REVIEW AND EVALUATION OF CLINICAL DATA

Application Information

NDA: 19-839
Sponsor: Pfizer
Clock Date: 10/7/98

Drug Name

Generic Name: sertraline
Trade Name: Zoloft

Drug Characterization

Pharmacological Category: Antidepressant
Proposed Indication: Post Traumatic Stress Disorder (PTSD)
NDA Classification: 1S
Dosage Forms, Strengths, and Routes of Administration:
Oral Tablets 25mg, 50mg, 100mg

Reviewer Information

Clinical Reviewer: Earl D. Hearst, M.D.
Review Completion Date: 6/8/99

1.0 Material Reviewed

This NDA supplement received on 10/7/98 contains 45 volumes and includes a CDROM disk containing case report form tabulations. In addition there is a CANDA available through the Internet and on a lap-top provided to me by the sponsor along with word tables on flopy disks. There are also SAS and Jump files in the FDA electronic document room.

I have reviewed all narratives for patients meeting the criteria for adverse events leading to discontinuation and serious adverse events including vital signs and weight, laboratory analytes, and ECG intervals and heart rate. I have also reviewed case report forms for all subjects who discontinued due to an adverse event. The case report forms are consistent with the narratives and clinical summaries provided by the sponsor.

I requested the sponsor to provided me with information on the nature of the traumatic event and the time symptoms began in relationship to this event. This information was provided and reviewed.

There is no additional information in INDs (see section 2.2) directly relevant to this review.

The sponsor recently indicated they are reanalyzing the data because an investigator was thrown out due to misconduct. I have not yet seen these changes but the sponsor indicates that they effect less than 10% of the patients and do not influence the conclusions.

2.0 Background

2.1 Indication

The sponsor proposes using sertraline in the treatment of PTSD.

2.2 Related INDs and NDAs

The data contained in this application have been obtained from studies carried out under the following Applications:

IND#	Filing Date	Drug

2.3 Administrative History

NDA 19-839 for Zoloft® in the treatment of depression was approved on December 30, 1991. Supplemental NDAs for the use of sertraline in the treatment of obsessive-compulsive disorder and panic disorder were approved on October 25, 1996 and July 8, 1997, respectively. Sertraline use in pediatric OCD was approved on October 10, 1997.

Selection of rating scales to evaluate PTSD treatment was endorsed by a Protocol Design Advisory Panel held in July 1993.

On October 9, 1997, a pre-sNDA Meeting was held with the Division to discuss the proposed PTSD submission. As a follow-up to the pre-sNDA Meeting, a statistical analysis plan was provided to the Division on November 15, 1997 and discussed on January 20, 1998. Gender analysis was submitted to the Agency on August 21, 1998. The sNDA efficacy supplement for treatment of Posttraumatic Stress Disorder was submitted to the FDA on October 7, 1998.

Protocols 640 and 641 for sertraline in the treatment of PTSD were filed to IND [redacted] on February 23, 1994 and February 24, 1994, respectively. On November 21, 1995, Pfizer conducted interim analyses for administrative purposes which had been planned prospectively in each protocol (640 and 641). Forty-three sertraline subjects and forty-nine placebo subjects were included in the interim analysis of Protocol 640 and thirty-nine sertraline subjects and thirty-three placebo subjects in Protocol 641. The purpose of the interim analysis was to verify the assumptions in the sample size calculation for Protocol 671 and to determine if a fourth study should be added to the development program. The third protocol (671) of sertraline in the treatment of PTSD was filed to IND [redacted] on February 16, 1996. The first subject entered the study on May 1, 1996. The fourth protocol (682) of sertraline in the treatment of PTSD was filed to IND [redacted] on May 20, 1996.

2.4 Directions for Use

The sponsor's directions are listed below:

Panic Disorder and Posttraumatic Stress 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.

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

2.5 Foreign Marketing

No registration applications requesting approval of sertraline in the treatment of post-traumatic stress disorder have been filed with any regulatory authorities anywhere in the world other than in the U.S.

3.0 Chemistry

The dosage form formulations approved December 30, 1991 in NDA 19-839 and March 6, 1996 in a supplement to NDA 19-839 will be used for the new indication.

4.0 Preclinical Pharmacology

No nonclinical pharmacology, toxicology, or pharmacokinetic studies in animal models of post-traumatic stress disorder were conducted for the present submission.

5.0 Description of Clinical Data Sources

5.1 Primary Development Program

5.1.1 Study Type and Design/Patient Enumeration

The current submission for the use of sertraline in PTSD is based on data from four adequate and well-controlled clinical studies that completed as of the February 26, 1998 cut-off date. The studies are Protocols 93CE21-0640, 95CE21-0671, 93CE21-0641, and 96CE21-0682).

In addition, there are four ongoing protocols as of the February 26, 1998 cut-off date. Protocol 95CE21-0672 is a 24-week, open-label, flexible-dose extension study for subjects who have completed Protocol 671 or 682. Subjects who have completed and

responded to open-label treatment in Protocol 672 are eligible to enter Protocol 96CE21-703, which is a 28-week, double-blind, placebo-controlled study assessing relapse. The other two ongoing protocols (STL-NY-93-005 and STL-AUS-94-001) are double-blind, placebo-controlled trials of sertraline in the treatment of PTSD conducted outside of the United States and are non-IND studies.

Tables of all studies are presented below.

Table V.A.1 Table of Completed Controlled Studies (Primary Database)

Protocol #	Study Design	Sertraline Dosage (qd)	Total Randomized Sertraline/Placebo	Comments
93CE21-0640 Multicenter 12 sites	Double-blind Placebo-controlled Parallel Flexible dosing 12 weeks d.b. treatment 1 week placebo run-in	25 mg for first week 50-200 mg thereafter PM dosing (may switch to AM dosing)	100/108	Primary efficacy measures: CAPS-2, IES, CGI Severity and Improvement Identical to Protocol 93CE21-0641
93CE21-0641 Multicenter 10 sites	Double-blind Placebo-controlled Parallel Flexible dosing 12 weeks d.b. treatment 1 week placebo run-in	25 mg for first week 50-200 mg thereafter PM dosing (may switch to AM dosing)	86/83	Primary efficacy measures: CAPS-2, IES, CGI Severity and Improvement Identical to Protocol 93CE21-0640
95CE21-0671 Multicenter 14 sites	Double-blind Placebo-controlled Parallel Flexible dosing 12 weeks d.b. treatment 2 weeks placebo run-in	25 mg for first week 50-200 mg thereafter PM dosing (may switch to AM dosing)	94/93	Primary efficacy measures: CAPS-2, IES, CGI Severity and Improvement Identical to Protocol 96CE21-0682 Completers may enter 24-wk open-label extension study (95CE21-0672; see Section 8.7.1)
96CE21-0682 Multicenter 16 sites	Double-blind Placebo-controlled Parallel Flexible dosing 12 weeks d.b. treatment 2 weeks placebo run-in	25 mg for first week 50-200 mg thereafter PM dosing (may switch to AM dosing)	96/97	Primary efficacy measures: CAPS-2, IES, CGI Severity and Improvement Identical to Protocol 95CE21-0671 Completers may enter 24-wk open-label extension study (95CE21-0672; see Section 8.7.1)

Studies were completed before the cut-off date of February 26, 1998.

Table V.A.2 Table of Ongoing Studies (Secondary Database)

Protocol # *Investigator*	Study Design	Sertraline Dosage (qd)	# Subjects Planned	Comments
95CE21-0672 Multicenter U.S.	Open-label Flexible dosing 24 weeks treatment	25 mg for first week 50-200 mg thereafter PM dosing (may switch to AM dosing)	320 maximum	Primary efficacy measures: CAPS-2, IES, CGI Severity and Improvement Open-label extension study for subjects who completed double-blind treatment in Protocols 95CE21-0671 or 96CE21-0682 (see Section 8.5.1) Responders may enter 28-wk double-blind continuation study (96CE21-0703)
96CE21-0703 Multicenter U.S.	Double-blind Placebo-controlled Parallel Flexible dosing 28 weeks treatment	25-200 mg PM dosing (may switch to AM dosing)	320 maximum	Primary efficacy measures: CAPS-2, IES, CGI Severity and Improvement Double-blind continuation study for subjects who responded to open-label treatment in Protocol 95CE21-0672. Subjects are randomized to sertraline or placebo, and time to relapse is assessed. Subjects begin at their last dose from Protocol 95CE21-0672.
STL-NY-93-005 Israel *Zohar J*	Double-blind Placebo-controlled Parallel Flexible dosing 10 weeks d.b. treatment 1-2 weeks placebo run-in	50-200 mg AM dosing	60 efficacy evaluable	Primary efficacy measures: CAPS-2, CGI Severity and Improvement
STL-AUS-94-001 Australia *Crompton DR* *McFarlane A*	Double-blind Placebo-controlled Parallel Flexible dosing 25 weeks d.b. treatment 1 week placebo run-in	25 mg for first week 50-200 mg thereafter AM or PM dosing	150 efficacy evaluable	Primary efficacy measures: CAPS-2, CGI Ten sessions of cognitive behavior therapy given in conjunction with double-blind treatment

Studies ongoing as of February 26, 1998 cut-off date

. The U.S. clinical development program investigating the safety and efficacy of sertraline in the treatment of PTSD includes four completed, 12-week, flexible-dose, double-blind, placebo-controlled studies which form the basis for the current submission.

5.1.2 Demographics

As shown in the table below, 65% (246/376) of the sertraline group and 60% (231/381) of the placebo group were female. The subject sample was predominantly white, with approximately 20% of sertraline subjects and 15% of placebo subjects identified as non-white. Both treatment groups had a mean age of 40 years. Most subjects were between 18 and 44 years of age. Only 6 sertraline subjects and 7 placebo subjects were >65 years old.

Table V.C.1. Demographic Profile for Completed Controlled Studies Combined*

	Sertraline (N=376)		Placebo (N=381)	
Measure	**No.**	**(%)**	**No.**	**(%)**
Sex: No. (%)				
Female	246	(65.4)	231	(60.6)
Male	130	(34.6)	150	(39.4)
Race: No. (%)				
Asian	5	(1.3)	7	(1.8)
Black	52	(13.8)	43	(11.3)
White	301	(80.1)	323	(84.8)
Other	18	(4.8)	8	(2.1)
Age: (yrs)				
Mean ± S.D.	39.7 ± 11.0		39.7 ± 11.1	
18 - 44	236		233	
45 - 64	130		141	
>= 65	6		7	
Weight (lb.)				
Mean ± S.D.	174.8 ± 47.8		174.8 ± 45.7	

* all randomized subjects(includes 2 sertraline and 5 placebo patients who never received study drug)

Differences between groups were tested using the Pearson chi-squared statistic for race and sex, and F-test from two-way ANOVA for mean age and weight. There were no statistical differences between groups on any of these parameters.

5.1.3 Extent of Exposure (dose/duration)

The total patient-years of exposure for all sertraline-treated subjects (n=374) in the primary database was 73.5 years. The mean was 0.20 + .07 yr.

Table VIII.A.2: Sertraline Exposure According to Maximum Daily Dose and Duration of Therapy - Completed Controlled Studies

Duration of Therapy	25 mg	50 mg	75 mg	100 mg	150 mg	200 mg	>200 mg*	Total	(%)
01 - 07	9	0	0	0	0	0	1	10	2.67
08 - 14	6	10	0	0	0	0	0	16	4.28
15 - 21	2	7	1	4	0	0	0	14	3.74
22 - 28	1	3	0	4	3	0	0	11	2.94
29 - 42	0	3	0	6	6	2	0	17	4.55
43 - 56	0	1	0	5	8	2	0	16	4.28
57 - 70	0	2	0	1	4	4	0	11	2.94
71 - 84	2	2	0	25	29	76	1	135	36.10
>= 85	0	4	0	25	31	83	1	144	38.50
Total	20	32	1	70	81	167	3	374	100.00
(%)	5.35	8.56	0.27	18.72	21.66	44.65	0.80	100.00	

* Includes Subject 94N0177-176, who ingested 425 mg sertraline (see SAE narratives for more information).

Sertraline was administered to a total of 374 safety analyzable subjects in the four completed PTSD studies. In addition, 376 safety analyzable subjects received placebo. The mean duration of exposure for sertraline subjects was 72 days (range of 2-114 days). The mean duration of exposure for placebo subjects was 74 days (range of 1-109 days). The majority of patients received 100-200mg of sertraline for greater than 71 days, as seen in the table above.

Table VIII.A.3 Mean Daily Dose By Visit Week - All Safety Analyzable Subjects

Week	Sertraline (mg)			Placebo (mg equivalent)		
	N	Mean	SD	N	Mean	SD
Week 1	374	24.8	5.6	375	24.6	2.5
Week 2	358	44.5	10.0	364	45.7	8.9
Week 3	337	78.4	28.1	354	83.6	25.9
Week 4	325	106.2	39.0	337	115.4	38.8
Weeks 6	312	131.4	52.0	327	144.5	51.7
Weeks 8	297	142.6	52.0	308	156.5	49.2
Weeks 10	286	149.0	51.1	293	161.2	50.7
Weeks 12	272	152.2	49.1	286	162.9	50.1

Mean daily dose was 24.8 mg during week 1 in sertraline subjects, increasing to 106.2 mg during week 4 and 142.6 mg during weeks 7

and 8. During weeks 11 and 12, mean sertraline dose was 152.2 mg/day. Mean placebo dose increased in a similar fashion to 163 mg/day during weeks 11 and 12. The average sertraline dosage during weeks 11 and 12 of therapy was 152.2 mg/day.

5.1.4 Disposition

Premature discontinuation of therapy occurred in 28% (104/374) of sertraline subjects and 25% (95/376) of placebo subjects. 8.6% of all sertraline-treated subjects and 4.8% of all placebo-treated subjects discontinued due to adverse events. Five sertraline subjects (1%) and no placebo subjects discontinued due to laboratory abnormalities. Four sertraline subjects (1%) and 9 placebo subjects (2%) discontinued due to insufficient clinical response. Discontinuation due to treatment emergent adverse events during the first week of treatment occurred in 1% of sertraline and 1% of placebo subjects.

Table VIII.B Rates of Discontinuation by Treatment Group and Reason - All Safety Analyzable Subjects

Reason for Discontinuation	% Discontinued Sertraline (n=374)	% Discontinued Placebo (n=376)
Withdrawn Consent	5.9	8.8
Adverse Event	8.6	4.8
Lost To Follow Up	6.7	4.5
Protocol Violation	2.4	2.1
Other	1.6	2.7
Insufficient Clinical Response	1.1	2.4
Laboratory Abnormality	1.3	0.0
Does Not Meet Entrance Criteria	0.3	0.0
Total % Discontinued	27.8%	25.3%

Includes subject 93N0179/598 (Protocol 641, Treatment=placebo; male) who discontinued due to adverse events which had onset prior to randomization and thus are not considered treatment emergent.

5.2 Secondary Sources

5.2.1 Non-IND Studies

There are two Non-IND studies with which the sponsor has been associated.

STL-NY-93-005 Title: A ten week single center parallel group, double-blind, comparative, placebo controlled, dose titration study of the safety, efficacy and toleration of sertraline (50mg to 200mg) in the treatment of outpatients with post-traumatic stress disorder.

STL-AUS-94-001 Title: A 25 week, multicenter, parallel group, double blind, randomized, placebo controlled dose titration study of the efficacy, toleration and safety of sertraline (25mg-200mg) in combination with cognitive behavior therapy in the treatment of post traumatic stress disorder in a non-veteran outpatient population.

Both studies were terminated early and there are no final reports. Serious adverse events were captured and are in the database. See table of ongoing studies in section 5.1.1.

5.2.2 Post-Marketing Experience

Zoloft used in PSTD is not marketed anywhere is the world. The sponsor had provided an analysis of postmarketing use of sertraline for PTSD which I summarize in the safety section.

5.2.3 Literature

The sposnsor has provided a literature review described below.

A review of the worldwide literature on the use of sertraline in post-traumatic stress disorder (PTSD) was conducted using five commercial databases:

The search included the terms of PTSD, post-traumatic stress disorder, post traumatic stress disorder, posttraumatic stress disorder, PTSS, post-traumatic stress syndrome, post traumatic stress syndrome, posttraumatic stress syndrome and traumatic neurosis and included all clinical and preclinical studies in publication (including original articles, review articles, letters and editorials) by the cut-off date of 26 February 1998. Ms. Karen Erani, Manager, Information Retrieval of the corporate Information Center conducted the search, and the literature was reviewed by Kathleen S. Ice, Ph.D., Associate Director, Clinical and Scientific Affairs, both of Pfizer, Inc. There were no preclinical studies

identified in the search, and foreign language publications consisted of review articles. The complete list of references is provided.

The sponsor states that there were no reports of any WHO-coded adverse event not already included in the product labeling, nor was any adverse event reported with unexpected frequency. The conclusion of the Pfizer reviewer is that no findings were noted which adversely affect the conclusions of this submission with regard to the safety of sertraline in patients with PTSD.

I have reviewed the sponsor's synopses of relevant articles and agree that there are no new safety or efficacy issues identified.

5.3 Adequacy of Clinical Experience

The exposure to sertraline appears to be of an adequate duration and dosage and the clinical experience is otherwise satisfactory.

5.4 Data Quality and Completeness

The data quality appears to be adequate and complete in that the specified scales and tests were appropriate, performed, with results collected and analyzed. The sponsor provided data to show treatment response in patients with low and high scores on the HAM-D but did not analyze PTSD response independently from response to depression.

6.0 Summary of Human Pharmacokinetics

No human pharmacokinetics or bioavailability studies were conducted in subjects with post-traumatic stress disorder for the present submission.

7.0 Efficacy Findings

7.1 Overview of Studies Pertinent to Efficacy

This section summarizes the four placebo-controlled studies (640, 671, 641 and 682) in the treatment of outpatients with PTSD. The designs of all four completed trials were similar; further,

Protocols 640 and 641 were identical to each other, as were Protocols 671 and 682. Subjects in all four studies were required to meet DSM-III-R criteria for a principal diagnosis of PTSD and were not allowed to have a primary diagnosis meeting DSM-III-R criteria for most other mood, anxiety or psychotic disorders, as determined by Structured Clinical Interview for DSM-III-R (SCID). All studies were conducted at U.S. research centers. Protocols 640, 671 and 682 were conducted primarily at civilian sites, while Protocol-641 was conducted at Veterans Administration (VA)-medical centers. There were no protocol restrictions as to the type of subject (civilian or veteran) that could be enrolled at a site. The intent-to-treat efficacy sample included all randomized subjects who had at least one dose of study medication and one post baseline efficacy evaluation.

At the Baseline visit, subjects in all four studies were required to have a score on the Clinician-Administered PTSD Scale Part 2 CAPS-2) of at least 50 in order to be randomized.

Each study had a 12-week, multicenter, double-blind, placebo-controlled, parallel-group, flexible dose (50 mg, 100 mg, 150 mg, 200mg) design using a 25 mg starting dose and a single-blind placebo run-in period (one week in Protocols 640 and 641; two weeks in Protocols 671 and 682). The sponsor states that a dose-titration design was utilized in the PTSD program because fixed dose studies conducted in depression, obsessive-compulsive disorder and panic disorder failed to yield evidence of a dose-response relationship.

Dosing.

In all four studies, subjects were started on a dose of 25 mg per day sertraline or matching placebo for one week. At the End of Week 1 visit, in the absence of any dose-limiting adverse events, subjects were titrated up to 50 mg per day. Thereafter, dosage was flexibly titrated in accordance with the subject's clinical response, in 50 mg weekly increments or decrements, to a maximum daily dose of 200 mg.

Primary Efficacy Variables.

The prospectively defined primary efficacy variables in all four studies were the Clinician-Administered PTSD Scale Part 2 (CAPS-2) total severity score, the Impact of Event Scale (IES) total score, and the Clinical Global Impressions ratings of Severity of Illness (CGI-S) and Improvement (CGI-I). Selection of these types of ratings to evaluate PTSD treatment was endorsed by a panel of U.S. experts at a meeting held in New York (March 1998) and a panel of experts from Europe, Israel, South Africa and the U.S. held in France (May 1998), as well as a pre-study Advisory Panel held prior to the start of Protocol 640. The Davidson Self-Rating PTSD scale

also known in the literature as the Davidson Trauma Scale; DTS) was denoted as a secondary efficacy measure at the time these trials were run as it was relatively new and validation was not complete.

Secondary Efficacy Variables. One secondary efficacy measure, the Hamilton Depression Scale (HAM-D), was administered in all four protocols. In addition, the Hamilton Anxiety Scale (HAM-A), the Civilian Mississippi Scale for PTSD (Mississippi), the Disorders of Extreme Stress - Not Otherwise Specified scale (DES-NOS), and the Pittsburgh Sleep Quality Index (PSQI) were administered in Protocols 640 and 641. In Protocols 671 and 682, additional secondary efficacy ratings were the Quality of Life scale and the Health and Work Questionnaire, the latter being a pharmacoeconomic evaluation.

Statistical Analysis:

In all studies, subject evaluations were conducted at one-week or two-week intervals, but secondary rating scales were administered only at Baseline and the final or termination visit. The Davidson scale was administered at every visit. The endpoint was 12 weeks or the last evaluation visit for all four studies.

The primary efficacy analyses were intent-to-treat analyses performed on the efficacy measures from every subject who received at least one dose of double-blind medication and had a baseline plus one on-treatment efficacy evaluation. Primary efficacy analyses assessed change from baseline to endpoint, where endpoint was defined as the last observation.

All statistical tests were two-sided and were performed in SAS at the 0.05 level of significance. Analysis of covariance models which included terms for treatment, site, treatment-by-site, and baseline (the covariate) effects were used to analyze the change from baseline on all efficacy variables except CGI Improvement. Type III sums of squares were used to assess statistical significance. The actual endpoint score was used for analysis of CGI Improvement since the change from baseline is implicit in this rating. The post-hoc responder analysis assessed subjects with at least a 30% decrease in the CAPS-2 total severity score and/or a CGI Improvement score of 1 or 2. The responder analysis used a Mantel-Haenszel chi-square statistic stratifying on site.

STUDY RESULTS:

0641

In study 641 done in a VA setting the sertraline-treated group did not differ from the placebo group at endpoint on any of the primary

efficacy variables. The secondary rating scales (Davidson, DES-NOS, Mississippi, HAM-A, HAM-D, and PSQI) did not show any differences between the two treatment groups at endpoint, as well.

0682

In study 682 the sertraline-treated group did not improve significantly compared to the placebo group at endpoint on any of the primary efficacy variables. On the IES, the placebo group was significantly improved compared to the sertraline group (-13.6 v. -19.7; p=0.017).

The sponsor considers two of the four completed studies to be supportive of their indication and I will describe these two studies in detail.

Protocol 93CE21-0640

Investigators/Sites

Please see complete list of investigators in the appendix.

Objectives

The objective of this study was to show the efficacy and safety of Zoloft in PTSD.

Study Design

Protocol 640 was a double-blind, 12-week comparison of flexible doses of sertraline and matching placebo conducted at 12 study sites.

Rating Scales

See general study discussion above.

Analysis

See general study discussion above.

Study Outcome

Patient Disposition

Please see appendix table of completer rates by week. 74.5% of sertraline and 71.2% of placebo patients completed week 12. At my request the sponsor provided tables showing weekly improvement in patients at time of drop out. In general the Zoloft patients had improved about the same or slightly more than placebo patients at time of drop out.

Demographics

Subjects were primarily white females, with significantly fewer males in the sertraline group compared to the placebo group (16/100 v. 30/108; p = 0.041). Subjects were approximately 37 years old with a mean duration of illness of approximately 12 years. The most common traumatic event was physical/sexual assault, with an approximate time since traumatic event of 18 years. Forty-nine percent of subjects had been diagnosed with a comorbid secondary depression. Please see appendix table.

Dosing Information

The mean final dose of sertraline was 125 mg/day at endpoint and 146 mg/day for weeks 11 and 12. The mean duration of treatment was 73 days in the sertraline group and 72 days in the placebo group.

Concomitant Medications

The appendix table presents the concomitant medication taken by subjects during the studies. 76% of sertraline-treated subjects and 81% of placebo-treated subjects took concomitant medication during double-blind treatment. Ibuprofen, acetaminophen, aspirin, and chloral hydrate were the medications most commonly taken in both treatment groups.

RESULTS:

My analysis indicated the following results.

In the CAPS-2, Sertraline does not win at weeks 1,2,3,4,6,8,10,12 for OC. The LOCF wins at week 12 P=.043 but at no other time.

In the IES, Sertraline does not win at weeks 1,2,3,4,6,8,10,12 for OC. The LOCF wins at week 12 P=.018 but at no other time.

In the CGI-S, Sertraline not win at weeks 1,2,3,4,6,8,10,12 for OC. The LOCF wins at week 12 P=.037 but at no other time.

In the CGI-I, Sertraline does not win at weeks 1,2,3,4,6,8,10,12 for OC. The LOCF wins at week 8 P=.041, week 10 P=.031, week 12 P=.001 but at no other time.

EFFICACY CONCLUSION STUDY I

No efficacy is seen in this study until week 12 and then it is only seen in females. This efficacy does not appear to be independent of the patient's mood (see predictors of response 7.3.1).

Protocol 95CE21-0671

Investigators/Sites

Please see complete list of investigators in the appendix.

Objectives

The objective of this study was to show the efficacy and safety of Zoloft in PTSD.

Study Design

Protocol 671 was a double-blind, 12-week comparison of flexible doses of sertraline and matching placebo conducted at 14 study sites.

Patient Disposition

Please see appendix table of completer rates by week. Sixty-nine percent of sertraline subjects and 73% of placebo subjects of the safety-analyzable population completed 12 weeks of treatment. At my request the sponsor provided tables showing weekly improvement in patients at time of drop out. In general the Zoloft patients had improved about the same or slightly more than placebo patients at time of drop out.

Demographics

Ninety-three subjects in the sertraline group and 90 in the placebo

group were included in the intent-to-treat analysis. Subjects were primarily white females, approximately 40 years old with a mean duration of illness of approximately 12 years. The most common traumatic event was physical/sexual assault, with time since traumatic event approximately 18 years. Thirty-six percent of subjects had been diagnosed with a comorbid secondary depression. Please see appendix table.

Dosing

The mean final dose of sertraline was 133 mg/day at endpoint and 151mg/day for weeks 11 and 12. The mean duration of treatment was 73 days in the sertraline group and 72 days in the placebo group.

Concomitant Medication

The appendix table presents the concomitant medication taken by subjects during the studies. 76% of sertraline-treated subjects and 81% of placebo-treated subjects took concomitant medication during double-blind treatment. Ibuprofen, acetaminophen, aspirin, and chloral hydrate were the medications most commonly taken in both treatment groups.

Rating Scales

See general study discussion above.

Analysis

See general study discussion above.

Efficacy Results

In the CAPS-2, Sertraline beats placebo at endpoint (OC) p=.016 and at week 2, P=.041, week 4 P=.00020, week 6 P=.011, week 8 P=.006, week 10 P=.004 and week 12 P=.023. The LOCF wins at weeks 2,4,6,8 and 10.. See appendix tables.

In the IES (OC), Sertraline beats placebo at week 10, P=.041, week 12 P=.049. The LOCF does not win at any time. See appendix tables.

In the CGI-S, Sertraline beats placebo at endpoint (OC) p=.012 and at week 4, P=.012, week 10 P=.030, week 12 P=.011,but does not win at weeks 1,2,3,6,8. The LOCF wins at week 4 P=.025, week 6 P=.024, week 10 P=.048, week 12 P=.012 but at no other time. See appendix tables.

In the CGI-I, Sertraline beats placebo at endpoint (OC) p=.016 and at week 1 P=.000, week 4 P=.000, week 6 P=.032, week 10 P=.008. The LOCF wins at weeks 1,4,6,8,10 and 12. See appendix tables.

EFFICACY CONCLUSION-STUDY 2

This study shows more consistent efficacy throughout the study period. Once again there is only a case for efficacy in females and this is influenced by mood improvement (see 7.3.1).

7.3 Summary of Data Pertinent to Important Clinical Issues

7.3.1 Predictors of Response

DOSE:

In each of the four completed studies, the starting dose of sertraline was 25 mg daily for one week, after which the dose was to be increased to 50 mg daily in the absence of dose-limiting adverse events. Thereafter, the daily dose could be titrated between 50 mg and 200 mg in weekly 50 mg increments or decrements based on clinical response and adverse events.

Mean daily dose was 24.8 mg during week 1 in sertraline subjects, increasing to 106.2 mg during week 4 and 142.6 mg during weeks 7 and 8. During weeks 11 and 12, mean sertraline dose was 152.2 mg/day. Mean placebo dose increased in a similar fashion to 163 mg/day during weeks 11 and 12. There is no evidence of a dose-response relationship.

AGE:

The majority of subjects in these studies were under 65 years of age (n = 13 for the four protocols), so no conclusions can be reached regarding the efficacy of sertraline in the treatment of PTSD in the elderly. There were no intrastudy differences in age distribution between sertraline and placebo groups

RACE:

The study population was predominately white (82%; 624/757 subjects), and no analysis was conducted stratified by race.

GENDER:

The sponsor concedes that the efficacy of sertraline in the treatment of PTSD may be different in men and women. A combined

analysis of the two positive studies was conducted to assess the difference in the efficacy of sertraline in men and women. See appendix table.

Seventy-six percent (76%) of the subjects were women. In women there was a significant difference between the sertraline and placebo groups in all efficacy measures. There were no significant differences in the efficacy measures between sertraline-treated men and placebo-treated men.

TRAUMATIC EVENT

Subjects were stratified by whether their traumatic event was one of physical/sexual assault or of another type. For the three PTSD rating scale totals, the change from baseline to the last observation was analyzed within men and women separately by analysis of covariance with the following effects included in the model: change= baseline, study, treatment, event, event by treatment. The clinical global improvement score was analyzed by the same model without a baseline covariate. Site effects were not used in this analysis because some sites had zero subjects in some strata.

The traumatic event in women was predominately physical/sexual assault (71.5%) while physical/sexual assault was the traumatic event in only 30.9% of the men. The sponsor states that sertraline is significantly efficacious in both strata of women. When men are stratified according to type of traumatic event the numbers of subjects in each stratum are small and no conclusions can be drawn
from this analysis.

IMPROVEMENT IN DEPRESSION AS PREDICTOR OF PTSD IMPROVEMENT

Dave Smith, Ph.D., FDA statistician and I attempted to see if there is improvement in PSTD scales independent from depression improvement. We tested the depression item on the HAM-D depression instrument regarding mood improvement. We defined depressed mood non-improvers as those patients with a difference between baseline depressed mood score to last visit depressed mood score of 0 or less. Depressed mood improvers were defined similarly with a difference of 1 or more. Therefore, patients whose depressed mood worsened or remained the essentially the same from the beginning of the study were considered to be depressed mood non-improvers. All other patients were classified as depressed mood improvers.

All statistical tests were two-sided and were performed in SAS at the 0.05 level of significance. Analysis of covariance models which included terms for improvement group (depressed mood improvers or non-improvers) and baseline HAM-D, which was treated as a covariate, were used to analyze the change from baseline PTSD on all three instruments.

The table below compares the response to PTSD scales for mood item improvers vs. non-improvers and contrasts that against the sertraline vs. placebo response on PTSD scales. This table shows that patients had a more consistent response on PTSD scales based on mood item improvement rather than whether they took sertraline or placebo.

MOOD ITEM CHANGES

Table 4.13. P-values for comparing depressed mood improvers vs. depressed mood non-improvers and sertraline vs. placebo with respect to PTSD instruments.

		Men		Women		Combined	
PTSD Instr.	Factor	640/671	All 4	640/671	All 4	640/671	All 4
CAPS-2	Dp. Mood	0.0997	0.0001	0.0001	0.0001	0.0001	0.0001
	Sertraline	0.7615	0.6698	0.0045	0.0534	0.0058	0.1227
CGI-S	Dp. Mood	0.0093	0.0001	0.0001	0.0001	0.0001	0.0001
	Sertraline	0.6472	0.5236	0.0176	0.0445	0.0182	0.1744
IES	Dp. Mood	0.1734	0.0001	0.0001	0.0001	0.0001	0.0001
	Sertraline	0.7026	0.6243	0.1472	0.2436	0.1053	0.4973

The next set of tables show various combinations of the variables mood item improved/mood item unchanged and sertraline/placebo

Table 4.14. P-values for comparing subgroups among males in Studies 640 and 671 only. The subgroups under consideration are combinations of depressed mood improvers vs. depressed mood non-improvers and sertraline vs. placebo with respect to PTSD instruments. A large negative mean difference from baseline implies patient benefit.

Males in Studies 640 and 671 (Pooled)					
CAPS-2					
	Mean Diff. From BL	Pbo. / No Dep. Imp.	Pbo. / Dep. Imp.	Sert. / No Dep. Imp.	Sert. / Dep. Imp.
Pbo. / No Dep. Imp.	-24.0	—			
Pbo. / Dep. Imp.	-32.5	0.188	—		
Sert. / No Dep. Imp.	-25.4	0.828	0.344	—	
Sert. / Dep. Imp.	-34.1	0.143	0.831	0.268	—
CGI-S					
		Pbo. / No Dep. Imp.	Pbo. / Dep. Imp.	Sert. / No Dep. Imp.	Sert. / Dep. Imp.
Pbo. / No Dep. Imp.	-0.7	—			
Pbo. / Dep. Imp.	-1.5	0.014	—		
Sert. / No Dep. Imp.	-0.9	0.490	0.099	—	
Sert. / Dep. Imp.	-1.5	0.021	0.988	0.119	—
IES					
		Pbo. / No Dep. Imp.	Pbo. / Dep. Imp.	Sert. / No Dep. Imp.	Sert. / Dep. Imp.
Pbo. / No Dep. Imp.	-11.0	—			
Pbo. / Dep. Imp.	-18.7	0.058	—		
Sert. / No Dep. Imp.	-15.6	0.243	0.492	—	
Sert. / Dep. Imp.	-16.4	0.211	0.628	0.873	—

Table 4.15. P-values for comparing subgroups among females in Studies 640 and 671 only. The subgroups under consideration are combinations of depressed mood improvers vs. depressed mood non-improvers and sertraline vs. placebo with respect to PTSD instruments. A large negative mean difference from baseline implies patient benefit.

Females in Studies 640 and 671 (Pooled)					
CAPS-2					
	Mean Diff. From BL	Pbo. / No Dep. Imp.	Pbo. / Dep. Imp.	Sert. / No Dep. Imp.	Sert. / Dep. Imp.
Pbo. / No Dep. Imp.	-14.3	—			
Pbo. / Dep. Imp.	-39.8	0.001	—		
Sert. / No Dep. Imp.	-25.3	0.002	0.001	—	
Sert. / Dep. Imp.	-44.6	0.001	0.255	0.001	—
CGI-S					
		Pbo. / No Dep. Imp.	Pbo. / Dep. Imp.	Sert. / No Dep. Imp.	Sert. / Dep. Imp.
Pbo. / No Dep. Imp.	-0.4	—			
Pbo. / Dep. Imp.	-1.6	0.001	—		
Sert. / No Dep. Imp.	-0.8	0.015	0.001	—	
Sert. / Dep. Imp.	-1.8	0.001	0.282	0.001	—
IES					
		Pbo. / No Dep. Imp.	Pbo. / Dep. Imp.	Sert. / No Dep. Imp.	Sert. / Dep. Imp.
Pbo. / No Dep. Imp.	-8.8	—			
Pbo. / Dep. Imp.	-22.9	0.001	—		
Sert. / No Dep. Imp.	-13.3	0.057	0.001	—	
Sert. / Dep. Imp.	-23.8	0.001	0.758	0.001	—

Table 4.16. P-values for comparing subgroups among all patients combined in Studies 640 and 671. The subgroups under consideration are combinations of depressed mood improvers vs. depressed mood non-improvers and sertraline vs. placebo with respect to PTSD instruments. A large negative mean difference from baseline implies patient benefit.

All patients in Studies 640 and 671 (Pooled)					
CAPS-2					
	Mean Diff. From BL	Pbo. / No Dep. Imp.	Pbo. / Dep. Imp.	Sert. / No Dep. Imp.	Sert. / Dep. Imp.
Pbo. / No Dep. Imp.	-17.0	—			
Pbo. / Dep. Imp.	-37.5	0.001	—		
Sert. / No Dep. Imp.	-25.3	0.008	0.001	—	
Sert. / Dep. Imp.	-42.5	0.001	0.173	0.001	—
CGI-S					
		Pbo. / No Dep. Imp.	Pbo. / Dep. Imp.	Sert. / No Dep. Imp.	Sert. / Dep. Imp.
Pbo. / No Dep. Imp.	-0.5	—			
Pbo. / Dep. Imp.	-1.5	0.001	—		
Sert. / No Dep. Imp.	-0.8	0.017	0.001	—	
Sert. / Dep. Imp.	-1.7	0.001	0.276	0.001	—
IES					
		Pbo. / No Dep. Imp.	Pbo. / Dep. Imp.	Sert. / No Dep. Imp.	Sert. / Dep. Imp.
Pbo. / No Dep. Imp.	-9.4	—			
Pbo. / Dep. Imp.	-21.6	0.001	—		
Sert. / No Dep. Imp.	-13.8	0.031	0.001	—	
Sert. / Dep. Imp.	-22.4	0.001	0.763	0.001	—

These tables help to indicate the extent to which both sertraline and placebo patients improve depending on whether their mood improves or not.

7.3.2 Size of Treatment Effect

The sponsor has provided the table below indicating the size of the treatment effect.

Table VII.G Treatment Effect Sizes - Protocols 640 and 671

	Protocol 640		Protocol 671	
	SERT Effect Size	Pbo-Subtracted Effect Size	SERT Effect Size	Pbo-Subtracted Effect Size
CAPS-2	-1.49	-0.31	-1.26	-0.37
Impact of Event	-1.56	-0.26	-1.35	-0.41
Davidson	-1.26	-0.48	-1.10	-0.47
CGI Severity	-1.18	-0.32	-1.04	-0.39

The effect size within each treatment group is the change from baseline divided by its standard deviation.

7.3.3 Choice of Dose

The following table indicates that the mean dosing for these patients is in the range recommended by the sponsor in their proposed labeling.

Table VIII.A.3 Mean Daily Dose By Visit Week - All Safety Analyzable Subjects

Week	Sertraline (mg)			Placebo (mg equivalent)		
	N	Mean	SD	N	Mean	SD
Week 1	374	24.8	5.6	375	24.6	2.5
Week 2	358	44.5	10.0	364	45.7	8.9
Week 3	337	78.4	28.1	354	83.6	25.9
Week 4	325	106.2	39.0	337	115.4	38.8
Weeks 6	312	131.4	52.0	327	144.5	51.7
Weeks 8	297	142.6	52.0	308	156.5	49.2
Weeks 10	286	149.0	51.1	293	161.2	50.7
Weeks 12	272	152.2	49.1	286	162.9	50.1

7.3.4 Duration of Treatment

There is insufficient data to support any efficacy claim beyond three weeks of treatment.

7.4 Conclusions Regarding Efficacy Data

Some things are easier than others to conclude from the efficacy data. It is clear that there is no data for efficacy in males in any of the four studies individually or combined. There is data for symptom reduction in study 640 seen only in females at week 12 (LOCF) but not week 12 (OC). There is more data seen at several weeks in study 671 indicating that females only have symptom reduction.

It is more difficult to characterize the nature of the symptom reduction seen only in females. Quite a bit of the effect on PTSD scales seems to be correlated with an improvement in the HAM-D. Whether Zoloft independently treats PTSD or simply treats associated comorbidity is difficult to determine.

8.0 Safety Findings

8.1 Methods

A total of 757 subjects (376 sertraline, 381 placebo) were randomized to double-blind medication in the completed PTSD studies as of the February 26, 1998 cut-off date of the present submission.

Of these, 750 subjects (374 sertraline, 376 placebo) received at least one dose of study medication and had at least one further contact with the study site. These 750 subjects comprise the "safety analyzable" population that forms the basis of the analyses in this summary.

The safety data from these four completed PTSD studies form the basis of this integrated summary of safety. Information is included on premature discontinuations of therapy, treatment emergent adverse events, serious adverse events, laboratory abnormalities, vital signs, body weight, and electrocardiography findings. In addition, as of the February 26, 1998 cut-off date, there are four ongoing PTSD studies including a total of 457 subjects receiving sertraline or placebo. Any serious adverse events from these ongoing studies that were entered into Pfizer's early alert system as of the cut-off date are discussed in this summary.

Serious adverse events were defined as events which: a) were fatal, b) were life-threatening or potentially life-threatening, c) resulted in permanent disability, d) required hospitalization or prolongation of a hospital stay, e) involved cancer, a congenital anomaly, or were the result of a drug overdose, or f) were deemed serious by the investigator.

All volunteered or observed treatment emergent adverse events were to be recorded and assessed by the investigator for relationship to study drug and severity. "Treatment emergent" was defined as beginning or worsening in severity after the subject was randomized, if the subject took at least one dose of study medication. Any objective test finding (e.g., an abnormal laboratory test result) which resulted in a change in study drug dosage or discontinuation of study drug was to be reported as an adverse event. Adverse event tables are organized according to body system and the preferred adverse event terms are used as listed in the Pfizer World Health Organization (WHO) Adverse Event Coding Glossary. In computing incidence of adverse events for a given table, a subject reporting more than one episode of the same adverse event, even of differing severity, was counted once and the highest level of severity was used. The incidence rates of subjects with any adverse event and of individual adverse events were compared between treatment groups using Fisher's exact test (2-tail). Adverse events occurring up to 7 days after the last dose of study drug are included in these analyses.

Laboratory safety evaluations were performed on all subjects receiving sertraline or placebo at baseline, at the end of week 6, and at end of week 12 (or when the subject discontinued the study). Clinical laboratory testing was performed at a central laboratory

At screening,

subjects with significant laboratory abnormalities in the investigator's opinion, as well as subjects with elevated liver function tests as specified in the protocols, were not to enter the studies. Laboratory evaluations made up to 7 days after the last dose of study drug are included in these analyses. Three methods were used to evaluate abnormal laboratory data that occurred during the studies, as listed below.

1. Premature discontinuations because of laboratory abnormalities.

2. Clinically significant laboratory test abnormalities using the threshold value criteria listed in Table 9.1.1 as adopted in sertraline Safety Update II for NDA #19-839, submitted to the U.S. Food and Drug Administration on 10/30/91.

3. Statistical comparison of the change from baseline in each laboratory parameter in the sertraline and placebo treatment groups. In addition, for hematology and serum chemistry parameters, the baseline and maximum (or minimum) laboratory values of each subject in each treatment group were graphically represented on scatterplots.

In all completed studies, blood pressure and heart rate were measured at every visit, after the subject had been sitting for 5 minutes.

In the completed studies, a 12-lead electrocardiogram was obtained at baseline and at the end of treatment (or when the subject discontinued from the study).

In all completed studies, body weight was measured at every visit.

The more commonly encountered adverse experiences were assessed using data from the placebo-controlled trials. Less frequent, but more grave adverse experiences were investigated by examining any death, reasons for premature discontinuation from clinical trials and the sponsor's safety reports of potentially serious adverse events from all studies.

8.2 Deaths

There were no deaths which occurred during or within 30 days of study discontinuation or poststudy (greater than 30 days following study discontinuation) for any study.

8.3 Assessment of Dropouts

8.3.1 Overall Pattern of Dropouts

The dropout rates for Sertraline and placebo due to adverse events were 8.6 vs 4,8. Please see table below.

Rates of Discontinuation by Treatment Group and Reason - All Safety Analyzable Subjects

Reason for Discontinuation	% Discontinued Sertraline (n=374)	% Discontinued Placebo (n=376)
Withdrawn Consent	5.9	8.8
Adverse Event	8.6	4.8
Lost To Follow Up	6.7	4.5
Protocol Violation	2.4	2.1
Other	1.6	2.7
Insufficient Clinical Response	1.1	2.4
Laboratory Abnormality	1.3	0.0
Does Not Meet Entrance Criteria	0.3	0.0
Total % Discontinued	27.8%	25.3%

Includes subject 93N0179/598 (Protocol 641, Treatment=placebo; male) who discontinued due to adverse events which had onset prior to randomization and thus are not considered treatment emergent.

8.3.2 Adverse Events Associated with Dropout

The discontinuation rate due to treatment-emergent adverse events/laboratory abnormalities at any time during the studies was 10% (37/374) in sertraline subjects and 5% (17/376) in placebo subjects. Sertraline was not associated with any statistically significant increased incidence of clinically significant abnormalities of laboratory parameters, vital signs, or body weight as compared to placebo.

Nausea and headache were the most common treatment-emergent adverse events leading to discontinuation in sertraline subjects.

Adverse Events Associated with Discontinuation - All Safety Analyzable Subjects
Protocols 640, 641, 671, 682

	Sertraline		Placebo	
Adverse Events	Subject N	Incidence (%)	Subject N	Incidence (%)
Nausea	7	(1.9)	1	(0.3)
Headache	5	(1.3)	2	(0.5)

The table above lists adverse events associated with discontinuation with an incidence > 1% in sertraline-treated subjects.

8.4 Search for Serious Adverse Events

Any serious adverse event occurring during the study or within 30 days after the last administration of study drug was to be reported regardless of causality. Any event that occurred greater than 30 days after the last administration of study drug was to be reported if the investigator felt that the event was causally related to study drug.

The serious adverse events which were entered into Pfizer's early alert safety database as of the February 26, 1998 cut-off date are presented for both completed and ongoing studies. Serious adverse events occurred in 2% (8/374) of sertraline subjects and 1% (5/376) of placebo subjects in the completed studies. As of the cut-off date, 5 sertraline subjects (with 7 events) and 5 subjects receiving blinded therapy experienced serious adverse events in the ongoing studies. None of these events were considered to be treatment-related by the investigator.

Serious adverse events among sertraline subjects were one of each of the following except where indicated: delirium (attributed to multiple sclerosis), suicide attempt, homicidal ideation, suicidal ideation (two subjects), head fracture, agitation, and cholecystitis.

Ten subjects out of a total of 457 subjects treated in studies ongoing as of February 26, 1998 (secondary database) experienced 12 serious adverse events. Among subjects treated with sertraline or blinded therapy, there was one of each of the following serious

adverse events, except where noted: fetal death, ovarian cyst (two subjects), basal cell carcinoma of the eyelid, bone graft, chest pain, pharyngeal constriction, breast reduction surgery, hernia, accidental hand laceration, paroxysmal atrial fibrillation, and suicidal ideation. None of the serious adverse events were considered by the investigator to be related to sertraline or blinded medication.

These events are listed in the safety appendix. I have reviewed this list and find no new or worrisome events that differ from the serious adverse events in the original submission.

Dropouts and deaths have been discussed in previous sections. Laboratory abnormalities, overdoses, withdrawal phenomena and pregnancy related events will be discussed in subsequent sections of this review.

8.5 Other Safety Findings

8.5.1 ADR Incidence Tables

8.5.1.1 Appropriateness of Adverse Event Categorization and Preferred Terms

Adverse event tables are organized according to body system and the preferred adverse event terms are used as listed in the Pfizer World Health Organization (WHO) Adverse Event Coding Glossary. I have reviewed this list and find the organization to be reasonable.

8.5.1.2 Incidence in Controlled Clinical Trials

At least one treatment emergent adverse event was reported by 88% (329/374) of sertraline-treated subjects and 80% (302/376) of placebo-treated subjects. The most frequent treatment emergent adverse events (10% incidence) in sertraline-treated subjects were diarrhea, headache, nausea, insomnia, somnolence, dry mouth, and malaise. The treatment emergent adverse events that occurred in at least 5% of sertraline subjects and with an incidence at least twice that of placebo were dry mouth, fatigue, anorexia, decreased libido, and tremor.

The adverse events reported in this submission are similar to those previously reported for the indications of depression, obsessive-compulsive disorder, and panic disorder, and reflected in the current labeling.

8.5.1.3 Post Marketing Spontaneous Reports

The sponsor had provided an analysis of postmarketing use of sertraline for PTSD. It is reproduced in truncated form in italics below.

Over 3,590,000,000 patient days of therapy with sertraline have been experienced worldwide through March 1998, since the drug was first launched in 1991. Sertraline has been approved for use in depression, obsessive-compulsive disorder, and panic disorder. Serious adverse events from spontaneous or literature reports of patients treated with sertraline for any indication (approved or unapproved) are entered into Pfizer's early alert safety database. This database was searched for spontaneous or literature reports of serious adverse events in patients treated for PTSD reported up to the data cut-off date of February 26, 1998. Thirteen such serious adverse events were found (Table 14). Only limited information is available for these events. Hypercholesterolemia in one patient and leukopenia in another patient were thought to be possibly related to sertraline by the reporters of the events; all other events were either not considered to be related to sertraline or were not assessed for relationship to sertraline by the reporters of the events. The most common event was intentional overdose, which was reported in five patients (see Section 8.10.12). All of the patients survived.

8.5.2 Laboratory Findings

5/374 of sertraline subjects and no placebo subjects prematurely discontinued study drug due to laboratory test abnormalities. Four of the five subjects had elevated SGOT and SGPT; maximum values for these subjects ranged from 50 to 172 U/L for SGOT and from 111 to 460 U/L for SGPT. The elevations were ascribed to hepatitis in one subject and to alcohol consumption in another subject. The last available follow-up values for these two subjects were 123 and 91 U/L, respectively, for SGOT and 111 and 121 U/L, respectively, for SGPT. In the other two subjects, the elevations were attributed to sertraline. In these subjects, values returned to normal after discontinuation of study drug. The fifth subject had decreases in hematocrit (from 30% to 27%) and hemoglobin (from 9.2 to 8.1 g/dL) attributed to a history of anemia. No follow-up values are available for this subject. None of these abnormalities were considered serious adverse events. No subjects discontinued due to vital sign abnormalities, electrocardiogram abnormalities, or weight changes.

The following sections will provide proportions of patients in the double-blind placebo-controlled trial who met arbitrarily defined criteria for changes in laboratory variables of possible clinical

significance. There will also be comparisons of sertraline versus placebo regarding mean changes in baseline parameters of laboratory values.

8.5.2.1 Clinical Chemistry Findings

There was no statistical difference in the incidence of laboratory test abnormalities in treated subjects (57 abnormalities in 46 subjects) as compared to placebo-treated subjects (66 abnormalities in 50 subjects). Mean changes from baseline in sertraline subjects which were significantly different from placebo included SGOT, SGPT, alkaline phosphatase, total protein, albumin, cholesterol, and uric acid. Sertraline treated subjects had higher mean change values for SGOT (3.11 vs -.13), SGPT (4.50 vs.67), Alk Phos (5.10 vs 1.43), total protein (7.33 vs4.16), cholesterol (13.31 s-2.90)

The chemistry criteria used in this section appear in the safety appendix along with the tables of proportions of patients in the double-blind placebo-controlled trial who fell outside the defined criteria for changes.

There were no significant changes in the proportions of patients exceeding defined criteria except for elevated SGPT where sertraline had 1.3% and Placebo .6%.

8.5.2.2 Hematology Findings

Mean changes from baseline in sertraline subjects which were significantly different from placebo included white blood count, red blood cells, neutrophils. These mean changes were small in magnitude and of minimal clinical importance.

The hematology criteria used in this section appear in the safety appendix along with the tables of proportions of patients in the double-blind placebo-controlled trial who fell outside the criteria for changes.

There were no significant changes in the proportions of patients exceeding defined criteria.

8.5.2.3 Urinalysis

The urinalysis criteria used in this section appear in the safety appendix along with the tables of proportions of patients in the double-blind placebo-controlled trial who fell outside the defined

criteria for changes.

There were no significant changes in the proportions of patients exceeding defined criteria.

There were no changes in urinary mean values reported.

8.5.3 Vital Signs

The sponsor provides the incidence of clinically significant abnormalities in vital signs in sertraline-treated subjects and placebo-treated subjects as determined by the following criteria: heart rate >120 bpm or <50 bpm; systolic blood pressure >180mmHg or <90mmHg; diastolic blood pressure >105 mmHg or <50 mmHg. In addition, in order to be classified as a clinically significant abnormality, the change from baseline was required to be greater than or equal to: 15 bpm for heart rate, 20 mmHg for systolic blood pressure and 15 mmHg for diastolic blood pressure. According to the above criteria there were 20 clinically significant abnormalities of vital signs among 19/370 (5%) sertraline-treated subjects compared with 17 such abnormalities among 17/368 (5%) placebo-treated subjects. None of the abnormalities were serious or warranted subject discontinuation. There were no statistically significant differences in the incidence of clinically significant vital sign abnormalities between the sertraline and placebo treatment groups.

The only statistically significant (p =.05) difference between the sertraline and placebo treatment groups in the mean change from baseline to final visit in any vital sign was heart rate. The mean decrease from baseline of 0.99 bpm (-1%) in sertraline-treated subjects compared with a mean increase of 1.31 bpm (+2%) in placebo-treated subjects is without clinical significance.

There were 12 sertraline subjects with low BP compared to 4 on placebo p=.07.

In all completed studies, body weight was measured at every visit. On the basis of a threshold criterion of a 7% change in weight from baseline during the study, 2/370 (1%) subjects in the sertraline group versus 7/367 (2%) subjects in the placebo group experienced a clinically significant weight gain, and 13/370 (4%) subjects in the

sertraline group versus 9/367 (2%) in the placebo group experienced a clinically significant weight loss. None of the weight changes led to discontinuation. The incidence of these body weight abnormalities was not significantly different in the sertraline and placebo treatment groups. The mean change in weight from baseline to final visit was -1.87 lbs for the sertraline group and +0.04 lbs for the placebo group. These changes are statistically significantly different (p=.05).

The vital sign criteria used in this section appear in the safety appendix along with the tables of proportions of patients in the double-blind placebo-controlled trial who fell outside the defined criteria for changes.

8.5.4 ECGs

Treatment-emergent clinically insignificant electrocardiogram abnormalities occurred in 9% of both sertraline (29/307) and placebo (28/306) subjects. No subjects had clinically significant electrocardiogram abnormalities. No subjects discontinued due to electrocardiogram abnormalities.

The ECG criteria used in this section appear in the safety appendix along with the tables of proportions of patients in the double-blind placebo-controlled trial who fell outside the arbitrarily defined criteria for changes.

There were no statistically significant changes in the proportions of patients exceeding defined criteria

There were no significant parameters among mean changes from baseline.

8.5.5 Special Studies

None done.

8.5.6 Withdrawal Phenomena/Abuse Potential

There was no new evidence of withdrawal signs or of indications of abuse potential in the four completed trials of sertraline for the treatment of Posttraumatic Stress Disorder. There is no significant change from previous data and recommendations in this section.

8.5.7 Human Reproduction Data

No human reproductive studies were included in this submission.

Of the 750 safety analyzable subjects in the completed controlled trials, two discontinued prematurely due to pregnancy, one in the sertraline group (93N0168/52) and one in the placebo group (94N0158/189). Of the 457 safety analyzable subjects in the ongoing trials as of the February 28, 1998 cut-off date, one subject (96N0192/1049) became pregnant after receiving 29 days of blinded therapy in Protocol 96CE21-0703. The patient had previously received 159 days of 100 mg/day open-label sertraline treatment. The patient discontinued treatment upon learning that she was pregnant. One month later her pregnancy terminated because of fetal death. The cause of the fetal death was unknown but not considered treatment related by the investigator. The subject was taking no concomitant medications. Previous pregnancy history is under investigation.

There is no significant change from previous data and recommendations in this section.

8.6 Overdose Experience

As of the February 26, 1998 data cut-off date, there was one reported case of sertraline overdosage in the completed and ongoing PTSD studies. Subject #94N0177-176 (Protocol 640) was a 39-year old white female who ingested 425 mg of sertraline in an attempt to obtain symptomatic relief following an encounter with a previous assailant. She suffered no sequelae of the overdose.

Five overdoses have been entered into Pfizer's early alert safety database as of February 26, 1998 from spontaneous or literature reports of patients treated with sertraline for PTSD. Only limited

information is available for these events. All of the patients survived. The amount of sertraline ingested by the five patients was 300 mg, 400 mg, 750 mg, 1500 mg, and an unknown amount. Three of the patients also overdosed on other medications at the same time. The patient that took 1500 mg was a 35-year old white female who also ingested 1000 mg of diphenhydramine at the same time. She was admitted to the hospital with decreased alertness, and electrocardiography revealed mild T wave changes. She also had a high blood alcohol level. The patient was treated with an orogastric lavage and a large number of pill fragments were returned. She was discharged from the hospital the next day.

8.7 Summary of Important Events Considered Drug Related

Weight:

On the basis of a threshold criterion of a 7% change in weight from baseline during the study, 2/370 (1%) subjects in the sertraline group versus 7/367 (2%) subjects in the placebo group experienced a clinically significant weight gain, and 13/370 (4%) subjects in the sertraline group versus 9/367 (2%) in the placebo group experienced a clinically significant weight loss. None of the weight changes led to discontinuation.

Liver Functions:

Four subjects had elevated SGOT and SGPT; maximum values for these subjects ranged from 50 to 172 U/L for SGOT and from 111 to 460 U/L for SGPT. The elevations were ascribed to hepatitis in one subject and to alcohol consumption in another subject. The last available follow-up values for these two subjects were 123 and 91 U/L, respectively, for SGOT and 111 and 121 U/L, respectively, for SGPT. In the other two subjects, the elevations were attributed to sertraline. In these subjects, values returned to normal after discontinuation of study drug.

EKG:

No subjects had clinically significant electrocardiogram abnormalities. No subjects discontinued due to electrocardiogram abnormalities.

8.8 Important Events Considered Not Drug Related

Certain events have been discussed elsewhere in this document and have been excluded from this list (i.e., deaths, overdoses, dropouts and changes in laboratory values).

The rest of the serious adverse events are considered not drug related and they are displayed in the Appendix of serious adverse events.

8.9 Summary of Drug Interactions

8.9.1 Drug-Demographic Interactions

GENDER:

89% (216/244) of females and 87% (113/130) of males in the sertraline group had treatment emergent adverse events, with 11% of females and 9% of males who received sertraline discontinuing due to treatment emergent adverse events. Headache, nausea, insomnia, and diarrhea were the most common (20%) treatment emergent adverse events in females. In males, diarrhea and headache were most common (20%).

AGE:

The sponsor presents the incidence of treatment emergent adverse events in 3 age groups: 18-44 years, 45-64 years, and 65 years. The percentage of sertraline subjects with treatment emergent adverse events was similar in the 18-44 year (90%; 213/238) and 45-64 year (85%; 111/130) age groups, as was the percentage of sertraline subjects discontinuing due to treatment emergent adverse events (10% for each age group). Incidences of individual adverse events were also comparable in these two groups. The number of sertraline subjects in the 65 year age group (n=6) was too small to allow meaningful interpretation.

RACE:

Among subjects receiving sertraline, 90% (271/300) of white subjects, 86% (44/51) of black subjects, and 61% (14/23) of subjects of other races reported treatment emergent adverse events. The incidence of discontinuation due to treatment emergent adverse events in sertraline subjects was 9% (28/300), 10% (5/51), and 17% (4/23) in these groups, respectively. The small sample size of

black and other non-white patients does not provide sufficient basis to draw meaningful conclusions about possible differences in sertraline tolerability with respect to race.

8.9.2 Drug-Disease Interactions

No potentially significant medical concern has been identified in subjects with PTSD that was not previously established in the safety profile of non-PTSD subjects as documented in previous submissions to NDA 19-839 and are reflected in the current labeling.

8.9.3 Drug-Drug Interactions

No new drug interactions have been reported with this submission. 76% of sertraline-treated subjects and 81% of placebo-treated subjects took concomitant medication during double-blind treatment. Ibuprofen, acetaminophen, aspirin, and chloral hydrate were the medications most commonly taken in both treatment groups.

9.0 Labeling Review

The labeling has been changed to include the larger data base now available. PTSD has been inserted in all areas where the indications are listed. The safety tables have been updated with PTSD columns. These listings appear to be correct. The significant changes are in the indications section where the sponsors add the indication and try to minimize the lack of effect in males.

10.0 Conclusions

There are no safety issues identified in subjects with PTSD that were not previously established in the safety profile of non-PTSD subjects as reflected in the current labeling.

There is little to no efficacy in males. There is some degree of efficacy in females who have a simultaneous improvement in mood (see 7.3.1).

11.0 Recommendations

The sponsor did not demonstrate efficacy in the full population that was intended. The efficacy they demonstrated was in a subpopulation (females) and then was highly associated with mood improvement.

This drug is currently available for use and I see no need to grant a new indication that is not fully proven for both men and women. My choice would be to describe these trials in the appropriate labeling section pointing out the gender differences and the high correlation with mood improvement.

/S/ 9/13/99

Earl D. Hearst, M.D.
Medical Reviewer

file/tlaughren/ehearst/ahomonnay

10-19-99

I disagree with Dr. Hearst's conclusion that Zoloft was not shown to be effective in PTSD overall. In fact, if the p-values had not been significant for the overall hypotheses, there would have been no basis for subgroup explorations. I agree that these explorations do suggest that the effects were derived predominantly from the women in those studies, however, as discussed at the PDAC meeting for this application, it might well be something other than gender that is driving the result. In any case, I agree with the majority of PDAC members who strongly urged FDA to approve Zoloft for PTSD in general, with a description of the exploratory analyses in the Clincical Trials section, as we ordinarily do in such situations. I also disagree with Dr. Hearst's suggestion that the correlations between the PTSD and the HAMD responses in some way diminish the evidence for effectiveness of Zoloft in PTSD. In fact, the exploratory analyses conducted by Drs. Smith and Hearst actually support the independence of the PTSD effect. Dr. Hearst's review is deficient in omitting what in my view are the most pertinent data, i.e., (1) the evidence that, with or without comorbid depression at baseline, there is evidence of a PTSD effect, and (2) the evidence for an effect on the cluster of items specific to PTSD. His suggestion, as an alternative to approving Zoloft for PTSD, to "describe these trials in the appropriate labeling section..." is without any clear meaning. See my 10-19-99 memo to the file for my more detailed comments on this application and my recommendation that Zoloft be approved for the treatment of PTSD.

/S/
TL, PDP

INDEX

APPENDIX

Table V.B List Of Investigators and Sites for Completed Controlled Studies

640 Principal Investigators	Study Sites
Jessy Colah, M.D., and Renuka Tank, M.D.	One Brookdale Plaza at Linden Boulevard Brooklyn, NY 11212
Kathleen Brady, Ph.D., M.D.	171 Ashley Avenue Charleston, SC 29425-0742
Paul Newhouse, M.D.	1 South Prospect Street Burlington, VT 05401
Barbara Rothbaum, Ph.D.[a]	Building B, Suite 6100 1365 Clifton Road NE Atlanta, GA 30322
Hisham Hafez, M.D., and Philip Santora, M.D.[a]	29 Northwest Blvd. Nashua, NH 03063
Peter Londborg, M.D.	901 Boren Avenue, Suite 940 Seattle, WA 98104
Teri Pearlstein, M.D.	345 Blackstone Blvd. Providence, RI 02906
Bessel van der Kolk, M.D., Ph.D.	227 Babcock Street Brookline, MA 02146
Wayne Phillips, M.D., Ph.D.	1650 38th Street Suite 105 W Boulder, CO 80301
Katherine Shear, M.D.[b]	3811 O'Hara Street Pittsburgh, PA 15213
Richard H. Weisler, M.D.	900 Ridgefield Drive Suite 320 Raleigh, NC 27609
William Patterson, M.D.	2120 Lynngate Drive Birmingham, AL 35216
Phebe Tucker, M.D.[a]	P.O. Box 26901 Oklahoma City, OK 73190-3048
641 Principal Investigators	**Study Sites**

Neal Kline, M.D.,and Mark Rapaport, M.D.[a]	3350 La Jolla Village Drive San Diego, CA 92161
June Corwin, Ph.D.	423 East 23rd Street New York, NY 10010
Israel Liberzon, M.D.	2215 Fuller Road Ann Arbor, MI 48105
Matthew J. Friedman, M.D., Ph.D.	White River Junction, VT 05009-0001
Joseph Westermeyer, M.D., Ph.D., M.P.H	One Veterans Drive Minneapolis, MN 55417
Jonathan Davidson, M.D.	508 Fulton Street Durham, NC 27705
Bruce Kagan, M.D.[b]	11301 Wilshire Blvd. Ward 207C Los Angeles, CA 90073
Dewleen G. Baker, M.D.	3200 Vine Street Cincinnati, OH 45220
Bruce Perry, M.D., Ph.D.	2002 Holcombe Blvd Houston, TX 77030
Mark H. Hamner, M.D.	109 Bee Street Charleston, SC 29401-5755
Thomas A. Mellan, M.D.	1201 N.W. 16th Street Miami, FL 33125
671 Principal Investigators	**Study Sites**
Gregory Asnis, M.D.	111 East 210 Street Bronx, NY 10467
Dewleen Baker, M.D.	3200 Vine Street Cincinnati, OH 45220

Robert Bielski, M.D.	26105 Orchard Lake Rd. Suite 301 Farmington Hills, MI 48334
Kathleen Brady, M.D., Ph.D.	171 Ashley Avenue Charleston, SC 29425-0742
Jonathan Davidson, M.D.[a]	3rd FLoor, Purple Zone, Room 3712 Trent Drive Durham, NC 27710
Edna Foa, Ph.D.and Richard J. Kavoussi, M.D.[b]	3200 Henry Avenue Philadelphia, PA 19129
Susanna Goldstein, M.D.	65 Central Park West #1-BR New York, NY 10023
Mark Hegel, Ph.D., and C. Lewis Ravaris, M.D., Ph.D.	One Medical Center Dr. Lebanon, N.H. 03756
Jonathan M Himmelhoch, M.D.[a]	3501 Forbes Avenue, Oxford Bldg., Room 738 Pittsburgh, PA 15213
Henry Lahmeyer, M.D.	310 Happ Road Suite 205 Northfield, IL 60093
Peter Londborg, M.D.	Cabrini Medical Tower 901 Boren Avenue, Suite 1800 Seattle, WA 98104
Teri Pearlstein, M.D.	345 Blackstone Boulevard Providence, RI 02906
Murray Rosenthal, D.O. and Andrew J. Ferber, R.N. MSN	9449 Balboa Avenue, Suite 205 San Diego, CA 92123
Barbara Rothbaum, Ph.D., and Philip T. Ninan, M.D.	1701 Uppergate Drive - Room 126 Atlanta, GA 30322
Ward Smith, M.D.[a]	1849 NW Kearney Portland, OR 97209

Phebe Tucker, M.D.	P.O. Box 26901 Oklahoma City, OK 73109-3048
682 Principal Investigators	**Study Sites**
Jon Bell, M.D.	4200 E. 9th Avenue Denver, CO 80262
Jessy Colah, M.D.[b] and Renuka Tank, M.D.	1335 Linden Blvd. Brooklyn, NY 11212
Lynn Cunningham, M.D.[a]	301 North Sixth Street Suite 330 Springfield, IL 62701-1098
Eugene A. DuBoff, M.D.	4704 Harlan Street, Suite 430 Denver, CO 80212
David Goldstein, M.D.	3750 Reservior Road Washington, DC 20007-2197
Wayne K. Goodman, M.D.[a]	1600 SW Archer Road Gainesville, FL 32608
Jon F. Heiser, M.D.[a]	1000 Dove Street Suite 200 Newport Beach, CA 92660-2814
Richard Maddock, M.D.	4430 V. Street Sacramento, CA 95817
Bharat Nakra, M.D.[a]	16216 Baxter Road, Suite 320 Chesterfield, MO 63017
William Patterson, M.D.	2120 Lyngate Drive Birmingham, AL 35216
Mark Pollack, M.D.[b]	WACC 815 15 Parkman Street Boston, MA 02114

Jeffrey Rausch, M.D.	1515 Pope Avenue Augusta, GA 30912-3800
Peter D. Londborg, M.D.	901 Boren Avenue, Suite 1800 Seattle, WA 98104
Teri Pearlstein, M.D.	345 Blackstone Boulevard Providence, RI 02906
Kathleen Brady, Ph.D., M.D.	171 Ashley Avenue Charleston, SC 29425-0742
Mark Hegel, Ph.D.	1 Medical Center Drive Lebanon, NH 03766
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Barbara Rothbaum, Ph.D.	1701 Uppergate Drive - Room 126 Atlanta, GA 30322