE) 2	90.8 (1.11)	93.2 (1.13)	0.118
Endpoint (SD) [3]	60.3 (28.13)	72.2 (27.75)	
Change from baseline (SE) 2	-31.3 (1.87)	-21.4 (1.90)	0.001

1. Defined as subjects with a CGI-I rating of 1 or 2. Values are least square adjusted mean scores or changes from baseline to endpoint and standard errors. [3] Values are mean scores and standard deviations.

STL-NY-94-004: Primary Efficacy Parameters at Endpoint–ITT Population

Primary Efficacy Parameters	Sertraline (N=134)	Placebo (N=69)	p-value
Treatment Responders[1] (%) at Endpoint	71.0 (53.0)	20 (29.0)	0.001
Duke BSPS Total Score[2]			
Baseline	47.26 (0.79)	45.65(1.10)	
Change from baseline	-16.44 (1.22)	-8.56 (1.71)	0.001
Duke BSPS Fear Factor Score			
Baseline	19.62 (0.32)	19.13 (0.45)	
Change from baseline	-6.61 (0.51)	-3.07 (0.71)	0.001
Duke BSPS Avoidance Factor Score[2]			
Baseline	19.60 (0.35)	19.57 (0.49)	
Change from baseline 2	-6.65 (0.54)	-3.40 (0.75)	0.001
Duke BSPS Physiologic Factor Score			
Baseline	8.04 (0.29)	6.95 (0.40)	
Change from baseline 2	-3.16 (0.26)	-2.09 (0.36)	0.016
FQ-SPS Total Score 2			
Baseline	23.14 (0.59)	21.63 (0.82)	
Change from baseline	-7.84 (0.68)	-2.60 (0.94)	0.001

[1]Defined as subjects with a CGI-I of 1 or 2. [2]Values are least square adjusted mean scores or least square adjusted mean changes from baseline to endpoint and standard errors. [2]All baseline scores were comparable different between groups except the BSPS physiologic factor score (p = 0.027).

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

19-839/S-045

20-990/S-011

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

CLINICAL PHARMACOLOGY/BIOPHARMACEUTICS REVIEW

DRUG: Zoloft® (Sertraline HCL) **PRIMARY REVIEWER:** Andre Jackson
NDA:19-839/SEI-045
20-990/SEI-011 **TYPE: New Indication Supplement**
FORMULATION:Tablets/Oral Concentrate **STRENGTH: 25, 50 and 100 mg tablets, 20 mg liquid concentrate**
APPLICANT: Pfizer Inc. **SUBMISSION DATE: 1-18-02**
8-15-02

EXECUTIVE SUMMARY

The sponsor is proposing a new indication (i.e., social anxiety disorder) for Zoloft® sertraline. This new indication is based upon two successful clinical studies (STL NY-94-004-50 mg research capsule) and (R-0601-25 mg and 50 mg commercial tablets). The sponsor intends to continue marketing the current tablet formulation for this new indication. Although a bioequivalence study was not essential since the commercial tablets, at a lower strength were used in the pivotal study R-0601, the firm submitted the data from earlier bioequivalence studies in order to provide a link between the two dosage forms (i.e., capsules and tablets). The sponsor conducted bioequivalence studies under protocols 050-006, 050-008 and 050-009. Study 050-006 was a relative bioavailability study comparing the 100 mg commercial capsule and the 100 mg research capsule to a solution. Study 050-008 compared the 100 mg tablet and the 100 mg commercial capsule to the 100 mg research capsule as the reference while study 050-009 compared the 100 mg commercial tablet to the 100 mg research capsule as the reference.

The bioequivalence data from 050-009 has been reanalyzed by the firm applying the current 90% confidence intervals (CI) for AUC and Cmax. The 90% CI indicated that the 100 mg research capsule and the 100 mg commercial tablet were bioequivalent.

The in vitro dissolution method used the current NDA method. The 100 mg commercial tablet is compositionally proportional to the 25 mg and 50 mg commercial tablets used in the clinical efficacy studies for social anxiety disorder. The 25 mg and 50 mg tablets used in the current clinical studies for social anxiety pass the specification [Q= [redacted] in 30 min] using the NDA dissolution method.

The sponsor's proposed label changes of the currently approved label relates to specific information about social anxiety disorder with no changes in the pharmacokinetics section.

Recommendation: The bioequivalence studies provided in this new indication supplement for Zoloft submitted to the Division of Neuropharmacological Drug Products to fulfill the new claims supports the bioequivalence of the research capsule and the commercial tablet. This submission is acceptable from the OCPB perspective.

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Overall Summary of Findings: The sponsor is proposing a new indication for Zoloft® sertraline (i.e., social anxiety disorder). This new indication is based upon two successful clinical studies (STL NY-94-004-50 mg research capsule) and (R-0601-25 mg and 50 mg commercial tablets). The sponsor intends to continue marketing the current marketed tablet formulation for this new indication. Although a bioequivalence study was not essential since the commercial tablets, at a lower strength were used in the pivotal study R-0601, the firm submitted the data from earlier bioequivalence studies in order to provide a link between the two clinical studies for social anxiety disorder. The sponsor conducted bioequivalence studies under protocols 050-006, 050-008 and 050-009. Study 050-006 was a relative bioavailability study comparing the 100 mg commercial capsule and the 100 mg research capsule to a solution. Study 050-008 compared the 100 mg commercial tablet and the 100 mg commercial capsule to the 100 mg research capsule as reference while study 050-009 compared the 100 mg commercial tablet to the 100 mg research capsule.

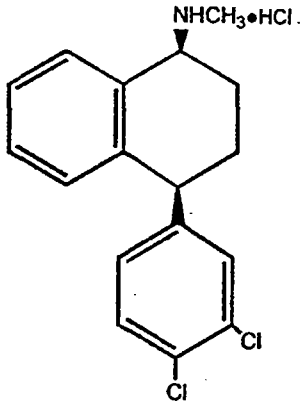
This Clinical Pharmacology/Biopharmaceutics review will focus only on results from the study 050-009 which gives a direct link between commercial tablets and research capsules since all of these studies have been submitted and previously reviewed by OCPB. The bioequivalence data from 050-009 has been reanalyzed by the firm applying the current 90% confidence intervals (CI) for AUC and Cmax. The 90% CI indicated that the 100 mg commercial tablet was bioequivalent to the 100 mg research capsule.

The 25 mg and 50 mg tablets used in the current clinical studies for social anxiety disorder pass the specification [Q= ——— in 30 min] using the NDA dissolution method.

Recommendation: The bioequivalence studies provided in this new indication supplement for Zoloft submitted to the Division of Neuropharmacological Drug Products to fulfill the new claims supports the bioequivalence of the research capsule and the commercial tablet. This submission is acceptable from the OCPB perspective.

Introduction and Background:

ZOLOFT® (sertraline hydrochloride) is a selective serotonin reuptake inhibitor (SSRI) for oral administration. It has a molecular weight of 342.7. Sertraline hydrochloride has the following chemical name: (1S-cis)-4-(3,4-dichlorophenyl)-1,2,3,4-tetrahydro-N-methyl-1-naphthalenamine hydrochloride. The empirical formula $C_{17}H_{17}NCl_2 \cdot HCL$ is represented by the following structural formula:



Sertraline hydrochloride is a white crystalline powder that is slightly soluble in water and isopropyl alcohol, and sparingly soluble in ethanol. ZOLOFT is supplied for oral administration as scored tablets . The mechanism of action of sertraline is presumed to be linked to its inhibition of CNS neuronal uptake of serotonin (5HT). Studies at clinically relevant doses in man have demonstrated that sertraline blocks the uptake of serotonin into human platelets. *In vitro* studies in animals also suggest that sertraline is a potent and selective inhibitor of neuronal serotonin reuptake and has only very weak effects on norepinephrine and dopamine neuronal reuptake. *In vitro* studies have shown that sertraline has no significant affinity for adrenergic (alpha1, alpha2, beta), cholinergic, GABA, dopaminergic, histaminergic, serotonergic (5HT1A, 5HT1B, 5HT2), or benzodiazepine receptors; antagonism of such receptors has been hypothesized to be associated with various anticholinergic, sedative, and cardiovascular effects for other psychotropic drugs. The chronic administration of sertraline was found in animals to downregulate brain norepinephrine receptors, as has been observed with other drugs effective in the treatment of major depressive disorder. Sertraline does not inhibit monoamine oxidase. In man, following oral once-daily dosing over the range of 50 to 200 mg for 14 days, mean peak plasma concentrations (Cmax) of sertraline occurred between 4.5 to 8.4 hours post-dosing. The average terminal elimination half-life of plasma sertraline is about 26 hours. Based on this pharmacokinetic parameter, steady-state sertraline plasma levels should be achieved after approximately one week of once-daily dosing. Linear dose-proportional pharmacokinetics were demonstrated in a single dose study in which the Cmax and area under the plasma concentration time curve (AUC) of sertraline were proportional to dose over a range of 50 to 200 mg. Consistent with the terminal elimination half-life, there is an approximately two-fold accumulation, compared to a single dose, of sertraline with repeated dosing over a 50 to 200 mg dose range. The single dose bioavailability of sertraline tablets is approximately equal to an equivalent dose of solution.

In a relative bioavailability study comparing the pharmacokinetics of 100 mg sertraline as the oral solution to a 100 mg sertraline tablet in 16 healthy adults, the solution to tablet ratio of geometric mean AUC and Cmax values were 114.8% and 120.6%, respectively. 90% confidence intervals (CI) were within the range of 80-125% with the exception of the upper 90% CI limit for Cmax which was 126.5%.

The effects of food on the bioavailability of the sertraline tablet and oral concentrate were studied in subjects administered a single dose with and without food. For the tablet, AUC was slightly increased when drug was administered with food but the Cmax was 25% greater, while the time to reach peak plasma concentration (Tmax) decreased from 8 hours post-dosing to 5.5 hours. For the oral concentrate, Tmax was slightly prolonged from 5.9 hours to 7.0 hours with food.

Sertraline undergoes extensive first pass metabolism. The principal initial pathway of metabolism for sertraline is N-demethylation. N-desmethylsertraline has a plasma terminal elimination half-life of 62 to 104 hours. Both *in vitro* biochemical and *in vivo* pharmacological testing have shown N-desmethylsertraline to be substantially less active than sertraline. Both sertraline and N-desmethylsertraline undergo oxidative deamination and subsequent reduction, hydroxylation, and glucuronide conjugation. In a study of radiolabeled sertraline involving two healthy male subjects, sertraline accounted for less than 5% of the plasma radioactivity. About 40-45% of the administered radioactivity was recovered in urine in 9 days. Unchanged sertraline was not detectable in the urine. For the same period, about 40-45% of the administered radioactivity was accounted for in feces, including 12-14% unchanged sertraline.

Desmethylsertraline exhibits time-related, dose dependent increases in AUC (0-24 hour), Cmax and Cmin, with about a 5-9 fold increase in these pharmacokinetic parameters between day 1 and day 14.

Current Submission:

The current submission contains the reanalysis of bioequivalence study data previously submitted to the FDA in 1987-1988 comparing:

1.Study 050-006-relative bioavailability-100 mg commercial capsule and the 100 mg research capsule to a solution.

2. Study 050-008-comparing the 100 mg commercial tablet and the 100 mg research capsule to the 100 mg commercial capsule as reference.

3.Study 050-009 comparing the 100 mg commercial tablet to the 100 mg research capsule.

These studies were submitted to establish a bioequivalence link between the capsule and tablet formulations used in clinical efficacy studies for social anxiety disorder (STL NY-94-004-50 mg research capsule) and (R-0601-25 mg and 50 mg commercial tablets). Only study 050-009 will be reviewed for this NDA since it has the only direct comparison between the research capsule and commercial tablet.

CLINICAL PHARMACOLOGY

QUESTION BASED REVIEW

Are the 100 mg commercial tablets bioequivalent to the 100 mg research capsules.

In a single dose bioequivalence study 005-009 the sponsor compared the 100 mg commercial tablets to the 100 mg research capsules in 18 subjects. Point estimates and 90% CI for Cmax and AUC(0-inf) were: 99.5% (90.0-110.0); 96% (90.0-112.5).

Are the formulations for the 25 mg and 50 mg tablets used in the clinical studies for social anxiety disorder compositionally proportional to the 100 mg tablet used in the bioequivalence study,

FORMULATION AND DISSOLUTION

Qualitative/Quantitative Compositions for Formulations

Sertraline Hydrochloride Film Coated Tablets:
25 mg, 50 mg and 100 mg, Formulation IDS: US Marketed Tablets

Component	Grade	25 mg tablet Mg. Per Tablet	50 mg tablet Mg Per Tablet	100 mg tablet Mg Per Tablet
Sertraline Hydrochloride	Pfizer	[redacted]	[redacted]	[redacted]
Dibasic Calcium Phosphate, Dihydrate	USP	[redacted]	[redacted]	[redacted]
Microcrystalline Cellulose	NF	[redacted]	[redacted]	[redacted]
Hydroxypropyl Cellulose	NF	[redacted]	[redacted]	[redacted]
Purified Water	USP	(as required)	(as required)	(as required)
Sodium Starch Glycolate		[redacted]	[redacted]	[redacted]
Magnesium Stearate	NF	[redacted]	[redacted]	[redacted]
[redacted] Light Green	Pharm	[redacted]	[redacted]	[redacted]
[redacted] Light Blue	Pharm	[redacted]	[redacted]	[redacted]
[redacted] Light Yellow	Pharm	[redacted]	[redacted]	[redacted]
Total mg/unit		[redacted]	[redacted]	[redacted]

The 50 mg and 25 mg tablets used in the clinical study are compositionally proportional to the 100 mg commercial tablets used in the bioequivalence study and they also have comparable dissolution and met the dissolution specification for sertraline of Q=[redacted] in 30 min.

Conclusion:

These results show that the 100 mg commercial capsules and 100 commercial tablets are bioequivalent.

Labeling comments:

The sponsor's proposed label changes of the currently approved label relates to specific clinical information about social anxiety disorder with no changes in the pharmacokinetics section.

Andre J. Jackson, Ph.D.
Reviewer, Neuropharmacological Drug Section, DPE I
Office of Clinical Pharmacology and Biopharmaceutics

R. Baweja 10/21/02

Concurrence: Ray Baweja, Ph.D.
Team Leader, Neuropharmacological Drug Section, DPE I
Office of Clinical Pharmacology and Biopharmaceutics

cc: HFD-120 NDA 19-839 SEI-045
20-990 SEI-011
/MO/ A. Mosholder
HFD-860 /CSO/P. David
/Biopharm/A. Jackson
/TL Biopharm/R. Baweja
/DD DPE1/M. Mehta

APPENDIX

Phase 1 Study 050-009

Objective: To determine the bioequivalence of a commercial tablet formulation to the research capsule of sertraline in a two-way crossover study.

Summary: The comparison of a tablet formulation with the research capsule by AUC, Cmax and Tmax indicated that bioequivalence was achieved. Using the research capsule as the reference formulation, the percentage differences were -3.4%, point estimate 0.96, for AUC (90% confidence limits of 90-112%) and -1.4%, point estimate 0.99, for Cmax (90% confidence limits of 90-110%). The overall mean values for Tmax and half-life were 6.0 hours and 19 hours, respectively, and did not differ by formulation administered.

Methods: This study was an open crossover design, in 18 subjects, comparing the bioequivalence of two formulations of sertraline. 100 mg dosage strengths of a tablet (FID# JV-87-032) and the research capsule (FID# JV-82-004) were used. Each subject received a single dose of each of the two formulations, separated by an interval of at least 14 days. Subjects fasted overnight for 10-12 hours prior to dosing and continued to fast for 4 hours following drug administration after which they each received an identical standard meal. Subjects were randomly divided into drug order groups based on order of entry into the study. Each dose was administered in the morning with 240 ml of water.

Blood sufficient to provide 5 ml plasma samples was collected in ——— tubes at hours 0 (baseline just prior to dosing) and at 1, 2, 4, 6, 8, 12, 16, 24, 36, 48, 72, and 96 hours post-dosing. The plasma was

Plasma samples were assayed for sertraline using a ——— method (see Appendix A). The lower limit of quantitation was — ng/ml. In this particular study, a single standard curve over the concentration range of ——— ng/ml was utilized. Plasma samples with concentrations of sertraline above the upper limit of quantitation were re-assayed using a smaller sample aliquot. Plasma concentrations less than— ng/ml were reported as zero.

Area under the plasma concentration-time curve (AUC) from time zero to the last time t-with a measurable concentration (Cp) was calculated using a linear trapezoidal approximation. AUC from time t to infinity was calculated by C /Kel, with Kel being the elimination rate constant. AUC(0-inf) was the sum of AUC0-t) + AUCext. Kel was calculated by least squares regression of log plasma concentrations from 12 hours to the last measurable time point used in the calculation. The elimination half-life (t /2) was calculated

by 0.693/Kel. The maximum plasma concentration (Cmax) was determined by inspection of the plasma concentrations and Tmax was defined as the time where Cmax was first observed.

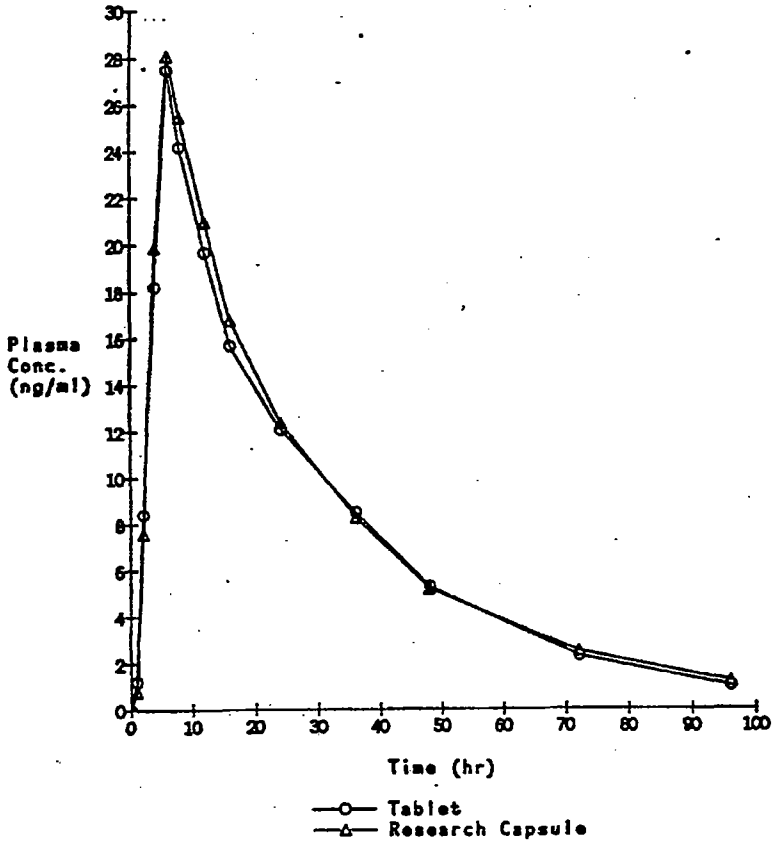
Results:

Subject demographic characteristics:

Number of subjects	18-All males
15-44	18
Mean Age(yrs) Range	26.5 20-43
Mean weight Weight range	72.5 61.8-83.6
White Black Other	14 3 1

000087

FIGURE 1.
Sertraline Plasma Concentrations Following a 100 mg Tablet or Research Capsule Dose. (mean data of 18 subjects)
Bioequivalence Study #009-599.



next

6 98

Figure 1. Mean plasma concentration graph for 100 mg commercial tablet and research capsule formulation in study 050-009.

Analytical

The assay methodology provided for Study 050-009 is the same assay method used in Studies 050-006 and 050-008.

Table 1. Results for the low calibration curve

Concentration Added(ng/ml)	Concentration Found(sd)	%CV	Accuracy %
[redacted]	[redacted](0.13)	12	109
[redacted]	[redacted](0.15)	6.1	100
[redacted]	[redacted]0.32)	6.6	97
[redacted]	[redacted]0.54)	7.3	99
[redacted]	[redacted](0.46)	4.5	101
[redacted]	[redacted](0.40)	3.2	100

Table 2. Validation data for the high calibration curve

Concentration Added(ng/ml)	Concentration Found(sd)	%CV	Accuracy %
[redacted]	[redacted]0.35)	7.9	89
[redacted]	[redacted]0.50)	5.1	98
[redacted]	[redacted](0.91)	4.4	104
[redacted]	[redacted]0.85)	2.8	101
[redacted]	[redacted]1.2)	3.1	99
[redacted]	[redacted]2.40)	5.1	96

Assay Stability:

Seven month stability data for Study 050-009 is provided below:

[redacted] Frozen Human Plasma Stability

Plasma Concentration (ng/mL)

Nominal Conc.	Time 0 wk	1 wk	4 wk	3 mo	7 mo
[redacted]					
[redacted]					

Study dates and assay dates for studies 050-006, 050-008, and 050-009 are provided below:

Study	Day 1 of Dosing	Final PK Sample	Final Assay
050-006	06-Jan-87	09-Mar-87	23-Apr-87
050-008	01-May-87	10-Jul-87	17-Sept-87
050-009	14-Feb-88	03-Mar-88	29-Apr-88

The frozen human plasma stability study for Sertraline is acceptable since it covers the longest period for sample storage of 5 months.

Table 3. Summary of pharmacokinetic parameters in male subjects. Values are mean (sd).

Parameter	Commercial Tablet	Research Capsule	Ratio(tablet/capsule)
AUC(0-inf) ng.hr/ml	794(409)	822(461)	0.96
Cmax ng/ml	27.8(6.9)	28.2(8.6)	0.99
Tmax,hr	6.0(1.2)	6.1(0.5)	0.99
Kel,hr-1	0.0353(0.0068)	0.0366(0.0095)	0.97
T1/2 ,hr	19.6*	18.9*	1.04

* Harmonic mean

Table 4.Confidence Intervals for study 050-009

Study 050-009	
Capsule treatment as reference	
Parameter	Tablet/Capsule
AUC(0-inf)	(90.0%,112.5%)
Cmax	(90.9%,110.0%)

Drug Dissolution: The current method and specification for the tablets are: USP Apparatus II(paddle), 900 ml of pH 4.5 0.05 M sodium acetate buffer, 75 rpm, samples collected at: 15 min, 30 min, 45 min and 60 min with [redacted] dissolution in 30 min.

FIRM	PFIZER GLOBAL RESEARCH AND DEVELOPMENT, GROTON LABORATORIES,						PFIZER INC	
DRUG	SERTRALINE HYDROCHLORIDE							
NDA	19-839							
			- Drug Product Dissolution Testing					
		Lot Number/			Speed of	Collection		
	Dosage Form	Formulation ID/	Dissolution	Medium and	Rotation	Times	Number of Units Tested/	Individual Data Points
	And Strength	(Study Number)	Apparatus	Temperature	(rpm)	(min)	%Label Claim Dissolved	(%Label Claim Dissolved)
							6 Capsules	6 Capsules
						15	[redacted]	[redacted]
Sertraline HCl		ED-G-138-X86/		pH 4.5,				
100 mg		JV-82-004	USP 2	0.05 M sodium	75	30	[redacted]	[redacted]
Capsules		(Study 050-008		acetate buffer				
		and 050-009)		37° C±0.5°C		45	[redacted]	[redacted]
						60	[redacted]	[redacted]
							6 Tablets	6 Tablets
						15		
							[redacted]	[redacted]
Sertraline HCl		ED-G-222-987/		pH 4.5,				
						30		

100 mg Tablets		JV-87-032	USP 2	0.05 M sodium	75			
		(Study 050-009)		acetate buffer				
						45		
						60		

		Lot Number/			Speed of	Collection		
	Dosage Form	Formulation ID/	Dissolution	Medium and	Rotation	Times	Number of Units Tested/	Individual Data Points
	and Strength	(Study Number)	Apparatus	Temperature	(rpm)	(min)	%Label Claim Dissolved	(%Label Claim Dissolved)
							6 Capsules	6 Capsules
	Sertraline HCl	D950409/		pH 4.5,		15		
	50 mg	JV-87-027	USP 2	0.05 M sodium				
	Capsules	(Study STL-NY-		acetate buffer	75	30		
		94-004 and STL-		37^0 C±O.5^{0}C				
		NY-94-004C)				45		
						60		
							6 Tablets	6 Tablets
						15		
	Sertraline HCl	ED-G-054-387/		pH 4.5,				
	100 mg Tablet	JV-87-032	USP 2	0.05 M sodium	75	30		
		(Study 050-008)		acetate buffer				

				37^0 C+O.5^{0}C		45		
						60		
	Dosage Form and Strength	Lot Number/ Formulation ID/ (Study Number)	Dissolution Apparatus	Medium and Temperature	Speed of Rotation (rpm)	Collection Times (min)	Number of Units Tested/ %Label Claim Dissolved	Individual Data Points (%Label Claim Dissolved)
							6 Tablets	6 Tablets
						15		
	Sertraline HCl	N8073-G2/		pH 4.5,				
9198	25 mg Tablet	QC2186	USP 2	0.05 M sodium	75	30		
		(Study R-0601)		acetate buffer				
				37^0 C+O.5^{0}C		45		
						60		
							6 Tablets	6 Tablets
						15		
	Sertraline HCl	N8033-GI/		pH 4.5,				
2199	50 mg Tablet	QC1457	USP 2	0.05 M sodium	75	30		
		(Study R-0601)		acetate buffer				
				37^0 C+O.5^{0}C		45		
						60 (')		
	"Based on the current specification, a 60 minute sample was not performed.							

	Office of Clinical Pharmacology and Biopharmaceutics						
	New Drug Application Filing and Review Form						
		General Information About the Submission					
		Information					Information
NDA Number	19-839 (SEI-045)/20-990 (SEI-011			Brand Name		Zoloft®	
OCPB Division (I, II, III)	I			Generic Name		Sertraline	
Medical Division	Neuropharmacology			Drug Class		SSRI	
OCPB Reviewer	Andre Jackson, Ph.D.			Indication(s)		Social Anxiety Disorder	
OCPB Team Leader	Ray Baweja, Ph.D.			Dosage Form		25, 50, and 100 mg tablets, 20 mg/ml liquid concentrate	
				Dosing Regimen		50-200 mg/day flexible dosing	
Date of Submission	1/18/02			Route of Administration		Oral	
Estimated Due Date of OCPB Review	8/15/02			Sponsor		Pfizer	
PDUFA Due Date	11/22/02			Priority Classification		Standard	
Division Due Date	9/1/02						
		Clin. Pharm. and Biopharm. Information					
		"X" if included at filing	Number of studies submitted		Number of studies reviewed	Critical Comments If any	
STUDY TYPE							
Table of Contents present and sufficient to locate reports, tables, data, etc.		X					
Tabular Listing of All Human Studies		X					
HPK Summary		X					
Labeling		X					
Reference Bioanalytical and Analytical Methods		X					
I. Clinical Pharmacology							
Mass balance:							
Isozyme characterization:							
Blood/plasma ratio:							
Plasma protein binding:							
Pharmacokinetics (e.g., Phase I) -							
Healthy Volunteers-							
	single dose:						
	multiple dose:						
Patients-							
	single dose:						
	multiple dose:						
Dose proportionality -							
fasting / non-fasting single dose:							
fasting / non-fasting multiple dose:							
Drug-drug interaction studies -							

In-vivo effects on primary drug:							
In-vivo effects of primary drug:							
	In-vitro:						
Subpopulation studies -							
	ethnicity:						
	gender:						
	pediatrics:						
	geriatrics:						

	renal impairment:				
	hepatic impairment:				
PD:					
	Phase 2:				
	Phase 3:				Clinical Efficacy Trials that
					used both tablets and capsules
PK/PD:					
Phase 1 and/or 2, proof of concept:					
	Phase 3 clinical trial:				
Population Analyses -					
	Data rich:				
	Data sparse:				
II. Biopharmaceutics					
Absolute bioavailability:					
Relative bioavailability -					
	solution as reference:				
alternate formulation as reference:					
Bioequivalence studies -					
traditional design; single / multi dose:		X	3	1	Studies 050-006, 050-008, and
					050-009 were conducted to
					compare the capsules and
					tablets used in the clinical
					trials.
replicate design; single / multi dose:					
Food-drug interaction studies:					
Dissolution:		X	1	1	
(IVIVC):					
Bio-waiver request based on BCS					
BCS class					
III. Other CPB Studies					
Genotype/phenotype studies:					
Chronopharmacokinetics					
Pediatric development plan					
Literature References					
Total Number of Studies			4	2	

Background:

Zoloft® is a selective serotonin reuptake inhibitor (SSRI) for oral administration. Clinically, sertraline is indicated for the treatment of depression, obsessive-compulsive disorder, panic disorder, and posttraumatic stress disorder. In addition, sertraline has received an approvable letter for the treatment of premenstrual dysphoric disorder (PMDD). In the current submission, the sponsor is proposing a new indication for sertraline to treat social anxiety disorder. For this new indication to be submitted in a supplemental NDA, the sponsor has conducted three trials in order to evaluate the clinical efficacy of sertraline on social phobia.
In the three clinical studies that the sponsor conducted, both capsule (Studies STL-NY-94-004 and STL-N/S-95-003) and tablet (Study R-0601) formulations of sertraline were administered to patients. The sponsor intends to market the current marketed tablet formulation for this new indication. In order to link the clinical studies together, the sponsor conducted bioequivalence (BE) studies to compare the bioavailability of the two formulations used. As a result of conducting the BE studies, the sponsor discovered that the commercial capsule (FID# JV 86-013) that was used in the clinical trials was not bioequivalent to the marketed tablet (FID# JV 87-032) and research capsule (FID# JV 82-004) based on Study 050-008. Prior to this submission, the sponsor submitted results of Study 050-009 in the original NDA, resulting in the conclusion that the marketed tablet and research capsule formulations were bioequivalent. In Study 050-006, the sponsor determined that the research capsule (FID# JV 82-004) was bioequivalent to the commercial capsule (FID# JV 86-013).
During the internal discussion held on November 7, 2001, the division of Neuropharmacological Drug Products discussed the sponsor's proposal. The medical officer stated that the clinical trials (R-0601 and STL-NY-94-004) according to the sponsor demonstrate efficacy for sertraline in the treatment of social phobia. Since commercial tablets were used in one of the pivotal studies (R-0601), BE information is not absolutely critical. The three BE studies among tablets and capsules (050-006, -008, and –009) along with dissolution data can be reviewed and used as supportive data. In addition, during the review, the median effective doses in both trials, 0601 and 004, will be compared to see if results are similar when tablets and capsules are used.
Filability and QBR comments
"X" if yes Comments
Application filable ? X
Comments sent to firm ? Comments were communicated to the firm on 11/8/01, that the supplement should include full reports of the BE studies (050-006, -008, and –009), a re-analysis of the pharmacokinetic parameters in these 3 studies using current BE tests and employing as the reference the lots corresponding to the commercial tablet formulation. In addition, the complete set of individual dissolution data on all formulations, and the rationale underlying their assessment of the BE relationship of the capsule and tablet be included (See review of submission dated 11/14/01).
QBR questions (key issues to be considered) 1. Are the capsules and tablet formulations used in the clinical trials bioequivalent?
2. Does a dose-response relationship exist for Zoloft in the treatment of Social Anxiety Disorder?
Other comments or information not included above
Primary reviewer Signature and Date
Secondary reviewer Signature and Date
CC: NDA 19-839 (SEI-045)/20-990 (SEI-011), HFD-850 (Lee), HFD-120 (Homonnay), HFD-860 (Jackson, Baweja, Marroum, Mehta), CDR (Clin. Pharm./Biopharm.)

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS (OCPB) REVIEW

NDA: **19-839/20-990** Submission Date: **10/26/01**

OCPB Receipt Date: **11/1/01**

Drug:	**Zoloft® (Sertraline HCl)**
Strength(s):	**25, 50, and 100 mg tablets, 20 mg/ml liquid concentrate**
Indications:	**Social Anxiety Disorder**
Applicant:	**Pfizer (Groton, CT)**
Type:	**Pre-sNDA Meeting Briefing Document**
Date of Review:	**11/9/01**
Primary Reviewer:	**Gerald J. Fetterly, Ph.D.**

Background:

Zoloft® is a selective serotonin reuptake inhibitor (SSRI) for oral administration. Clinically, sertraline is indicated for the treatment of depression, obsessive-compulsive disorder, panic disorder, and posttraumatic stress disorder. In addition, sertraline has received an approvable letter for the treatment of premenstrual dysphoric disorder (PMDD). In the current submission, the sponsor is proposing a new indication for sertraline to treat social anxiety disorder. For this new indication to be submitted in a supplemental NDA, the sponsor has conducted three trials in order to evaluate the clinical efficacy of sertraline on social phobia.

In the current submission, the sponsor had one clinical pharmacology question that stated:

1. ***Are the clinical studies and the available bioequivalence information summarized in the briefing document sufficient to support the social phobia indication?***

Table 1

Table 1. Sertraline NDA Bioequivalence Studies – Formulations Compared and Outcomes

Study	N (enrolled)	N (PK evaluable)	Formulation A	Formulation B	Study Conclusion
050-006 (3 way open single dose crossover)	25	24	FID# JV 82-004 lot# ED-G-164-X83 100 mg research cap	FID# JV 86-013 lot# ED-G-146-X86 100 mg comm cap	Bioequivalent
			FID# JV 86-015 lot# ED-G-144-Z86 100 mg solution	FID# JV 86-013 lot# ED-G-146-X86 100 mg comm cap	Bioequivalent
			FID# JV 86-015 lot# ED-G-144-Z86 100 mg solution	FID# JV 82-004 lot# ED-G-164-X83 100 mg research cap	Bioequivalent
050-008 (3 way open single dose crossover)	19	17	FID# JV 82-004 lot# ED-G-138-X86 100 mg research cap	FID# JV 87-032 lot# ED-G-054-387 100 mg US comm tab	Bioequivalent (AUC) Not bioequivalent (Cmax)
			FID# JV 82-004 lot# ED-G-138-X86 100 mg research cap	JV 86-013 lot# ED-G-146-X86 100 mg comm cap	Not bioequivalent
			FID# JV 87-032 lot# ED-G-054-387 100 mg US comm tab	JV 86-013 lot# ED-G-146-X86 100 mg comm cap	Not bioequivalent
050-009 (2 way open single dose crossover)	18	18	FID# JV 82-004 lot# ED-G-138-X86 100 mg research cap	FID# JV 87-032 lot# ED-G-222-987 100 mg US comm tab	Bioequivalent

In the three clinical studies that the sponsor conducted, both capsule (Studies STL-NY-94-004 and STL-N/S-95-003) and tablet (Study R-0601) formulations of sertraline were administered to patients. The sponsor intends to market the current marketed tablet formulation for this new indication. In order to link the clinical studies together, the sponsor conducted bioequivalence (BE) studies (see Table 1) to compare the bioavailability of the two formulations used. As a result of conducting the BE studies, the sponsor discovered that the commercial capsule (FID# JV 86-013) that was used in the clinical trials was not bioequivalent to the marketed tablet (FID# JV 87-032) and research capsule (FID# JV 82-004) based on Study 050-008. Prior to this submission, the sponsor submitted results of Study 050-009 in the original NDA, resulting in the conclusion that the marketed tablet and research capsule formulations were bioequivalent. In Study 050-006, the sponsor determined that the research capsule (FID# JV 82-004) was bioequivalent to the commercial capsule (FID# JV 86-013).

Sponsor's justification:

Although the research capsule (FID# JV 82-004) was found to be inequivalent to the commercial tablet (FID# JV 87-032) and commercial capsule (FID# JV 86-013)

formulation of sertraline in Study 008, the research capsule is bioequivalent to the commercial capsule (FID# JV 86-013) and tablet (FID# JV 87-032) in Studies 006 and 009. Thus, the sponsor provides a justification for Study 005-008 in that the pharmacokinetic profiles of sertraline were associated with higher variability, resulting in the inequivalence of the research capsule with the commercial tablet and states that results of all three bioequivalence (BE) studies should be considered together. In addition, since a dose-response relationship does not exist for sertraline within the recommended dose range, small changes in plasma levels will not affect the clinical outcome of the drug.

During the internal discussion held on November 7, 2001, the division of Neuropharmacological Drug Products discussed the sponsor's proposal. The medical officer stated that the clinical trials (R-0601 and STL-NY-94-004) according to the sponsor demonstrate efficacy for sertraline in the treatment of social phobia. Since commercial tablets were used in one of the pivotal studies (R-0601), BE information is not absolutely critical. The three BE studies among tablets and capsules (050-006, -008, and –009) along with dissolution data can be reviewed and used as supportive data. In addition, during the review, the median effective doses in both trials, 0601 and 004, will be compared to see if results are similar when tablets and capsules are used.

Comments:

1. **As a result of the inequivalence between the commercial capsule (FID# JV 86-013) and the marketed tablet (FID# JV 87-032), the sponsor is requested to submit the current justification along with a rationale supporting that a small change in sertraline pharmacokinetics would not impact the clinical efficacy of the drug.**
2. **When the NDA is filed, the sponsor should provide all three BE studies and conduct the appropriate statistical analysis, including 90% confidence intervals on C_{max} and AUC. Also, the tablet formulation should be used as the reference product where it is appropriate during the statistical analysis.**

3. **The sponsor should submit comparative dissolution and composition of all tablets and capsules used in clinical trials.**

Recommendation:

The information to support the bioequivalence of sertraline formulations in the treatment of social phobia is acceptable to the Office of Clinical Pharmacology and Biopharmaceutics for filing the sNDA provided the comments above are addressed. The comments were conveyed to the sponsor during a telephone conference held on November 8, 2001. No action is necessary at this time.

Gerald J. Fetterly, Ph.D. Gerald Fetterly 11/14/01

RD/FT Initialed by Ramana Uppoor, Ph.D. Uppoor 11/14/01

cc: NDA 19-839/20-990, HFD-120, HFD-860 (Mehta, Uppoor, Fetterly), Central Document Room (Clin. Pharm./Biopharm. File)

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

19-839/S-045

20-990/S-011

ADMINISTRATIVE DOCUMENTS

 Version in NDFS

EXCLUSIVITY SUMMARY for NDA # 19-839/S-045 & 20-990/S-011

Trade Name Zoloft® Tablets Generic Name sertraline HCl

Applicant Name Pfizer HFD-120
Approval Date 2/7/03

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 questions about the submission.

   a) Is it an original NDA? YES/__/ NO /_X__/

   b) Is it an effectiveness supplement? YES /_X__/ NO /__/

      If yes, what type(SE1, SE2, etc.)? SE-1

   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 /_X_/ 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 /_X__/ NO /__/

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

3 years

e) Has pediatric exclusivity been granted for this Active Moiety?

YES /_X__/ NO /__/

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9.

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? (Rx to OTC) Switches should be answered No - Please indicate as such).

YES /___/ NO /_X_/

If yes, NDA # _____ Drug Name _____

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9.

3. Is this drug product or indication a DESI upgrade?

YES /___/ NO /_X_/

IF THE ANSWER TO QUESTION 3 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9 (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 /_X__/ NO /__/

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA # 19-839 _____

NDA # 20-990 _____

NDA # _____ _____

2. Combination product.

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 9. 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 /_X__/ NO /___/

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9.

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.

For the purposes of this section, studies comparing two products with the same ingredient(s) are considered to be bioavailability studies.

(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 /_X__/ 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 9:**

_____

_____

(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 /_X__/

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

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 /_X__/

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:

Investigation #1, Study # R-0601

Investigation #2, Study # STL-NY 94-004

Investigation #3, Study # _____

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 /_X__/

Investigation #2 YES /___/ NO /_X__/

Investigation #3 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:

NDA # _____ Study # _____
NDA # _____ Study # _____
NDA # _____ Study # _____

(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 /_X__/

Investigation #2 YES /___/ NO /_X__/

Investigation #3 YES /___/ NO /___/

If you have answered "yes" for one or more investigations, identify the NDA in which a similar investigation was relied on:

NDA # _____ Study # _____

NDA # _____ Study # _____

NDA # _____ Study # _____

(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"):

Investigation #_1_, Study # R-0601
Investigation #_2_, Study # STL-NY 94-004
Investigation #__, Study # _____

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 /_X__/ Explain: _____

_____

_____

Investigation #2

IND # _____ YES /___/ ! NO /_X__/ 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 /_X__/ Explain _____ ! NO /___/ Explain _____

_non-US Study conducted by Pfizer_____

! _____ ! _____

Investigation #2

YES /_X__/ Explain _____ ! NO /___/ Explain _____

_non-US study conducted by Pfizer_____ !

_____ ! _____

(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 /_X__/

If yes, explain: _____

_____

_____

_____ Date_____

Signature of Preparer

Title:Regulatory Health Project Manager

_____ _____

Signature of Office of Division Director Date

cc:
Archival NDA
HFD-120/Division File
HFD-120/Homonnay
HFD-093/Mary Ann Holovac
HFD-104/PEDS/T.Crescenzi

Form OGD-011347
Revised 8/7/95; edited 8/8/95; revised 8/25/98, edited 3/6/00

13.0 PATENT AND EXCLUSIVITY INFORMATION

1. Active Ingredient (Tablet and Solution): (1S-cis)-4(3,4-dichlorophenyl) -1,2,3,4-tetrahydro-N-methyl-1-naphthalenamine hydrochloride

2. Strengths:

   a) Tablet: 25, 50 and 100mg sertraline
   b) Solution: 20 mg/ml sertraline

3. Trade Name (Tablet and Solution): Zoloft

4. Dosage Forms/Route of Administration:

   a) Tablet: Tablets/Oral
   b) Solution: Oral Concentrate

5. Application Firm Name: Pfizer Inc.

6. NDA Numbers:

   a) Tablet: 19-839
   b) Solution: 20-990

7. Exclusivity Period:

   a) Tablet: N/A
   b) Solution: Thirty-six months (3 years) from the date of approval of the Oral Solution NDA 20-990

8. Applicable Patent Numbers And Expiration Dates

   a) Tablet: 4,536,518 December 30, 2005
   4,962,128 November 2, 2009
   5,248,699 August 13, 2012

   b) Solution: 4,536,518 December 30, 2005
   4,962,128 November 2, 2009
   *5,248,699 August 13, 2012

* U.S. Patent 5,248,699 claims the crystalline polymorph of sertraline hydrochloride that is the drug substance (ingredient) used to manufacture the Zoloft oral concentrate and is therefore being listed in Section 13.0 of this sNDA for 20-990.

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: January 28, 2003

FROM: Thomas P. Laughren, M.D.
Team Leader, Psychiatric Drug Products
Division of Neuropharmacological Drug Products
HFD-120

SUBJECT: Recommendation for Approval Action for
Zoloft tablets (sertraline) for the treatment of social anxiety disorder

TO: File NDA 19-839/S-045 and NDA 20-990/S-011
[**Note:** This overview should be filed with the 12-11-02 response to our 11-19-02 approvable letter.]

In our 11-19-02 approvable letter, we requested the following information:
-Documentation for the change in the analysis plan for the long-term trial
-A safety update
-A regulatory status update
-A world literature update
-Response to proposed labeling

Pfizer responded with a 12-11-02 submission that adequately addressed all of these requests. The 12-11-02 submission was reviewed by Robert Levin, M.D., from the clinical group.

Documentation for the change in the analysis plan for the long-term trial:
-The positive outcome of the long-term trial (STL-NY-94-004C) was dependent on the changed definition of relapse (presumably the change was made on 8-22-99, prior to data analysis). However, the analysis plan was not officially amended with this change, and we did not have any actual documentation for the change. Thus, we requested that Pfizer provide such documentation.
-Pfizer indicates that this change was made using internal e-mail by the project clinician on 8-22-99, and was implemented by the project statistician on 8-24-99. A copy of the finalized analysis plan (signed off on 9-7-99) is included, and this documents the change in the definition of relapse (see page 5, appendix IV).
-Comment: In my view, this is an adequate response to this request.

Safety Update:
-The only new data were spontaneous reports, and there were no new findings that would impact on the approval decision or on labeling (see Dr. Levin's review).

Regulatory Status Update:
-As of 11-19-02, Zoloft is approved for social anxiety disorder in 16 countries (see Dr. Levin's review).

World Literature Update:
-There were no new pertinent published papers to review (see Dr. Levin's review).

Response to Proposed Labeling:
-Pfizer accepted all of our proposed language regarding the new claim for social anxiety disorder. They also added other language that had been approved in the interim, and made some minor additional changes to integrate the social anxiety disorder claim. We reached agreement on final labeling as of 1-24-03.

Conclusions and Recommendations
-I believe that Pfizer has submitted sufficient data to support the conclusion that Zoloft is effective and acceptably safe in the treatment of social anxiety disorder, both short-term and longer-term. I recommend that we issue the attached approval letter with the mutually agreed upon final labeling.

cc:
Orig NDA 19-839/S-045 & NDA 20-990/S-011
HFD-120
HFD-120/TLaughren/RKatz/RLevin/AMHomonnay

DOC: MEMZLFSA.AP1

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/s/

Thomas Laughren
1/28/03 03:36:14 PM
MEDICAL OFFICER

Appears This Way
On Original

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: November 6, 2002

FROM: Thomas P. Laughren, M.D.
Team Leader, Psychiatric Drug Products
Division of Neuropharmacological Drug Products
HFD-120

SUBJECT: Recommendation for Approvable Action for
Zoloft tablets (sertraline) for the treatment of social anxiety disorder

TO: File NDA 19-839/S-045 and NDA 20-990/S-011
[**Note:** This overview should be filed with the 1-18-02
original submission.]

1.0 BACKGROUND

Sertraline is a selective serotonin reuptake inhibitor currently approved and marketed for depression, OCD, panic disorder, PTSD, and PMDD, in an immediate release tablet, i.e., Zoloft (NDA 19-839, originally approved for depression 12-30-91; subsequent approvals for OCD on 10-25-96, panic disorder 7-8-97), PTSD on 12-7-99, and PMDD on 5-16-02. Zoloft is also available as an oral concentrate (NDA 20-990). S-045 and S-011 provide data in support of a new claim for sertraline in tablet and concentrate form in the treatment of social anxiety disorder in a dose range of 50-200 mg/day, on a once daily basis. At the present time, there is only one other drug approved for the treatment of social anxiety disorder, i.e., Paxil.

We held a preNDA meeting with the sponsor on 6-8-99. They identified two completed nonUS studies (004 and 003) that they intended to submit as primary support for the new claim. Data analysis had not been done at that point, and there was much discussion of the proposed analysis plans. The sponsor also presented plans for a 12-week US study (601). We also discussed the eventual need for longer-term efficacy data and pediatric data.

In a premeeting package for a second preNDA meeting, the sponsor indicated that study 601 was completed and that they also had data from a relapse prevention phase of study 004 that would support longer-term efficacy. They noted that studies 004 and 601 were now considered the two pivotal trials.

We decided at our premeeting (11-1-01) that the sponsor likely had sufficient data for filing, and we would not need a general meeting. However, a potential biopharmaceutical concern was identified, and a brief teleconference was held (11-8-01) to plan an approach to resolving this issue (see biopharmaceutics later).
Studies in support of this claim were conducted under IND 18,004.

Since the proposal is to use the currently approved Zoloft formulations for this additional claim, there was no need for chemistry or pharmacology reviews reviews of this supplement. As noted, there was a need for a biopharmaceutics review, and this was done by Andre Jackson, Ph.D., from OCPB. The focus was primarily on clinical data. The primary review of the efficacy and safety data was done by Robert Levin, M.D., from the clinical group. Fanhui Kong, Ph.D., from the Division of Biometrics, also reviewed the efficacy data.

The original supplements for this expanded indication (S-045 and S-011) were submitted 1-18-02.

We decided not to take these supplements to the Psychopharmacological Drugs Advisory Committee (PDAC).

2.0 CHEMISTRY

As Zoloft is a marketed product, there were no CMC issues requiring review for this supplement.

3.0 PHARMACOLOGY

As Zoloft is a marketed product, there were no pharmacology/toxicology issues requiring review for this supplement.

4.0 BIOPHARMACEUTICS

The new claim is supported by two studies, one of which used a 50 mg research capsule (004) and the other used 25 and 50 mg commercial tablets (601). Although a BE study was not essential, since study 601 used the marketed tablets, Pfizer submitted results from earlier BE studies to establish the linkage between the research capsules and the marketed tablets. These were older studies, so the results had to be reanalyzed using the current 90% CI approach, and OCPB concluded that BE had been established. Dissolution data submitted were also judged to be acceptable.

It should be noted that the sponsor has obtained pediatric PK data in other programs, and labeling already addresses pediatric PK.

5.0 CLINICAL DATA

5.1 Efficacy Data

5.1.1 Overview of Studies Pertinent to Efficacy

Our review of efficacy was focused on the results of three short-term studies of sertraline in social anxiety disorder (R-0601, STL-NY 94-004, and STL-N/S 95-003), and one longer-term study (STL-NY 94-004C).

5.1.2 Summary of Study R-0601

This was a randomized, double-blind, parallel group, 12-week, flexible-dose, multicenter (20 US sites) study comparing sertraline, in a dose range of 50 to 200 mg/day, and placebo in adult outpatients meeting DSM-IV criteria for generalized social anxiety disorder. Randomization was preceded by a 7-day single-blind placebo run-in. Treatment was initiated at 25 mg for 1 week, then increased to 50 mg for the second and third week. At the end of the third week, patients who were not optimally controlled but who were tolerating assigned treatment could be increased to 100 mg. Dose increases could occur similarly at the ends of week 5 to 150 and week 6 to 200 mg. Doses could be adjusted within the final 6 weeks in the 50-200 mg/day range, as needed. Following the 12-week phase, patients taking more than 50 mg/day were tapered at a rate of 50 mg/day, every 4 days.

The primary endpoints were: (1) proportion of patients who were responders, defined as subjects with a CGI-I score of 1(very much improved) or 2(much improved) at endpoint, and (2) change from baseline to endpoint (12 weeks) in the Liebowitz Social Anxiety Scale (LSAS), an assessment that was administered at the ends of weeks 1,2,3,4,6,8, and 12. There were numerous secondary endpoints. The primary analysis model was CMH with centers as strata, for CGI-I, and ANCOVA with treatment and investigator as main effects and baseline score as covariate, for LSAS, using LOCF in our usual intent-to-treat population (all randomized patients who received at least one dose of assigned treatment, and had baseline and at least one followup LSAS assessment).

Of 520 subjects screened, there were 415 patients randomized (sertraline=211; placebo=204). There were n=401 patients in the ITT sample (sertraline=205; placebo=196). There were substantial dropouts before reaching the 12 week endpoint, with the % completing to 12 weeks ranging from 69% for placebo to 72% for sertraline. The patients were about 60% male, about 70% Caucasian, and the mean age was about 35 years. The mean daily sertraline dose for completers during weeks 9 to 12 in this trial was 173 mg/day.

Sertraline was superior to placebo on both primary endpoints:

Efficacy Results on CGI-I Responders for Study R-0601 (LOCF)

	% Responders on CGI-I at Endpoint	[P-value(vs pbo)]
Sertraline (n=205)	**47%**	**p=0.001**
Placebo (n=196)	**26%**	

Efficacy Results on LSAS Total Score for Study R-0601 (LOCF)

	Baseline LSAS	Obaseline LSAS	[P-value(vs pbo)]
Sertraline (n=205)	**90.8**	**-31.3**	**p=0.001**
Placebo (n=196)	**93.2**	**-21.4**	

The OC analyses for CGI-I and LSAS also statistically significantly favored sertraline over placebo at week 12 (p=0.001 for both). Analyses of secondary outcomes also generally favored sertraline over placebo. Dr. Kong performed a Wilcoxon nonparametric test for LSAS, since the data failed on a normality test, and the result again was highly favorable for sertraline (p=0.0001). An evaluation by investigator revealed consistent findings favoring sertraline across centers, and an analysis by gender also showed positive results for sertraline in both strata.

Comment: Both Drs. Levin and Kong considered this a positive study, and I agree.

5.1.3 Summary of Study NY94-004

This was a randomized, double-blind, parallel group, 20-week, flexible-dose, multicenter (10 Canadian sites) study comparing sertraline, in a dose range of 50 to 200 mg/day, and placebo (2:1 ratio, sertraline to placebo) in adult outpatients meeting DSM-IV criteria for generalized social anxiety disorder. Randomization was preceded by a 7-day single-blind placebo run-in. Treatment was initiated at 50 mg for 4 weeks, at which point patients who were not optimally controlled but who were tolerating assigned treatment could be increased to 100 mg until the end of week 7. Dose increases could occur similarly at the ends of week 7 to 150 mg and week 10 to 200 mg. Doses could not be raised after week 10, but could be reduced for intolerance, but not below 50 mg/day.

The six primary endpoints were: (1) proportion of patients who were responders, defined as subjects with a CGI-I score of 1(very much improved) or 2(much improved) at endpoint; (2) change from baseline to endpoint (20 weeks) in several measures of the Duke Brief Social Phobia Scale (BSPS): (a) total score; (b) fear factor score; © avoidance factor score; (d) physiologic factor score; and, (3) change from baseline to endpoint (20 weeks) in the Marks Fear Questionnaire-Social Phobia Subscale (FQ-SPS) total score. These assessments were administered at the ends of weeks 1,2,4,7,10,13,16, and 20. There were numerous secondary endpoints. The primary analysis model was CMH with centers as strata, for CGI-I responders, and ANCOVA with treatment and investigator as main effects and baseline score as covariate, for continuous outcomes, using LOCF in our usual intent-to-treat population (all randomized patients who received at least one dose of assigned treatment, and had baseline and at least one followup LSAS assessment).

There were 204 patients randomized (sertraline=135; placebo=69). There were n=203 patients in the ITT sample (sertraline=134; placebo=69). There were substantial dropouts before reaching the 20

week endpoint, with the % completing to 20 weeks ranging from 78% for placebo to 77% for sertraline. The patients were about 55% male, about 94% Caucasian, and the mean age was about 36 years. The mean daily sertraline dose for completers during weeks 17 to 20 in this trial was 159 mg/day.

Sertraline was superior to placebo on all six primary endpoints:

Efficacy Results on 6 Primary Endpoints (LOCF at Week 20 for ITT) for Study 94-004			
Endpoint	**Sertraline**	**Placebo**	**P-Value**
Duke BSPS (mean change from BL)			
Total Score	**-16.4**	**-8.6**	**0.001**
Fear Factor	**-6.6**	**-3.1**	**0.001**
Avoidance Factor	**-6.7**	**-3.4**	**0.001**
Physiologic Factor	**-3.2**	**-2.1**	**0.001**
CGI-I & FQ-SPS			
CGI-I/% Respnders	**53%**	**29%**	**0.001**
FQ-SPS/Total/OBL	**-7.8**	**-2.6**	**0.001**

The OC analyses also statistically significantly favored sertraline over placebo at week 20 for 5 of the 6 primary outcomes. Analyses of secondary outcomes also generally favored sertraline over placebo. Dr. Kong performed Wilcoxon nonparametric test for all four BSPS measures, since the data failed on a normality test, and the results again were highly favorable for sertraline. An evaluation by investigator revealed consistent findings favoring sertraline across centers, and an analysis by gender also showed positive results for sertraline in both strata.

Comment: Both Drs. Levin and Kong considered this a positive study, and I agree.

5.1.4 Summary of Study STL-N/S 95-003

Since the sponsor acknowledged that this was a negative study, one not conducted for registration purposes, it was agreed that they needed to submit only a summary report. It was a 24-week RCT comparing sertraline (50-150 mg/day) vs pbo, with or without exposure therapy, in the treatment of social anxiety disorder. It was conducted at 47 sites in Norway and Sweden. It was a large study, with approximately 200 patients per group. The analysis was complex, essentially a factorial analysis, involving both drug treatment and exposure therapy. The primary outcomes were based on CGI-Lebowitz severity total score. There was no difference between drug and placebo on this

outcome. It is noteworthy that the mean daily sertraline dose for completers at week 24 in this trial was 113 mg/day, compared to doses of 173 and 159 in the previous two positive trials.

Comment: While ordinarily we would require the mention of a negative trial in labeling, this study appears to have been planned and conducted primarily by an academic group, and not for registration purposes. Thus, I am inclined to agree that the results need not be mentioned in labeling.

5.1.5 Summary of Study STL-NY 94-004C

Results from study STL-NY 94-004C were submitted in support of a claim for the longer-term efficacy of sertraline in social anxiety disorder. This 10 center Canadian study recruited adult patients with social anxiety disorder who had completed study STL-NY 94-004 and who were responders (CGI-I ≤ 2), either while taking sertraline or placebo. The sertraline responders (n=50) were randomly assigned to double-blind treatment with either sertraline (referred to as sertraline/sertraline [s/s] group) or placebo (referred to as sertraline/placebo [s/p] group) in a 1:1 ratio. Placebo responders (n=15) were continued on placebo (referred to as placebo/placebo [p/p] group). A total of n=50 patients were randomized (and met modified ITT criteria), with n=25 receiving sertraline and n=25 receiving placebo. Patients were instructed to take the same sertraline dose during this phase that they had been taking at the end of 004; placebo patients were tapered off sertraline. This double-blind discontinuation phase ran for up to 24 weeks. Patients were seen monthly during this period.

There were six protocol specified co-primary endpoints: (1) rate of relapse, where relapse was defined as (a) an increase in the CGI-S score of ≥ 2, or (b) discontinuation due to lack of efficacy; (2) change from baseline in CGI-S score; (3) change from baseline in CGI-I score; (4) proportion of responders, where response is CGI-I of ≤ 2; (5) change from baseline in BSPS total score; (6) change from baseline in FQ-SPS total score. It is noteworthy that the definition of relapse was changed from the original protocol to include discontinuation due to lack of efficacy in an 8-22-99 amendment, prior to data analysis. However, an amended analysis plan for the protocol was not submitted to the IND and there was no other documentation for this change. Although the sponsor included statistical tests for comparisons of both s/s vs s/p and s/s vs p/p, I will comment only on the s/s vs s/p comparison, since this is the only comparison of regulatory interest. The analyses were CMH for categorical variables and ANCOVA or ANOVA for continuous variables. Analyses were based on an ITT sample including all randomized patients who received at least 1 dose of assigned treatment and had baseline and at least one post-randomization efficacy assessment.

Patients in this study were roughly 60% male, 100% Caucasian, and the mean age was roughly 36 years. The mean maximum sertraline dose at endpoint in the double blind phase was 139 mg/day. The overall rates of discontinuation prior to reaching the 24 week nominal endpoint were as follows:

Sertraline:	3/25 (12%)
Placebo:	9/25 (60%)

5.1.6 Comment on Other Important Clinical Issues Regarding Zoloft in Social Anxiety Disorder

Evidence Bearing on the Question of Dose/Response for Efficacy

Neither of the 2 positive acute studies provided any information pertinent to the question of dose response for efficacy. Labeling will simply describe how patients were dosed in these 2 trials.

Clinical Predictors of Response

Exploratory analyses were done to detect subgroup interactions on the basis of gender, and these analyses suggested treatment effects in both strata.

Size of Treatment Effect

The effect size as measured by difference between drug and placebo in change from baseline in the LSAS observed in study 0601 was similar to that seen in the positive trials for Paxil, the only other drug approved for social anxiety disorder. I consider this a sufficient effect to support a claim for this product in social anxiety disorder.

Duration of Treatment

As noted, study 004C provides evidence of longer-term efficacy for sertraline in social anxiety disorder.

5.1.7 Conclusions Regarding Efficacy Data

The sponsor has, in my view, provided sufficient evidence to support the claim of both short-term and longer-term efficacy for Zoloft in social anxiety disorder.

5.2 Safety Data

Dr. Levin's safety review of this NDA was based predominantly on the safety data from the three acute studies, i.e., 601, 004, and 003, and also the longer-term trial (004C).

Given our prior knowledge of the risks associated with Zoloft in the other populations for which this drug is approved, the focus in the safety review was on any differences between the recognized safety profile in these other populations with that observed in the social anxiety disorder population.

It should be noted that the sponsor has obtained pediatric safety data in other programs, and labeling already addresses pediatric safety.

5.2.1 Overview of Adverse Event Profile for Zoloft in Social Anxiety Disorder

In a pool of studies 601 and 004, the following adverse events were ≥ 5% for sertraline and ≥ twice placebo: insomnia, nausea, diarrhea, dizziness, dyspepsia, libido decreased (male), ejaculation disorder, dry mouth, fatigue, increased sweating, tremor, influenza-like symptoms, and anorexia. A similar profile of common and drug-related adverse events was seen in the longer-term trial. There were no unexpected effects on vital signs, body weight, ECGs, or clinical laboratory parameters. Overall, the adverse events profile for Zoloft in the social anxiety disorder population was similar to that observed for this drug in the other populations in which it is approved.

5.2.2 Conclusions Regarding Safety of Zoloft in Social Anxiety Disorder

There were no new safety findings to suggest a substantially different safety profile for Zoloft in social anxiety disorder compared to that seen in the other populations in which it is approved.

5.3 Clinical Sections of Labeling

We have modified 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

The sponsor provided a literature review focused on sertraline and social anxiety disorder, including 13 references. Dr. Levin examined a review of this literature provided by the sponsor and indicated that it revealed no new safety findings that would impact on the labeling of Zoloft.

7.0 FOREIGN REGULATORY ACTIONS

To my knowledge, Zoloft is not approved for the treatment of social anxiety disorder anywhere at this time. We will ask for an update on the regulatory status of Zoloft for the treatment of social anxiety disorder in the approvable letter.

8.0 PSYCHOPHARMACOLOGICAL DRUGS ADVISORY COMMITTEE (PDAC) MEETING

We decided not to take these supplements to the PDAC.

9.0 DSI INSPECTIONS

Two domestic sites were inspected, i.e., Drs. Duboff and Smith for 601, and also 1 Canadian site, i.e., Dr. Pecknold for 004. 256 and 493, and [redacted] for 493. While there were minor deviations at two of the sites, overall, the data were judged to be acceptable.

10.0 LABELING 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, we have made changes to the sponsor's draft dated 1-18-02.

10.2 Foreign Labeling

Zoloft is not approved for the treatment of social anxiety disorder anywhere at this time.

10.3 Approvable Letter

The approvable letter includes draft labeling and requests for a literature update and a regulatory status update.

11.0 CONCLUSIONS AND RECOMMENDATIONS

I believe that Pfizer has submitted sufficient data to support the conclusion that Zoloft is effective and acceptably safe in the treatment of social anxiety disorder, both short-term and longer-term. However, we do need to request documentation for the change in the analysis plan for the longer-term trial. I recommend that we issue the attached approvable letter with our labeling proposal and the above noted requests for updates, in anticipation of final approval.

cc:
Orig NDA 19-839/S-045 & NDA 20-990/S-011
HFD-120
HFD-120/TLaughren/RKatz/RLevin/AMHomonnay

DOC: MEMZLFSA.AE1

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/s/

Thomas Laughren
11/6/02 09:10:04 AM
MEDICAL OFFICER

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DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Division of Scientific Investigations
Office of Medical Policy
Center for Drug Evaluation and Research
Food and Drug Administration
Rockville MD 20857

CLINICAL INSPECTION SUMMARY

DATE: August 27, 2002

TO: Anna Marie Homonnay-Weikel, R.Ph., Regulatory Project Manager
Robert Levin, M.D., Medical Officer
Division of Neuropharmacological Drug Products, HFD-120

THROUGH: Antoine El-Hage, Ph.D., Branch Chief AEH 8/28/02
Good Clinical Practice Branch II, HFD-47
Division of Scientific Investigations

FROM: Ni A. Khin, M.D., Medical Officer
Good Clinical Practice Branch II, HFD-47
Division of Scientific Investigations

SUBJECT: Evaluation of Clinical Inspections

NDA: NDA 19-839/SE1-045
NDA 20-990/SE1-011

APPLICANT: Pfizer, Inc.

DRUG: Zoloft (sertraline hydrochloride) Tablets and Oral Concentrate

CHEMICAL CLASSIFICATION: Type 6

THERAPEUTIC CLASSIFICATION: Type S, Standard Review

INDICATION: Social Phobia

CONSULTATION REQUEST DATE: March 18, 2002

ACTION GOAL DATE: November 22, 2002

I. BACKGROUND:

Sertraline hydrochloride is a selective serotonin reuptake inhibitor, which is currently marketed under the brand name of Zoloft. Zoloft is approved in the U.S. for use in the treatment of major depressive disorder, obsessive compulsive disorder, panic disorder and post traumatic stress disorder. In this supplemental NDA, the sponsor has requested the use of Zoloft in social phobia.

Inspection assignments were issued on April 19, 2002 for two domestic sites, Drs. Eugene DuBoff and Ward Smith, for Protocol R-0601 entitled "A Multicenter, Randomized, Double-Blind, Placebo-Controlled Trial of Sertraline for Acute Treatment of DSM-IV Generalized Social Phobia in Outpatients." Inspection assignment was also issued for non-U.S. site, Dr. John Pecknold, for Protocol STL-NY-94-004 entitled "A Twenty-Week, Prospective, Randomized, Multicenter, Parallel Group, Double-Blind, Dose-Titration Comparison of the Safety, Efficacy and Tolerability of Sertraline (50-200 mg/day) and Placebo in the Treatment of DSM-IV Generalized Social Phobia in Outpatients"; and Protocol STL-NY-94-004C entitled "A Twenty-Four Week Continuation of Study STL-NY-94-004 of Sertraline (50-200mg/day) or Placebo in the Treatment of DSM-IV Generalized Social Phobia in Outpatients." These investigators enrolled a large number of subjects in the clinical trial. The purpose of the assignments was to validate data in support of pending NDA 19-839/SE1-045 and NDA 20-990/SE1-011.

II. RESULTS (by site):

Protocol R-0601 (U.S. Study)

NAME	CITY	STATE	ASSIGNED DATE	RECEIVED DATE	CLASSIFICATION
DuBoff	Denver	CO	04-19-2002	07-02-2002	VAI*
Smith	Portland	OR	04-19-2002	06-14-2002	NAI

Protocols STL-NY-94-004 and STL-NY-94-004C (Canadian Study)

NAME	CITY	STATE	ASSIGNED DATE	RECEIVED DATE	CLASSIFICATION
Pecknold	Verdun	Quebec	04-19-2002	08-13-2002	VAI*

* Currently, the letter to the investigator is with the Office of Chief Counsel (OCC) for review.

DUBOFF, M.D.

At this clinical site, protocol R-0601, for treatment of Generalized Social Phobia, was inspected. Records for 12 of 34 subjects were audited. All subjects received adequate informed consent. No serious adverse events occurred during the study. Inspectional concern regards qualifications of raters performing CGI-I and LSAS Scales, both primary efficacy variables: 1) A total of 8 subjects reviewed did not have the same CGI-I rater for each visit. Specifically, 4 subjects (——— , had different raters for more than one visit and 4 other subjects (——— had a different rater for one visit during the study. 2) Two raters rated the LSAS for several subjects prior to being qualified as raters by the sponsor; for 9 subjects, a qualified rater with inter-rater reliability did not perform the LSAS at each visit.

We note that the study was conducted between 1999-2001 and ——— was listed for ECG analysis. There is an ongoing investigation of ——— in regards to

duplicate ECGs in other studies conducted during the same period. Overall, data appear to be acceptable.

SMITH, M.D.

This site enrolled 36 subjects for protocol R-0601; 6 subjects were screen failures. Of the 30 subjects randomized to receive sertraline or placebo, 4 subjects discontinued and 26 subjects completed the protocol. The reasons for discontinuation included lost to follow up, protocol violation, adverse event (1 subject) and personal reasons.

Review of 7 subjects' records found no objectionable conditions. No serious adverse events were reported at this site. Every subject received informed consent. Data appear acceptable.

PECKNOLD, M.D.

At this Canadian site, 21 subjects were randomized to receive either Zoloft or placebo. During the 20-week study in protocol STL-NY-94-004, 2 subjects discontinued from placebo group only. Twelve subjects entered the 24-week continuation study, protocol STL-NY-94-004C. No significant adverse events reported. No objectionable conditions noted. DSI noted omissions of some required elements of consent form such as description of benefits to be expected from the research, alternative treatment section, confidentiality of records and contact information in regards to research questions or research-related injury. All subjects signed the consent form. Overall, data appear acceptable.

III. OVERALL ASSESSMENT OF FINDINGS AND GENERAL RECOMMENDATIONS

As stated above, DSI notes that there was some concerns on qualifications of raters performing primary efficacy measures (CGI-I and LSAS Scales) at Dr. DuBoff's site and some informed consent deficiency at Dr. Pecknold's site. Overall, data from these sites appear acceptable for use in support of pending NDA supplement.

Key to Classifications
NAI = No deviation from regulations. Data acceptable
VAI = Minor deviations(s) from regulations. Data acceptable
VAIr= Deviation(s) form regulations, response requested. Data acceptable
OAI = Significant deviations for regulations. Data unreliable
Pending = Inspection not completed

5/28/02

Ni A. Khin, M.D.
Medical Officer
Good Clinical Practice Branch II, HFD-47
Division of Scientific Investigations

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

Date: March 19, 2002

To: Joanne Rhodes, MD, MPH, GCPB Division Director
and
Ni Khin, M.D., GCPB Reviewer/HFD-47

From: Russell Katz, MD
Director, Division of Neuropharmacological Drugs
HFD-120

Through: Thomas Laughren, MD
Medical Teamleader, Psychiatric Drugs

Subject: **Request for Clinical Inspections**
NDA 19-839/S-045
Pfizer, Inc.

Protocol/Site Identification:

As discussed with you, the following protocols/sites essential for approval have been identified for inspection. These sites are listed in order of priority.

Indication	Protocol #	Site (Name and Address)
Social anxiety disorder	STL-NY-94-004C	1 Canadian Site

Note: International inspection requests or requests for five or more inspections require sign-off by the ORM Division Director and forwarding through the Director, DSI.

Goal Date for Completion:

We request that the inspections be performed and the Inspection Summary Results be provided by (September 31, 2002). We intend to issue an action letter on this application by (November 22, 2002).

Should you require any additional information, please contact Ms. Anna Marie Homonnay

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/s/

Russell Katz
3/20/02 10:53:07 AM

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FDA MEETING MINUTES

Date: June 8, 1999
IND: 18,004
Location: Woodmont II, Conference Room E
Firm: Pfizer Pharmaceuticals
Drug: Zoloft (sertraline HCl) Tablets
Indication: Social Phobia
Meeting Type: pre-sNDA
Participants:

FDA Division of Neuropharmacological Drug Products Attendees:

Russell Katz, M.D.	Acting Director
Thomas Laughren, M.D.	Medical Team Leader, PDP
Susan Molchan, M.D.	Medical Reviewer
Kun Jin, Ph.D.	Team Leader, Biostatistics
Dr. Siddiqui	Biostatistician

Pfizer Attendees:

Iwona Jeske DuPont, Ph.D.	Team Leader
Christopher Wohlberg, M.D., Ph.D.	Clinician
Arkady Rubin, Ph.D.	Biostatistician
Martha Brumfield, Ph.D.	Regulatory Affairs
Andrea Garrity	Regulatory Affairs

BACKGROUND:

This meeting was requested by Pfizer to discuss the content of a supplemental new drug applicatioon for Zoloft^{R} for the treatment of social phobia. Pfizer has completed two placebo controlled dose titration studies of 20-24 weeks duration.

DISCUSSION:

- The study designs were discussed and FDA indicated they should be sufficient to demonstrate an effect in this disorder.

- The Division agreed that although different rating scales, including both clinician and patient rated scales, had been employed for each study, the scales mapped reasonably well to the diagnostic criteria for social anxiety disorder and should be adequate.

- For both studies 003 and 004, several outcomes were identified as primary. Thus, it was noted that, for both studies, it would be necessary to show superiority to placebo at a 0.05 level of significance on all primary outcomes in order for each study to be considered positive.

- It was also noted that we will want to look at both OC and LOCF analyses for both studies, and it will be necessary for any discrepancies between these two approaches to be explained.

- It was noted that, for both studies, it would be necessary to show that statistical plans were developed and submitted to the IND in advance of the analyses being conducted.

- Since Study 003, which involved a full factorial design, i.e., sertraline vs placebo and exposure therapy vs no exposure therapy,

- In conformance with the new Pediatric Rule, usage in the pediatric population and juvenile animal studies should also be addressed.

- The sponsor confirmed that data from all trials would be available for audit if necessary.

-

ACTION ITEMS:

- The final protocols should be submitted to the IND as soon as possible with the study designs clearly specified.
- Final statistical analysis plans should be developed, written up, and submitted to the IND prior to data analysis.

Signature, minutes preparer: Anna M. Homonnay-Weikel
Anna M. Homonnay-Weikel
Project Manager

Concurrence Chair: Thomas P. Laughren 7-9-99
Thomas Laughren, M.D
Teamleader, Psychiatric Drug Products

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HFD-120/IND 18,004
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HFD-120/Laughren/Molchan
HFD-120/Homonnay

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Social Phobia Clinical Program

Christopher Wohlberg, MD, PhD
Clinical and Scientific Affairs
Pfizer, Inc.

Social Phobia Clinical Program

- Meeting Objectives:
  - To reach consensus on the following questions
    1. Are the study designs of the completed trials adequate to support this indication?
    2. Are the endpoints appropriate to assess the pharmacological effects of treatment in social phobia?
    3. Are the analyses sufficient to adequately measure these changes?

Overview of Social Phobia

- Lifetime prevalence of approximately 13% (National Comorbidity Study, 1996)
- Third most prevalent psychiatric disorder (behind depression and generalized anxiety disorder - WHO Study on Psychological Problems in General Health Care)
- Onset generally between 15-20 years of age, equally distributed between males and females
- Not just "shyness," it causes functional, social and occupational impairment

Social Phobia Clinical Program

- Discussion Items:
  - ***Are the study designs of the completed trials adequate to support this indication?***
  - Are the endpoints appropriate to assess the pharmacological effects of treatment in social phobia?
  - Are the analyses sufficient to adequately measure these changes?

Pfizer Social Phobia sNDA Studies

Protocol	n enrolled	Description	Duration of Treatment	Primary Endpoints	Secondary Endpoints
COMPLETED					
STL-N/S-95-003 (Scandinavia)	375	multicenter, double-blind, randomized, placebo-controlled flexible dose study in outpatients	24 weeks	SPS CGI-L	BSPS FNE FQ-SPs
STL-NY-94-004 (Canada)	204	multicenter, double-blind, randomized, placebo-controlled flexible dose study in outpatients	20 weeks	BSPS CGI-I FQ-SPs	CGI-S CGI-L SPAI SADS FNE

STL-NY-94-004

- 20 week, randomized, multicenter, parallel, placebo-controlled trial comparing the efficacy of sertraline to placebo in the treatment of generalized social phobia
- DSM-IV diagnosis of generalized social phobia
- 2:1 randomization of sertraline : placebo, 204 patients enrolled
- Single-blind, 1 week placebo run-in followed by flexible dose titration of 50-200mg of sertraline or placebo-equivalent per day

STL-NY-94-004

- Inclusion / exclusion criteria
  - Outpatients aged 18 - 60 years
  - Primary diagnosis of DSM-IV Generalized Social Phobia, present for at least one year
  - At least moderate illness at baseline (CGI-S $\geq$ 4)
  - DSM-IV diagnosed Avoidant Personality Disorder allowed
  - Comorbid Major Depression allowed ***only if*** it post-dated the onset of Social Phobia by at least 5 years ***and*** the MADRS score at baseline was $\leq$ 19
  - Patients excluded with diagnosis of panic disorder, agoraphobia, OCD, eating disorder, substance abuse, bipolar disorder

STL-NY-94-004

- Primary endpoints
  - Marks Fear Questionnaire
    - Change from baseline to endpoint score on the social phobia subscale
  - Duke Brief Social Phobia Scale
    - Change from baseline to endpoint on total score
  - CGI-I
    - Treatment response defined as score of 1 or 2 at Final Visit

STL-N/S-95-003

- 24 week, multicenter (Norwegian and Swedish sites), randomized, double-blind trial comparing sertraline +/- exposure therapy to placebo +/- exposure therapy
- DSM-IV diagnosed Generalized Social Phobia
- 2 X 2 factorial design, 375 patients enrolled
  - Sertraline, 95 — Sertraline + Exposure, 95
  - Placebo, 92 — Placebo + Exposure, 93
- One week single-blind placebo run-in period followed by flexible titration of 50 - 150mg of sertraline or placebo equivalent per day
- Assessments performed by family physicians after obtaining training and certification in exposure therapy

STL-N/S-95-003

- Inclusion / Exclusion criteria
  - Outpatients in general practice aged 18 to 65 years
  - DSM-IV diagnosis of primary, generalized social phobia for at least one year
  - Liebowitz CGI-Overall Severity score at baseline greater than or equal to 4 (moderately ill)
  - Comorbid Major Depression and Panic Disorder allowed if they post-dated the onset of Social Phobia ***and*** the MADRS score is < 20 at baseline
  - Patients excluded with the diagnosis of substance abuse, PTSD, OCD, and bipolar disorder
  - Benzodiazepine usage allowed under 'exceptional' circumstances though patients were instructed not to use benzodiazepines during the study

STL-N/S-95-003

- Primary endpoints
  - CGI Liebowitz Social Anxiety Scale
    - Change from baseline to endpoint overall score
  - Social Phobia Scale
    - Change from baseline to endpoint total score
  - Response rate
    - defined as CGI-L-I score 1 or 2, CGI-L-S score < 3, and >50% reduction in SPS score compared to baseline
    - Protocol defines subjects as responders, partial responders and nonresponders

Pfizer Clinical Program Summary

- 2 international trials of social phobia
- A total of 579 patients
  - 318 sertraline, 251 placebo
- Treatment duration of 20-24 weeks
- Dose titration studies comparing sertraline to placebo in both studies and sertraline +/- exposure therapy in one study

Social Phobia Clinical Program

- Discussion items:
  - Are the study designs of the completed trials adequate to support this indication?
  - ***Are the endpoints appropriate to assess the pharmacological effects of treatment in social phobia?***
  - Are the analyses sufficient to adequately measure these changes?

Pfizer Social Phobia sNDA Studies

Protocol	n Enrolled	Description	Duration of Treatment	Primary Endpoints	Secondary Endpoints
COMPLETED					
STL-N/S-95-003 (Scandinavia)	375	multicenter, double-blind, randomized, placebo-controlled flexible dose study in outpatients	24 weeks	⇒ *SPS* CGI-L	BSPS ⇒ *FNE* ⇒ *FQ-SPs*
STL-NY-94-004 (Canada)	204	multicenter, double-blind, randomized, placebo-controlled flexible dose study in outpatients	20 weeks	BSPS CGI-I ⇒ *FQ-SPs*	CGI-S CGI-L ⇒ *SPAI* ⇒ *SADS* ⇒ *FNE*

Social Phobia Rating Scales

- Multiple rating scales employed, each measuring symptoms of social phobia
- Cross-validation studies of scales have demonstrated high degree of correlation between these scales
- Both clinician- and patient-rated scales used in studies 003 and 004

Social Phobia Clinical Program

- Discussion items:
  - Are the study designs of the completed trials adequate to support this indication?
  - Are the endpoints appropriate to assess the pharmacological effects of treatment in social phobia?
  - ***Are the analyses sufficient to adequately measure these changes?***

Statistical Analysis
STL-NY-94-004

- ITT evaluation of efficacy is considered primary
- Primary efficacy evaluations are based on endpoint (LOCF) values (treatment response and CGI-I) or changes from baseline to endpoint (all other efficacy parameters)
- ANCOVA will be used for continuous variables and CMH for categorical measures
- Two-sided statistical tests, 0.05 level of significance

Statistical Analysis STL-N/S-95-003

- Factorial Design
  - What would be of primary interest to the division?
    - Sertraline alone (n=95) vs placebo alone (n=92)
    - Sertraline +/- exposure (n=190) therapy vs placebo +/- exposure therapy (n=185)

Statistical Analysis
STL-N/S-95-003

- ITT evaluation of efficacy is considered primary
- Primary efficacy evaluations are based on endpoint (LOCF) values (treatment response and CGI-L-I) or changes from baseline to endpoint (all other efficacy parameters)
- ANCOVA for continuous variables and categorical linear model for categorical variables appropriate to factorial design (the factors are drug and therapy)
- Two-sided statistical tests, 0.05 level of significance

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

19-839/S-045

20-990/S-011

CORRESPONDENCE

Laughren, Thomas P

From: Laughren, Thomas P
Sent: Tuesday, January 28, 2003 3:50 PM
To: Homonnay Weikel, Anna M
Subject: NDA 19-839/S-045/Zoloft/SocAnx

Anna Marie,

I have written a brief approval memo and entered it into DFS. The package is fine, both letter and labeling. I have checked on the 2 items you indicated as needing MO review; these are both fine (I've initialed them). I've returned the package to you, with a hardcopy of my memo.

Thanks,

Tom

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********** -COMM. JOURNAL- ********** DATE MAY-16-2002 ***** TIME 14:59 *** P.01

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Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation I

FACSIMILE TRANSMITTAL SHEET

DATE: May 16, 2002

To: Graydon Elliot

Company: Pfizer Inc.

Fax number: (212) 857-3558

Phone number: (212) 733-0948

Subject:

From: Anna Marie H. Weikel, R.Ph.
Regulatory Health Project Manager
Division of Neuropharmacological Drug Products

Fax number: (301) 594-2859

Phone number: (301) 594-5535

Total no. of pages including cover: 1

Please provide the following electronic data sets for NDA 19-839/-045:
The statistical analysis data sets for the efficacy analysis for studies: 601, 94-004, 94-004C and 95-03. The SAS code for efficacy analysis for studies: 601, 94-004, 94-004C and 95-003.

Thank You

Document to be mailed: ☐YES ☑NO

Homonnay Weikel, Anna M

From: Khin, Ni Aye
Sent: Wednesday, March 20, 2002 3:37 PM
To: Homonnay Weikel, Anna M; Levin, Robert; Kong, Fanhui
Subject: NDA 19-839/SE1-045

Hi all,

I would like to let you know that the following sites are our DSI pick for inspection:

For protocol R60, 2 US sites:

1) 98-S-7005 Eugene DuBoff, Denver, CO (n=37)
2) 98-S-7016 Ward Smith, Portland, OR (n=36)

For protocol STL-NY-94-004 and 004C, the Canadian site for inspection:

1) Center 342 John Pecknold, Verdun, Quebec (n=21 for 20 week study, n=12 for relapse prevention)

Let me know if you wish to change any of these sites. Unless I hear from the Statistical Reviewer with any other specific site/concern for the Canadian site by end of next week, I will start with above sites for assignment. Thanks.

--Ni

********** -COMM. JOURNAL- ********** DATE JAN-29-2002 ***** TIME 12:09 *** P.01

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********** - ***** - 3015942859- *********

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation I

FACSIMILE TRANSMITTAL SHEET

DATE: January 29, 2002

To: Graydon Elliot

Company: Pfizer Inc.

Fax number: (212) 857-3558

Phone number: (212) 733-0948

Subject:

Total no. of pages including cover: 3

Supplement Acknowledgement Letter

From: Anna Marie Homonnay, R.Ph.
Regulatory Health Project Manager
Division of Neuropharmacological Drug Products

Fax number: (301) 594-2859

Phone number: (301) 594-5535

Document to be mailed: ☐YES ☑NO

NDA 19-839/S-045
NDA 20-990/S-011

PRIOR APPROVAL SUPPLEMENT

Pfizer Inc.
Attention: Graydon Elliott
Director, Regulatory Affairs
235 East 42nd Street
New York, NY 10017-5755

Dear Mr. Elliott:

We have received your supplemental drug applications submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for the following:

Name of Drug Product: Zoloft® (sertraline HCl) Tablets
Zoloft® (sertraline HCl) Oral Concentrate

Supplement Number: 19-839/S-045
20-990/S-011

Review Priority Classification: Standard (S)

Date of Supplement: January 18, 2002

Date of Receipt: January 22, 2002

These supplements provide for the treatment of Social Anxiety Disorder as a new indication.

Unless we notify you within 60 days of our receipt date that the application is not sufficiently complete to permit a substantive review, this application will be filed under section 505(b) of the Act on As March 22, 2002 in accordance with 21 CFR 314.101(a). If the application is filed, the primary user fee goal date will be November 22, 2002.

If you should have any questions, please call Anna Marie Homonnay, R.Ph., Regulatory Project Manager, at (301) 594-5535.

Sincerely,

{See appended electronic signature page}

John S. Purvis
Chief, Project Management Staff
Division of Neuropharmacological Drug Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Anna-Marie Homonnay
1/29/02 11:08:35 AM

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