CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

Application Number: NDA 19839/S-017 AND S-018

Trade Name: ZOLOFT

Generic Name: SERTRLINE HYDROCHLORIDE

Sponsor: PFIZER PHARMACEUTICALS

Approval Date: OCTOBER 10, 1997

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION: NDA 19839/S-017, S-018

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	Included	Pending Completion	Not Prepared	Not Required
Approval Letter	X			
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Approvable Letter			X	
Final Printed Labeling		X		
Medical Review(s)	X			
Chemistry Review(s)				X
EA/FONSI				X
Pharmacology Review(s)				X
Statistical Review(s)	X			
Microbiology Review(s)				X
Clinical Pharmacology Biopharmaceutics Review(s)	X			
Bioequivalence Review(s)			X	
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Correspondence				

CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number: NDA 19839/S-017 AND S-018

APPROVAL LETTER

NDA 19-839/S-017/S-018

Pfizer Pharmaceuticals
Attention: Margaret Longshore, Ph.D.
Director, Regulatory Affairs
235 East 42nd Street
New York, New York 10017-3184

OCT 10 1997

Dear Dr. Longshore:

Please refer to your supplemental new drug applications dated December 19, 1996 (S-017) and December 20, 1996 (S-018) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Zoloft (sertraline Hydrochloride) 25, 50 and 100 mg tablets.

We acknowledge receipt of your additional communications dated March 26, July 14, July 17, August 19, and August 21, 1997.

The User Fee goal dates for these applications are December 19, 1997 (S-017) and December 23, 1997 (S-018).

Supplemental application S-017 provides clinical data supporting the use of Zoloft in the treatment of obsessive compulsive disorder in the pediatric population, and S-018 provides clinical data regarding sertraline's abuse potential.

We have completed our review of these supplemental applications, 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 marked-up draft labeling (see ATTACHMENT). Accordingly, these supplemental applications are approved effective on the date of this letter.

Labeling

The labeling accompanying this letter should be used for marketing this drug product. This final labeling is almost entirely based on an Agency telefacsimile sent to you dated August 14, 1997. We note your agreement to that version of labeling in a telephone conversation held on August 20, 1997, between representatives of Pfizer and the Agency, and a telephone conversation dated August 22, 1997, between Dr. Jeannette Barrett of your firm and Mr. Paul David of this Agency. An additional paragraph, not previously provided to your firm, but discussed with your representatives (October 9, 1997), has been added to the Pediatric Use section. For convenience, all labeling changes made since your last approved labeling (Label Code: 70-4721-00-3) appear as shaded text (redlined) in the attached labeling.

Please submit three copies of the introductory promotional material 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 material and the package insert directly to:

Food and Drug Administration
Division of Drug Marketing, Advertising and Communications, HFD-40
5600 Fishers Lane
Rockville, Maryland 20857

The final printed labeling (FPL) must be identical to the enclosed marked-up draft labeling. These revisions are terms of the supplemental NDAs approval. Marketing the product before making the agreed upon revisions in the product's labeling may render the product misbranded and an unapproved new drug.

Please submit 20 copies of the printed labeling, ten of which are individually mounted on heavy-weight paper or similar material.

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

We remind you that you must comply with the requirements for an approved NDA set forth under 21 CFR 314.80 and 314.81.

If you have any questions, please contact Mr. Paul A. David, Project Manager, at (301) 594-5530.

Sincerely yours,

10/10/97

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

ATTACHMENT

cc:
ORIG NDA 19-839/S-017/S-018
HF-2/MedWatch
HFD-2/ORM
HFD-40/LStockbridge
HFD-92/DDM-DIAB
HFD-101/LCarter
HFD-120/DIV FILE
HFD-120/PLeber/TLaughren/AMosholder/RGlass
HFD-120/GFitzgerald/BRosloff
HFD-120/PDavid
HFC-130/JAllen
HFD-170/MKlein/BHayes
HFD-222/New Drug Chemistry Division Director
HFD-613
HFD-713/TSahlroot/DHoberman
HFD-735/DPE
HFD-860/RBaweja/MMehta
HFI-20/Press Office
District Office
rd:08/15/97pd;
ft:08/22/97pd (no ~~revisions~~)
Doc #DAVID\LTRZLOCD.AP1
SUPPLEMENTAL APPLICATIONS APPROVAL

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: NDA 19849/S-017 AND S-019

MEDICAL REVIEW(S)

REVIEW AND EVALUATION OF CLINICAL DATA
ADDENDUM

NDA	19-839 (Supplement: SES-017)
SPONSOR:	Pfizer Inc.
DRUG:	Sertraline (Zoloft)
MATERIAL REVIEWED:	Supplement for Pediatric Labeling: Vol. 16 &17
REVIEW SUBMITTED:	8/1/97
DATE OF ADDENDUM:	8/15/97
MEDICAL OFFICER:	Roberta L. Glass, M.D.

A bibliography and reprints of clinical information regarding the use of sertraline in the pediatric population was included in this supplement submission. The cut-off dates for the literature search was listed as February to April, 1996. The submission included a collection of approximately 80 articles and letters to the editor from US journals. There were several case reports of sertraline induced mania or hypomania in the pediatric population (Ghaziuddin, 1994; Minnery, 1995; Tierney, 1995; Heimann, 1996). Other case reports of note were: 1) a 17 y.o. male on lithium and sertraline undergoing surgery with anesthesia whose symptoms resembled malignant hyperthermia (Stuebing, 1995), 2) a case of sertraline intoxication in a 9 y.o. male who manifested symptoms of hypertension, hallucinations, coma, hyperthermia, and tremors--resembling a serotonin syndrome (Kaminski, 1994), and 3) a case report of a new born who experienced a withdraw syndrome when his nursing mother discontinued sertraline three weeks postpartum (Kent, 1995).

Otherwise, the sponsor's literature search did not reveal any unexpected adverse events.

Roberta L. Glass 8/15/97

Roberta L. Glass, M.D.
Medical Officer, DNDP

NDA 19-839/SES-017
HFD 120: LaughrenT/MosholderA/DavidP/HobermanD/GlassR
HFD 710: Hoberman/Sahlroot

8-22-97

We will follow up on cases of possible withdrawal. S-017 can now be approved. See memo to file.

James P. Laughren, MD
TL, DDP

REVIEW AND EVALUATION OF CLINICAL DATA

NDA	**19-839 (Suppliment:SES-017)**
SPONSOR:	**Pfizer Inc.**
DRUG:	**Sertraline (Zoloft)**
MATERIAL SUBMITTED:	**Supplement for Pediatric Labeling including: Protocol 90CE21-0498: "Double-Blind Comparison of Sertraline and Placebo in Children and Adolescents with Obsessive-Compulsive Disorder, and Protocol 90CK21-0525: "Tolerance and Pharmacokinetics of sertraline after Single and Multiple Dosing in Children and Adolescents with Obsessive-Compulsive Disorder or Depression."**
DATE SUBMITTED:	**12/19/96**
DATE RECEIVED:	**12/19/96**
MEDICAL OFFICER:	**Roberta L. Glass, M.D.**
REVIEW COMPLETED:	**8/1/97**

Contents of Review

1.0 Material Utilized in Review

1.1 Material from NDA/IND

This review covers the 20 volumes of the 12/19/96 supplement submission to NDA 19-839, Supplement SES-017.

1.2 Related Reviews

The following reviews were used to supplement the sponsor's submission:

2)
Clinical Safety Review of NDA #19-839 (Zoloft®), Supplement #02 by Dr. James F. Knudsen, Ph.D.,M.D. (3/28/96), 3) Statistical Review and Evaluation of the current submission [Vol 1, 4, and 5] by David Hoberman, Ph.D. (Draft: 7/24/97) 4) Memorandum of 10/25/96 by Thomas P. Laughren, M.D., and 5) Basis of Approval for Sertraline NDA 19-839 (12/91).

2.0 Background

2.1 Indication

The sponsor is currently pursing an indication for obsessive-compulsive disorder (OCD) in children (aged 6-12) and adolescents (aged 13-17). In the DSM-IV, OCD is defined as a disorder in which individuals experience recurrent thoughts or repetitive behaviors which interfere with daily functioning, are time consuming, or cause significant distress. Of the five drugs approved for OCD in adults (clomipramine, fluoxetine, fluvoxamine, paroxetine , and sertraline) only clomipramine and fluvoxamine are approved for OCD in children. This submission for sertraline presents studies which include children and adolescents ranging as young as 6 y.o. to 17 y.o.; fluvoxamine's labeling mentions studies of children and adolescents 8-17 y.o., whereas clomipramine's labeling refers to studies of children and adolescents in the 10 -17 y.o. range.

2.2 Important Information from Related INDs and NDAs and from Pharmacologically Related Agents

The present submission appears to include any critical data concerning sertraline (Zoloft®) for the indication of OCD in children and adolescents. No other INDs or NDAs were consulted.

2.3 Administrative History

Pfizer is the sponsor for NDA 19-839 for Zoloft® (sertraline) which was approved for the use of depression in adults on December 30, 1991 and for OCD in adults on October 25, 1996.

2.4 Directions for Use

The current labeling for patients with OCD or depression indicates that the initial recommended dosage is 50 mg qd with a suggested range of 50-200 mg; it is also recommended that dose changes occur at intervals of not less than one week.

The proposed labeling states that "as with adults," the initial dose for the pediatric OCD patients is 50 mg daily. Beyond that, it does not give specific instructions for children/adolescents. The remaining dosage information refers to a dose range of 50-200 mg/day for antidepressant or antiobsessive effectiveness without clearly indicating that the antidepressant effectiveness has been established in adults only.

2.5 Foreign Marketing

As of July 15, 1997, sertraline is on the market in thirty-nine countries and specific indications for OCD were required in thirty of those countries. Other than this current submission to the FDA, there has been no submissions made to other countries for the approval of pediatric use.

3.0 Chemistry

There are no chemistry issues to be addressed. There is only a tablet form of Zoloft® available which may limit its utility in children unable/unwilling to swallow a tablet.

4.0 Animal Pharmacology

There was no new data submitted in this supplement.

5.0 Description of Clinical Data Sources

This submission includes the clinical data from protocols 90CE21-0498 (a twelve week placebo-controlled efficacy study with 92 subjects exposed to sertraline), 90CK21-0525 (a 51 day open label pK study with 61 subjects), 91CE21-0536 (an open label extension of Study 498 with 67 subjects previously treated with placebo), 91CK21-0550 (open label extension of Study 525), the OCD final safety update submitted on December 7, 1995 (with cut-off of June 30, 1995), and serious adverse experiences occurring as of June 30, 1995 from 38 pediatric subjects participating in two ongoing depression studies (STL-CDN-94-002 and R-0246) (Please note that the safety data from the depression studies is only for serious adverse event). This submission includes all safety data from 220 children/adolescents exposed to sertraline in the OCD studies and the serious adverse experiences of the 38 children/adolescents in the depression studies as indicated in the following table (which is extracted from the sponsor's submission):

Summary of Exposure In Pediatric Population

PROTOCOL	SERTRALINE	PLACEBO
90CE21-0498	92	95
90CK21-0525	61	
91CE21-0536*	67	
91CK21-0550**	No new sertraline exposure	
STL-CDN-94-002	3	
R-0246	35	
Total Exposure	258	95

*Extension to Protocol 498
**Extension to Protocol 525

The following table is a summary of studies included in the safety submission:

TABLE OF ALL STUDIES IN THIS SUBMISSION	
90CE21-0498-US	Double-blind, placebo controlled, randomized, twelve center, multiple oral dose trial; pediatric population with OCD [stratified for age: 1) children (6-12 yo): sertraline/n=53, pbo/n=54; 2) adolescents (13-17 yo): sertraline/n=39, pbo/n=41. TOTALS: sertraline: n=92 and placebo: n=95]; forced titration to 200 mg qd or highest dose tolerated up to 200 mg; twelve weeks. Open label extension is study 91CE21-0536.

TABLE OF ALL STUDIES IN THIS SUBMISSION	
90CK21-0525-US	Open, randomized, parallel, six center, multiple oral dose trial; pediatric population with OCD (n=16) and depression (n=61) [stratified for age: 1) children (6-12 yo) : sertraline/n= 29; 2) adolescents (13-17 yo): sertraline/n=32; forced titration to 200 mg qd or highest dose tolerated up to 200 mg; fifty-one days. Open label extension is study 91CK21-0550.
R-0246	Open, safety, multiple oral dose trial; outpatient pediatric population (13-19 yo) with major depression; [Sertraline: n=35 (as of 6/20/95)]; Dose range 50-200 mg qd.
STL-CDN-94-002 Canada	Open, safety, multiple oral dose trial; outpatient pediatric population (12-18 y.o.) with major depression or dysthymia ; [Sertraline: n=3 (as of 6/30/95)]; Dose range 50-200 mg qd.

In addition, a pharmacokinetic study (Study #050-020) in young adults and elderly subjects was included in this submission; this study will be reviewed by HFD-860.

6.0 Human Pharmacokinetics

The current labeling states that the pharmacokinetic properties in adults achieve the C_{max} between 4.5 to 8.4 hours with an average elimination half-life of 26 hours. Steady-state levels are expected to be achieved approximately after one week of once a day dosing. When administered with food, the AUC had a slight increase, but the C_{max} was 25% greater and the t_{max} was reduced to 5.5 hours (t_{max}= 8 hours without food). The main metabolite of sertraline is N-desmethylsertraline which has an elimination half life of 62-104 hours and is thought to be much less active than sertraline. The sponsor reported that data from 31 adult OCD patients receiving 200 mg/day of sertraline for 10 weeks had levels of 85.3±42.1 ng/ml of sertraline and 143 ±66.8 ng/ml of desmethylsertraline. According to the Summary Basis of Approval for sertraline, a study in 24 adult subjects taking a single 100 mg dose resulted in a C_{max} value of 23-26 ng/ml and an AUC value of 683 -700 ng·h/ml.

In study 498, a twelve week placebo-controlled efficacy study with 92 pediatric subjects taking sertraline (refer to Section 7.0 for details of study), the pharmacokinetics were assessed only in subjects whose plasma levels were drawn 10 to 24 hours after administration of sertraline. Median collecting time was approximately 21 hours after dosing which the sponsor described as the trough levels . Two-thirds of the subjects were taking 200 mg daily and the remainder were taking doses in a range of 25-175 mg/day. The following data of plasma concentration levels were calculated only from subjects who had been titrated to sertraline 200 mg/day:

	Sertraline levels (200 mg/day) (ng/ml)	Desmethylsertraline (ng/ml)
Week 4 (n=35)	88.07±50.93	128.25 ± 66.82
Week 8 (n=34)	85.85±40.77	148.13 ± 97.36
Week 12 (n=30)	84.05±38.32	128 ± 61.47

Pharmacokinetics were also assessed in study 525, a 51 day open label study, in which pediatric subjects received a single 50 mg dose of sertraline, followed by a seven day washout period, and then followed by 42 days of daily dosing of sertraline using one of two titration schedules: 1) a titration in increments of 25 mg every 3-4 days, or 2) a titration of increasing increment of 50 mg every seven days; the targeted dose of both groups was 200 mg of sertraline daily. In addition to baseline values, blood draws were collected on Day 1 at 1, 2, 3, 4, 6, 8, 12, 16, 24, 36, and 48 hours. On days 8, 14, 21, 28, and

42, levels were taken just before sertraline ingestion and at times 1, 2, 4, 6, 8, 16, and 24 hours after ingestion. After the last dose given on day 42, blood samples were collected at 36, 48, 72, 120, 168, and 216 hours after discontinuation. The pharmacokinetic results for this study were the following:

- After a single 50 mg dose of sertraline:

	6-12 yo Subjects n=25	13-17 y o Subjects n=29
C_{max}(ng/ml)	23.5 ± 10.9	16.3 ± 5.76
t_{max} (hrs)	5.8 ± 2.1	6.2 ± 3.0
AUC(ng h/ml)	299 ± 145	214 ± 59.9

- After the last day of dosing 200mg (Day 42):

	6-12 yo Subjects n= 19 to 20	13-17 y o Subjects n=22 to 27
C_{max} (ng/ml)	165 ± 72.3	123 ± 47.0
C_{min} (ng/ml)	96.9 ± 52.7	81.7 ± 38.0
T_{max} (hrs)	7.1 ± 3.3	9.5 ± 6.1
AUC(ng h/ml)	3107 ± 1450	2296 ± 882
$t_{½}$ (hrs)	26.2 ± 8.35	27.8 ± 8.22

Pharmacokinetic Summary

It appears to be a consistent finding that the pharmacokinetic properties of sertraline differ in the group of 6-12 year old children and 13-17 year old adolescents. In both studies, the AUC and the C_{max} were higher in the younger group. However, the sponsor calculated that when the dosage was normalized by body weight, the apparent age effect was eliminated.

In study 498, the 6-12 y.o. age group had a 68.4% higher plasma level of sertraline than the 13-17 y.o. group ($p<0.0001$). The sponsor again reported that this age effect was negligible when normalized by body weight. One could speculate that a lower dose may be adequate for younger children.

This data is to be reviewed by HFD-860 (Biopharm.).

7.0 Efficacy Findings

Study 90CE21-0498 was the only efficacy study to support an OCD indication in the pediatric population for sertraline.

Protocol 90CE21-0498

Investigators/Location

The following investigators participated in this study at twelve-sites throughout the United States:

Neal Cutler, M.D.--California Clinical Trials, Beverly Hills, CA
Joseph Biederman, M.D.--Massachusetts General Hospital, Boston, MA
John March, M.D.--Duke University Medical Center, Durham, NC
Hans Steiner, M.D.--Children's Hospital at Stanford, Stanford, CA
Roberto Dominguez, M.D.--Miami, FL
James M. Ferguson, M.D.--Murray, UT
Murray Rosenthal, D.O.--San Diego, CA
Ed Cook, M.D.--University of Chicago, Chicago, IL
Robert Riesenberg, M.D.--Biobehavioral Research Center, Decatur, GA
Betty Muller, M.D.--New Orleans, LA
Daren Wagner,M.D.--University of Texas Medical Branch, Galveston, TX
Floyd Sallee, M.D.--Medical University of South Carolina

Study Plan

Objectives

The objective of this study was to test the safety and efficacy of sertraline in outpatient non-depressed children (ages 6-12 years) and adolescents (ages 13-17 years) with a diagnosis of obsessive compulsive disorder (OCD).

Population

Inclusion criteria for this study required physically healthy male or female outpatients aged 6 to 17 years old who met the DSM-III-R criteria for OCD without comorbid depression. To fulfill these criteria, subjects were required to obtain a total score of 17 or less on the Hamilton Depression rating scale at baseline with the intent to rule out major depression; also, a score of 0 or 1 on the first item of the HAM-D was required [indicating that depressed mood was either "absent (0)" or "these feelings (depressed mood) were indicated only on questioning (1)"]. In addition, a baseline score of 7 or above on the NIMH Global Obsessive Compulsive Rating Scale at the end of the washout period was required. Laboratory values and ECGs were required to be normal; abnormal values must be clinically insignificant and LFT values were required to be less than twice the upper limit of normal. Pregnant or lactating females were excluded; all participating females must have agreed to use a medically approved form of contraception during the study . Any patient with an Axis I diagnosis, other than OCD, was to be excluded from the study. Subjects were not permitted to receive any form of behavior or psychotherapy during the study.

Design

This twelve week study was a double-blind, placebo-controlled, multicenter, outpatient, parallel design preceded by a single-blind placebo washout lead-in. The method of subject recruitment is unclear from the protocol. A history and physical, rating scales (Ham-D, NIMH), routine serum laboratory tests, ECG, and serum pregnancy test were performed in the washout period. After one week of the washout period, vitals and rating scales (Ham-D, NIMH, CY-BOCS, CGI) were to be administered. Placebo responders should have been eliminated before the 12 week double-blind period began. All rating scales,

vital signs, and laboratory tests were repeated at each visit (See Appendix 1 for schedule). Plasma level and serum pregnancy test would be performed at weeks 2, 6, and 10. ECGs would be performed at the end of Weeks 1,4, and 10. Subjects discontinuing the study within the first four weeks for lack of efficacy were to be replaced.

Subjects were randomly assigned to either placebo or sertraline group and stratified by two age groups: children (6-12 y.o.) and adolescents (ages 13-17 y.o.). Children (6-12 y.o.) had an ascending titration schedule of once daily dosing with increasing increments of 25 mg every 3-4 days until reaching a maximum dose of sertraline 200 mg or the highest tolerated dose. The adolescent group (ages 13-17 y.o.) had a titration schedule of once daily dosing with increasing increments of 50 mg every seven days until reaching the maximum dose of sertraline 200 mg or the highest tolerated dose. Psychotropic drugs (other than the test medication), anticoagulants, antiarrhymics, insulin, and narcotic agents were not allowed during the study. Medications allowed on a prn basis included antiasthma agents, antibiotics, anit-inflamatory agents, antianginal agents, antacids, antinauseants, terfenadine (the only antihistamine allowed); hormones, diuretics, oral hypoglycemic agents, and antihypertensives were allowed if the dose was stable and the medication had been taken for six months prior to the begining of the study.

Analysis Plan

The protocol in this submission does not include an analysis plan.

Study Conduct/Outcome

Patient disposition

It is unclear from this submission how many subjects were screened. The submission states that 187 subjects were randomized and received double-blind medication. In addition to these 187 subjects, the submission makes reference to four additional subjects: two were randomized but did not partake in the double-blind study (they were not included in safety or efficacy analyses); one subject was erroneously given double-blind medication during the wash-out period and was discontinued; one subject reportedly withdrew consent after the screening phase before participating in the double-blind study.

Of the 187 evaluable subjects, 80% (74 of 92) of the sertraline-treated subjects and 86% (82 of 95) of the placebo-treated subjects completed the twelve week double-blind study. One placebo subject (90N0244/281) who discontinued for lack of efficacy within the first four weeks was replaced. The tables below summarize reasons for premature discontinuation and subject flow.

Reasons for Premature Discontinuations: Intent to Treat Sample

Reason for Dropout	Sertraline n=92 (%)	Placebo n=95 (%)
Lack of efficacy	3 (3.3)	2 (2.1)
Adverse Events*	12 (13.0)	3 (3.2)
Other	3 (3.3)	8 (8.4)
Completed	74 (80.4)	82 (86.3)

*Includes intercurrent illnesses

Subject Flow

Treatment	No. Randomized*	Intent to treat sample	Week 1 (%)	Week 2 (%)	Week 3 (%)	Week 4 (%)	Week 6 (%)	Week 8 (%)	Week 10 (%)	Week 12 (%)
Sertraline	94*	92	100	97.8	95.6	94.6	92.4	87	82.6	81.5
Placebo	95	95	100	94.7	92.6	92.6	91.6	87.4	87.4	86.3

*Two subjects were assigned randomized numbers, but did not participate in the double-blind study; please refer to statistical review.

Demographic characteristics

The following table summarizes the demographic characteristics of subjects in this trial.

Demographic Profile

Parameter	Sertraline (n=92)	Placebo (n=95)
AGE (years)		
Mean	12.5	12.7
Range	6-17	6-17
GROUPS		
6-12 Years	53	54
13-17 Years	39	41
SEX		
Male	52	47
Female	40	48
RACE		
White	78	79
Non-white	14	16
WEIGHT (lbs)		
Mean	105	105
Range	43-298	39-206

Summary of Subjects' Ages

AGE (years old)	Sertraline n=	Placebo n=
6	5	2
7	2	7
8	6	1
9	10	7
10	9	10
11	6	13
12	15	14
Subtotal	53	54
13	4	7
14	10	13
15	10	7
16	8	6
17	7	8
Subtotal	39	41
TOTAL Ss in Study 498	92	95

There was no statistically significant difference in the demographics of the sertraline and the placebo groups.

Baseline Illness Severity

The baseline scores for the CY-BOCS, the NIMH-OC rating scale, and the CGI were comparable for the sertraline and the placebo groups. Subjects ages 6-12 y.o. had a mean duration of illness of 3.4 years (range: 0.2- 8.0 yrs) in the sertraline group; the mean duration of illness for the placebo group was 4.2 years (range: 0.5-10 years). For the subjects aged 13-17 y.o., the sertraline group had a mean duration of illness of 6.1 years (range: 1-13 years); the placebo group had a mean duration of illness of 5.5 years (range: 0.5-12 years). Comorbidity of past or present diagnoses was recognized in 26 Ss (28%) in the sertraline group and in 25 Ss (26%)in the placebo group. The sponsor notes that ADHD was the most frequent comorbid illness in this population studied. There were 5 subjects (3 in the sertraline group and 1 in the placebo group) which the sponsor categorized as "unknown" for comorbid illness in the study report. Curiously, the Data Listings of patient characteristics(Vol 5 pp3-278 to 3-288) list comorbid diagnoses for nine subjects which appear to violate the exclusion criterion of depressive disorders [Eg. suicidal thoughts (1S), dysthymic disorder (4 Ss), depression (3 Ss), major depression (1 S)].

Dosing

Below is a table with the weekly mean dosing information:

Mean Weekly Dosing

Week	1	2	3	4	5	6	7	8	9	10	11	12
n=	91	90	88	87	84	82	78	77	77	75	75	72
Mean (mg)	44.0	87.3	131.4	167.7	176.6	173.0	176.6	176.4	177.3	176.8	177.0	177.6
SD (mg)	6.5	17.2	31.5	44.0	43.9	47.9	44.8	42.8	41.6	42.5	42.4	41.9

Concomitant Medications

Concomitant medications were taken by 75% of the sertraline group and by 70 % of the placebo group. According to the sponsor, acetaminophen and ibuprofen were the most frequent concomitant medications taken. Diphenhydramine was taken by 8% of the sertraline group compared to 1 % of the placebo group; albuteral inhaler by 4% of the sertraline group and 1% of the placebo group; chloral hydrate by 2% of the sertraline group and 0% of the placebo group.

Efficacy

Primary outcome measure

The primary efficacy variables were not defined in the protocol enclosed with this submission; however the study report listed the primary measurement variables as the CY-BOCS, the NIMH Global Obsessive Compulsive Scale and the CGI for Severity and Improvement. Using regression analysis of the

change of measurement scales, the sertraline group demonstrated a statistically significant improvement over placebo by Week 6 for the CY-BOCS (Week 6: p=0.043; endpoint: p=0.005) and the CGI Improvement (Week 6: p=0.008; endpoint: p=0.002). By Week 10, the sertraline group displayed a statistically significant improvement over the placebo group in the NIMH Scale (Week 10: p=0.024; endpoint: p=0.019). The CGI-Severity Scale showed statistical improvement over placebo at Week 10 only (Week 10: p=0.021; endpoint: p=0.089). Refer to Appendix 2 for details.

Subgroup Analyses

When comparing the two age groups, there appears to be a slightly greater improvement in the scores of the children ages 6-12 yo than the adolescent group (13-17 yo) (See Appendix 3). However, Dr. Hoberman, in his statistical review, concluded that this difference was not statistically significant. The sponsor reports that there was not a significant gender effect.

Overall Conclusions Regarding Efficacy

The data from this study provides statistical evidence that sertraline is effective in the treatment of OCD in children. It was not possible to obtain conclusive information regarding a dose-response relationship from this study. The sponsor's thrust was to force titration to the highest dose tolerated to a maximum of 200 mg, rather than assess the lowest effective dose.

It appears that depressive illnesses may not have been adequately excluded from the population. Despite the exclusion criteria, there were subjects listed as having comorbid depressive illnesses. Also, the Hamilton Depression Rating Scale, which is designed to be used in adults, was used to assess depression is this study; there are other rating scales (e.g. CDI) which are designed specifically to better assess depression in children. It presents a weakness in this study to not adequately assess depression during the drug trial especially given that some children made it in the study with depressive symptomatology despite the exclusion criteria.

As a point of comparison, the study for the pediatric supplement for fluvoxamine (NDA 20-243 Suppl 6) reviewed by Dr. Mosholder included subjects with ages ranging from 9-18 and showed that the CY-BOCS had an effect size of 2.66 points (comparing LOCF endpoint of treatment group and placebo); study 498 of this submission includes subject ranging in ages of 6-17 y.o. and demonstrated an effect size of 3.4 points.

In addition, the anafranil labeling reports on children with OCD between the ages 10-17. This submission includes the youngest subjects referred to thus far in any labeling for the indication of OCD based on data from seven children under age 8 y.o. on sertraline and nine children under age 8 on placebo.

8.0 Safety Findings

Safety data has been extracted from the current submission (including data from Protocol 498, 525, 536, & 550, and 38 other pediatric subjects in 2 ongoing depression studies).

8.1 Background and Methodology for Safety Review

8.1.1 Extent of Exposure

The total number of subjects exposed to sertraline described in this submission is 258 children and adolescents; however, there is incomplete data from the thirty-eight children/adolescents in the two

depression studies. As pointed out in the Safety Review by Dr. Knudsen, data from studies 498 and 525 showed that 81% (124/153) of the pediatric subjects were exposed to the maximum dose of 200 mg with a mean maximum dose of 185 mg/day; three percent of this population were reported to have taken sertraline for more than 6 months. Dr. Knudsen also calculated the mean duration of exposure to be 58 days with thirty-seven percent of the pediatric subjects reported to have received a mean daily dose of 150-200 mg. The total patient exposure years from studies 498 and 525 combined is 24.3.

8.1.2 Deaths

There were no deaths reported by the sponsor in this submission.

8.1.3 Dropouts

8.1.3.1 Overall Pattern of Dropouts

The following table delineates the reasons and rate of premature discontinuations from the double-blind placebo portion of study 498 (this table is also shown above in the efficacy portion of this review):

Premature Discontinuations- Study 498

Reason for Dropout	Sertaline n=92 (%)	Placebo n=95 (%)
Lack of efficacy	3 (3.3)	2 (2.1)
Adverse Events*	12 (13.0)	4 (4.2)
Other	3 (3.3)	7 (7.4)
Completed	74 (80.4)	82 (86.3)

*Includes intercurrent illness and laboratory abnormalities

The following table delineates the reasons and rate of premature discontinuations from the multiple dose portion of study 525:

Discontinuations by Treatment Group- Study 525

Reason for Dropout	Sertraline 6-12 y.o. n=29 (%)	Sertaline 13-17 n=32 (%)
Adverse Events	3 (10.3)	1 (3.1)
Other	3 (10.3)	1 (3.1)
Completed	23 (79.3)	30 (93.8)

8.1.3.2 Adverse Events Associated with Dropout

Please refer to Appendix 8 for a full listing of dropouts. The sponsor's table enumerating adverse events associated with dropout from the placebo controlled study 498 are in Appendix 5. The sponsor failed to provide an adverse events list across all the pediatric studies .

In his review, Dr. Knudsen pointed out that the most frequent reason for drop outs in children were psychiatric in nature (agitation, insomnia, impaired concentration) whereas the discontinuation in the reviewed adult OCD database were related more to gastrointestinal (nausea, vomiting) and psychiatric adverse events (insomnia, somnolence and anxiety).

8.1.4 Other Serious Adverse Events

In study 525, a 14 y.o. depressed male subject (92-N-0058/225) with conduct disorder made a serious suicidal gesture ingesting organophosphate insecticide, sertraline and lorazepam. He was hospitalized for one night, then discharged because "the suicidal ideation was thought to have resolved within 1 day." Subsequently, he made a second suicide attempt (injested chloral hydrate) in the next 24 hours and was readmitted to the hospital. This subject was not withdrawn from the study during either of these episodes.

8.1.5 Other Search Strategies

No other search strategies were used in this review.

8.1.6 Adverse Event Incidence Tables

The sponsor utilized the categories of adverse events developed by the WHO dictionary preferred terminology. Please refer to Appendix 5 for the sponsor's table of incidence and severity of adverse events. The adverse events which displayed a statistical difference ($p<0.05$) between the sertraline and placebo groups in study 498 were insomnia, nausea, agitation, and tremor.

The following is a table comparing adverse events which may be drug related which were reported in at least 5% of the pediatric sertraline group and occurred more than twice as frequently in the sertraline group than the placebo group; for comparison, also listed in this table are the same adverse events reported in the current labeling by adult subjects with OCD in premarket placebo-controlled clinical trials (please refer to the sponsor's draft labeling for a 2 % table) :

Common and Drug Related Adverse Events-from Study 498 and Current labeling

Adverse Event	Sertraline Child/Adol (n=92) # Ss (%)	Placebo Child/Adol (n=95) # Ss (%)	Sertraline Adults/OCD (n=533) %	Placebo Adults/OCD (n=373) %
Hyperkinesis	8 (9%)	4 (4%)	Not recorded (NR)	NR
Tremor	6 (6.5%)	0	8 %	1%
Insomnia	34 (37%)	12 (13%)	28 %	12%
Nervousness	14 (15%)	6 (6%)	7 %	6%

Adverse Event	Sertraline Child/Adol (n=92) # Ss (%)	Placebo Child/Adol (n=95) # Ss (%)	Sertraline Adults/OCD (n=533) %	Placebo Adults/OCD (n=373) %
Agitation	12 (13 %)	2 (2%)	6 %	3%
Nausea	16 (17%)	7 (7%)	30%	11%
Anorexia	12 (13%)	5 (5%)	11%	2%
Fatigue	7 (7.6%)	2 (2%)	14 %	10%
Rash	5 (5%)	1 (1%)	2 %	1%
Total Skin Disorders	15 (16%)	6(6%)	2%	1%

The adverse events considered common and drug related in the pediatric population, but not seen as commonly in adults were: nervousness, agitation, hyperkinesia, rash and other skin disorders.

8.1.7 Laboratory Findings

Laboratory test monitoring for study 498 included CBC, platlets, Chem 100 with LFTS, urinalysis, serum pregnancy tests; thyroid function studies were done on day 1 of the washout only. The sponsor utilized the same criteria as utilized in the Safety Update II and the OCD Supplemental NDA (#19 839, supplement 02) to determine clinically significant laboratory abnormalities. Please refer to Section 6.0 of this review for sertraline plasma level results.

Laboratory abnormalities were identified in 44 of the 92 subjects in the sertraline group and 44 of the 95 subjects in the placebo group. The following lists the clinically significant laboratory abnormalities present in the sertraline group:

Laboratory Abnormality	# of Ss in Sertraline Group (n=92)	# of Ss in Placebo Group (n=95)
Increased Eosinophils	8	9
Decreased Neutrophils	1	0
Increased RBC	1	0
Low Hemoglobin	4	2
Low Hematocrit	33	31
Urinalysis: Protein	3	3
LFT: Low Albumin	2	1
High SGOT	1	0
High SGPT	1	1
Uric Acid	1	0
Random Glucose	6	5

The low hematocrit seen in both the placebo and medication groups may be explained by repeated blood draws done during the study. The only discontinuation due to laboratory abnormalities occurred with a subject on placebo who was reported to have an elevated SGOT and SGPT. The following table lists

statistically significant mean changes from baseline for laboratory values for both the treatment and the placebo groups:

Mean change from baseline values-Study 498

	SGOT (U/L)	Uric Acid (mg/dl)	Total Cholesterol (mg/dl)	Eosinophil (%)
Sertraline	↑ 0.92	↓ 0.67	↑ 6.53	↑ 0.56
Placebo	↓ 0.62	↑0.09	↓ 6.67	↓ 0.14

No clinical symptoms were observed in relation to these laboratory abnormalities.

8.1.8 Vital Signs

Vital signs were measured at each visit. The sponsor adopted the following parameters from adult trials to establish abnormal criteria for this pediatric population: heart rate ≥ 120 bpm or ≤ 50 bpm; systolic blood pressure (standing or supine) ≥ 180 mmHG or ≤ 90 mm Hg; diastolic blood pressure (standing or supine) ≥ 105 mmHg or ≤ 50 mmHg. Pediatric normal values differ from adults for both blood pressure and heart rates, and it is questionable if using adult parameters allows for the most accurate assessment of abnormal changes. (Please refer to Appendix 6 for normal values of children).

Comparing the mean changes for the placebo and sertraline group for heart rate and blood pressure did not reveal a statistically significant difference. The follow list contains the number of subjects with clinically significant changes by treatment group.

Clinically Significant Vital Sign Changes-Study 498

Vital sign change	# of sertraline Ss (n=92)	# of placebo Ss(n=95)
Weight loss*	**5**	**0**
Weight gain	9	12
↑ Standing DBP	1	0
↓ Standing DBP	6	3
↑ Standing SBP	0	0
↓ Standing SBP	3	6
↑ Standing Pulse	1	2
↓ Standing Pulse	1	0
↑ Supine SBP	0	0
↓ Supine SBP	7	6
↑ Supine DBP	1	0
↓ Supine DBP	16	12

*** Based on ≥ 7% change in weight from baseline during this study; more helpful information might be the change in percent of the normalized growth curve by age.**

There is a statistically significant difference (p=0.0025) for the mean weight gain between the placebo (2.51 lbs. ± 3.44) and the sertraline group (0.68 ± 4.31). Weight loss appears to be more predominant in the sertraline group.

There were no clinically relevant episodes correlating with any of the significantly abnormal values.

8.1.9 Electrocardiogram findings

In study 498, electrocardiograms were obtained on day 1 of the washout period and at the end of week 1, 4, and 12 (or at discontinuation). The incidence of abnormal EKGs was not statistically significant when comparing placebo and the sertraline groups; the sponsor reported that none of these abnormal EKGs were clinically significant (individual readings were not included in the submission).

One subject displayed an EKG pattern of p-wave changes and sinus tachycardia at the week 12 visit. The sponsor notes that this subject had been treated with albuterol for asthmatic symptoms two days prior to this EKG reading; it is unclear if the subject had been receiving this treatment while the EKG was recorded. There were no discontinuations because of EKG findings.

8.2 Review of Systems

8.2.1 Cardiovascular

There was a statistically significant difference ($p<0.0001$) in cholesterol value changes when comparing placebo and sertraline groups. The sertraline group showed an increase of 7 mg/dl (↑4%) from baseline while the placebo group showed a mean decrease of 7 mg/d (↓5%). In his safety review, Dr. Knudsen made reference to a possible correlation between elevated cholesterol levels in childhood and an increased risk of cardiovascular disease.

According to the sponsor, there was only one incident in which the EKG appeared to be clinically significant with a EKG change in p-wave and sinus tachycardia which may be explained by the subjects concomitant use of albuterol (please refer to Section 8.1.9 for details). There were no withdraws or serious adverse events that appeared to be treatment emergent.

8.2.2 Gastrointestinal

There were no reported withdraws based on gastrointestinal symptoms. Nausea and anorexia were adverse events more commonly reported in the sertraline group than the placebo group.

8.2.3 Hemic and Lymphatic

Low hematocrits were observed in both the placebo and sertraline groups; this may be explained by repeated blood draws done during the study. A statistically significant difference in the eosinophil count was observed between the sertraline and the placebo group, but there did not appear to be any apparent clinical significance to this finding. There were no withdraws from the study based on these findings.

8.2.4 Metabolic and Endocrine

In the placebo controlled study 498, weight loss was statistically more prevalent in the sertraline group (5% compared to 0%); weight gain was observed more frequently in the placebo group. It is difficult to make definitive conclusions because of the brief observation period of 12 weeks. However, it would be expected that the pediatric group would be gaining weight as part of normal growth and development; it could be concluded that there is a medication related effect which results in weight loss instead of following a natural tendency towards weight growth.

8.2.5 Musculoskeletal

Besides one subject (92-N0053/513) who sustained a fractured lumbar vertebrae after a motor vehicle accident, there were no other reports of withdraws for musculoskeletal events.

8.2.6 Nervous

8.2.6.1 Suicidality

This submission gives reports on eight subjects who experienced suicidal ideation or attempts in the submitted pool of pediatric subjects. This included 3 incidents in study 525, 2 incidents in study 536 and 1 incident in study 550 (Please refer to the Appendix 7 for individual listing). Dr. Knudsen's safety report refers to one placebo subject in the placebo controlled study 498 (this was not able to be located in the current submission). In light of the fact that there were no incidents of suicidality occurring in the sertraline group of the double blind placebo controlled study, it is not possible at this time to comment on the effects of sertraline on this adverse event. The data from the open label extensions do not provide placebo controls and, therefore become difficult to interpret in terms of making conclusions regarding suicidality as an adverse event. In his review, Dr. Knudsen suggested that the pediatric population data base appeared to have a greater incidence of suicidality than the data base of OCD adults which he was reviewing. This was followed by a memo written by Dr. Laughren in which he discussed that the higher incidence seen in the pediatric population as compared to the adult population; he offered explanations that 1) the OCD studies in adults did not allow for comorbid depression whereas this pediatric data base did include subjects with depression, and 2) the pediatric data base included open label extensions without placebo controls and allowed for a longer period of observation than was used in the adult OCD data base.

8.2.6.2 Seizures

There were 3 reports of seizure disorders in the current submission. One incident was in the placebo controlled study 498 in which a fourteen y.o. female experienced a new onset tonic-clonic seizure; this subject, who had a positive family history for seizure disorder, was treated with carbamazepine and then re-challenged with sertraline 200 mg/day (no further information was provided). Two other cases occurred in the open label extension study 536; the first case was of a 15 y.o. female

with no history of seizure disorder who had a grand mal seizure and was treated with carbamazepine which she was reportedly not compliant with, and she experienced two more seizures. She was rechallenged with sertraline and switched to paroxetine prior to her third seizure. The second case in study 536 involved a 15 y.o. male with a history of two seizure episodes and autistic disorder who experienced a grand mal seizure and experienced a fourth seizure 6 months after withdrawing from the study; eventually he was treated with felbatol and the seizures were reported to be under control.

8.2.6.3 Other behavioral disturbances

Other relevant adverse events which lead to withdrawals were agitation, insomnia, fatigue, impaired concentration, emotional lability, panic attack, hyperactivity, and exacerbation of ADHD symptoms (please refer to Appendix 8 for individual cases). The table in section 8.1.6 (Common and Drug Related Adverse Events) demonstrates that tremor, insomnia, nervousness, agitation, and fatigue have a more prominent relative risk in the drug group than in the placebo group in the pediatric double blind study 498.

8.2.7 Respiratory

There were no adverse events which appeared to be drug related that affected this system. Of note, though, is that 4 % of the sertraline group used albuteral inhaler whereas only 1 % of the placebo group required this concomitant medication during the study. Also in the "two percent" table in the proposed labeling, epistaxis was listed as occurring in 2 % of the subjects, but did not occur in the placebo group.

8.2.8 Dermatologic

Skin disorders occurred more commonly in the sertraline group than the placebo group in the placebo controlled study 498 (please refer to Section 8.1.6). There were two withdraws from study 498 for skin disorders: 1) a 10 y.o. male with lichen nitidus on his body and face, and 2) a 14 y.o. female with a moderate body rash which began to resolve two days after the discontinuation of sertraline and treatment with diphenhydramine).

8.2.9 Special Senses

No adverse events were observed in this system.

8.2.10 Genitourinary

The urinalysis results for Study 498 showed some abnormal values for urine protein, glucose and casts; however there were no reports of clinical significance.

9.0 Labeling Review

Changes in the proposed labeling include a section of **Pediatric Pharmacokinetics**. There are two concerns that arise in this section. The sponsor makes reference to the pediatric pharmacokinetic study (525) and includes that the population was comprised of patients with **depression or** OCD; it could be misleading as this submission is for the pediatric indication of OCD not depression.

The labeling goes on to assert that there was a difference observed in the younger group of 6-12 y.o. compared to adults and yet contradicts this statement by stating that there is no need for dose adjustment for the pediatric patients. Actually, observing this difference in pharmacokinetic properties in both pediatric age groups may suggest that it would be important to consider different dosing regimens especially for the younger children aged 6-12 y.o.

As stated previously, the modification of the dosage and administration of the proposed labeling states that "as with adults," the initial dose for the pediatric OCD patients is 50 mg daily. Beyond that, it does not give specific instructions for children/adolescents. The remaining dosage information refers to a dose range of 50-200 mg/day for antidepressant or antiobsessive effectiveness without clearly indicating that the antidepressant effectiveness has been established in adults only.

Under the section of **Pediatric Use** it is questionable for the sponsor to state that "....Zoloft was well tolerated in doses up to 200 mg/day."

10.0 Conclusions

The placebo controlled study 498 provides statistical support for the efficacy of sertraline in children and adolescents for the treatment of OCD. However, as discussed, this study intended to exclude a population which suffered from depression, but appears to have not achieved that goal. There were several subjects with comorbid depressive illnesses who were participants in the study, and the Hamilton Depression Scale used during the study does not adequately assess depression in children. There also was no monitoring for depressive symptomatology assessed during the study. This may have presented a confounding variable.

From the data in study 498, weight loss appears to be a drug related adverse event. This finding in a 12 week study becomes even more concerning as this is a medication which may be prescribed for long term use. Also, the monitoring of children's weight and height would be more accurate to plot on standardized growth charts which are readily available.

It appears that the sponsor has not given much thought to the dosage regimen in the pediatric population. It is quite common for medication in this population to be prescribed on a mg/kg basis. This concept of dosing sertraline seems to follow logically when considering that the age group of 6-12 y.o. displays pharmacokinetic properties which are uniquely different than adults. With a dosing of mg/kg, the practioner could gauge more accurate dosing and perhaps minimize interference with normal growth and development. Information regarding the lowest effective dose is unfortunately lost in a study design which uses forced titration.

Lastly, it could be pondered as to whether or not this data includes enough exposure information to include children as young as 6 y.o. in the approved labeling.

11.0 Recommendations

This supplement is recommended to be approvable. As stated above, there are issues which it is recommended that the sponsor address more carefully. An addition to the labeling to monitor growth in the pediatric population may be considered; this could minimize the potential to cause weight loss and interfere with development during these vulnerable years.

It is also recommended that the sponsor submit a literature search and composite of postmarketing reports. Informally, we are aware of one death from acute pulmonary edema in a 14 y.o. female and an incident of priapism in a 15 y.o. male.

Roberta L Glass 8/1/97

Roberta L. Glass, M.D.
Medical Officer, DNDP

NDA 19-839/SES-017
HFD 120: LaughrenT/MosholderA/DavidP/HobermanD/GlassR
HFD 710: Hoberman/Sahlroot

8-22-97

S-017 can now be approved.
See memo to file for
more detailed comments.

Thomas P. Laughren, MD
TL, PDP

Appendix 1

Study 498 Schedule from Sponsor's Submission

	Day 1 of Washout	End of Washout	End of Week 1	2	4	6	8	10	12*
Medical/Psychiatric Social History	X								
Physical Exam	X								X
Rating Scales:									
Ham-D	X	X							
NIMH General OC Rating	X	X	X	X	X	X	X	X	X
CY-BOCS		X	X	X	X	X	X	X	X
CGI		X	X	X	X	X	X	X	X
BP/Pulse/Wt/Ht.	X	X	X	X	X	X	X	X	X
Labs	X		X	X	X	X	X	X	X
ECG	X		X		X				X
Plasma Level	X				X		X		X
Serum Pregnancy	X				X		X		X

* or when a patient is discontinued

Appendix 2

Study 498 Efficacy Tables from Sponsor's Submission

PROTOCOL: 90CE21-0498
STUDY: DOUBLE-BLIND COMPARISON OF SERTRALINE AND PLACEBO IN CHILDREN AND ADOLESCENTS WITH OBSESSIVE COMPULSIVE DISORDER

SUMMARY OF EFFICACY ANALYSES AT ENDPOINT

	Adjusted Mean Change from Baseline* ± Standard error		p-values	
	Sertraline (N=92)	Placebo (N=95)	Sertraline vs Placebo	Age Group
CY-BOCS:	-6.8 ± 0.67	-5.4 ± 0.62	0.085	0.929
MIMH:	-2.2 ± 0.29	-1.3 ± 0.27	0.019	0.449
CGI:				
Severity	-1.8 ± 0.14	-0.7 ± 0.13	0.089	0.586
Improvement	2.7 ± 0.14	3.3 ± 0.13	0.002	0.661

*Adjusted for site and baseline value

PROTOCOL: 90CE21-0498
STUDY: DOUBLE-BLIND COMPARISON OF SERTRALINE AND PLACEBO IN CHILDREN AND ADOLESCENTS WITH OBSESSIVE COMPULSIVE DISORDER

SUMMARY OF EFFICACY ANALYSES AT EACH WEEK AND AT ENDPOINT: CY-BOCS

	Adjusted Mean Change from Baseline* Standard error						p-values	
	Sertraline			Placebo			Sertraline vs Placebo	Age Group
	N	Mean	Std Err	N	Mean	Std Err		
Week 1	90	-1.2	0.41	94	-0.6	0.39	0.232	0.331
Week 2	92	-2.8	0.53	89	-1.2	0.52	0.036	0.476
Week 4	88	-4.2	0.68	88	-2.4	0.65	0.056	0.180
Week 6	83	-5.8	0.80	85	-3.6	0.76	0.043	0.246
Week 8	78	-6.7	0.81	83	-4.2	0.78	0.032	0.582
Week 10	75	-7.5	0.85	82	-3.8	0.81	0.002	0.595
Week 12	73	-8.0	0.95	82	-4.2	0.88	0.004	0.731
Endpoint	92	-6.8	0.87	95	-3.4	0.82	0.005	0.929

*Adjusted for age group, site, treatment by site and baseline value

PROTOCOL: 90CE21-0498
STUDY: DOUBLE-BLIND COMPARISON OF SERTRALINE AND PLACEBO IN CHILDREN AND ADOLESCENTS WITH OBSESSIVE COMPULSIVE DISORDER

SUMMARY OF EFFICACY ANALYSES AT EACH WEEK AND AT ENDPOINT: MIMH

	Adjusted Mean Change from Baseline* Standard error						p-values	
	Sertraline			Placebo			Sertraline vs Placebo	Age Group
	N	Mean	Std Err	N	Mean	Std Err		
Week 1	90	-0.2	0.11	94	-0.3	0.10	0.609	0.237
Week 2	92	-0.5	0.15	89	-0.6	0.15	0.815	0.937
Week 4	88	-1.1	0.19	88	-0.9	0.18	0.485	0.160
Week 6	83	-1.7	0.23	85	-1.3	0.22	0.228	0.455
Week 8	78	-2.0	0.25	83	-1.5	0.24	0.108	0.424
Week 10	75	-2.4	0.27	83	-1.5	0.26	0.024	0.336
Week 12	73	-2.5	0.32	82	-1.5	0.30	0.032	0.837
Endpoint	92	-2.2	0.29	95	-1.3	0.27	0.019	0.449

*Adjusted for age group, site, treatment by site and baseline value

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Study 498 Efficacy Tables from Sponsor's Submission

PROTOCOL: 98CE21-0498
STUDY: DOUBLE-BLIND COMPARISON OF SERTRALINE AND PLACEBO IN CHILDREN AND ADOLESCENTS WITH OBSESSIVE COMPULSIVE DISORDER

SUMMARY OF EFFICACY ANALYSES AT EACH WEEK AND AT ENDPOINT: CGI Severity

	Adjusted Mean Change from Baseline* Standard error						p-values	
	Sertraline			Placebo			Sertraline vs Placebo	Age Group
	N	Mean	Std Err	N	Mean	Std Err		
Week 1	90	-0.2	0.06	94	-0.2	0.05	0.923	0.481
Week 2	91	-0.2	0.08	89	-0.2	0.08	0.838	0.289
Week 4	87	-0.5	0.10	88	-0.3	0.09	0.174	0.885
Week 6	83	-0.8	0.12	85	-0.6	0.11	0.348	0.927
Week 8	78	-1.0	0.13	83	-0.7	0.13	0.126	0.942
Week 10	74	-1.1	0.14	83	-0.7	0.13	0.021	0.512
Week 12	73	-1.2	0.16	82	-0.8	0.14	0.091	0.213
Endpoint	92	-1.0	0.14	95	-0.7	0.13	0.069	0.586

*Adjusted for age group, site, treatment by site and baseline value

PROTOCOL: 98CE21-0498
STUDY: DOUBLE-BLIND COMPARISON OF SERTRALINE AND PLACEBO IN CHILDREN AND ADOLESCENTS WITH OBSESSIVE COMPULSIVE DISORDER

SUMMARY OF EFFICACY ANALYSES AT EACH WEEK AND AT ENDPOINT: CGI Improvement

	Adjusted Mean Standard error*						p-values	
	Sertraline			Placebo			Sertraline vs Placebo	Age Group
	N	Mean	Std Err	N	Mean	Std Err		
Week 1	90	3.6	0.07	94	3.8	0.07	0.491	0.863
Week 2	92	3.5	0.09	89	3.7	0.09	0.195	0.351
Week 4	88	3.2	0.12	88	3.5	0.12	0.079	0.450
Week 6	83	3.0	0.13	85	3.3	0.12	0.008	0.689
Week 8	78	2.7	0.13	83	3.2	0.12	0.009	0.720
Week 10	74	2.6	0.15	83	3.2	0.14	0.004	0.564
Week 12	73	2.6	0.14	82	3.2	0.13	0.002	0.741
Endpoint	92	2.7	0.14	95	3.3	0.13	0.002	0.661

*Adjusted for age group, site, and treatment by site

Appendix 3

Study 498 Efficacy Tables by Age Group from Sponsor's Submission

PROTOCOL: 90CE21-0498
STUDY: DOUBLE-BLIND COMPARISON OF SERTRALINE AND PLACEBO IN CHILDREN AND ADOLESCENTS WITH OBSESSIVE COMPULSIVE DISORDE

SUMMARY OF EFFICACY VARIABLES AT ENDPOINT BY AGE GROUP

ADJUSTED MEAN CHANGE FROM BASELINE ± STANDARD ERROR*

	Patients 6 - 12 years				Patients 13 - 17 years			
	Sertraline (N = 53)		Placebo (N = 54)		Sertraline (N = 39)		Placebo (N = 41)	
	Adj. Mean ±	Std. Err.	Adj. Mean ±	Std. Err.	Adj. Mean ±	Std. Err.	Adj. Mean ±	Std. Err.
CY-BOCS:	-7.32 ±	1.08	-2.74 ±	1.07	-6.03 ±	1.28	-4.16 ±	1.19
NIMH:	-2.19 ±	0.36	-0.96 ±	0.36	-2.13 ±	0.43	-1.58 ±	0.40
CGI:								
Severity	-1.10 ±	0.18	-0.69 ±	0.17	-0.91 ±	0.21	-0.68 ±	0.20
Improvement	2.71 ±	0.17	3.41 ±	0.17	2.77 ±	0.20	3.21 ±	0.19

*Adjusted for age group, site, site-by-treatment and baseline value

Appendix 4

Study 498 Adverse Events from Sponsor's Submission

PROTOCOL: 90CE21-0498
STUDY : DOUBLE-BLIND COMPARISON OF SERTRALINE AND PLACEBO IN CHILDREN AND ADOLESCENTS WITH OBSESSIVE COMPULSIVE DISORI

INCIDENCE AND SEVERITY OF ADVERSE EXPERIENCES.

ADVERSE EXPERIENCE	SERTRALINE PATIENT INCIDENCE NO. PTS. (%)	SERTRALINE SEVERITY MILD	SERTRALINE SEVERITY MODERATE	SERTRALINE SEVERITY SEVERE	PLACEBO PATIENT INCIDENCE NO. PTS. (%)	PLACEBO SEVERITY MILD	PLACEBO SEVERITY MODERATE	PLACEBO SE
TOTAL NO. PATIENTS	92				95			
NO. OF PTS. WITH ADVERSE EXPERIENCE	86				69			
NO. OF PTS. DISCONTINUED DUE TO ADV. EXP.	10 (10.9%)				2 (2.1%)			
CENTR & PERIPH NERV SYST DISORDERS								
HEADACHE	33 (35.9%)	23	8	2	23 (24.2%)	14	8	
DIZZINESS	11 (12.0%)	8	3	0	6 (6.3%)	1	5	
HYPERKINESIA	8 (8.7%)	2	5	1	4 (4.2%)	3	0	
TREMOR	6 (6.5%)	5	1	0	0 (0.0%)	0	0	
URINARY INCONTINENCE	3 (3.3%)	0	2	1	2 (2.1%)	0	2	
TWITCHING	2 (2.2%)	1	1	0	0 (0.0%)	0	0	
PARESTHESIA	1 (1.1%)	0	1	0	1 (1.1%)	1	0	
CONVULSIONS	1 (1.1%)	0	0	1	0 (0.0%)	0	0	
DYSPHONIA	1 (1.1%)	1	0	0	0 (0.0%)	0	0	
HYPERTONIA	0 (0.0%)	0	0	0	1 (1.1%)	1	0	
PSYCHIATRIC DISORDERS								
INSOMNIA	34 (37.0%)	13	19	2	12 (12.6%)	5	7	
NERVOUSNESS	14 (15.2%)	3	10	1	6 (6.3%)	2	2	
SOMNOLENCE	12 (13.0%)	8	3	1	10 (10.5%)	7	3	
AGITATION	12 (13.0%)	3	7	2	2 (2.1%)	0	1	
AGGRESSIVE REACTION	4 (4.3%)	0	4	0	3 (3.2%)	1	1	
PARONIRIA	3 (3.3%)	2	1	0	3 (3.2%)	3	0	
CONCENTRATION IMPAIRED	3 (3.3%)	1	2	0	0 (0.0%)	0	0	
MANIC REACTION	3 (3.3%)	0	2	1	0 (0.0%)	0	0	
ANXIETY	2 (2.2%)	1	1	0	1 (1.1%)	0	0	
EMOTIONAL LABILITY	2 (2.2%)	1	0	1	1 (1.1%)	1	0	
THINKING ABNORMAL	2 (2.2%)	0	0	2	0 (0.0%)	0	0	
SOMNAMBOLISM	1 (1.1%)	1	0	0	1 (1.1%)	1	0	
DEPRESSION	1 (1.1%)	1	0	0	0 (0.0%)	0	0	

-- (CONTINUED) --

EACH ADVERSE EXPERIENCE WAS TABULATED ONCE PER PATIENT REGARDLESS OF THE NUMBER OF TIMES IT WAS REPORTED BY THAT PATIENT, THE MOST SEVERE OCCURRENCE IS SHOWN.

Appendix 4
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Study 498 Adverse Events from Sponsor's Submission

PROTOCOL: 90CE21-0498
STUDY : DOUBLE-BLIND COMPARISON OF SERTRALINE AND PLACEBO IN CHILDREN AND ADOLESCENTS WITH OBSESSIVE COMPULSIVE DISOF

INCIDENCE AND SEVERITY OF ADVERSE EXPERIENCES.

	SERTRALINE				PLACEBO			
ADVERSE EXPERIENCE	PATIENT INCIDENCE NO. PTS. (%)	SEVERITY MILD	MODERATE	SEVERE	PATIENT INCIDENCE NO. PTS. (%)	SEVERITY MILD	MODERATE	S
HALLUCINATIONS	1 (1.1%)	0	0	1	0 (0.0%)	0	0	
AMNESIA	0 (0.0%)	0	0	0	1 (1.1%)	1	0	
CONFUSION	0 (0.0%)	0	0	0	1 (1.1%)	1	0	
SUICIDE IDEATION	0 (0.0%)	0	0	0	1 (1.1%)	1	0	
GASTRO-INTESTINAL DISORDERS								
NAUSEA	16 (17.4%)	10	5	1	7 (7.4%)	4	1	
DIARRHEA	12 (13.0%)	8	4	0	11 (11.6%)	7	4	
ABDOMINAL PAIN	11 (12.0%)	8	3	0	16 (16.8%)	10	5	
DYSPEPSIA	6 (6.5%)	3	2	1	7 (7.4%)	5	2	
VOMITING	5 (5.4%)	3	1	1	5 (5.3%)	2	2	
FLATULENCE	4 (4.3%)	3	1	0	4 (4.2%)	4	0	
CONSTIPATION	0 (0.0%)	0	0	0	3 (3.2%)	3	0	
GASTRITIS	0 (0.0%)	0	0	0	1 (1.1%)	1	0	
AUTONOMIC NERVOUS SYSTEM DISORDERS								
ANOREXIA	12 (13.0%)	9	2	1	5 (5.3%)	2	3	
APPETITE INCREASED	3 (3.3%)	2	1	0	4 (4.2%)	2	2	
MOUTH DRY	1 (1.1%)	1	0	0	3 (3.2%)	2	1	
SYNCOPE	1 (1.1%)	0	0	1	1 (1.1%)	0	1	
FLUSHING	1 (1.1%)	1	0	0	0 (0.0%)	0	0	
BODY AS A WHOLE - GENERAL DISORDERS								
FATIGUE	7 (7.6%)	5	2	0	2 (2.1%)	2	0	
CHEST PAIN	4 (4.3%)	2	1	1	1 (1.1%)	1	0	
FEVER	3 (3.3%)	3	0	0	1 (1.1%)	0	1	
MALAISE	2 (2.2%)	2	0	0	0 (0.0%)	0	0	
BACK PAIN	1 (1.1%)	1	0	0	0 (0.0%)	0	0	
HOT FLUSHES	0 (0.0%)	0	0	0	2 (2.1%)	2	0	

-- (CONTINUED) --

EACH ADVERSE EXPERIENCE WAS TABULATED ONCE PER PATIENT REGARDLESS OF THE NUMBER OF TIMES IT WAS REPORTED BY THAT PATIENT THE MOST SEVERE OCCURRENCE IS SHOWN.

Appendix 4
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Study 498 Adverse Events from Sponsor's Submission

PROTOCOL: 90CE21-0498
STUDY : DOUBLE-BLIND COMPARISON OF SERTRALINE AND PLACEBO IN CHILDREN AND ADOLESCENTS WITH OBSESSIVE COMPULSIVE DISOF

INCIDENCE AND SEVERITY OF ADVERSE EXPERIENCES.

ADVERSE EXPERIENCE	SERTRALINE PATIENT INCIDENCE NO. PTS. (%)	SERTRALINE SEVERITY MILD	SERTRALINE SEVERITY MODERATE	SERTRALINE SEVERITY SEVERE	PLACEBO PATIENT INCIDENCE NO. PTS. (%)	PLACEBO SEVERITY MILD	PLACEBO SEVERITY MODERATE
PAIN	0 (0.0%)	0	0	0	2 (2.1%)	2	0
CONTUSION	0 (0.0%)	0	0	0	1 (1.1%)	0	1
SKIN AND APPENDAGES DISORDERS							
RASH	5 (5.4%)	3	1	1	1 (1.1%)	0	1
SKIN DISORDER	2 (2.2%)	2	0	0	0 (0.0%)	0	0
RASH ERYTHEMATOUS	1 (1.1%)	1	0	0	2 (2.1%)	2	0
SWEATING INCREASED	1 (1.1%)	0	1	0	2 (2.1%)	1	1
PRURITUS	1 (1.1%)	0	1	0	1 (1.1%)	1	0
ACNE	1 (1.1%)	0	1	0	0 (0.0%)	0	0
ALOPECIA	1 (1.1%)	1	0	0	0 (0.0%)	0	0
RASH PUSTULAR	1 (1.1%)	1	0	0	0 (0.0%)	0	0
SKIN ODOR ABNORMAL	1 (1.1%)	1	0	0	0 (0.0%)	0	0
URTICARIA	1 (1.1%)	1	0	0	0 (0.0%)	0	0
RESPIRATORY SYSTEM DISORDERS							
PHARYNGITIS	3 (3.3%)	1	2	0	5 (5.3%)	3	2
RESPIRATORY DISORDER	2 (2.2%)	2	0	0	4 (4.2%)	2	2
EPISTAXIS	2 (2.2%)	1	1	0	0 (0.0%)	0	0
COUGHING	1 (1.1%)	1	0	0	4 (4.2%)	3	1
HYPERVENTILATION	1 (1.1%)	0	1	0	0 (0.0%)	0	0
RHINITIS	1 (1.1%)	1	0	0	0 (0.0%)	0	0
BRONCHOSPASM	0 (0.0%)	0	0	0	2 (2.1%)	2	0
METABOLIC AND NUTRITIONAL DISORDERS							
WEIGHT DECREASE	3 (3.3%)	2	1	0	0 (0.0%)	0	0
WEIGHT INCREASE	1 (1.1%)	1	0	0	3 (3.2%)	2	1
REPRODUCTIVE DISORDERS, FEMALE							
DYSMENORRHEA	1 (1.1%)	0	1	0	1 (1.1%)	0	1

-- (CONTINUED) --

EACH ADVERSE EXPERIENCE WAS TABULATED ONCE PER PATIENT REGARDLESS OF THE NUMBER OF TIMES IT WAS REPORTED BY THAT PATIENT THE MOST SEVERE OCCURRENCE IS SHOWN.

Appendix 4
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Study 498 Adverse Events from Sponsor's Submission

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PROTOCOL: 90CE21-0498
STUDY : DOUBLE-BLIND COMPARISON OF SERTRALINE AND PLACEBO IN CHILDREN AND ADOLESCENTS WITH OBSESSIVE COMPULSIVE DI

INCIDENCE AND SEVERITY OF ADVERSE EXPERIENCES.

	SERTRALINE				PLACEBO			
ADVERSE EXPERIENCE	PATIENT INCIDENCE NO. PTS. (%)	SEVERITY MILD	MODERATE	SEVERE	PATIENT INCIDENCE NO. PTS. (%)	SEVERI MILD	MODERATI	
BREAST PAIN FEMALE	1 (1.1%)	1	0	0	0 (0.0%)	0	0	
MENSTRUAL DISORDER	1 (1.1%)	1	0	0	0 (0.0%)	0	0	
VISION DISORDERS								
EYE ABNORMALITY	1 (1.1%)	1	0	0	0 (0.0%)	0	0	
MYDRIASIS	1 (1.1%)	0	1	0	0 (0.0%)	0	0	
VISION ABNORMAL	1 (1.1%)	1	0	0	0 (0.0%)	0	0	
VASCULAR (EXTRACARDIAC) DISORDERS								
PURPURA	2 (2.2%)	1	1	0	1 (1.1%)	0	1	
MUSCULO-SKELETAL SYSTEM DISORDERS								
MYALGIA	1 (1.1%)	1	0	0	1 (1.1%)	1	0	
ARTHRALGIA	0 (0.0%)	0	0	0	1 (1.1%)	1	0	
ARTHROSIS	0 (0.0%)	0	0	0	1 (1.1%)	0	1	
URINARY SYSTEM DISORDERS								
CYSTITIS	1 (1.1%)	0	1	0	0 (0.0%)	0	0	
DYSURIA	0 (0.0%)	0	0	0	2 (2.1%)	1	1	
HEARING AND VESTIBULAR DISORDERS								
EARACHE	1 (1.1%)	1	0	0	0 (0.0%)	0	0	
RESISTANCE MECHANISM DISORDERS								
HERPES SIMPLEX	1 (1.1%)	1	0	0	0 (0.0%)	0	0	

---- (END) ----

EACH ADVERSE EXPERIENCE WAS TABULATED ONCE PER PATIENT REGARDLESS OF THE NUMBER OF TIMES IT WAS REPORTED BY THAT PATIE
THE MOST SEVERE OCCURRENCE IS SHOWN.

PAGE: 4

Appendix 5

Study 498 Adverse Events Associated with Dropouts from Sponsor's Submission

PROTOCOL: 90CE21-0498
STUDY : DOUBLE-BLIND COMPARISON OF SERTRALINE AND PLACEBO IN CHILDREN AND ADOLESCENTS WITH OBSESSIVE COMPULSIVE DISOR

INCIDENCE OF DISCONTINUATIONS ASSOCIATED WITH ADVERSE EXPERIENCES.

ADVERSE EXPERIENCE	SERTRALINE NO. PTS. (%)	PLACEBO NO. PTS. (%)	P-VALUE#
TOTAL NO. PATIENTS	92	95	
NO. OF PTS. DISCONTINUED DUE TO ADV. EXP.	10 (10.9%)	2 (2.1%)	0.017
PSYCHIATRIC DISORDERS			
AGITATION	3 (3.3%)	0 (0.0%)	0.117
INSOMNIA	2 (2.2%)	1 (1.1%)	0.617
CONCENTRATION IMPAIRED	2 (2.2%)	0 (0.0%)	0.241
NERVOUSNESS	1 (1.1%)	1 (1.1%)	1.000
AGGRESSIVE REACTION	1 (1.1%)	0 (0.0%)	0.492
EMOTIONAL LABILITY	1 (1.1%)	0 (0.0%)	0.492
CENTR & PERIPH NERV SYST DISORDERS			
CONVULSIONS	1 (1.1%)	0 (0.0%)	0.492
HYPERKINESIA	0 (0.0%)	1 (1.1%)	1.000
SKIN AND APPENDAGES DISORDERS			
RASH	1 (1.1%)	0 (0.0%)	0.492
BODY AS A WHOLE - GENERAL DISORDERS			
FATIGUE	1 (1.1%)	0 (0.0%)	0.492

---- (END) ----

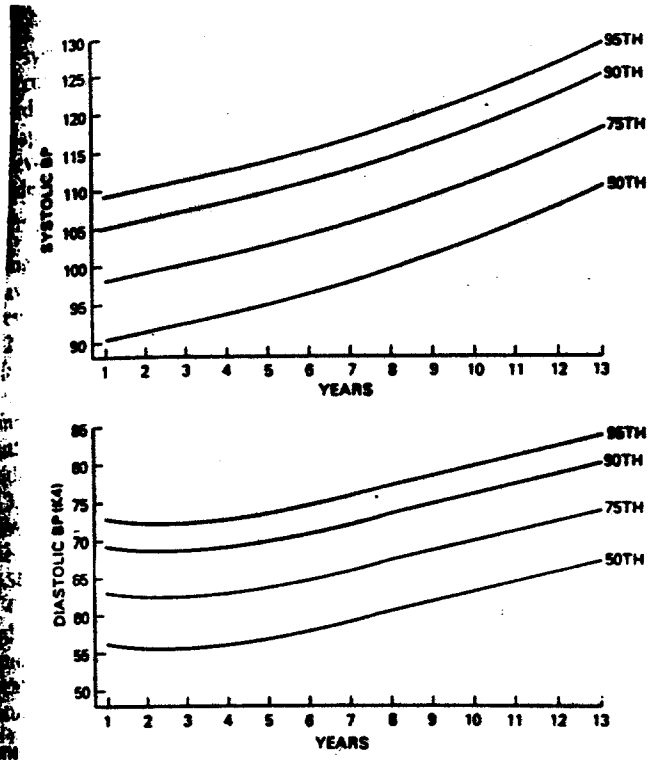
EACH ADVERSE EXPERIENCE WAS TABULATED ONCE PER PATIENT REGARDLESS OF THE NUMBER OF TIMES IT WAS REPORTED BY THAT PATIENT.
BASED ON FISHER'S EXACT (2-TAIL) TEST

Appendix 6

Normal Values for Pediatric Cardiac Vitals Signs
From Nelson Textbook of Pediatrics (1996)

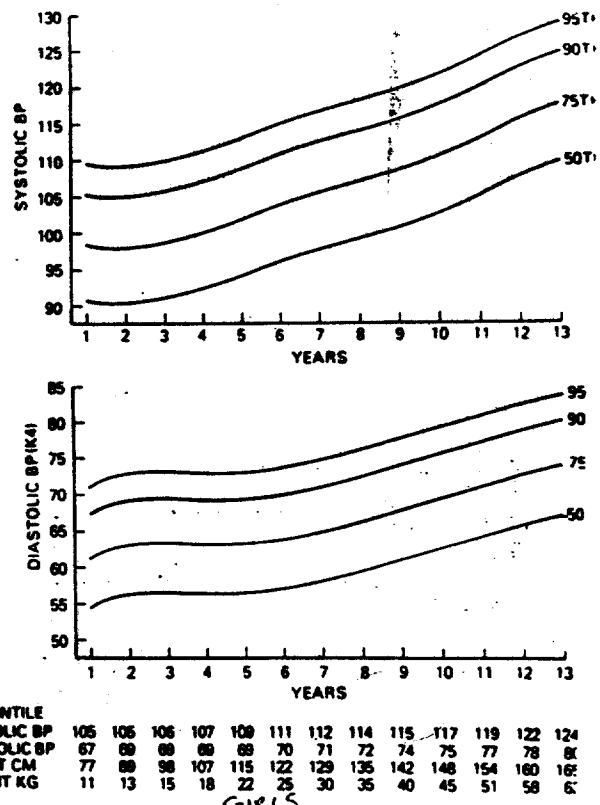
■ **TABLE 380–4 Pulse Rates at Rest**

Age	Lower Limits of Normal		Average		Upper Limits of Normal	
Newborn	70/min		125/min		190/min	
1–11 mo	80		120		160	
2 yr	80		110		130	
4 yr	80		100		120	
6 yr	75		100		115	
8 yr	70		90		110	
10 yr	70		90		110	
	Girls	*Boys*	*Girls*	*Boys*	*Girls*	*Boys*
12 yr	70	65	90	85	110	105
14 yr	65	60	85	80	105	100
16 yr	60	55	80	75	100	95
18 yr	55	50	75	70	95	90



BOYS

Figure 380–3. Age-specific percentiles for BP measurements in boys—1–13 yr of age; Korotkoff phase IV (K4) used for diastolic BP. (From National Heart, Lung, and Blood Institute, Bethesda, MD: Report of the second task force on blood pressure control in children—1987. Reproduced by permission of Pediatrics. Vol 79, p 1. Copyright © 1987.)



GIRLS

Figure 380–4. Age-specific percentiles of BP measurement girls—1–13 yr of age; Korotkoff phase IV (K4) used for dias BP. (From National Heart, Lung, and Blood Institute, Beth MD: Report of the second task force on blood pressure contr children—1987. Reproduced by permission of Pediatrics. Vo p 1. Copyright © 1987.)

Appendix 6
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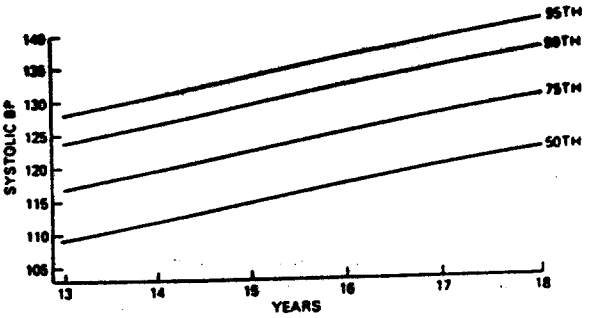
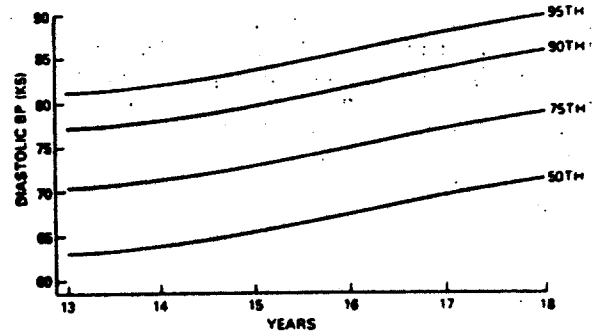
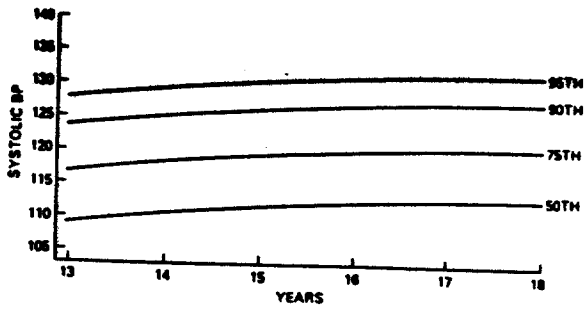
Normal Values for Pediatric Cardiac Vitals Signs
From Nelson Textbook of Pediatrics (1996)

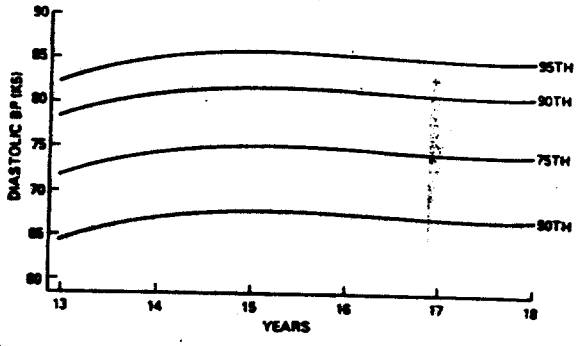




90TH PERCENTILE						
SYSTOLIC BP	124	126	129	131	134	136
DIASTOLIC BP	77	78	79	81	83	84
HEIGHT CM	168	172	176	182	184	184
WEIGHT KG	62	68	74	80	84	86

Figure 380–5. Age-specific percentiles of BP measurements in boys—13–18 yr of age; Korotkoff phase V (K5) used for diastolic BP. (From National Heart, Lung, and Blood Institute, Bethesda, MD: Report of the second task force on blood pressure control in children—1987. Reproduced by permission of Pediatrics. Vol 79, p 1. Copyright © 1987.)





90TH PERCENTILE						
SYSTOLIC BP	124	125	126	127	127	127
DIASTOLIC BP	78	81	82	81	80	80
HEIGHT CM	165	168	169	170	170	170
WEIGHT KG	63	67	70	72	73	74

Figure 380–6. Age-specific percentiles of BP measurements in girls—13–18 yr of age; Korotkoff phase V (K5) used for diastolic BP. (From National Heart, Lung, and Blood Institute, Bethesda, MD: Report of the second task force on blood pressure control in children—1987. Reproduced by permission of Pediatrics. Vol 79, p 1. Copyright © 1987.)

Appendix 7

Individual Listing of Suicide Attempts

Study 525:

1. (92-N-0058/225): a 14 y.o. male with major depression and conduct disorder who was taking 200 mg qd of sertraline had two suicide attempts during the study on days 35 and 37; he was not withdrawn from the study (Please refer to Section 8.1.3 for further detail)
2. (92-N-0062/4) : an 8 yo depressed male on 200 mg of sertraline tied a tie around his neck and cut his feet with a razor and withdrew from the study on day 36; he had no previous history of suicidality or self mutilation.
3. (92-N-0070): s 13 y.o. male with major depression became suicidal, irritable, and agitated and withdrew from the study on day 22 after being titrated to 150 mg qd of sertraline.

Study 536:

1) (91-N-0242/217) a 17 y.o. female with OCD who was on 200 mg in the study for 136 days and was taking 200 mg qd of sertraline for 55 days attempted suicide by taking an overdose of antihistamines
2) (91-N-0242/221) a 15 yo female with OCD and PTSD who was on 200 mg qd for 74 days and was hospitalized for suicidal ideation.

Study 550:

1) 17 yo female with major depression (92-N-0059/229) who had been taking 50 mg qd for 8 days ant was hospitalized for suicidal ideation. She withdrew from the study, but continued sertraline 200 mg qd, and was noted to make another suicide gesture three weeks later.

Study R-0246:

1) (94-S-0503/4) an 18 yo male with major depression and ADHD and who had been on 50 mg qd of sertraline was hospitalized on day 16 for self-inflicted superficial cuts on his chest and arms
2) (94-S-0501/110) a 12 y.o., male with depression who had been taking 50 mg qd of sertraline was hospitalized for a suicidal gesture and aggressive behavior on day 14.

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Appendix 8

Adverse Events Associated with Dropout

Dropouts and Associated Adverse Event-Study 498

Site/Subject #	Age/Sex	Treatment/Duration/ Final Dose (mg)	Adverse Event
92N0054/524	9/M	sertraline/ 32 d/ 200	Exacerbation of ADHD symptoms*
92N0008/308	11/M	sertraline/ 33 d/ 50	Increased agitation-Moderate
92N0008/305	12/M	sertraline/ 28 d/ 100	Increased aggressiveness and agitation-Moderate
92N0008/304	10/M	sertraline/ 7 d / 50	Lichen nitidus on body and face
92N008/298	6/M	sertraline/ 27 d / 150	Severe insomnia and increased irritability
90N0247/251	14/F	sertraline/ 13 d/ 100	Moderate body rash
90N0246/242	12/M	sertraline/ 57 d/ 100	Mild fatigue and insomnia
90N0246/43	8/F	sertraline/ 18 d/ 150	Impaired concentration
90N0242/222	14/F	sertraline/ 74 d/ 200	New Onset Seizure*
90N0241/270	14/F	sertraline/ 48 d/ 200	Severe emotional lability
90N0241/265	15/M	sertraline/ 29 d/ 200	Severe panic attack
90N0241/75	10/F	sertraline/ 40 d/ 50	Exacerbation of ADHD-moderate
92N0052/509	10/F	placebo	Elevated SGPT and SGOT
92N0008/306	7/M	placebo	Severe increased irritability
92N0008/297	10/F	placebo	URI
90N0247/250	13/F	placebo	Mild hyperactivity/decreased sleep

*Serious Adverse Event

Dropouts and Associated Adverse Event-Study 525

Subject #	Age/Sex	Treatment/ Final Daily Dose (mg)/Duration	Adverse Event
92-N-0058/14	11/M	sertraline/200 mg/35 d	Exacerbation of Oppositional Defiant Disorder*
92-N-0058/18	7/M	sertraline/125 mg/24 d	Hyperactivity
92-N-0062/4	8/M	sertraline/200 mg /36 d	Self-mutilation and restlessness
92-N-0070/218	13/M	sertraline 150 mg/22 d	Irritability, agitation and suicidal ideation
91N0068/11	11/M	sertraline/50 mg/ 16 d	Elected to withdraw prior to visit #3
91N0068/19	6/M	sertraline/50 mg/ 1 d	Refused heparin well insertion
92N0058/14	14/M	sertraline/ 200 mg/ 35 d	Discontinued due to "oppositional defiant disorder"

Appendix 8
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Adverse Events Associated with Dropouts

Subject #	Age/Sex	Treatment/ Final Daily Dose (mg)/Duration	Adverse Event
92-N-0058/14	11/M	sertraline/200 mg/35 d	Exacerbation of Oppositional Defiant Disorder*
92-N-0058/18	7/M	sertraline/125 mg/24 d	Hyperactivity
92-N-0062/4	8/M	sertraline/200 mg /36 d	Self-mutilation and restlessness
92-N-0070/218	13/M	sertraline 150 mg/22 d	Irritability, agitation and suicidal ideation
92N0058/25	11/F	sertraline/ 50 mg/ 1 d	Lost to follow up

*Serious Adverse Event

Dropouts and Associated Adverse Event-Study 536

Subject #	Age/Sex	Treatment/ Final Daily Dose (mg)/ Duration	Adverse Event
92-N-0053/513	10/M	sertraline/125 mg/67 d	Oppositional behavior*
91-N-0247/49	10/F	sertraline/150 mg/ 141 d	Aggressive behavior*
91-N-0242/217	17/F	sertraline/ 200 mg/ 55 d	Suicide attempt*
91-N0242/221	15/F	sertraline/200 mg/74 d	suicidal ideation**
91-N-0242/223	15/F	sertraline/100 mg/ 15 d	New onset Seizure* p.2-61 Vol 3
92-N-0055	15/M	sertraline/50 mg/ 4 d	Grand mal seizure*
91-N-0242/21	12/M	sertraline/ 200 mg/ 206 d	Cervical Injury 2° wrestling accident
92-N-0053/823	12/F	sertraline/ 75 mg/43 d	Mononucleosis

*Serious Adverse Event
**Continued in study

Dropouts and Associated Adverse Event-Study 550

Subject #	Age/Sex	Treatment/ Final Daily Dose (mg)	Adverse Event
92-N-0071/211	14/F	sertraline 200 mg	Motor vehicle accident

Dropouts and Associated Adverse Event-Study R-0246

Subject #	Age/Sex	Treatment/ Final Daily Dose (mg)/ Duration	Adverse Event
94-S-0503/4	18/M	sertaline 50 mg/16 d	Self-inflicted cuts to chest and arms
94-S-0501/104	14/M	sertraline 50 mg/57 d	Worsening of oppositional behavior
94-S-0501/110	12/M	sertraline 50 mg/14 d	Aggressive behavior and suicidal gesture

REVIEW AND EVALUATION OF CLINICAL DATA

NDA:	19-839
SPONSOR:	Pfizer
DRUG:	Sertraline HCL (Zoloft)
MATERIAL SUBMITTED:	SLR-018 Labeling Supplement: Abuse Potential
DATE SUBMITTED:	12/20/96
DATE RECEIVED:	12/23/96
PDUFA DUE DATE:	12/23/97
MEDICAL OFFICER:	Andrew Mosholder, M.D.

I. BACKGROUND

This labeling supplement contains proposed labeling regarding sertraline's lack of abuse potential. The sponsor has provided the following supporting information: results of a clinical study of sertraline abuse potential in recreational drug users, results of four pre-clinical studies with monkeys of sertraline abuse potential, and a world literature bibliography. This submission was reviewed by the Division of Anesthetic Critical Care and Addiction Drug Products (HFD-170) by Drs. Hayes and Klein.

Pfizer has proposed the following new labeling pertaining to this topic under the section "Drug Abuse and Dependence:"

> Physical and Psychological Dependence--In human and animal studies, Zoloft has not demonstrated potential for abuse and there is no evidence that it causes either tolerance or physical or 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 positive subjective effects indicative of abuse potential. In contrast, subjects rated alprazolam and d-amphetamine significantly greater than placebo on measures of drug liking, euphoria, and abuse potential. Zoloft did not produce either the stimulation and anxiety associated with d-amphetamine or the sedation and psychomotor impairment associated with alprazolam. Zoloft does not function as positive reinforcer in rhesus monkeys trained to self administer cocaine, nor does it substitute as a discriminative stimulus for either d-amphetamine or pentobarbital in rhesus monkeys. There are no reports of Zoloft abuse or diversion for non-prescription use. As with any CNS active drug, however, physicians should carefully evaluated patients for history of drug abuse and follow such patients closely, observing them for signs of misuse or abuse (e.g., development of tolerance, incrementation of dose, drug seeking behavior).

II. MATERIAL SUBMITTED

A. Clinical Study 8ACP21-0377

Please refer to the consult report from HFD-170 for further details about this study. The trial was conducted by Dr. Edward Sellers of the University of Toronto in Ontario. The purpose of this study was to investigate the abuse potential of sertraline compared to placebo, d-amphetamine and alprazolam. Adult males with a history of substance abuse were the intended subjects. This was a single dose, randomized, double-blind cross over study. Subjects were screened with physical

examination, routine clinical laboratory, ECG, urine drug screen, and a secobarbital challenge test (the latter to ensure that they were capable of distinguishing secobarbital 150 mg from single-blind placebo). After screening, the patients received the following five oral sinlge dose treatments in randomized order, separated by one week: sertraline 100 mg, sertraline 200 mg, alprazolam 1 mg, d-amphetamine 10 mg, and placebo. The study included numerous assessments such as an automated video tracking test, and a variety of subjective rating scales. For a complete description of the outcome measures please refer to the consult report by Drs. Hayes and Kline.

For a more detailed summary of the study results please refer to the consultation report by Drs. Hayes and Kline. Twenty subjects out of twenty-three who were randomized completed the study. Results of the drug "liking" question are shown below.

Double blind single dose treatment	Number of subjects who stated they would like to take drug again (out of n=20)
Alprazolam 1 mg	19*
D-amphetamine 10 mg	16*
Sertraline 100 mg	6
Sertraline 200 mg	4
Placebo	9

*statistically significant in comparison to placebo

Neither dose of sertraline nor d-amphetamine had a statistically significant effect verse placebo on the visual tracking test; however, alprazolam produced significantly poorer performance compared to placebo.

Although the weaknesses of the study are well described in the consultation from HFD-170, on balance, this study did produce evidence that under controlled conditions subjects with a history of drug abuse were more likely to experience administration of d-amphetamine or alprazolam as a pleasurable experience than either dose of sertraline tested. This does not, of course, establish that sertraline is free of abuse potential completely, but simply that its abuse potential was less than that of amphetamine or alprazolam under the same conditions.

B. Non Clinical Data

These experiments will be reviewed by the HFD-120 Pharmacology team and have also been reviewed by HFD-170. Stated briefly, monkeys trained to administer themselves cocaine were not prone to self administer sertraline. Furthermore, monkeys trained to discriminate drugs of abuse from placebo were not able to similarly discriminate sertraline from placebo.

C. Literature Search

The sponsor conducted a electronic literature search covering the period January 19, 1985 through March 1996. Copies of publications were provided in the submission. Pfizer concluded that there was no evidence of abuse potential for sertraline in the literature. The sponsor also reported that they surveyed the 1994 Drug Abuse Warning Network (DAWN) data on hospital emergency room

episodes related to drug abuse for reports involving sertraline, and again concluded there is no evidence suggesting widespread abuse of sertraline. Finally, Pfizer contacted the National Institute on Drug Abuse (NIDA) and was informed that sertraline is not considered by NIDA to be a drug of abuse.

In their consult, Drs. Hayes and Kline have highlighted a number of literature references which refer to a withdrawal syndrome after discontinuation of a serotonin reuptake inhibitor. However, it appears that these reports apply chiefly to paroxetine rather than sertraline. This phenomenon is currently noted in the paroxetine labeling. Indeed, the consult report notes that because paroxetine inhibits its own metabolism to a much greater extent than sertraline, clearance upon discontinuation of the drug would be expected to increase for paroxetine, thereby leading to a more rapid decline of plasma drug levels and exacerbated withdrawal symptoms.

Drs. Hayes and Kline also note a report by Markel and Associates in the Journal of Pediatrics (vol. 125, pp. 817-819, 1994) describing two adolescent patients who were felt to have exacerbated LSD flashbacks while prescribed sertraline. Although this report is of theoretical interest in terms of the proposed mechanism (i.e., that this is a serotonin mediated phenomenon), my own opinion is that these two reports are not persuasive in themselves, given the high background incidence of LSD flashback.

D. Post-Marketing Data

Drs. Hayes and Kline include in their consult an analysis of spontaneous post-marking reports involving terms related to drug abuse with Zoloft. My own interpretation is that while there are a number of such reports, a conclusive interpretation of these reports would involve review of the individual cases, since it is quite possible that many of them involve concomitant drugs or substances of abuse. Without such a review of the individual cases I am hesitant to draw conclusions based on the number of reports.

The consult note also contains an analysis of DAWN data, showing emergency room mentions of Zoloft. There have been 4000-7000 such mentions yearly for the past several years, and these do include a number of reports of recreational use. Drs. Hayes and Kline have recommended that this data be included in the Zoloft labeling. I am inclined, however, to see the same difficulty here as with the spontaneous postmarketing event reports: without an individual review of the cases, these data are difficult to interpret.

III. CONCLUSION AND RECOMMENDATIONS

In my opinion, this supplement may be approved and the Zoloft labeling be may be amended to reflect the results of the clinical study submitted. The sponsor's proposed labeling is shown at the beginning of this review; Drs. Hayes and Kline have proposed alternative labeling which appears on page 23 of their consult report.

I would like to propose a different version of labeling for the Drug Abuse and Dependence section, drawing on both the sponsor's and the consultants' proposals, as follows:

> In animal studies, Zoloft does not demonstrate stimulant or barbiturate-like (depressant) abuse potential. 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 that were observed with the other

two drugs. 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 misuse or abuse (e.g. development of tolerance, incrementation of dose, drug seeking behavior).

6/26/97

Andrew Mosholder, M.D.
Medical Officer

cc:NDA 19-839
Division file
HFD-120:Laughren\David\Fitzgerald\Rosloff\Mosholder
HFD-170:Hayes\Kline

8-22-97

We have been able to reach agreement with Pfizer on modified language for the section and it can now be approved. See memo to file for more detailed response.

James P. Laughren, MD
TL, PDP

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: NDA 19839/S-017 AND S-018

STATISTICAL REVIEW(S)

Statistical Review and Evaluation

NDA#: 19-839/SE5-017

Applicant: Pfizer, Inc.

Name of drug: Zoloft (sertraline)

Documents Reviewed: **Vols 1, 4, and 5 of submission dated December 19, 1996 by sponsor**

Medical Officer: Roberta Glass, M.D., HFD-120

Background

The sponsor has submitted **one** placebo controlled, double-blind, randomized, multicenter trial (0498) evaluating the efficacy of Zoloft for OCD (obsessive compulsive disorder) in children and adolescents. Children are defined as ages 6-12 and adolescents are defines as ages 13-17.

Design

This was a 12 week study among 12 investigators with the first 3 weeks devoted to titration from 25-200 mg/d in children and 50-200 mg/d in adolescents. Ninety-four (94) patients were randomized to Zoloft and 95 to placebo. The numbers of children randomized to Zoloft and placebo were 55 and 54, respectively. Patients were randomized within age group. Two (2) patients randomized to Zoloft did not receive medication and were not included in analyses. Two (2) centers which enrolled 5 or less patients were combined with each other, while the enrollments in the other 10 centers were between 9 and 31 patients.

Efficacy measures were The Children's Yale-Brown Obsessive Compulsive Scale (CY-BOCS), the NIMH Global Obsessive Compulsive Rating Scale, and CGI's for Severity and Improvement.

The protocol does not contain either a statistical analysis plan, nor a sample size calculation. It says only that 160 patients will be enrolled. The ANCOVA model described in the study included factors for treatment, site, treatment x site interaction, age group, gender, and the interactions of age group and treatment, gender and age group, gender and treatment and gender, age, group and treatment (a second order interaction) with the baseline value of the particular analyzed scale as the covariate. However, the models eventually used to produce the reported p-values in **Table 2a** (see below) contain only treatment, site, treatment x site interaction, age group, and baseline of the analyzed scale as a covariate. Presumably, the additional factors and interactions were not significant in the 'full' model.

Results (All tables and Figures were supplied by the sponsor)

Examination of baseline characteristics did not reveal evidence of any serious imbalance in potential prognostic factors (See **Table 1**) or responses on the rating scales (**Table 2**).

The numbers of patients who discontinued the trial were 18 (3 due to insufficient clinical response) in the Zoloft group and 13 in the placebo group (2 due to insufficient clinical response).

Table 3a displays the summery of results and p-values comparing the two treatment groups. See **Figures 1-4** for graphical displays of mean scores over time for the clinical endpoints and **Figure 5** for the percentages of patients who achieved 'clinical improvement'. **Table 3b** displays results by the two age groups. **Table 4** displays the results by investigator. Seven (7) of the 11 'sites' produced results for which results with Zoloft were favorable in comparison to placebo.

Discussion

It may be useful to compare these results with those of up to 200 mg in a trial of Luvox in essentially the same age groups. In that study (RH.114.02.01), there were the same number of adolescents (ages 12 to 17), but half the number of children (8 to 11) as in the current study under review. The average baseline declines in the CY-BOCS were -9.7 and -3.5 in the Luvox and placebo groups respectively in the "children" subgroup, while they were -4.1 and -3.2 in the "adolescent" subgroup, respectively. The age group by treatment interaction test produced a p-value of .075, suggesting perhaps that the drug was either inactive or minimally active in adolescents (given that the treatment difference is so small in that subgroup).

In the Zoloft trial, the respective declines in the CY-BOCS were -7.3 and -2.7 in the "children" group, and -6.0 and -4.2 in the "adolescent" subgroup. Although it appears at first glance that the treatment effect may be larger in children (ages 6-12), a test for interaction is not close to statistical significance. One should note that 1) the treatment difference in the Zoloft trial in the "adolescent" subgroup was twice that in the Luvox trial and 2) the treatment difference in the Zoloft trial was an average of 1.6 points less than the difference in the Luvox trial. All one can say at this point is that there is a suggestion that "children" may respond better to up to 200 mg Zoloft than "adolescents". More data in other SSRI's is needed to support an hypothesis that there may be a 'drug class' phenomenon occurring.

David Hoberman, Ph.D.
Mathematical Statistician

concur: Dr. Sahlroot JTS 8/28/97

Dr. Chi Chi 8/25/97

cc:
NDA# 19-839/SE5-017
HFD/120/Dr. Leber
HFD-120/Dr. Laughren
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HFD-120/Mr. Purvis
HFD-120/Mr. Hardiman
HFD-344/Dr. Barton
HFD-710/Dr. Chi
HFD-710/Dr. Sahlroot
HFD-710/Dr. Hoberman
HFD-710/chron

TABLE 1

SUMMARY OF PATIENT CHARACTERISTICS

		Patients 6 - 12 years			Patients 13 - 17 years			All Patients		
		Sertraline	Placebo	P-value	Sertraline	Placebo	P-value	Sertraline	Placebo	P-va
Sex:	Males	33	31		19	16		52	47	
	Females	20	23		20	25		40	48	
	Total	53	54	0.608	39	41	0.382	92	95	0.
Race:	White	50	46		28	33		78	79	
	Black	1	5		2	5		3	8	
	Hispanic	0	4		3	2		3	6	
	Asian	0	0		1	0		1	0	
	Other	2	1		5	1		7	2	
	Total	53	54	0.139	39	41	0.258	92	95	0.
Age:	N	53.0	54.0		39.0	41.0		92.0	95.0	
	Mean	10.3	10.6		15.6	15.4		12.5	12.7	
	Standard Dev.	1.9	1.8		1.3	1.5		3.1	2.9	
	Minimum	6.4	6.2		13.2	13.0		6.4	6.2	
	Maximum	12.9	13.0	0.306	17.8	18.0	0.644	17.8	18.0	0.
Weight:	N	53	54		39	41		92	95	
	Mean	83	82		136	135		105	105	
	Standard Dev.	24	24		39	31		41	38	
	Minimum	43	39		77	82		43	39	
	Maximum	149	140	0.908	298	206	0.800	298	206	0.
Tanner Stage:	N	52.0	51.0		36.0	40.0		88.0	91.0	
	Mean	1.8	1.8		4.1	4.2		2.7	2.9	
	Standard Dev.	1.0	0.9		1.1	0.6		1.5	1.5	

		Sertraline	Placebo	P-value	Sertraline	Placebo	P-value	Sertraline	Placebo	P-v
Ham-D	N	53	54		39	41		92	95	
	Mean	5.3	4.6		6.0	5.7		5.6	5.0	
	Standard Dev.	3.8	3.6		5.2	4.1		4.4	3.8	
Duration of Illness	N	53.0	54.0		39.0	41.0		92.0	95.0	
	Mean	3.4	4.2		6.1	5.5		4.5	4.7	
	Standard Dev.	2.1	2.8		3.5	3.3		3.0	3.1	
Comorbidity	Yes	16	16		10	9		26	25	
	No	35	37		28	31		63	68	
	Unknown	2	1		1	1		3	2	
	Total	53	54	0.896	39	41	0.695	92	95	0.
Hollingshead Classification	I	5	10		6	5		11	15	
	II	10	5		2	5		12	10	
	III	21	23		20	21		41	44	
	IV	15	15		10	9		25	24	
	V	2	1		1	1		3	2	
	Total	53	54	0.441	39	41	0.843	92	95	0.

		Sertraline	Placebo
Age :			
	6	5	2
	7	2	7
	8	6	1
	9	10	7
	10	9	10
	11	6	13
	12	15	14
	13	4	7
	14	10	13
	15	10	7
	16	8	6
	17	7	8
	Total	92	95

TABLE 2

SUMMARY OF COMPARISON OF EFFICACY VARIABLES AT BASELINE

	Sertraline		Placebo		P-values	
	N	Mean ± Standard Deviation	N	Mean ± Standard Deviation	Treatment	Age Group
CY-BOCS:	92	23.36 ± 4.56	95	22.25 ± 6.15	0.2109	0.6516
NIMH:	92	9.18 ± 1.47	95	9.07 ± 1.55	0.5653	0.0793
CGI:						
Severity	92	4.65 ± 0.73	95	4.55 ± 0.81	0.2668	0.5434

SUMMARY OF EFFICACY VARIABLES AT BASELINE BY AGE GROUP

	Patients 6 - 12 years						Patients 13 - 17 years					
	Sertraline			Placebo			Sertraline			Placebo		
	N	Mean ±	Std. Dev.	N	Mean ±	Std. Dev.	N	Mean ±	Std. Dev.	N	Mean ±	Std. Dev.
CY-BOCS:	53	24.02 ±	4.56	54	21.33 ±	6.61	39	22.46 ±	4.47	41	23.46 ±	5.32
NIMH:	53	9.21 ±	1.50	54	8.87 ±	1.58	39	9.15 ±	1.46	41	9.34 ±	1.49
CGI:												
Severity	53	4.70 ±	0.75	54	4.50 ±	0.84	39	4.59 ±	0.72	41	4.61 ±	0.77

TABLE 3a

SUMMARY OF EFFICACY ANALYSES AT ENDPOINT

	Adjusted Mean Change from Baseline* ± Standard error		p-values	
	Sertraline (N=92)	Placebo (N=95)	Sertraline vs Placebo	Age Group
CY-BOCS:	-6.8 ± 0.87	-3.4 ± 0.82	0.005	0.929
NIMH:	-2.2 ± 0.29	-1.3 ± 0.27	0.019	0.449
CGI:				
Severity	-1.0 ± 0.14	-0.7 ± 0.13	0.089	0.586
Improvement	2.7 ± 0.14	3.3 ± 0.13	0.002	0.661

*Adjusted for site and baseline value

TABLE 3b

SUMMARY OF EFFICACY VARIABLES AT ENDPOINT BY AGE GROUP

ADJUSTED MEAN CHANGE FROM BASELINE ± STANDARD ERROR*

	Patients 6 - 12 years				Patients 13 - 17 years			
	Sertraline (N = 53)		Placebo (N = 54)		Sertraline (N = 39)		Placebo (N = 41)	
	Adj. Mean ±	Std. Err.	Adj. Mean ±	Std. Err.	Adj. Mean ±	Std. Err.	Adj. Mean ±	Std. Err.
CY-BOCS:	-7.32 ±	1.08	-2.74 ±	1.07	-6.03 ±	1.28	-4.16 ±	1.19
NIMH:	-2.19 ±	0.36	-0.96 ±	0.36	-2.13 ±	0.43	-1.58 ±	0.40
CGI:								
Severity	-1.10 ±	0.18	-0.69 ±	0.17	-0.91 ±	0.21	-0.68 ±	0.20
Improvement	2.71 ±	0.17	3.41 ±	0.17	2.77 ±	0.20	3.21 ±	0.19

'djusted for age group, site, site-by-treatment and baseline value

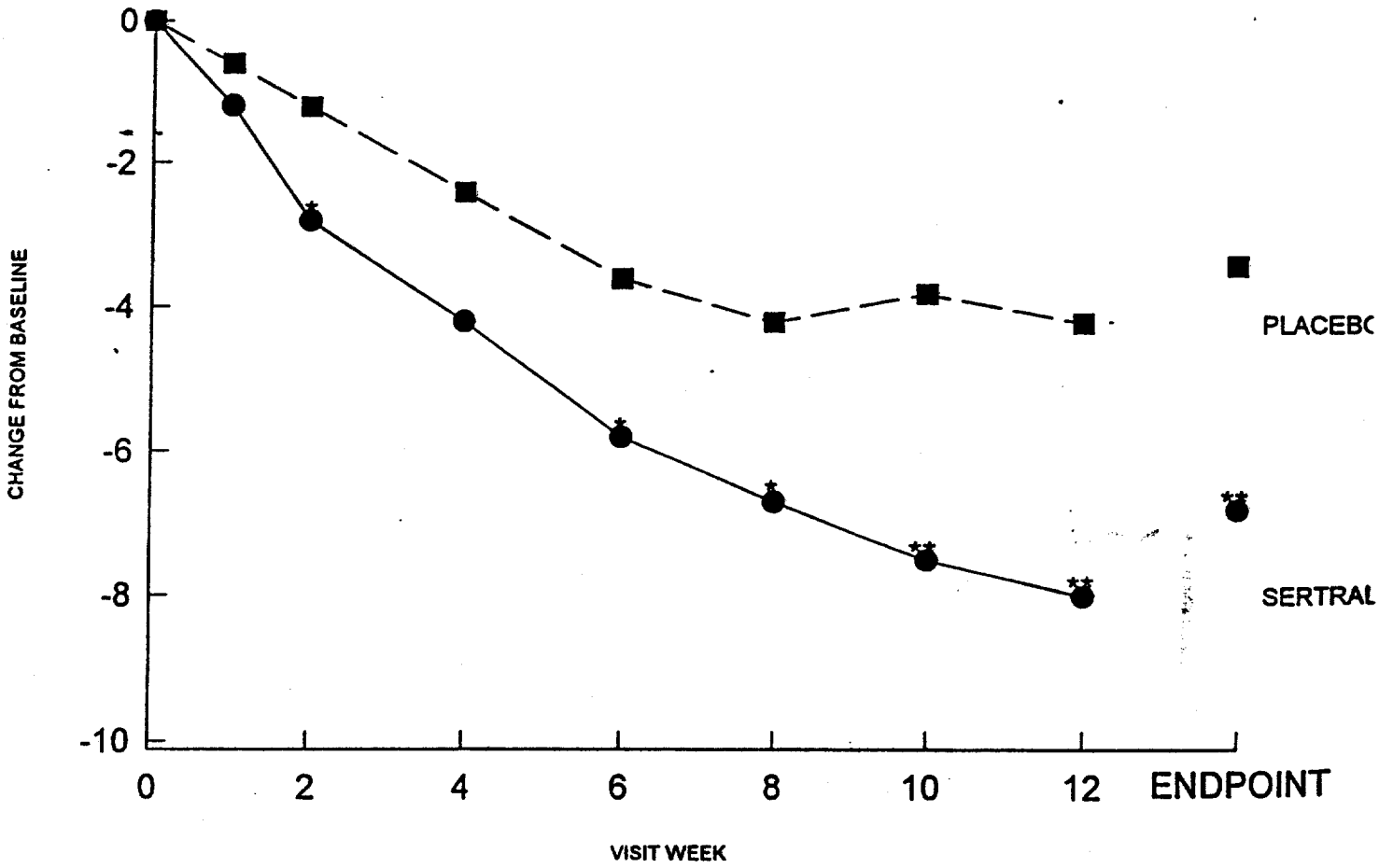
Table 4

Change from Baseline in Y-BOCS by Site and Treatment

Site	Sertraline	Placebo
90N0241	-7.06 ± 1.83 (N = 16)	-8.07 ± 1.90 (N = 15)
90N0242	-3.31 ± 2.21 (N = 11)	-2.19 ± 2.23 (N = 11)
90N0243	-12.08 ± 3.00 (N = 6)	-1.96 ± 2.99 (N = 6)
90N0244	-10.61 ± 2.98 (N = 6)	0.44 ± 3.00 (N = 6)
90N0246	-11.15 ± 2.04 (N = 13)	-5.03 ± 2.11 (N = 12)
90N0247	-4.49 ± 2.83 (N = 7)	-7.40 ± 2.60 (N = 8)
91N0033	-9.08 ± 4.26 (N = 3)	0.68 ± 3.37 (N = 5)
92N0008	-5.47 ± 2.33 (N = 10)	-4.22 ± 2.46 (N = 9)
92N0052	-8.22 ± 3.00 (N = 6)	-3.18 ± 2.99 (N = 6)
92N0054	-5.09 ± 2.31 (N = 10)	-7.80 ± 2.17 (N = 12)
90N0245/92N0047	1.90 ± 3.66 (N = 4)	1.45 ± 3.37 (N = 5)

FIGURE 1

RE 1. SUMMARY OF EFFICACY ANALYSES AT EACH WEEK: CY-BOCS

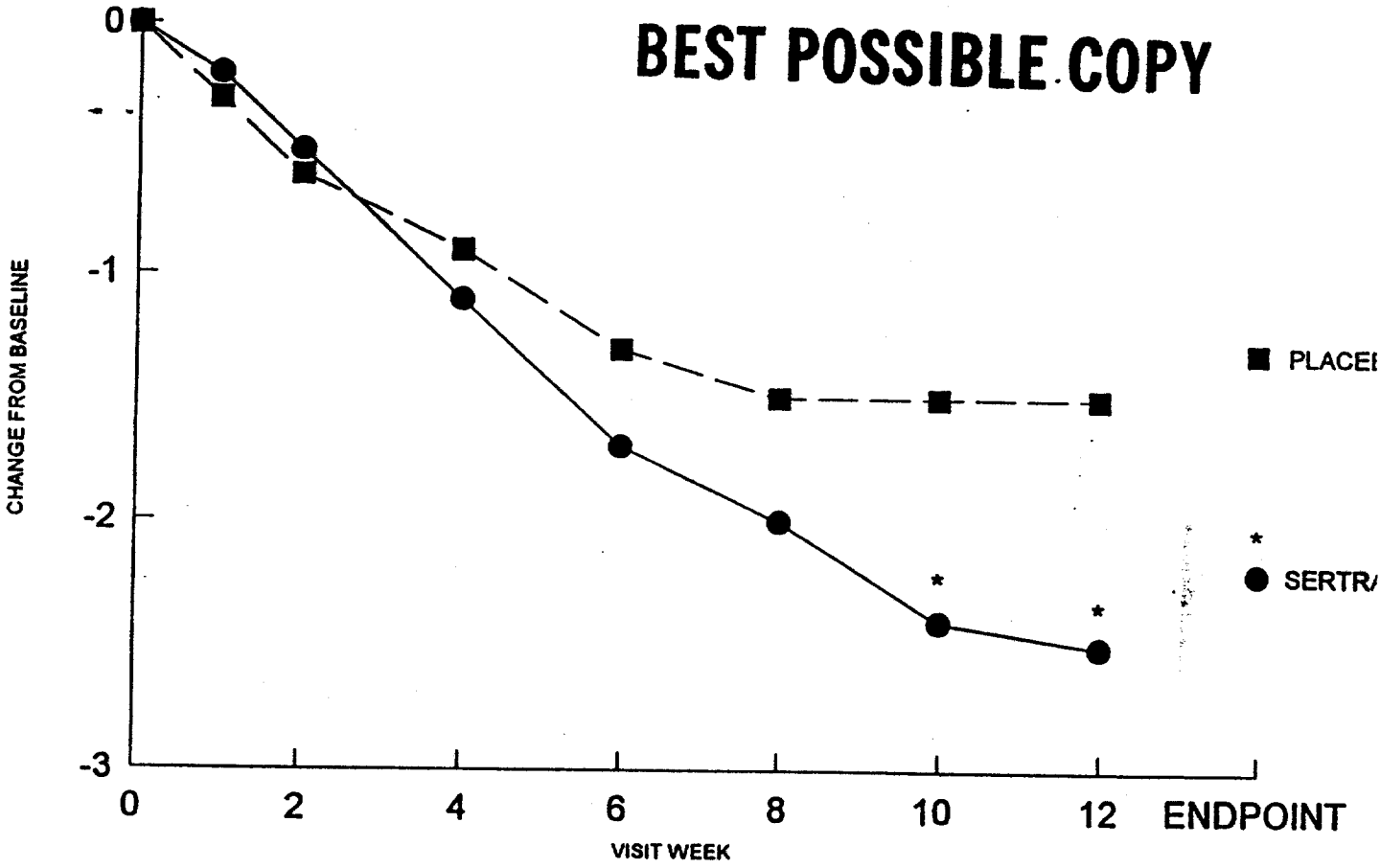


* p <0.05
** p <0.01

S498F1 SPW

FIGURE 2

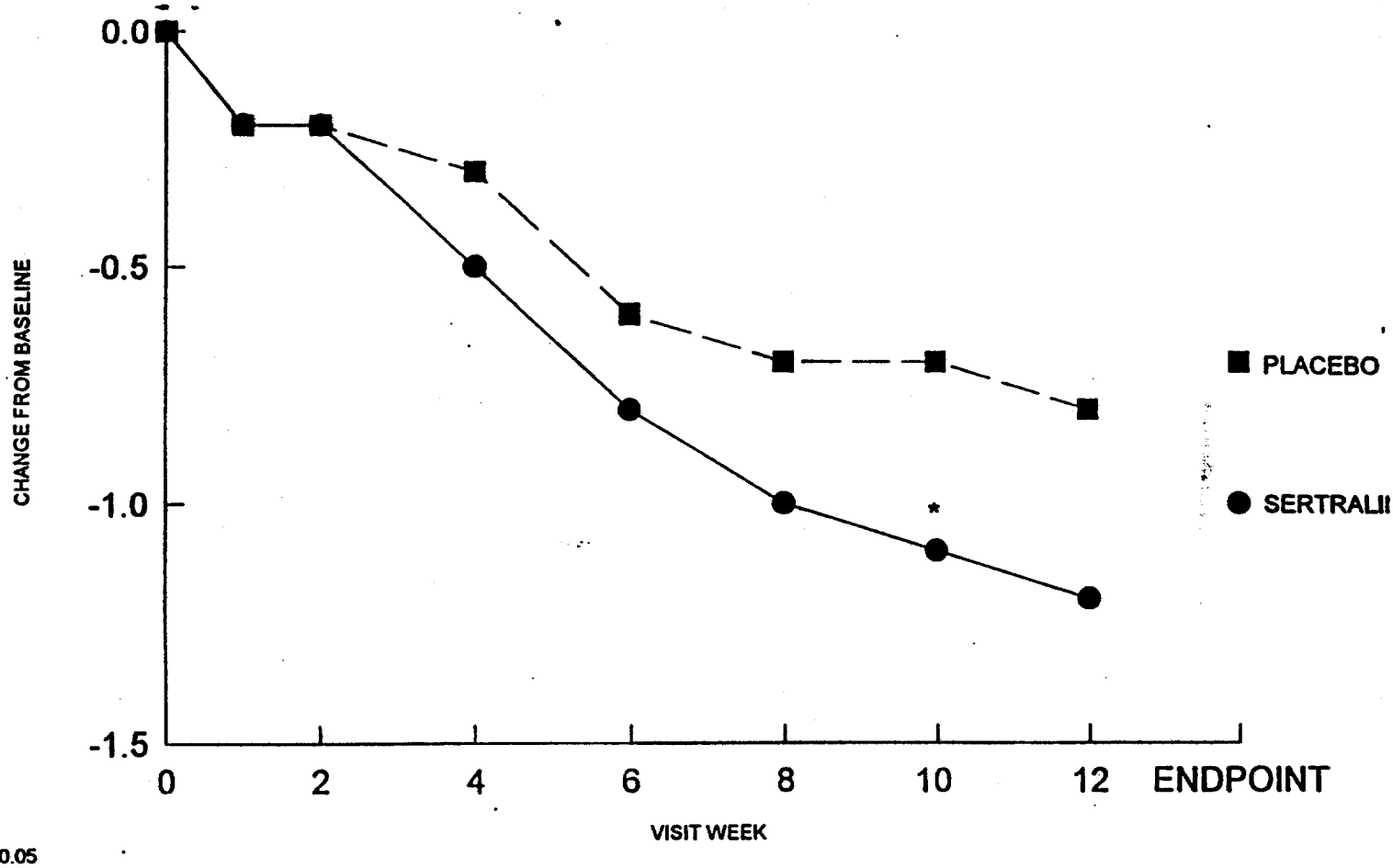
JRE 2. SUMMARY OF EFFICACY ANALYSES AT EACH WEEK: NIMH



* p <0.05

FIGURE 3

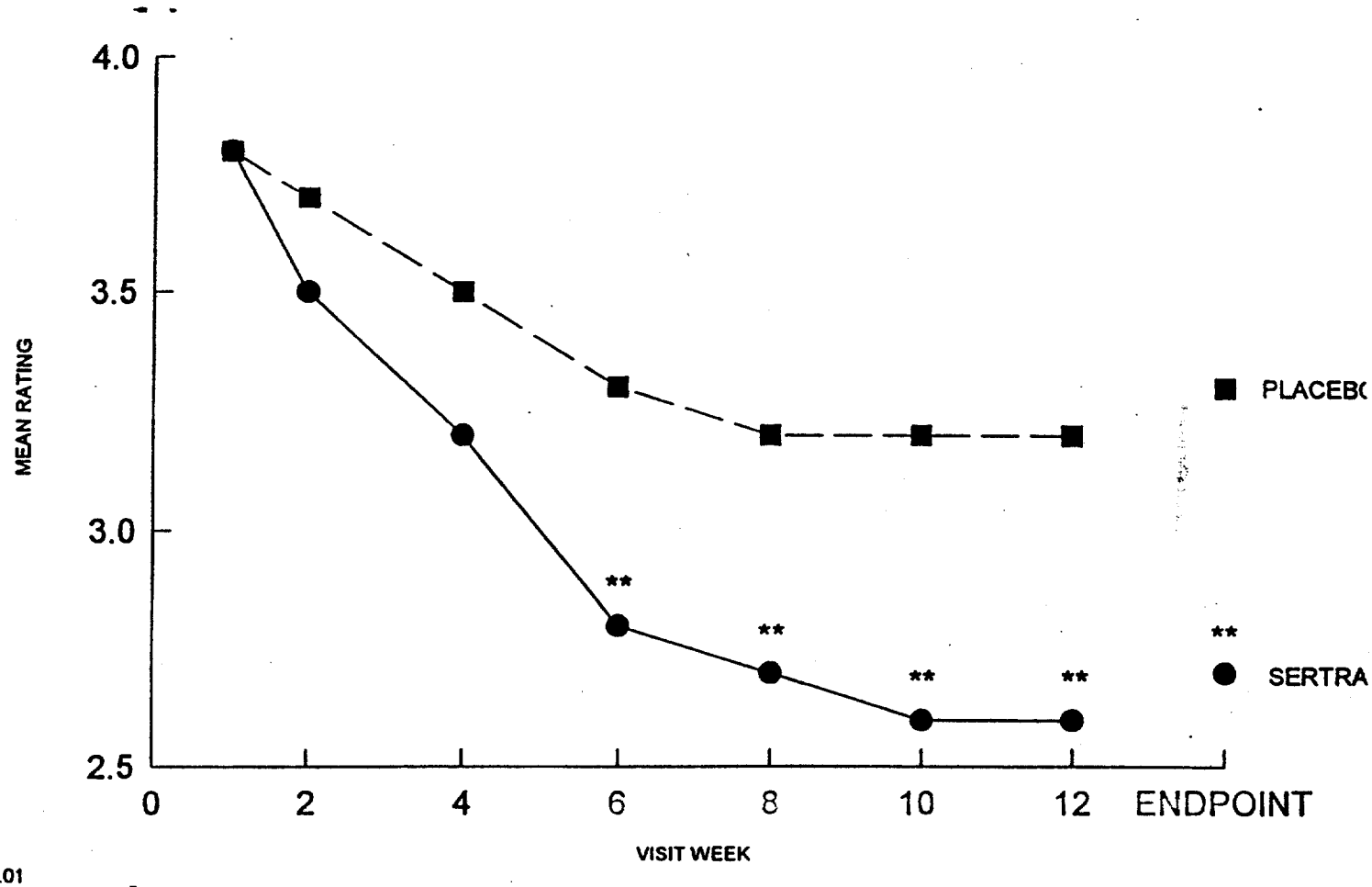
FIGURE 3. SUMMARY OF EFFICACY ANALYSES AT EACH WEEK: CGI SEVERITY



* p <0.05

FIGURE 4

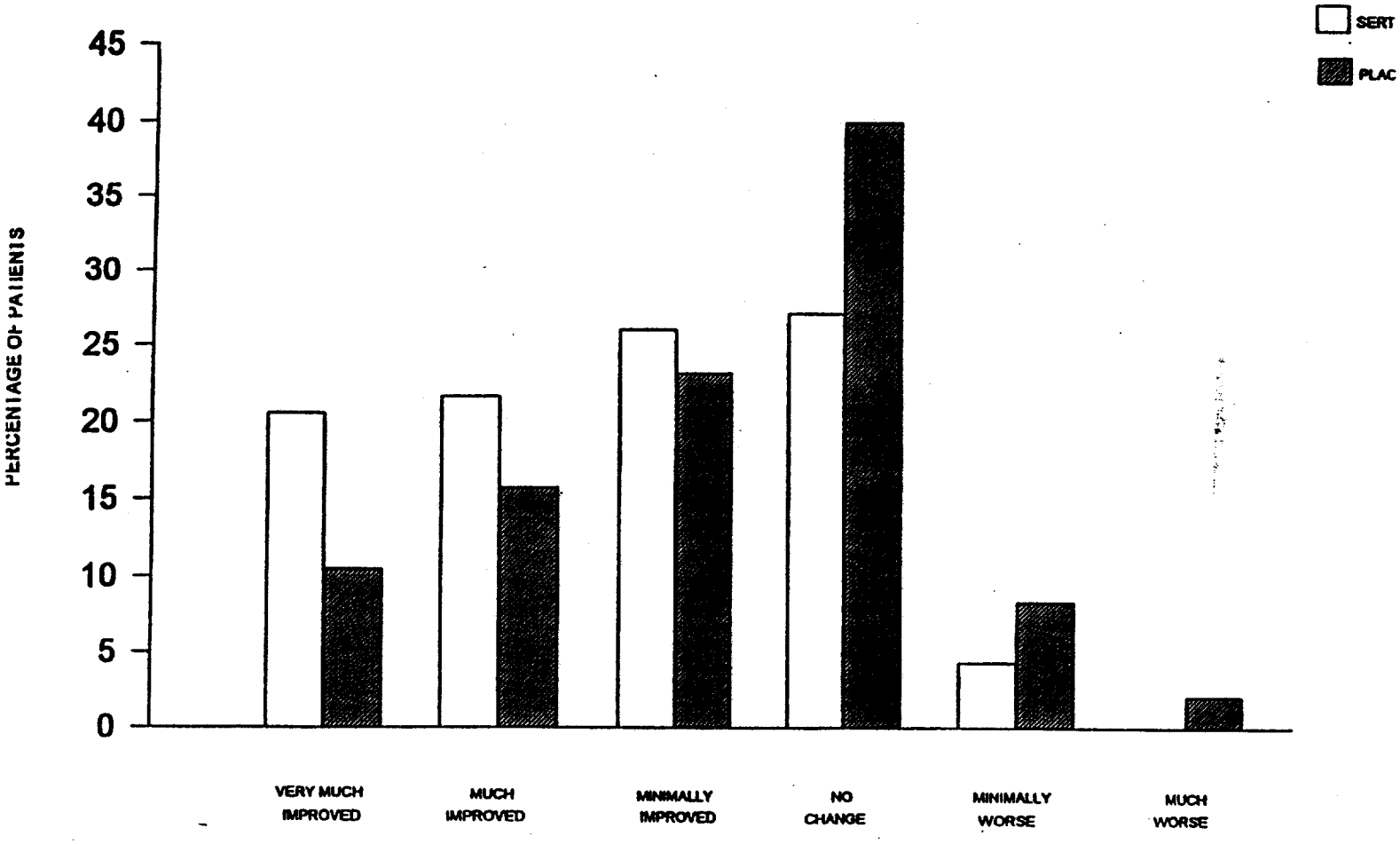
FIGURE 4. SUMMARY OF EFFICACY ANALYSES AT EACH WEEK: CGI IMPROVEMENT



** p <0.01

FIGURE 5

FIGURE 5. SUMMARY OF EFFICACY ANALYSES AT ENDPOINT: CGI IMPROVEMENT



CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: NDA 19839/S-017 AND S-018

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

OFFICE OF CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW

NDA 19,839
Sertraline HCl 50 mg and 100 mg tablets (Zoloft)
Reviewer: Raman Baweja, Ph.D.

Pfizer, Inc., New York, N.Y. 10017
Submission Dates: December 19, 1996

OCPB Receipt Date: January 6, 1997

REVIEW OF A PHARMACOKINETIC STUDY IN PEDIATRIC PATIENTS

Sertraline Hydrochloride 50 mg, 100 mg, 150 mg and 200 mg tablets were approved in December 1991 and the sponsor decided to market 50 mg and 100 mg tablets. In this submission of December 19, 1996, the sponsor has performed a pharmacokinetic study titled "Tolerance and Pharmacokinetics of Sertraline after Single and Multiple Dosing in Children and Adolescents with Obsessive-Compulsive Disorder or Depression" (Protocol 90CK21-0525). Details of the study are presented in Attachment 1.

Briefly described, there were 61 pediatric patients who were enrolled in the study with 44 patients with the symptoms of depression, 16 with obsessive compulsive disorder, and 1 patient who had both the symptoms. There were 28 females and 33 males. The study was a six-site, open label parallel study. The patients were divided into two age-stratified groups -- 6 to 12 year old (n=29; mean age 10 years), and 13 to 17 years old (n=32; mean age 15 years old). Initially, all patients received a 50 mg single dose of sertraline followed by a 7-day washout period. On day 8, one of two stated daily dose escalation schemes was begun, i.e., 25 mg increments or 50 mg increments - see Appendix I for details of the doses in the escalation schemes. In the 6-12 years old patients there were 15 in Scheme A and 14 in Scheme B, and in the 13-17 year old patients there were 16 patients each in Scheme A and Scheme B.

Focus in the discussion of results will be for doses of sertraline at steady state. It should be noted that this study used 25 mg and 50 mg capsules and not the approved tablets.

The analytical assay involved using an internal standard, CP-53,630-1, and was gas chromatography with electron capture detection. Overall, the assay appears validated.

Results: Attachment 2 shows the AUC24, Cmax and Cmin for the 6-12 years old group and for the 13-17 years old group.

AUC24: At the highest dose of 200 mg a day, AUC24 was 3107±1450 ng*hr/ml and 2296±882 ng*hr/ml, respectively. Normalizing these values to a "dose in mg/Kg of body weight" basis yields AUC24 values of 666±305 ng*hr/ml//mg/Kg and 655±226 ng*hr/ml//mg/Kg which are very comparable. Likewise, the 150 mg q d dosing yields 629±259 ng*hr/ml//mg/Kg and 593±187 ng*hr/ml//mg/Kg, a difference of 6 %. At the lower doses of 50 mg and 100 mg daily dosing, these normalized values are equally close between the two groups.

Cmax and Cmin: This comparability between the two groups was also seen across corresponding

doses for both Cmax and Cmin values normalized also on a "dose in mg/Kg of body weight" basis (Attachment 2).

Pediatrics vs Adults: A cross study comparison of these two pediatric groups was made with 22 healthy adults who received 200 mg/day of sertraline for 30 days (Study 050-020; Attachment 3). AUC and Cmax values for the young adult group normalized on a "dose in mg/Kg of body weight" basis were 864.8 ng*hr/ml and 47.8 ng/ml, respectively. A comparison of these normalized pharmacokinetic parameters showed that relative to the adults, the 6-12 year olds had both AUC and Cmax values that were about 22 % lower than the adults. The adults serve as the reference because the drug was studied in the original NDA in adults. Similarly, the 13-17 year old also showed AUC and Cmax values that were also about 22 % lower than those seen in adults.
Based on these results it appears that administration of sertraline to pediatric patients does not require adjustment of dosage.

Comment to the Clinical Division:

The sponsor has provided labelling information for the pediatric population (Attachment 4). Comparison of the pharmacokinetic parameters between the pediatric age groups and adults should be based on comparison of dose/Kg normalized data. Thus, the pediatric to adult comparison sentence should be changed in the labelling to appropriately describe the comparison on a "dose in mg/Kg of body weight" basis as follows:

"Relative to the adults, both the 6-12 year olds and the 13-17 year olds showed about 22 % lower dose normalized AUC24 and Cmax values. This suggests that administration of sertraline to pediatric patients does not require adjustment of dosage."

Recommendation: Labelling should now include information on pediatric pharmacokinetics.

Raman Baweja 5/22/97.
Raman Baweja, Ph.D.
Team Leader

RD/FT Initialed by M. Mehta, Ph.D. 5/30/97

cc: NDA 19,839, HFD-120, HFD-860 (Baweja, Mehta, Malinowski), Drug files (Barbara Murphy, Central Documents Room).

Attachment I (1/2)

PHARMACOKINETICS/BIOAVAILABILITY STUDY SYNOPSIS

Study Title: Tolerance and Pharmacokinetics of Sertraline after Single and Multiple Dosing in Children and Adolescents with Obsessive Compulsive Disorder or Depression

Protocol No.: 90CK21-0525

Investigator: [See preceding list]

Study Location: [See preceding list]

NO FURTHER DOCUMENTS ATTACHED TO COPY

Study Objective: To determine the pharmacokinetics of and tolerance to sertraline after single and multiple dose administration to pediatric patients with obsessive compulsive disorder or depression.

Study Population: Subjects were 61 pediatric psychiatric patients who met DSM-III-R criteria for either major depression (n=44), obsessive compulsive disorder (n=16), or both (n=1). Twenty-eight patients were female, 33 were male. Fifty-one patients were Caucasian, 6 were black, and 4 had other ethnic backgrounds. Age (mean ± SD) for all patients was 12.8 ± 2.7 yr, weight was 113 ± 37.2 lb. They were divided into two age-stratified groups (ages 6-12, and ages 13-17 years). The patients who were 6 to 12 years old (mean age ± SD, 10.4 ± 1.7 yr; n=29) had a mean body weight of 94.4 ± 28.9 lb, and the patients who were 13 to 17 years old (mean age ± SD, 14.9 ± 1.4 yr; n=32) had a mean body weight of 129 ± 36.5 lb. All subjects were in good health as determined by their medical histories, physical exams and clinical laboratory tests. Approximately one third (20/61) of the patients carried secondary psychiatric diagnoses, most commonly attention deficit disorder.

Dosage Form: Sertraline was administered in this study in the form of 25 and 50 mg capsules.

Study Design: This was a six-site, open-label parallel study. Initially, all patients received a single 50 mg dose of sertraline followed by a 7-day washout. On day 8, daily sertraline dosing was begun according to one of two titrations as shown below:

Titration A (25 mg increments)		Titration B (50 mg increments)	
Study Day	Dose (mg/day)	Study Day	Dose (mg/day)
8-10	25	8-14	50
11-14	50	15-21	100
15-17	75	22-28	150
18-21	100	29-42	200
22-24	125		
25-28	150		
29-31	175		
32-42	200		

Attachment I (contd.) (2/2)

Within each age group, 15 age 6-12 year old patients were in the A and 14 in the B titration groups, and 16 age 13-17 year old patients each were in the A and B titration groups.

Seven ml blood samples were collected at the following times on day 1: just prior to dosing (0 hr), and then at 1, 2, 3, 4, 6, 8, 12, 16, 24, 36 and 48 hrs. On days 8, 14, 21, 28, and 42, blood samples were collected immediately prior to drug administration (0 hr) and at 1, 2, 4, 6, 8, 16, and 24 hrs. Additional blood samples were collected after the last dose (day 42) at 36, 48, 72, 120, 168, and 216 hrs. Physical examinations, including an ECG, and measurement of vital signs, were performed during the screening period (up to one month prior to study) and at the end of the study on the last blood collection day (day 51). Blood pressure and pulse rate were recorded 45 minutes prior to drug administration (0 hr) and 4 hrs postdose on days 1, 8, 14, 21, 28, 42 and at the completion of the study (day 51). Clinical laboratory testing was performed during the screening period (up to one month prior to study), within 96 hours prior to the first administration of study drug, on day 14, and at the end of the study (day 51) prior to discharge from the study site. A urine drug screen was obtained during the screening period and on day 14.

For patients with obsessive compulsive disorder, the following rating scales were completed by the investigator 48 hours prior to dosing (baseline) and at the end of day 42 or upon study discontinuation.

1. Children's Yale-Brown Obsessive Compulsive Scale (CY-BOCS).
2. NIMH Global Obsessive Compulsive Scale.
3. Clinical Global Impressions (CGI) of Severity of Illness and Improvement.

Only the CGI was done for patients with major depression.

Analytical Method: Sertraline,

Attachment 2 (1/8)

SERTRALINE PEDIATRIC PK STUDY 0525
TABLE 2A - SUMMARY STATISTICS FOR PHARMACOKINETIC PARAMETERS*

DRUG: SERTRALINE
PARAMETER: AUC(24), ng-h/mL

DAY	EVENT	AGE 6-12 YEARS			AGE 13-17 YEARS			OVERALL
		TITRATION A	TITRATION B	OVERALL	TITRATION A	TITRATION B	OVERALL	
1	SINGLE DOSE OF 50 MG	355 ± 157 (13)	239 ± 105 (12)	299 ± 145 (25)	203 ± 44.5 (15)	225 ± 72.8 (14)	214 ± 59.9 (29)	253 ± 115 (54)
8	SINGLE DOSE OF 25/50 MG**	142 ± 70.4 (12)	227 ± 70.7 (10)	n.d.	89.5 ± 30.1 (13)	226 ± 70.4 (11)	n.d.	n.d.
14	LAST DOSE @ 50 MG	548 ± 191 (10)	394 ± 155 (8)	480 ± 188 (18)	369 ± 115 (11)	435 ± 178 (9)	399 ± 147 (20)	437 ± 170 (38)
21	LAST DOSE @ 100 MG	1435 ± 480 (10)	1061 ± 417 (8)	1269 ± 479 (18)	888 ± 297 (10)	921 ± 270 (9)	903 ± 277 (19)	1081 ± 426 (37)
28	LAST DOSE @ 150 MG	2381 ± 874 (9)	1960 ± 742 (9)	2170 ± 816 (18)	1394 ± 406 (13)	1772 ± 397 (10)	1558 ± 437 (23)	1827 ± 695 (41)
42	LAST DOSE @ 200 MG	3659 ± 1259 (10)	2555 ± 1476 (10)	3107 ± 1450 (20)	2013 ± 914 (13)	2704 ± 688 (9)	2296 ± 882 (22)	2682 ± 1242 (42)

* TABLE VALUES ARE MEAN ±SD (NO. OF PATIENTS).
** 25 MG FOR TITRATION A, 50 MG FOR TITRATION B.
n.d. = NOT DETERMINED BECAUSE DOSES WERE DIFFERENT BETWEEN TITRATION GROUPS.

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DRUG: SERTRALINE

TABLE 2A - SUMMARY STATISTICS FOR [illegible]

PARAMETER: AUC(24) NORMALIZED BY DOSE IN MILLIGRAMS PER KILOGRAM OF BODYWEIGHT (ng-h/ml/(mg/kg))

DAY	EVENT	AGE 6-12 YEARS			AGE 13-17 YEARS			OVERALL
		TITRATION A	TITRATION B	OVERALL	TITRATION A	TITRATION B	OVERALL	
1	SINGLE DOSE OF 50 MG	272 ± 124 (13)	205 ± 81.4 (12)	240 ± 109 (25)	235 ± 55.0 (15)	240 ± 64.4 (14)	238 ± 58.7 (29)	239 ± 85.0 (54)
8	SINGLE DOSE OF 25/50 MG**	224 ± 107 (12)	192 ± 54.9 (10)	n.d.	204 ± 67.7 (13)	231 ± 51.5 (11)	n.d.	n.d.
14	LAST DOSE @ 50 MG	471 ± 241 (10)	338 ± 136 (8)	412 ± 207 (18)	453 ± 183 (11)	458 ± 165 (9)	455 ± 171 (20)	435 ± 188 (38)
21	LAST DOSE @ 100 MG	615 ± 292 (10)	458 ± 135 (8)	546 ± 243 (18)	533 ± 247 (10)	528 ± 166 (9)	530 ± 207 (19)	538 ± 222 (37)
28	LAST DOSE @ 150 MG	703 ± 316 (9)	554 ± 173 (9)	629 ± 259 (18)	556 ± 207 (13)	640 ± 153 (10)	593 ± 187 (23)	609 ± 219 (41)
42	LAST DOSE @ 200 MG	770 ± 316 (10)	561 ± 268 (10)	666 ± 305 (20)	596 ± 242 (13)	741 ± 180 (9)	655 ± 226 (22)	660 ± 263 (42)

* TABLE VALUES ARE MEAN ±SD (NO. OF PATIENTS).
** 25 MG FOR TITRATION A, 50 MG FOR TITRATION B.
n.d. = NOT DETERMINED BECAUSE DOSES WERE DIFFERENT BETWEEN TITRATION GROUPS.

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Att. 2

(3/8)

SERTRALINE PEDIATRIC PK STUDY 0525

DRUG: SERTRALINE
PARAMETER: Cmax, ng/mL

TABLE 2A - SUMMARY STATISTICS FOR PHARMACOKINETIC PARAMETERS*

DAY	EVENT	AGE 6-12 YEARS			AGE 13-17 YEARS			OVERALL
		TITRATION A	TITRATION B	OVERALL	TITRATION A	TITRATION B	OVERALL	
1	SINGLE DOSE OF 50 MG	26.9 ± 11.5 (13)	19.8 ± 9.20 (12)	23.5 ± 10.9 (25)	15.3 ± 4.54 (15)	17.4 ± 6.84 (14)	16.3 ± 5.76 (29)	19.6 ± 9.17 (54)
8	SINGLE DOSE OF 25/50 MG**	8.73 ± 3.73 (12)	14.0 ± 3.99 (11)	n.d.	5.07 ± 1.62 (14)	14.5 ± 4.91 (12)	n.d.	n.d.
14	LAST DOSE @ 50 MG	31.9 ± 10.4 (10)	24.9 ± 10.6 (8)	28.8 ± 10.8 (18)	22.1 ± 7.55 (11)	25.5 ± 8.85 (9)	23.6 ± 8.12 (20)	26.1 ± 9.72 (38)
21	LAST DOSE @ 100 MG	84.3 ± 26.7 (10)	59.7 ± 20.5 (8)	73.3 ± 26.7 (18)	51.8 ± 17.8 (10)	51.6 ± 15.2 (9)	51.7 ± 16.1 (19)	62.2 ± 24.2 (37)
28	LAST DOSE @ 150 MG	134 ± 51.9 (9)	113 ± 36.7 (9)	124 ± 45.0 (18)	77.0 ± 20.2 (13)	101 ± 18.8 (10)	87.5 ± 22.7 (23)	103 ± 38.4 (41)
42	LAST DOSE @ 200 MG	193 ± 65.3 (10)	138 ± 71.5 (10)	165 ± 72.3 (20)	106 ± 43.3 (13)	148 ± 42.6 (9)	123 ± 47.0 (22)	143 ± 63.3 (42)

* TABLE VALUES ARE MEAN ±SD (NO. OF PATIENTS).
** 25 MG FOR TITRATION A, 50 MG FOR TITRATION B.
n.d. = NOT DETERMINED BECAUSE DOSES WERE DIFFERENT BETWEEN TITRATION GROUPS.

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Att. 2

SERTRALINE PEDIATRIC PK STUDY 0525
TABLE 2A - SUMMARY STATISTICS FOR PHARMACOKINETIC PARAMETERS*

(4/8)

DRUG: SERTRALINE
PARAMETER: Cmax NORMALIZED BY DOSE IN MILLIGRAMS PER KILOGRAM OF BODYWEIGHT (ng/ml/(mg/kg))

		AGE 6-12 YEARS			AGE 13-17 YEARS			
DAY	EVENT	TITRATION A	TITRATION B	OVERALL	TITRATION A	TITRATION B	OVERALL	OVERALL
1	SINGLE DOSE OF 50 MG	20.9 ± 9.89 (13)	17.0 ± 7.07 (12)	19.0 ± 8.70 (25)	17.7 ± 5.12 (15)	18.6 ± 6.41 (14)	18.2 ± 5.69 (29)	18.6 ± 7.18 (54)
8	SINGLE DOSE OF 25/50 MG**	14.0 ± 6.50 (12)	12.1 ± 3.27 (11)	n.d.	11.7 ± 3.61 (14)	15.2 ± 3.75 (12)	n.d.	n.d.
14	LAST DOSE @ 50 MG	27.0 ± 11.9 (10)	21.1 ± 8.39 (8)	24.3 ± 10.7 (18)	27.1 ± 12.0 (11)	27.0 ± 8.50 (9)	27.0 ± 10.3 (20)	25.8 ± 10.4 (38)
21	LAST DOSE @ 100 MG	35.7 ± 15.4 (10)	26.0 ± 7.05 (8)	31.4 ± 13.1 (18)	31.2 ± 15.1 (10)	29.9 ± 10.9 (9)	30.6 ± 12.9 (19)	31.0 ± 12.8 (37)
28	LAST DOSE @ 150 MG	40.1 ± 19.8 (9)	32.0 ± 8.61 (9)	36.0 ± 15.4 (18)	30.8 ± 11.1 (13)	36.8 ± 9.38 (10)	33.4 ± 10.6 (23)	34.6 ± 12.8 (41)
42	LAST DOSE @ 200 MG	40.5 ± 16.1 (10)	30.3 ± 13.0 (10)	35.4 ± 15.2 (20)	31.6 ± 12.4 (13)	40.6 ± 11.6 (9)	35.3 ± 12.7 (22)	35.3 ± 13.7 (42)

* TABLE VALUES ARE MEAN ±SD (NO. OF PATIENTS).
** 25 MG FOR TITRATION A, 50 MG FOR TITRATION B.
n.d. = NOT DETERMINED BECAUSE DOSES WERE DIFFERENT BETWEEN TITRATION GROUPS.

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DRUG: SERTRALINE
PARAMETER: Cmin, ng/mL

TABLE 2A - SERTRALINE PEDIATRIC PK STUDY 0525
SUMMARY STATISTICS FOR PHARMACOKINETIC PARAMETERS* (5/8)

Att. 2

DAY	EVENT	AGE 6-12 YEARS			AGE 13-17 YEARS			OVERALL
		TITRATION A	TITRATION B	OVERALL	TITRATION A	TITRATION B	OVERALL	
1	SINGLE DOSE OF 50 MG	9.86 ± 5.80 (13)	5.57 ± 2.37 (12)	7.80 ± 4.92 (25)	5.53 ± 1.76 (15)	5.76 ± 1.95 (14)	5.64 ± 1.82 (29)	6.64 ± 3.73 (54)
8	SINGLE DOSE OF 25/50 MG**	3.98 ± 1.79 (12)	6.15 ± 2.45 (10)	n.d.	3.27 ± 1.16 (14)	6.84 ± 2.18 (12)	n.d.	n.d.
14	LAST DOSE @ 50 MG	16.6 ± 10.0 (12)	10.3 ± 4.88 (11)	13.5 ± 8.44 (23)	13.3 ± 6.36 (15)	14.7 ± 7.06 (13)	13.9 ± 6.60 (28)	13.8 ± 7.41 (51)
21	LAST DOSE @ 100 MG	37.2 ± 12.7 (11)	27.9 ± 12.4 (11)	32.6 ± 13.2 (22)	24.3 ± 8.97 (14)	33.4 ± 14.6 (13)	28.7 ± 12.7 (27)	30.4 ± 12.9 (49)
28	LAST DOSE @ 150 MG	79.6 ± 48.7 (11)	53.1 ± 27.5 (11)	66.3 ± 40.9 (22)	47.6 ± 23.1 (14)	58.3 ± 17.3 (11)	52.3 ± 21.1 (25)	58.9 ± 32.3 (47)
42	LAST DOSE @ 200 MG	117 ± 48.3 (10)	76.8 ± 51.2 (10)	96.9 ± 52.7 (20)	71.5 ± 42.4 (15)	94.4 ± 28.3 (12)	81.7 ± 38.0 (27)	88.2 ± 44.9 (47)

* TABLE VALUES ARE MEAN ±SD (NO. OF PATIENTS).
** 25 MG FOR TITRATION A, 50 MG FOR TITRATION B.
n.d. = NOT DETERMINED BECAUSE DOSES WERE DIFFERENT BETWEEN TITRATION GROUPS.

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DRUG: SERTRALINE
PARAMETER: Cmin NORMALIZED BY DOSE IN MILLIGRAMS PER KILOGRAM OF BODYWEIGHT (ng/ml/(mg/kg))

TABLE 2A - SERTRALINE PEDIATRIC PK STUDY 0525 [illegible]
SUMMARY STATISTICS FOR PHARMACOKINETIC PARAMETERS*

Att. 2 (6/8)

DAY	EVENT	AGE 6-12 YEARS			AGE 13-17 YEARS			OVERALL
		TITRATION A	TITRATION B	OVERALL	TITRATION A	TITRATION B	OVERALL	
1	SINGLE DOSE OF 50 MG	7.18 ± 3.47 (13)	4.82 ± 1.95 (12)	6.05 ± 3.03 (25)	6.38 ± 1.90 (15)	6.11 ± 1.78 (14)	6.25 ± 1.81 (29)	6.16 ± 2.43 (54)
8	SINGLE DOSE OF 25/50 MG**	6.30 ± 2.85 (12)	5.24 ± 1.99 (10)	n.d.	7.54 ± 2.95 (14)	7.03 ± 1.63 (12)	n.d.	n.d.
14	LAST DOSE @ 50 MG	13.2 ± 7.87 (12)	9.14 ± 4.62 (11)	11.3 ± 6.71 (23)	15.5 ± 7.54 (15)	15.4 ± 6.45 (13)	15.5 ± 6.92 (28)	13.6 ± 7.09 (51)
21	LAST DOSE @ 100 MG	15.8 ± 8.49 (11)	11.8 ± 4.38 (11)	13.8 ± 6.91 (22)	14.5 ± 6.44 (14)	17.6 ± 5.45 (13)	16.0 ± 6.08 (27)	15.0 ± 6.49 (49)
28	LAST DOSE @ 150 MG	21.4 ± 11.4 (11)	15.2 ± 6.83 (11)	18.3 ± 9.68 (22)	18.2 ± 7.49 (14)	20.9 ± 5.41 (11)	19.4 ± 6.66 (25)	18.9 ± 8.14 (47)
42	LAST DOSE @ 200 MG	24.7 ± 11.8 (10)	16.9 ± 9.43 (10)	20.8 ± 11.1 (20)	20.4 ± 11.1 (15)	24.8 ± 7.19 (12)	22.4 ± 9.63 (27)	21.7 ± 10.2 (47)

* TABLE VALUES ARE MEAN ±SD (NO. OF PATIENTS).
** 25 MG FOR TITRATION A, 50 MG FOR TITRATION B.
n.d. = NOT DETERMINED BECAUSE DOSES WERE DIFFERENT BETWEEN TITRATION GROUPS.

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SERTRALINE PEDIATRIC PK STUDY 0525
TABLE 2A - SUMMARY STATISTICS FOR PHARMACOKINETIC PARAMETERS*

Att. 2 (7/8)

DRUG: SERTRALINE
PARAMETER: Tmax, h

DAY	EVENT	AGE 6-12 YEARS			AGE 13-17 YEARS			OVERALL
		TITRATION A	TITRATION B	OVERALL	TITRATION A	TITRATION B	OVERALL	
1	SINGLE DOSE OF 50 MG	6.02 ± 2.42 (13)	5.60 ± 1.81 (12)	5.82 ± 2.11 (25)	6.39 ± 3.34 (15)	5.93 ± 2.66 (14)	6.17 ± 2.98 (29)	6.00 ± 2.60 (54)
8	SINGLE DOSE OF 25/50 MG**	7.33 ± 4.29 (12)	5.70 ± 1.53 (11)	n.d.	11.9 ± 5.92 (14)	6.03 ± 1.48 (12)	n.d.	n.d.
14	LAST DOSE @ 50 MG	6.83 ± 3.55 (10)	5.76 ± 4.33 (8)	6.36 ± 3.83 (18)	6.42 ± 3.57 (11)	6.06 ± 3.96 (9)	6.26 ± 3.65 (20)	6.30 ± 3.69 (38)
21	LAST DOSE @ 100 MG	5.41 ± 1.89 (10)	5.29 ± 1.51 (8)	5.36 ± 1.68 (18)	4.85 ± 1.40 (10)	6.44 ± 4.06 (9)	5.61 ± 3.00 (19)	5.48 ± 2.42 (37)
28	LAST DOSE @ 150 MG	7.12 ± 3.65 (9)	5.80 ± 1.21 (9)	6.46 ± 2.72 (18)	7.19 ± 4.13 (13)	8.24 ± 4.32 (10)	7.65 ± 4.15 (23)	7.13 ± 3.60 (41)
42	LAST DOSE @ 200 MG	6.82 ± 3.46 (10)	7.41 ± 3.27 (10)	7.12 ± 3.29 (20)	10.4 ± 7.24 (13)	8.29 ± 4.18 (9)	9.51 ± 6.14 (22)	8.37 ± 5.08 (42)

* TABLE VALUES ARE MEAN ±SD (NO. OF PATIENTS).
** 25 MG FOR TITRATION A, 50 MG FOR TITRATION B.
n.d. = NOT DETERMINED BECAUSE DOSES WERE DIFFERENT BETWEEN TITRATION GROUPS.

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SERTRALINE PEDIATRIC PK STUDY 0525
TABLE 2A - SUMMARY STATISTICS FOR PHARMACOKINETIC PARAMETERS

DRUG: SERTRALINE
PARAMETER: t1/2 (H)

Att. 2 (8/8)

DAY	EVENT	AGE 6-12 YEARS TITRATION A	AGE 6-12 YEARS TITRATION B	AGE 6-12 YEARS OVERALL	AGE 13-17 YEARS TITRATION A	AGE 13-17 YEARS TITRATION B	AGE 13-17 YEARS OVERALL	OVERALL
42+	LAST DOSE @ 200 MG	30.0 ± 9.02 (9)	22.8 ± 6.33 (10)	26.2 ± 8.35 (19)	26.2 ± 7.73 (14)	29.8 ± 8.68 (12)	27.8 ± 8.22 (26)	27.1 ± 8.22 (45)

* TABLE VALUES ARE MEAN ±SD (NO. OF PATIENTS).
\+ BASED ON TERMINAL PHASE OUT TO 216 HOURS.

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Attachment 3

SYNOPSIS

PROTOCOL 050-020: PHASE I MULTIPLE DOSE STUDY TO COMPARE THE PHARMACOKINETIC PARAMETERS OF SERTRALINE AND DESMETHYLSERTRALINE BETWEEN NORMAL, HEALTHY ELDERLY AND YOUNG VOLUNTEERS

PRINCIPAL INVESTIGATOR:

A. STUDY DESIGN:

Protocol 050-020 was an open-label, multiple-dose study to compare the pharmacokinetics of sertraline and desmethylsertraline at steady state in elderly male and female subjects (≥65 years) and young male and female subjects (18-45 years). Subjects were to be normal and healthy. Each subject was to receive sertraline once daily for 30 days according to a titrated dose regimen up to 200 mg/day. All doses were to be taken in the morning with a standard breakfast. Plasma sertraline and desmethylsertraline levels and follow-up side effect and laboratory test data were to be collected through at least 336 hours after the final dose on the 30th day (total of 44 study days), when a final physical examination was to be performed.

B. SUBJECTS:

	Young		Elderly	
	Male	Female	Male	Female
Entered Treatment	12	14	14	13
Completed Treatment	12	11	13	11
Discontinued Study	0	3 (a)	1	2
Assessed for pharmacokinetics	11	11	11	11

(a) One subject discontinued during the follow-up period after completion of the dose regimen.

C. DRUG ADMINISTRATION:

Dose Titration Over 30 Days

1 x 50 mg tablet (3 days)
2 x 50 mg tablet (3 days)
3 x 50 mg tablet (3 days)
4 x 50 mg tablet (21 days)

D. RESULTS:

1. PHARMACOKINETICS (mean values after 30 days of dosing except where otherwise noted; N=11/group)

	Sertraline			
	Young		Elderly	
	Male	Female	Male	Female
AUC0-24 (ng·hr/ml)	2076	3063	2590	2667
Cmax (ng/ml)	117.5	165.6	135.4	147.1
Tmax (hr)	6.9	6.7	7.8	6.4
Kel (hr^{-1})	0.0309	0.0216	0.0189	0.0191
Half-life (hr)	22.4	32.1	36.7	36.3
% Unbound drug/Day 1	1.61	1.55	1.50	1.34
% Unbound drug/Day 30	1.53	1.50	1.43	1.39

Avg. wt. = 67.3 kg

Attachment 4.

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 depression 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 (24) of 2296 ng-hr/mL, mean Cmax of 123 ng/mL, and mean half-life of 27.8 hr.[1] 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 (24) of 2570 ng-hr/mL, mean Cmax of 142 ng/mL, and mean half-life of 27.2 hr.[2] Relative to the adults, the 6-12 year olds exhibited a 21% higher AUC (24), a 16% higher Cmax, and a 4% shorter half-life, while the 13-17 year olds exhibited an 11% lower AUC (24), a 13% lower Cmax, and a 2% longer half-life. This suggests that administration of sertraline to pediatric patients does not require adjustment of dosage (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. The elimination half-life of sertraline was prolonged in a single dose study of patients with mild, stable cirrhosis, with a mean of 52 hours compared to 22 hours seen in subjects without liver disease. In hepatically impaired patients, it was observed that the Cmax and AUC were increased by 1.7 and 4.4 fold, respectively,

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: NDA 19839/S-017 AND S-018

ADMINISTRATIVE DOCUMENTS

EXCLUSIVITY SUMMARY for NDA # 19-839 SUPPL # SE5-017

Trade Name Zoloft Generic Name Sertraline Hydrochloride
Applicant Name Pfizer Pharmaceuticals HFD- 120

Approval Date 10-10-97

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.) SE5

   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 /___/ NO /_X_/

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

_____

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. Has a product with the same active ingredient(s), dosage form, strength, route of administration, and dosing schedule previously been approved by FDA for the same use?

YES /__/ NO /_X_/

If yes, NDA #___ Drug Name

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

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

YES /___/ NO /_X_/

IF THE ANSWER TO QUESTION 3 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (even if a study was required for the upgrade).

PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES
(Answer either #1 or #2, as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES /___/ NO /___/

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

NDA # _____ _____

NDA # _____ _____

NDA # _____ _____

2. Combination product.

If the product contains more than one active moiety (as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES /___/ NO /___/

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

NDA # _____ _____

NDA # _____ _____

NDA # _____ _____

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8. IF "YES," GO TO PART III.

PART III THREE-YEAR EXCLUSIVITY FOR NDA'S AND SUPPLEMENTS

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2, was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

YES /_X_/ NO /___/

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

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 /___/

APPEARS THIS WAY
ON ORIGINAL

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval **AND GO DIRECTLY TO SIGNATURE BLOCK ON PAGE 8:**

_____

_____

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES /__/ NO /_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: _____

_____

© 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 # 94-S-0501

Investigation #2, Study # 94-S-0503

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 # 94-S-0501

Investigation #2, Study # 94-S-0503

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 /_X_/ NO /___/ Explain: _____

_____

Investigation #2

IND # _____ YES /_X_/ NO /___/ Explain: _____

_____

(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study? N/A

Investigation #1

YES /___/ Explain _____ NO /___/ Explain _____

_____ _____

_____ _____

Investigation #2

YES /___/ Explain _____ NO /___/ Explain _____

_____ _____

_____ _____

c. Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES /___/ NO /_X_/

If yes, explain: _____

_____

_____

_____

Signature Date 8/14/97

Title: Project Manager, HFD-120

Signature of Division Director Date 8/15/97

cc: Original NDA Division File HFD-85 Mary Ann Holovac

M E M O R A N D U M

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

DATE: August 22, 1997

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 (sertraline) for Pediatric OCD

TO: File NDA 19-839/S-017
[**Note:** This overview should be filed with the 12-19-96
original submission.]

1.0 BACKGROUND

Zoloft (sertraline) is a selective serotonin reuptake inhibitor that was approved for the treatment of (1) depression on 12-30-91 (NDA 19-839), (2) obsessive compulsive disorder (OCD) on 10-25-96 (S-002), and (3) panic disorder (PD) on 7-8-97 (S-011). Supplement S-017 included data from a single clinical efficacy trial (Study 498) supporting the use of sertraline in the treatment of OCD in pediatric patients with this condition, in a dose range of 25-200 mg/day. It also included safety and pharmacokinetic data from a trial in pediatric patients with either depression or OCD (Study 525), from 2 extension trials, and from 2 ongoing depression trials.

Since the proposal is to use the currently approved Zoloft formulations for this expanded population, there was no need for chemistry or pharmacology reviews of this supplement. Consequently, the focus was on clinical data. The primary review of the efficacy and safety data was done by Roberta Glass, M.D. from the clinical group, and David Hoberman, Ph.D., from the Division of Biometrics also reviewed the efficacy data. The pharmacokinetic data were reviewed by Ray Baweja, Ph.D. from the biopharmaceutics group.

These studies (498 and 525) were conducted under IND The original supplement for OCD (S-017) was submitted 12-19-96.

It should be noted that, at the current time, there are 5 drugs specifically approved for the treatment of obsessive compulsive disorder (OCD) in the US. The first of these to be approved was Anafranil, a tricyclic antidepressant, and this was followed by the 4 SSRIs, 3 of which were originally approved and marketed in the US for the treatment of depression (Prozac, Paxil, and Zoloft). The fourth SSRI, Luvox, is approved only for OCD. Of these 5 drugs, data have been provided in support of use in pediatric OCD for both Anafranil and Luvox.

Anafranil and Luvox do not have separate indications for OCD in pediatric patients, but rather, they have general indications for OCD, along with a description of the clinical trials conducted in the pediatric age group with OCD under Clinical Pharmacology. This approach to labeling is in fact consistent with current thinking about OCD, i.e., an illness that typically has its onset in childhood and very often continues into adulthood. It is widely believed to be the same condition in both adults and children, both phenomenologically and regarding response to pharmacological treatment. This view supports both our approach to labeling and also the acceptablilty of basing an expansion of the claim into the pediatric age range on a single efficacy study.

We decided not to take this supplement to the Psychopharmacological Drugs Advisory Committee.

Since the submission was essentially complete, we decide to go directly to an approval action. The review team, up to the level of Team Leader, interacted with the sponsor over a period of several weeks to arrive at the version of labeling [LABZLOCD.AP2] that is included with the approval letter. We responded to the sponsor's labeling submitted with the 12-19-96 original submission with a counterproposal that was faxed to the sponsor on 8-14-97. The sponsor sent a counter-proposal by FAX on 8-19-97. We held a teleconference on 8-20-97, during which we were able to reach agreement on the version of labeling that is included with the approval packkage. The sponsor faxed two minor revisions to labeling on 8-21-97, both of which we considered acceptable. Thus, the sponsor is in agreement with the draft of labeling included with the approval letter [LABZLOCD.AP2].

2.0 CHEMISTRY

Zoloft is a marketed product, and there were no chemistry issues requiring review for this supplement.

3.0 PHARMACOLOGY

There were no pharmacology issues requiring review for this supplement.

4.0 BIOPHARMACEUTICS

Pharmacokinetic data were collected for 61 pediatric patients (n=29 in 6-12 age group and n=32 in 13-17 age group) with either depression or OCD who were treated with sertraline in an open manner (referred to as study 525). Dosing was for 6 weeks up to a maximum dose of 200 mg/day. These data were reviewed by Ray Baweja, Ph.D. from the biopharmaceutics group. In summary, these data suggest that the pharmacokinetic properties of sertraline are similar in adults and pediatric patients, with slightly lower exposures observed in pediatric patients (when dose normalized) compared to young adults (a cross study comparison). The sponsor has recommended no adjustment of dose for pediatric patients. While it is true that children and adolescents may actually clear sertraline with even slightly greater efficiency than young adults, I believe that it is important to alert prescribers to the fact that pediatric patients, especially young children, may require less aggressive dosing simply on the basis of their often much lower weights. I have proposed a modification of labeling to address this issue.

5.0 CLINICAL DATA

5.1 Efficacy Data

5.1.1 Summary of Study 90CE21-0498

As noted, this supplement provided data for a single study.

This was a randomized, 12-center (all US), double-blind, parallel group, 12-week, flexible-dose study comparing sertraline in a dose range of 25-200 mg/day (in children) or 50-200 mg/day (in adolescents) vs placebo for the treatment of OCD in 187 pediatric outpatients, ranging in age from 6 - 17 and meeting DSMIIIR criteria for OCD. Patients were stratified into 2 age groups: children (6-12) and adolescents (13-17). In addition to meeting diagnostic criteria, patients were required to (1) have at an NIMH-OC score of at least 7 at baseline, and (2) have a 24-item HAMD total score of ≤ 17 and item 1 score of 0 or 1 at baseline. In addition, they could not meet diagnostic criteria for Tourette's Disorder, other major Axis 1 disorders, or mental retardation.

The study began with a 1 week single-blind placebo phase, and was followed by the 12-week double-blind treatment phase. The initial dose was 25 mg in children and 50 mg in adolescents, and dosage was subsequently titrated during the first 4 weeks, in increments of 25 mg q 3-4 days, up to a maximum dose of 200 mg qd. The objective of titration was to get all patients up to 200 mg/day, unless there were dose limiting side effects, in which case, dose was reduced to a tolerable level. The only dose changes permitted after 4 weeks were decreases due to intolerance. The minimum dose was to be 25 mg/day in children and 50 mg/day in adolescents. Dosing was on a qd schedule, in the evening. An open label extension followed the double-blind phase for responding patients, and nonresponding patients could enter this phase after 6 weeks.

Efficacy assessments included: (1) C-YBOCS (ranges from 0-40); (2) NIMH-OC (ranges from 1-15); (3) CGI severity and improvement ratings for OCD (both range from 1-7). Assessments were done at baseline and at the ends of weeks 1, 2, 4, 6, 8, 10, and 12.

We focused on 4 key efficacy variables: (1) change from baseline in the C-YBOCS total score, NIMH-OC score, CGI severity score, and (2) CGI improvement score.

Patients were approximately 47% female, predominantly white, and the mean age was 13. The age distribution was slightly skewed toward the younger age group , i.e., 107 in the 6-12 group and 80 in the 13-17 group. The treatment groups were comparable at baseline on the demographic and key efficacy variables.

There were 92 patients assigned to sertraline and 95 to placebo. Of the placebo patients, 86% completed to 12 weeks, compared to 80% of sertraline patients. The mean sertraline dose for completers to week 12 was 178 mg/day.

The sponsor used ANCOVA as the primary analysis, with terms for treatment, site, treatment-by-site interaction, age, gender, and various other interaction terms. Baseline values of each scale were used as covariates. Dr. Hoberman reviewed the efficacy data from a statistical standpoint.

The results of this study are summarized in tables on pages 9-10 of this memo, i.e., a summary of the significance of pairwise comparisons by week for LOCF and OC of the intent-to-treat sample on p. 9 and a summary of effect sizes for the 4 key variables, as measured by difference between drug and placebo in mean change scores from baseline at week 12, on p. 10.

Sertraline was superior to placebo on reduction of C-YBOCS score, NIMH-OC score, and CGI improvement score, both in the LOCF analyses at endpoint and at the later visits in the OC analyses. There was a trend favoring sertraline over placebo on the CGI severity score. Although the treatment effect seemed to be somewhat more prominent in the children compared to the adolescents (e.g., mean change from baseline in C-YBOCS was -7.3 for sertraline vs -2.7 for placebo in children compared to -6.0 for sertraline vs -4.2 for placebo in adolescents), there was not a statistically significant age interaction. [Note: In the Luvox/OCD pediatric study, there was a difference in the same direction, however, in that instance the age difference was more prominent and represented a statistically significant interaction.]

Impression: Overall, I consider this a positive study, providing support for the effectiveness of sertraline as a treatment for OCD in a pediatric population.

1 page PURGED

information on a competitor's product

5.1.3 Conclusions Regarding Efficacy Data

I believe that Pfizer has provided evidence for the effectiveness of sertraline in the treatment of OCD in pediatric patients with this disorder. Given the general view that OCD is essentially the same disorder in adults and children, I consider one study sufficient to support extrapolation of the claim into the pediatric age group. A new indication is not needed. Rather, the claim can be extended by permitting this trial to be described in the Clinical Trials section of Clinical Pharmacology.

5.2 Safety Data

Since Zoloft has been available in the US for the treatment of depression in adults for approximately 6 years, more recently for both OCD and PD in adults, and elsewhere for the treatment of depression and OCD for several years, our approach to the safety data was, in part, to compare the findings from the relatively small pediatric OCD database with the adult databases for depression, OCD, and PD. Dr. Glass concluded that Zoloft is acceptably safe for use in the treatment of OCD in the pediatric age group, and I agree with that conclusion.

The safety data for this review were derived from several pediatric studies, including: 498 (described under Efficacy Data), 525 (described under Biopharmaceutics), and also 536, 550, 002, and 246. Study 536 was an extension protocol for study 498, study 550 was an extension protocol for study 525, and studies 002 and 246 are ongoing studies in pediatric depression. The total population of pediatric patients exposed to sertraline in the safety data base for this supplement was n=258. Exposure was relatively short-term.

No analysis of postmarketing reports for Zoloft related specifically to the treatment of pediatric patients with OCD was included in this supplement.

The mean age of patients in this study was 13, with roughly half in each of 2 age groups (6-12) and 13-17). Patients were also distributed roughly 50:50 by gender. The dose for sertraline was in a range of 25-200 mg/day, with a majority of patients being dosed at the higher end of this range.

There were no deaths in this study. Seizures were reported in 2 sertraline-exposed patients in an open extension (study 536) and in 1 sertraline-exposed patient in study 498. Suicidal ideation was observed in several patients, but could not be reasonably attributed to sertraline use.

In study 498, the only controlled trial in this database, dropouts were minimal for both sertraline and placebo. Dropouts for adverse events were 13% among sertraline patients compared to 4% in placebo patients. The most frequent reasons for dropout among sertraline patients included agitation, insomnia, and impaired concentration.

The common and drug-related adverse events overall from study 498 (incidence $\geq$ 5% and at least twice the placebo rate) included: hyperkinesis, tremor, insomnia, nervousness, agitation, nausea,

anorexia, fatigue, and rash. This list overlaps with the adverse events associated with sertraline in the adult depression and OCD databases.

Explorations of data from study 498 for laboratory, vital signs, and ECG variables, revealed several findings: (1) There was a slight mean increase in cholesterol among sertraline-treated patients (+6.5mg/dl) compared to a slight decrease among placebo patients (-6.7 mg/dl). (2) Overall, there was a slight weight increase in both groups, but this was less among sertraline-treated patients (+0.7 lbs) compared to placebo-treated patients (+2.5 lbs). Five sertraline-treated patients lost ≥7% of body weight compared to no placebo-treated patients.

In conclusion, the safety experience for sertraline in pediatric patients with OCD did not reveal any adverse findings that are unique for this population and none that would preclude its use in this population.

5.3 Clinical Sections of Labeling

As noted, we were able to reach agreement with the sponsor at the Team Leader level on final labeling.

6.0 WORLD LITERATURE

Dr. Glass reviewed the published literature for sertraline included in the supplement and discovered no previously unrecognized important safety concerns for this drug that would impact on an approval action or justify further changes in labeling at this time. However, there was a case of a neonate who experienced what was described as a "withdrawal reaction" when his nursing mother discontinued sertraline 3 weeks postpartum. We will search for other cases, independent of the action on this package, and make any future labeling changes as appropriate.

7.0 FOREIGN REGULATORY ACTIONS

Zoloft is marketed in a number of countries around the world, including the US, for the treatment of depression and OCD. To my knowledge, it is not yet marketed anywhere for the treatment of OCD in the pediatric age group.

8.0 PSYCHOPHARMACOLOGICAL DRUGS ADVISORY COMMITTEE (PDAC) MEETING

We decided not to take this supplement for the use of Zoloft in the treatment obsessive compulsive disorder in the pediatric age group to the PDAC.

9.0 DSI INSPECTIONS

DSI's current policy is to not conduct routine inspections for supplemental indications, but rather, only if there is some specific concern that would justify an inspection. There were no such issues, consequently none of the study sites for the key trial supporting the extension of the OCD claim into the pediatric age group have been inspected.

10.0 LABELING AND APPROVAL LETTER

10.1 Final Draft of Labeling Attached to Approval Package

As noted, we were able to reach agreement with the sponsor on the final labeling that is attached to the approval letter.

10.2 Foreign Labeling

Zoloft is not marketed anywhere at this time for the treatment of OCD in the pediatric age group.

10.3 Approval Letter

The approval letter includes final labeling and makes no phase 4 requests.

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 OCD in the pediatric age group. I recommend that we issue the attached approval letter with our mutually agreed upon final labeling.

cc:
Orig NDA
HFD-120
HFD-120/TLaughren/PLeber/RGlass/AMosholder/PDavid

DOC: MEMZLOCD.AP1

Summary of Significance Levels[1] (2-Sided) for Pairwise Comparisons (Sertraline vs Placebo) in Study 498							
Key Outcome Variables	Sertraline vs Placebo						
	Week[2]						
	1	2	4	6	8	10	12
C-YBOCS[3]							
LOCF							*
OC	-	*	*	*	*	*	*
CGI Severity[3]							
LOCF							t
OC	-	-	-	-	-	*	t
CGI Improvement[3]							
LOCF							*
OC	-	-	t	*	*	*	*
NIMH-OC[4]							
LOCF							*
OC	-	-	-	-	-	*	*

1 * = $p \leq 0.05$
t = $p \leq 0.10$
- = $p > 0.10$

2 End of weeks 1, 2, 4, 6, 8, 10, and 12

3 p-values for this variable based on ANCOVA

Size of Treatment Effect in Study 498			
CGI Improvement Score			
Group	Baseline[1]	Wk 12	Difference[2]
Placebo	-	3.3	
Sertraline	-	2.7	0.6
C-YBOCS Score			
Group	Baseline[3]	BL - Wk 12[4]	Difference[5]
Placebo	22	-3.4	
Sertraline	23	-6.8	3.4
NIMH-OC Score			
Group	Baseline[3]	BL - Wk 12[4]	Difference[5]
Placebo	9.1	-1.3	
Sertraline	9.2	-2.2	0.9
CGI Severity Score			
Group	Baseline[3]	BL - Wk 12[4]	Difference[5]
Placebo	4.6	-0.7	
Sertraline	4.7	-1.0	0.3

1 Baseline score not relevant for this variable
2 Difference between drug and placebo in mean CGI Improvement score at week 12
3 Mean score at baseline
4 Mean Change from baseline to week 12 (LOCF)
5 Difference in mean change from baseline to week 12 endpoint (LOCF) between sertraline and placebo

Memorandum

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

DATE: October 9, 1997

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

SUBJECT: Zoloft™ [sertraline hydrochloride] for Pediatric OCD
NDA 19-839/S-017 Approval Action Memorandum

TO: File NDA 19-839

This memorandum documents for the administrative file the basis for my decision to approve Pfizer's NDA 19-839/ S-017 for Zoloft that allows for sertraline's use in the management of OCD in a pediatric population.

Background

Zoloft (sertraline), an SSRI, was approved for use as an antidepressant in December of 1991. It was subsequently granted claims for use in both OCD (1996) and Panic disorder (1997). The current supplement in effect[1] seeks to extend the OCD use claim to patients within the pediatric age range.

Review documentation.

The information, test findings, and analyses supporting approval of this supplement are explicated in Dr. Laughren's August 22, 1997 memorandum recommending that action. The primary safety and efficacy review was conducted by Roberta Glass, M.D (8/1/97). Consultative reviews were performed by Dr. Hoberman (8/26/97) (Biometrics) and Dr. Baweja (Biopharmaceutics).

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[1] The supplement, as approved, will NOT lead to a change in the claimed use of Zoloft, but to the incorporation of statements in Zoloft product labeling that make reference to and/or apply to the use of Zoloft in children and adolescents with OCD. This is, in effect, an expansion of the OCD claim, albeit an implicit one.

Effectiveness in Use

Evidence providing direct support for the sponsor's claim that sertraline is effective in the management of OCD patients of pediatric age is derived from a single, double-blind, randomized controlled trial, 90CE21-0498. The 12 week long study was conducted at 12 US centers. Patients with OCD (DSM-IIIR), but without co-morbid depression[2], were randomized, after a week long, single blind, placebo run-in, to sertraline or placebo within two age defined strata:

children (6 to 12 years)- 53 to sertraline and 54 to placebo

adolescents (13 to 17 years)) 39 to sertraline and 41 to placebo

The protocol required patients to be titrated on a forced schedule employing once a day dosing. For children, the regimen began with a 25 mg/day dose that was advanced in 25 mg/day increments every 3 to 4 days to a maximum daily dose of 200 mg or, if that proved impossible, to the highest tolerable dose of the drug. For adolescents, the regimen called for an initial dose of 50 mg that was increased in 50 mg increments every 7 days until a dose of 200 mg or the highest possible dose below that value was attained.

The study protocol failed to identify a single "primary" outcome variable, specifying, instead, several "established" assessment instruments (CY-BOCS, the NIMH Global OCD scale and CGIs for both improvement and severity).

The randomization process appears to have produced roughly comparable groups at baseline as determined by a between group assessment of demographic and disease intensity assessment measures.(See Table 1 of Dr. Hoberman's review).

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[2] As documented by a baseline HAM D score of 17 and a Ham D.Item 1-depressed mood rating of 0 (absent) or 1(expression of depressed feelings only upon questioning)

Attrition over the 12 weeks of the trial was slightly greater among drug (about 20%) as among placebo (about 14%) randomized patients. The difference is in large part attributable to adverse drug associated events.

Both LOCF and OC analyses of the data were performed on all measures. Consistent, statistically significant, drug-placebo differences were obtained on the Observed Cases [OC] data subset analysis for the C-YBOCS at weeks 2, 4, 6, 8, 10 and 12. The CGI-improvement was also strongly positive for this subset, but the weekly scores for other measures, for the most part, failed to attain significance. Importantly, the LOCF 12 week analysis did achieve significance on 3 of the 4 major outcomes evaluated, failing only on the CGI severity where a trend (p 0.1) favoring sertraline was observed .

The point estimate of the treatment effect[3] of sertraline in children (e.g. 4.6 C-YBOCS units) was numerically larger than that observed in adolescents (e.g., 1.8 C-YBOCS units). Although I am mindful that a directionally identical and larger difference in estimated effect size was found in a study involving children and adolescents with OCD treated with fluvoxamine, I place little weight on these findings because the groups from which the estimates derive are not truly representative of the age groups they were chosen to represent (i.e., the study samples are samples of convenience and not a probability sample from the OCD population).

In sum, the results of a single adequate and well controlled clinical study carried out with children and adolescents provide direct support for the conclusion that sertraline is "effective in use" in the management of the signs and symptoms of OCD in that population. The study may also be viewed as confirming[4] the hypothesis, previously supported solely by

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[3] the difference in change from baseline average scores between the drug and placebo groups

[4] A substantive proportion of patients experience their onset of OCD in childhood. There is no basis to suspect that the pathogenesis of the signs and symptoms of OCD exhibited by such patients changes as they grow older. Accordingly, evidence documenting that sertraline is effective in adult patients with OCD of childhood onset can be reasonably interpreted as evidence that sertraline has anti-OCD activity in children. The evidence obtained in study 90CE21-0498 can,

extrapolation from the results of studies conducted primarily with older patients, that Zoloft is effective in the age group.

As is almost always the case, the evidence adduced in the clinical trial speaks primarily to "proof in principle" of sertraline's effectiveness in use. Vital questions concerning the persistence of sertraline effectiveness in extended use in this chronic disorder cannot be answered at this point in time in regard to either adults or children. Neither can the information available substantively address the question of sertraline's true value.

Safety for use and further revisions of zoloft Labeling

Zoloft has previously been found, within the meaning of the Act, to be "safe for use" in the management of OCD under the conditions of use recommended in its currently approved product labeling.

Reports submitted to this NDA supplement relating to Zoloft's use in children and adolescents with OCD have been reviewed and have been found to provide no adverse finding that would cause the agency to conclude that Zoloft is, within the meaning of the Act, less safe for use in the short term management of the signs and symptoms of OCD in the pediatric age patients than it is in adults.

It is noteworthy, however, that the supplement provides reports of experience gained with only 260 or so pediatric aged individuals treated over a relatively brief interval of time. Accordingly, my conclusion that sertraline is "safe for use" in children and adolescents rests as much on extrapolation from "safe passage" experience gained in adults treated with sertraline for its several approved indications (i.e., depression, panic, and OCD) as it does on the clinical experience gained with the drug in children and adolescents with OCD.

Although I concur fully with the review team's judgment that the information submitted is sufficient to justify the inclusion of statements

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therefore, be viewed as confirmation (independent substantiation) of that conclusion.

in Zoloft product labeling that specifically address the product's use in OCD patients of pediatric age, I believe that the proposed revisions should not be made unless they are accompanied by additional statements that draw attention to the limitations of all warrants of drug safety.

Specifically, in the absence of further qualification, I am concerned that the labeling tentatively agreed upon by the sponsor's representatives and the review team runs some risk of promoting an inference that Zoloft has been evaluated for safety in patients in the pediatric age group much more thoroughly than it actually has. Why I harbor this concern requires a brief digression about the nature of the evidence the agency ordinarily relies upon to make determinations about the safety of drug products.

The duration of the clinical tests upon which the agency relied to reach its original conclusion that Zoloft would be safe for use in adults with OCD are relatively brief (measured in weeks and months) in comparison to the average duration (years) of Zoloft's expected use in typical patients with OCD. The discrepancy noted is hardly unusual for drug products intended for use in the management of chronic illnesses. In fact, the discrepancy is a predictable consequence of the agency's current interpretation of the requirements of the Act.

The disconnect between the duration of premarket testing of new drugs and the expected duration of their use upon marketing, although not widely appreciated by the public, is widely recognized by members of the academic, regulatory and industrial communities. Indeed, the possibility that premarket testing may fail to detect rare and/or late occurring drug associated injury is repeatedly cited by experts as a major reason why an efficient and sensitive system of post-marketing surveillance is vital to the safety of the drug supply.

Unfortunately, the current system of post-marketing surveillance is not without its limitations. In particular, it is not especially sensitive to subtle adverse or untoward drug effects, and it is not very good at identifying events that occur only after a long latency if the events also occur spontaneously and commonly in the absence of drug treatment. For example, post-marketing surveillance would be unlikely, at least in the short run, to identify a drug that caused subtle defects in cognition,

changes in personality, or an increased likelihood that an individual would develop an illness or disability that occurs spontaneously in the population (e.g. diabetes, hypertension, etc.).

Thus, by virtue of their very nature, it is extremely difficult to predict on the basis of evidence collected either during drug development or from post-marketing surveillance whether or not drug induced injury of the kind postulated occurs, let alone, if it does, whether it will be common or rare in those exposed to a drug (e.g., consider the recent example of Phen/fen). Thus, the possibility that such kinds of drug induced injury may occur cannot be dismissed, and worse, the opportunity for such injury to occur would seem to be even greater in children who suffer from a chronic illness and are treated throughout their years of growth and development with a new drug. A drug, for example, could easily cause injuries of the kind identified and we would be unlikely to identify them them[5] using the methods and tests currently employed.

Accordingly, I am persuaded that it is intrinsically misleading to advance labeling representing Zoloft as being safe for use in children and adolescents without simultaneously making clear in product labeling the limitations of this implied regulatory warrant. Thus, the labeling under which I can agree to allow Zoloft to be marketed must contain, in addition to the new information already recommended by the review team, the following statement:"

> **Advisory note regarding the chronic use of sertraline in children and adolescents** (to be placed in the Precautions Section in the subsection "Pediatric Use")
>
> "The risks, if any, that may be associated with sertraline's extended use in children and adolescents with OCD have not be systematically

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5 It would be virtually impossible to determine in the absence of a controlled trial lasting for several years, for example, whether the chronic use of a new drug had an adverse effect on one or more aspects of a child's growth and development. Admittedly, if an adverse effect were unique enough, the risk might be detected, but even then, probably only after years of marketing (e.g., pemoline and the risk of fulminant hepatic necrosis).

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 relatively short term clinical studies and from 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[6]. "

Conclusion and Action:

The supplement is being approved under the labeling developed by the review team as modified by the text provided in this memorandum.

Paul Leber, M.D.
10/9/97

6 For reasons of equity, the division will ask the sponsors of all products implicitly or explicitly approved for use in children and adolescents to introduce a similar statement in their product labeling.

cc: NDA 19-839
HFD-101
Temple
HFD-120
Katz
Laughren
Glass
Mosholder
HFD-713
Sahlroot
Hoberman
HFD-860
Baweja

RETURN

Division of Anesthetic, Critical Care and Addiction Drug Products (HFD-170)
Abuse Liability Review

JUN 0 - 1997

CONSULT: Division of Neuropharmacological Drug Products (HFD-120)

NDA 19-839/SLR-018: LABELING SUPPLEMENT (1/21/97)

DRUG: ZOLOFT (SERTRALINE HYDROCHLORIDE) TABLETS
SPONSOR: PFIZER

REVIEWERS: Belinda Hayes, Ph.D. Belinda A. Hayes 5/21/97
Michael Klein, Ph.D. (Acting Team Leader) Michael Klein 5/21/97

DATE: May 21, 1997

SUMMARY:
Pfizer submitted a labeling supplement for SERTRALINE (Zoloft®). Sertraline is a highly selective serotonin reuptake inhibitor (SSRI). The drug was approved for treatment of depression on December 30, 1991. This Supplement addresses proposed changes in labeling concerning sertraline's abuse potential and was submitted for the purpose of updating the *Drug Abuse and Dependence Section* of the package insert. Sponsor submitted material including clinical and preclinical studies and literature review in support of their proposal that sertraline does not have any abuse potential.

The sponsor submitted the following for review:

1. Nonclinical abuse liability studies dealing with evaluation of sertraline's
   a. Reinforcing effects
   b. Discriminative stimulus effects
   c. Effect on behavior maintained by cocaine or food presentation in monkeys.
2. Clinical abuse liability study conducted in experienced drug abusers
   a. Double-blind, crossover, vs. two positive comparators (a central nervous system stimulant and depressant), vs. placebo.
   b. Psychometric performance and subjective responses were measured.
3. Literature Review of Selected Papers dealing with abuse and dependence of sertraline and SSRI substances.
4. A proposed label with rewrite of the **Drug Abuse and Dependence Section.**

In addition to reviewing the above studies, we have reviewed data from MedWatch relative to the NERABUSE costart terms indicative of abuse or dependence, data from the Drug Abuse Warning Network

(DAWN), and proposed an alternative version of the label.

NONCLINICAL PHARMACOLOGY:

Protocol 89PP21-0446: Sertraline self-administration, drug discrimination, and antagonism of cocaine self-administration in monkeys.

Investigator:

1. **Evaluation of the reinforcing effects of sertraline in rhesus monkeys.**

Rhesus monkeys (*Maccaca mulatta*) were fitted with iv catheters and trained to perform an operant response, lever pressing, to receive injections of cocaine during experimental sessions. Once the response rate for cocaine was stable between sessions, sertraline was substituted for cocaine to assess whether it would maintain lever-pressing behavior.

2. **Evaluation of the discriminative stimulus effects of sertraline in rhesus monkeys.**

Sertraline's discriminative stimulus properties were investigated for similarity to either pentobarbital, a CNS depressant, or d-amphetamine, a CNS stimulant. Sertraline (4.0-32 mg/kg ig) was administered in place of each training drug.

3. **Effects of sertraline on behavior maintained by cocaine or food presentation in monkeys.**

Sertraline's effect on cocaine- and food-maintained lever pressing using a self-administration paradigm was investigated. Purpose of the experiment was to investigate whether continuous infusions could decrease cocaine-maintained behavior (lever pressing) without affecting food-maintained behavior, which was intended to demonstrate support for its potential use as a therapy for cocaine abusers. Sertraline (0.1-8.0 mg/kg/24 hour) was administered continuously by iv infusion for at least 21 days and during this time daily experimental sessions were conducted in which the monkey could press a lever to receive cocaine injections or food pellets on alternate schedule within session.

Clinical Protocol 88CP21-0377

Report Date: 10-24-96

Title: Double-blind crossover study to investigate the abuse potential of sertraline, dextroamphetamine, alprazolam, and placebo in recreational drug users. (6-27-90 to 2-13-91).

PI:

Study publication: Zawertailo LA, Busto U, Kaplan HL, Sellers EM, "Comparative abuse liability of sertraline, alprazolam and dextroamphetamine in humans," J Clin Psychopharm, 1995,15:117-24.

Study Objectives: To investigate the abuse potential of sertraline compared to placebo, d-amphetamine and alprazolam.

Study Design: Double-blind, randomized, 5-way crossover study. Subjects were administered a single oral dose of one of the following treatments on each of 5 study days separated by 1 week intervals: sertraline 100 mg, sertraline 200 mg, d-amphetamine 10 mg, alprazolam 1 mg, placebo. A visual tracking test and 4 computerized subject-rated scales assessing drug liking and drug effect were administered 8 times on each treatment day: 1 hour and immediately prior to administration of the single dose of study drug and 1,2,3,4,5, and 8 hours after drug administration.

Subjects: Males (18-60 yoa) (N=200) experienced chronic users of 2 or more CNS depressants in past year. (CNS Depressants include: Alcohol <60 g/day; barbiturates, benzodiazepines, non-benzodiazepine sedatives and hypnotics and cannabis). Subjects were required to distinguish effects of a single dose of secobarbital (150 mg) from placebo in a single-blind screening evaluation using the same tests subsequently administered in db.

Psychomotor Performance & Subjective Rating Scales:
A visual tracking test and 4 computerized subject-rated scales were administered 8 times on each treatment day: 1 hour and immediately prior to administration of the single dose of study drug and 1, 2, 3, 4, 5, and 8 hours after drug administration: Visual tracking test, ARCI, Circumstances of Drug Use Questionnaire (CDUQ), Drug Perception and Preference Profile (DPPP), Mood Adjective Checklist (MACL).

1. Visual Tracking Test: A sinusoidal "road" on an oscilloscope with a "plane" icon under joystick control. Subject manipulates the joystick so as to keep plane positioned over the moving road. Three outcome measures: mean percent time over the road (PCTMEAN); mean root mean square of the distance in pixels from the road (RMSMEAN), & mean peak distance in pixels from road (MAXMEAN).
2. ARCI: 77 descriptors varying in concreteness and subjectivity from "speech in slurred" to "weird feeling" for each of which the subject selects a self-rating on a 4-point scale (mostly false, more false than true, more true than false, or mostly true). Each item is then recorded as a + or reverse item on

1 or more of 7 composite subscales:
1. sedation-motor, 2. sedation-mental, 3. unpleasantness-physical, 4. unpleasantness-dysphoria, 5. stimulation-motor, 6. stimulation-euphoria, & 7. abuse potential.

3. CDUQ: 16 hypothetical situations and for each situation, the subject is asked whether he would choose to take the test drug under those circumstances. A "yes" is qualified as choosing to take 1. Same dose. 2. Smaller dose, or 3. Larger dose. For "no", the subject selects a reason: 1. Because the test drug has the opposite effect from the desired
4. DPPP: 33 Multiple-choice questions designed to evaluate drug effects: 6 Items assess presence, strength & duration of effect. 7 Items assess drug liking and whether subject would take the drug again. 6 Items are self-ratings of cognitive, psychomotor, and mood effects. Remaining 14 items are comparisons with other drugs. 5 of these are objective comparisons, for which test drug's effect is rated as 1. Similar but stronger, 2. Similar, 3. Similar but weaker, 4. Non-existent, 5. Opposite, 6. A mixture, or 7. Never tried the comparator. The other 9 comparisons are preference items - including water, a cigarette, and coffee as comparators - for which the subject chooses whether he would take the test drug again or the comparator.
5. MACL: 33 Adjectives that subject rates from 0 (not at all) to 3 (definitely) to describe emotional state. Scores on clusters of 3 items are summed to derive scores on anxiety, aggression, elation, concentration, fatigue, social affection, sadness, skepticism, egotism, vigor.

Statistical Methods: For continuous variables (visual tracking test, ARCI, MACL and some DPPP data) peak change from time zero and AUC over the 8-hour testing period were compared among treatments with an ANOVA. CDUQ and several DPPP items were analyzed as categorical variables and compared among treatments using the Chi-square test. If overall treatment effect was significant, pairwise comparisons of active treatments vs. placebo were performed.

Procedures: Subjects were supposed to be excluded if they were on concurrent medications with a significant CNS effect during the study. Urine drug screens were to be performed on the day of the study. If a positive screen was attributable, in the investigator's opinion, to a drug that the subject reported taking more than 72 hours before study day, subject may not have been excluded. Other exclusion requirements were use of 2 or more CNS depressants for more than 3 weeks in 4 weeks prior to the study, the use of >60 g alcohol/day for more than 3 weeks in the 4 weeks prior to study, and taking alcohol on any study day.

Concomitant Medications: Protocol required that concomitant medications not be permitted on day of testing. Concomitant medications taken during the week between dosing, including OTC preparations were recorded, including dose and frequency (Table 1).

Table 1. Subject Incidence of Concomitant Medications.

Medication	# of Subjects	%
Cannabis	14	60.87
Acetaminophen	8	34.78
Multivitamins	6	26.09
Aspirin	5	21.74
Tylenol w/codeine	2	8.70
Vitamin C	2	8.70
Diazepam	2	8.70
Peptobosimol	1	4.35
Percocet	1	4.35
Ketoprofen	1	4.35
Triazolam	1	4.35
Oxycodone	1	4.35
Amino acids	1	4.35
Hismanal	1	4.35
Vitamin B	1	4.35
Matol	1	4.35
Chlortripilon	1	4.35
Vitamin A&D	1	4.35
Trihexaphenidyl HCl	1	4.35
Flexeril	1	4.35
Pen VK	1	4.35
Anacin	1	4.35
Vitamin E	1	4.35
Nyquil	1	4.35
Ventolin	1	4.35
TOTAL	20	86.96

Adverse Drug Experiences:

Table 2. Incidence (and %) of ADVERSE EXPERIENCES for 20 Study Completers (Placebo >10%)

ADE	Sertraline 100 mg	Sertraline 200 mg	Alprazolam 1 mg	dextroamphetamine 10 mg	PLACEBO
Pts.w/ ADE (TOTAL N)	17 (85%)	19 (95%)	20 (100%)	19 (95%)	15 (75%)
Somnolence	6 (30%)	5 (25%)	8 (40%)	1 (5%)	8 (40%)
Nervousness	3 (15%)	3 (15%)	3 (15%)	7 (35%)	2 (10%)
Euphoria	2 (10%)	4 (20%)	5 (25%)	4 (20%)	2 (10%)
Headache	4 (20%)	7 (35%)	5 (25%)	8 (40%)	9 (45%)
Dizziness	3 (15%)	5 (25%)	9 (45%)	4 (20%)	4 (20%)
Ataxia	1 (5%)	0 (0%)	3 (15%)	0 (0%)	2 (10%)
Fatigue	7 (35%)	8 (40%)	16 (80%)	1 (5%)	4 (20%)

PSYCHOMOTOR PERFORMANCE & SUBJECTIVE RATING SCALES

Two analysis variables were derived for each subject on each treatment day:

1. Peak change (maximum difference, positive or negative) from time 0 (just prior to drug administration) at any of the sampling times after drug administration.
2. AUC over the 8 hour sampling period (less time 0 value).

STUDY SUBJECTS

All Male (n=20) 26.0±6.5 yoa and 72.0±11.8 kg. 19 Caucasians.

RESULTS - SPONSOR SUMMARY:

Sertraline (100 mg):

1. Visual tracking test: no significant differences between drug and placebo.
2. ARCI: both peak (p=.033) and AUC (p=.040) analysis of the unpleasantness-physical subscale demonstrated significantly higher scores after administration of drug than after placebo.
3. CDUQ: proportion of subjects indicating that they would choose to take drug again did not significantly differ from placebo.
4. DPPP: subjects reported that they were significantly more alert (less sleepy) (p=.024) after drug than after placebo.
5. MACL: no significant placebo-drug differences.

Sertraline (200 mg):

1. Visual tracking test: no significant differences between drug and placebo.
2. RCI: both peak (p=<.001) and AUC (p=<.001) analysis of the unpleasantness-physical subscale demonstrated significantly higher scores after administration of drug than after placebo.
3. CDUQ: proportion of subjects indicating that they would choose to take drug again did not significantly differ from placebo.
4. DPPP: subjects reported they were more certain of feeling drug effect than from placebo (AUC p=.004) and rated current & maximal (peak p=.019, AUC p=.048) strength of the drug effect as greater.
5. MACL: no significant placebo-drug differences.

Table 3. ARCI (Peak minus time zero).

Battery	Sertraline 100 mg	Sertraline 200 mg	Alprazolam 1 mg	Dextroamphetamine 10 mg	Placebo
ARCI Sedation-Motor	Av:3.34 ±5.537 Range:	Av:4.45 ±6.378 Range:	Av:10.1 ±6.696 Range:	Av:4.55 ±5.404 Range:	Av: 3.0 ±5.272 Range:
ARCI Sedation-Mental	Av:5.95 ±7.783 Range:	Av: 9.5 ±7.388 Range:	Av: 12.55 ±8.841 Range:	Av: 3.1 ±7.033 Range:	Av: 5.95 ±7.345 Range:
ARCI Unpleasant -physical	Av:4.75 ± 4.587 Range:	Av:7.050 ± 5.276 Range:	Av:4.200 ±2.726 Range:	Av:4.200 ± 3.350 Range:	Av:2.450 ±3.395 Range:
ARCI Unpleasant -dysphoria	Av:1.850 ± 3.990 Range:	Av:3.60 ± 4.147 Range:	Av:3.65 ± 3.083 Range:	Av:2.00 ± 4.117 Range:	Av:0.900 ± 4.541 Range:
ARCI Stimulation -Motor	Av: 0.2 ± 2.840 Range:	Av: 1.2 ± 2.876 Range:	Av: 1.35 ± 2.621 Range:	Av: 2.65 ± 2.498 Range:	Av: 1.3 ± 2.342 Range:
ARCI Stimulation -Euphoria	Av: 1.050 ± 7.598 Range:	Av: 2.2 ± 8.224 Range:	Av: 5.25 ±8.632 Range:	Av: 7.1 ± 9.819 Range:	Av: 1.65 ± 4.534 Range:
ARCI Abuse Potential	Av: -0.85 ±6.596 Range:	Av: -2.1 ±7.684 Range:	Av: 2.6 ±6.202 Range:	Av: 2.65 ±6.319 Range:	Av: 0.05 ±4.979 Range:

Table 4. ARCI (AUC minus time zero).

Battery	Sertraline 100 mg	Sertraline 200 mg	Alprazolam 1 mg	Dextroamphetamine 10 mg	Placebo
ARCI Sedation-Motor	Av:13.025 ±25.999 Range:	Av:18.0 ±33.08 Range:	Av:32.4 ±30.028 Range:	Av:16.625 ±26.686 Range:	Av:11.675 ± 26.964 Range:
ARCI Sedation-Mental	Av:29.75 ±39.442 Range:	Av: 40.875 ±39.596 Range:	Av: 52.750 ±37.096 Range:	Av: 8.80 ±28.165 Range:	Av:25.425 ±32.066 Range:
ARCI Unpleasant -physical	Av:18.675 ± 22.507 Range:	Av:25.450 ± 24.610 Range:	Av:13.575 ±12.282 Range:	Av:14.825 ± 15.609 Range:	Av:9.175 ±12.501 Range:
ARCI Unpleasant -dysphoria	Av:8.750 ± 20.139 Range:	Av:14.0 ± 20.238 Range:	Av:13.1 ± 11.121 Range:	Av:6.25 ± 18.155 Range:	Av:3.850 ± 19.023 Range:
ARCI Stimulation -Motor	Av: 0.250 ± 11.978 Range:	Av: 3.25 ± 10.438 Range:	Av: 2.825 ± 10.994 Range:	Av: 7.575 ± 8.621 Range:	Av: 4.725 ± 9.430 Range:
ARCI Stimulation -Euphoria	Av: -3.375 ± 32.943 Range:	Av: -1.3 ± 28.274 Range:	Av: 12.625 ±23.459 Range:	Av: 17.650 ± 35.555 Range:	Av: 2.225 ± 20.195 Range:
ARCI Abuse Potential	Av: -7.05 ± 27.299 Range:	Av: -9.425 ± 28.028 Range:	Av: 7.079 ± 18.314 Range:	Av: 6.75 ± 19.753 Range:	Av: 2.026 ± 17.993 Range:

REVIEWERS COMMENTS ON STUDIES - CONCLUSIONS:

NONCLINICAL ABUSE LIABILITY ASSESSMENT

DISCRIMINATIVE STIMULUS EFFECTS. The drug discrimination paradigm is routinely used in the preclinical assessment of the abuse potential of a drug and it is widely accepted as an animal model for human subjective effects. In this paradigm, the animal is required to discriminate between a drug state and a non-drug state. Within the operant chamber, the animal is trained to elicit a response on one lever (e.g., right) following drug injection and on the opposite lever (left) following vehicle injection. Once the animal has learned to respond on the correct lever based on the interoceptive cues, novel drugs can be evaluated in order to

determine whether or not they elicit similar stimulus properties. There is a wealth of preclinical data to support the general statement that for many drugs their subjective effects in humans and their discriminative stimulus properties in animals (e.g., LSD-like, amphetamine-like, opiate-like) parallel one another (Schuster and Balster, 1977; Glennon and Rosecrans, 1981; Chait et al., 1984; Griffiths et al., 1985). Drugs that elicit similar subjective effects in humans are considered likely to produce similar discriminative stimulus effects in animals.

The discriminative stimulus properties of sertraline were evaluated in rhesus monkeys trained to discriminate either d-amphetamine (0.56-1.0 mg/kg, IG) or pentobarbital (10.0 mg/kg, IG) from saline in a discrete-trials shock avoidance/escape paradigm (Vanover et al., Pharmacol. Biochem. Behav. 41(4):789-93, 1992). After criterion was established, sertraline (4.0-32.0 mg/kg IG, 2 hour pre-injection time) was administered. To characterize the time course of sertraline's discriminative stimulus effect, the highest sertraline dose was tested in the pentobarbital-trained monkeys, and responding was primarily on the saline lever. Of the amphetamine-trained monkeys, 5 of 6 animals failed to generalize to the stimulus cue of d-amphetamine. The sixth monkey elicited 93% d-amphetamine-appropriate responding after receiving 20 mg/kg of sertraline. However, when this monkey received 20 mg/kg on a second occasion, only saline-appropriate responding resulted in 5 of 6 monkeys at pretreatment times of 60, 240, or 480 minutes. The sixth monkey elicited 100% d-amphetamine-lever responding when sertraline was administered 480 minutes prior to the discrimination task. The results suggest that sertraline does not possess typical CNS stimulant-like or pentobarbital-like subjective effects.

REINFORCING EFFECTS. The ability to function as a "positive reinforcer" (i.e., reinforcing efficacy) is another characteristic of all dependence-producing drugs. It is generally accepted in the scientific community that the ability of addictive drugs to serve as "positive reinforcers" is the core property that promotes the development and maintenance of addiction (Thompson and Schuster, 1968; Thompson and Unna, 1977; Balster, 1991). The self-administration paradigm is widely used to determine whether or not a drug can control behavior, that is, function as a positive reinforcer and to evaluate the abuse potential of the drug. The self-administration procedures using nonhuman primates and rats have been shown to be valid and reliable predictors of the potential of a substance to result in drug dependence (i.e., addiction). In this paradigm, the animals are trained to self-administer a known drug of abuse (e.g., cocaine). Once stable responding is maintained, test drugs are substituted for the training drug to determine if the animals will maintain responding

to the new drug. Preclinical studies have shown that there is a strong concordance between the types of drugs that serve as reinforcers in animals and the many illicit drugs associated with problems of addiction, dependence or abuse by man (Johanson and Balster, 1978; Griffiths et al., 1980; Johanson and Schuster, 1981; Johanson et al., 1987; Woolverton and Nader, 1990).

The reinforcing efficacy of sertraline was evaluated in primates (Vanover et al., Pharmacol. Biochem. Behav., 4(14):789-793, 1992). Rhesus monkeys were trained to self-administer cocaine (0.03 mg/kg/injection) under a fixed-ratio 10 schedule of drug delivery. Once stable responding was obtained, sertraline (0.05-0.4 mg/kg/injection) was substituted. Sertraline did not function as a positive reinforcer; it did not maintain self-administration behavior at levels above those maintained by saline.

POTENTIAL TREATMENT FOR COCAINE ADDICTION. The ability of sertraline to attenuate self-administration behavior was evaluated in rhesus monkeys (Kleven, M. And Woolverton, W., Drug Alcohol Depende., 31:149-158, 1993). Six rhesus monkeys were trained under a three-component multiple schedule of reinforcement; food was available for 600 sec. Under a fixed-ratio 30 schedule in the first and third component, cocaine (0.03 or 0.05 mg/kg/injection) was available for 1800 sec. Under a fixed-ratio 30 schedule. Once responding was stable, the effects of sertraline (0.1 - 8.0 mg/kg per 24 hours), mazindol (0.4 - 3.2 mg/kg, per 24 hours) and fluoxetine (0.4 - 3.2 mg/kg per 24 hours) on food- and cocaine-maintained behavior were evaluated. Sertraline and fluoxetine were continuously infused for 21 days; mazindol was infused continuously for at least the same number of sessions as had been required for the drug component to decline to low levels when saline was substituted for cocaine (i.e., 5 - 13 days). Both cocaine-maintained and food-maintained behavior was suppressed in a dose-dependent manner by the continuous infusion of each drug. Because of the lack of specificity, these results suggested that these monoamine uptake inhibitors may not be useful in the treatment of cocaine dependence.

NONCLINICAL SUMMARY.

The results from these published nonclinical data have shown that the sertraline behavioral profile is not similar to that of the psychostimulant amphetamine or the barbiturate pentobarbital. It did not possess amphetamine-like or pentobarbital-like discriminative stimulus effects (i.e., subjective effects). Furthermore, under conditions in which cocaine served as a reinforcer in rhesus monkeys, sertraline did not function as a positive reinforcer.

While the results from these preclinical studies have suggested that sertraline does not have amphetamine- and pentobarbital-like abuse potential, hallucinogen-like abuse potential can not be ruled out since sertraline is an indirect serotonergic compound. Some drugs with direct or indirect serotonergic activity have been shown to elicit hallucinogenic activity in man. Data obtained from MedWatch has included reports of hallucinations, euphoria, dependence and withdrawal symptoms associated with sertraline used in the treatment of depression.

SUMMARY OF CLINICAL STUDIES.

The incidence of ADEs across all drug conditions were observed and reported in the drug study. There was a large number of reports for patients taking placebo (15/20; 75%). Also a large number of ADEs were reported for subjects experiencing CNS and specifically psychiatric disorders. ADEs reported for subjects for Euphoria were for example: 10% in Sertraline 100 mg group, 20% in Sertraline 200 mg group, 25% in Alprazolam 1 mg group, 20% in d-Amphetamine 10 mg group and 10% in Placebo group. This high incidence has not been explained. Also, the Placebo group elicited high incidences of responses for the following: headache (45%), somnolence (40%), fatigue (20%), and dizziness (20%).

Positive comparators (alprazolam and dextroamphetamine) are not of the same pharmacologic type as sertraline. Another serotonergic agonist may have been a better positive control. Also, very large standard deviations and overlapping ranges were reported for the most important measurements, specifically those of the ARCI battery.

The study assessed only single dose administration, and did not deal with multiple dose administrations or a long term assessment. This study did not assess production of dependence or tolerance by the drug. Any assessment with respect to dependence and tolerance has not been proven by this trial. Inadequate controls were in place to ensure that other drugs were not being abused.

Regarding subject use of other drugs during the trial, there appears to be an inconsistency, not allowing recent drug/alcohol abuse prior to the study, but allowing between administration of study medications. Concomitant medications were taken by 20 (87%) of the 23 subjects who entered the study. A very large number of subjects used cannabis between subject drug administrations.

FDA Adverse Events Reporting System.

As of May 1997, 727 reports have been submitted since 1992 for

Zoloft. These 727 cases provided 221 COSTART terms. The majority of the adverse reports were reported in 1996 (212 cases). In 1992, 1993, and 1994 the number of cases reported were 89, 160, 165, and 96, respectively. The frequency of drug dependence COSTART terms are listed in Table 5 below. Withdrawal syndrome was the most frequent reported drug dependence COSTART term; it represented 43% of the total reported cases. Withdrawal symptoms have been observed after discontinuation, after abrupt withdrawal and has been reported in babies born to mothers taking Zoloft during pregnancy. Withdrawal symptoms have been observed in patients receiving 25, 50, 100, 150, and 200 mg/day. Sertaline's withdrawal syndrome has been reported in the literatute (Louie, A.K., *et al.*, Am. J. Psychiatry, 151:3, March 1994). See section on Worldwide Literature Update which follows this section.

Other COSTART terms reported to MedWatch were intentional overdose (21%), suicide attempts (19%), hallucination (15%), overdose (5%), tolerance (4%), euphoria (3%), drug dependence (2%), accidental overdose(2%), and drug dependence (0.14%).

There has been 117,707 emergency mentions of Zoloft from 1993 to 1995 in the Drug Abuse Warning Network (DAWN) (Table 6). While suicide was the primary ER mention; dependence, recreational use and other psychic effects were other motives for taking the drug (see Table). The demographic data revealed that the majority of the episodes involved women (63%, 70% and 68% for 1993, 1994, and 1995, respectively), aged 13-19, 20-29, and 30-39.

Table 5. Frequency of drug dependence COSTART terms reported for Zoloft from 1992 to the first quarter of 1997.

COSTART TERMS	COUNT	% OF TOTAL REPORTED
Withdrawal Syndrome	312	43%
Overdose Intent	157	21%
Suicide Attempts	136	19%
Hallucination	109	15%
Overdose	37	5%
Tolerance Inc	31	4%
Euphoria	18	3%
Drug Dependence	13	2%
Overdose Accidental	14	2%
Drug Dependence Addiction	1	0.14%

Table 6. Estimated Number of Emergency Department Zoloft Mentions, by Motive for Taking Substance(s), Age, Source and Gender 1993-1995.

ZOLOFT	YEARS		
	1993	1994	1995
TOTAL MENTIONS	4,184	7,116	6407
MOTIVE FOR TAKING SUBSTANCE(S)			
Dependence	21	192	183
Suicide	3,345	5,262	5141
Recreational Use	12	94	159
Other Psychic Effects	396	1099	635
Unknown/Other	161/249	461/10	*/80
AGE GROUP			
6-12	-	66	75
13-19	888	1,686	1,706
20-29	1,560	2,001	1,870
30-39	1,211	1,662	1,510
40-49	451	1,089	1,149
50-59	43	529	76
60-69	-	19	*
70-79	-	-	13
>=80	14	59	*
SEX			
Male	1,504	1,980	1,997
Female	2,621	4,985	4,323
Unknown	59	151	87

*: Estimated quantity less than 10.
Source: Office of Applied Studies, SAMHSA, Drug abuse Warning Network

WORLD LITERATURE UPDATE

Dates: 1-85 thru 3-96

Sources Searched: DIALOG thru MedLine, Embase, PsycInfo

Keywords Searched: **sertraline, substance abuse, drug abuse,** substance use disorders, substance dependence, drug dependence, drug tolerance, drug addition, withdrawal syndrome, substance withdrawal syndrome.

General Press* including 12 Databases: Newsearch, National Newspaper Index**, Reuters, Textline, PRNewswire, Promt, Newsletter, Business Dateline, Magazine Index, FDA Reports, Health & Wellness Papers.
*(1-87 thru 3-96) **(1991 thru 3-96)

Keywords Searched: sertraline, Zoloft, diversion, black market, abuse, liability, withdrawal and dependence.

Data from 1994 Drug Abuse Warning Network (DAWN) were reviewed. Also, an interview of Dr. James Cooper was conducted, who stated that he is not aware of any reports of sertraline abuse, and that he has no plans to initiate a review of sertraline due to the absence of these reports.

Summary of Significant Papers:
Fava, G.A. and Grandi, S., "Withdrawal syndromes after paroxetine and sertraline discontinuation," J. Clin. Psychopharmacol., 15(5), 374-375, 1995.

A withdrawal syndrome associated with discontinuation of the serotonin reuptake inhibitor paroxetine has recently been reported in patients with obsessive-compulsive disorder. The syndrome is characterized by: influenza-like symptoms (e.g., rhinorrhea, muscle aches), vertigo, nausea, diarrhea, fatigue, insomnia, and visual phenomena similar to the fortification spectra associated with migraine. Physical symptoms associated with paroxetine discontinuation could be cholinergically mediated, yet it has also been suggested the potential involvement of functional changes in the serotonin system, at least as to vertigo, emesis, and visual phenomena. References #1 and #2 were cited:

1. **Barr LC, Goodman WK, Price LH, "Physical symptoms associated with paroxetine discontinuation (letter). Am. J. Psychiatry, 1994;151-289.**

2. Keuthen NJ, Cyr P., Ricciardi JA, Minichiello WE, Buttolph ML, Jenike MA, "Medication withdrawal symptoms in obsessive-compulsive disorder patients treated with paroxetine (letter), J. Clin. Psychopharmacol. 1994; 14:206-7.

This withdrawal syndrome was observed in patients with serotonin reuptake inhibitors, 3 after discontinuation of paroxetine and 1 after discontinuation of sertraline. The circumstances of these withdrawal reactions and biochemical mechanisms underlying their occurrence were described.

1. Patient with depression: Paroxetine 40 mg/day (3 months); then 20 mg/day (3 days), then switched to desipramine. After 7 days, symptoms were severe vertigo, gait instability, malaise, muscle aches, and hypnagogic visual hallucinations (geometrical designs, abstract shapes, or scenes as from movies); no fever. Symptoms faded only after 10 days. Desipramine was substituted.
2. Patient with 2 year history of schizoaffective disorder, depressive type: Treated with a combination of haloperidol (3 mg/day p.o.) and paroxetine (40 mg/day) without apparent success. Paroxetine was stopped abruptly. After 10 days, patient experienced nausea, emesis, myalgia, psychomotor agitation, and middle insomnia, which disappeared in about 1 week. Desipramine was substituted.
3. Patient with major depression: Paroxetine (20 mg/day) for 4 months. One week after discontinuation, she developed fatigue, agitation, rhinorrhea, myalgia and middle insomnia which subsided in 10 days.
4. Patient with major depression: Sertraline (50 mg/day) with cognitive-behavioral treatment for 2 months. After 5 days, patient developed vertigo, gait instability, malaise, headache, and muscle aches which subsided in about 1 week.

The authors concluded the following:

1. Production of a withdrawal syndrome was confirmed.
2. The possibility that cholinergic mechanisms might be responsible were eliminated. In 2 of the 4 cases, withdrawal syndrome occurred despite treatment with desipramine which binds to the muscarinic cholinergic receptor with approximately equal affinity as paroxetine.
3. According to Keuthen *et al.*, addition of fluoxetine abruptly stopped the withdrawal effects of paroxetine. Therefore, the withdrawal syndrome should be serotonergically mediated. The chronic administration of serotonin reuptake inhibitors has been associated with down-regulation of 5-HT2 receptors and the desensitization of both the 5-HT2 receptor transmembrane signaling system and 5-HT autoreceptors It is then likely that the withdrawal syndrome may occur as a result of these functional changes. These syndromes developed after only a 3- to 4-month treatment.

4. A withdrawal syndrome was not observed in 19 patients referred to the Affective Disorders Program who had discontinued fluoxetine. This suggests that the withdrawal syndromes may not involve all serotonin reuptake inhibitors - at least to the same extent.
5. Fluoxetine would be expected to be the least likely to cause withdrawal syndromes, given the long half-life of norfluoxetine.
6. Paroxetine inhibits its own clearance thru P4502D6 so that its half-life is prolonged at higher doses and there is a disproportionate increase in paroxetine concentrations with dose increases. When the drug is discontinued, clearance rate accelerates as the level in plasma falls as result of rate decreased inhibition of P4502D6. These factors would be predicted to increase the likelihood of withdrawal reactions.
7. Sertraline would be expected to be a weaker inhibitor of P4502DC and would not be expected to have its clearance rate accelerated when drug is discontinued.
8. Clinicians should thus be aware that withdrawal symptoms may appear in some patients after these drugs are discontinued.
9. These serotonergically mediated withdrawal syndromes also raise concern about the possibility of sensitization of serotonergic systems by selective reuptake inhibitors, leading to increased vulnerability to depressive relapse in the long run.

I. Hindmarch & J.Z Bhatti "Psychopharmacological effects of sertraline in normal, healthy volunteers," Eur J. Clin Pharmacol., (1988), 35:221-3.

A db, pc crossover study was carried out in 10 normal healthy volunteers to investigate effects of sertraline 25 mg, 50 mg, 75 mg and 100 mg on aspects of cognitive functioning. Changes with respect to placebo in objective tests of psychomotor function (critical flicker fusion & choice reaction time) showed that sertraline had an alerting effect.

10 Healthy Female volunteers (25-45 yoa) received sertraline 25, 50, 75 and 100 mg, and placebo. Each subject acted as her own control and received 1 of 5 treatments on the morning of each test day. The order of treatments was randomized and balanced, with a 7 day washout between each administration. Psychomotor function was assessed using Critical Flicker Fusion as an index of overall CNS activity and Choice Reaction Time (CRT) as a measure of sensori-motor performance. Following baseline measurements, psychometric assessments were conducted 1.5, 3, 4.5, 6 and 7.5 hours after drug administration.

Sertraline produced significantly elevated CFF thresholds. CFF threshold is used to evaluate the range of psychotropic drug activity from sedation to stimulation. Sedatives (barbs and BZD)

generally reduce CFF threshold, whereas psychostimulants (amphetamines) increase it. Another group may have mood elevating or relatively mild energizing activity (e.g. hydergine or nomifensine) and also result in an elevation of CFF threshold. Sertraline's results concur with those obtained for nomifensine and zimeldine and indicate a mental alerting property of sertraline 25, 50, 75 and 100 mg. The absence of sertraline sedative action was further evident in the CRT results, relative to imipramine and amitryptiline. Sertraline 75 & 100 mg reduced total reaction time (CRT). Drowsiness occurred after all doses.

Hindmarch, I., Shillingford, J. And Shillingford, C. "The effects of sertraline on psychomotor performance in elderly volunteers," J. Clin. Psychiatry, 1990; 51[12, suppl B]: 34-36.

A db, pc crossover study investigating effects of 9 days' administration of sertraline and mianserin on cognitive and psychomotor performance of elderly volunteers. Each drug was given on a rising dose schedule for the first 5 days of treatment (sertraline 100 mg Day 1 &2, 150 mg Days 3&4, and 200 mg Day 5; mianserin 10 mg Days 1&2, 20 mg Days 3&4, and 30 mg Day5) with the highest dose (Mianserin 30 mg & sertraline 200 mg) being intended for the remainder of the study. To assess the effect of concomitant alcohol administration, alcohol (0.5 g/kg body weight) was given 6 hours after the last dose of each treatment. Available evidence showed the expected sedative effects on a number of psychometric tests. Single or multiple doses of sertraline did not affect objective measures of performance. The addition of alcohol did not affect the results which indicate that sertraline has a neutral psychomotor profile in the elderly and appears to have no additive depressant effects when taken with moderate amounts of alcohol.

Test batteries were used to measure reaction time, information processing, short-term memory, sensorimotor coordination, and peripheral attention. They included the CFF threshold, CRT, Linear Analogue Rating Scales for sedation, Immediate Memory Tests for numbers and words, and sensorimotor tracking. Tests were performed before treatment, 3 & 6 hours after treatment on Days 1 & 9, and 1 hour after the alcohol challenge on the final study day. Data demonstrated sedative effects of mianserin on a number of psychometric tests, indicating the sensitivity of the battery of tests used in study. Single or multiple doses of sertraline did not affect objective measures of performance. Sertraline had a slight effect on subjective measures (drowsiness) and alcohol did not alter these findings.

Sertraline exhibits neither CNS stimulant nor depressant effects in

therapeutic dosages. However, in db comparisons with placebo and amitriptyline in healthy volunteers, using doses up to 100 mg, sertraline improved vigilance, as assessed by ECG and psychometric measures. Author concluded that sertraline does not appear to exert any detrimental effect on objective measures of psychomotor and cognitive performance.

Louie, A. K., Lannon, R.A., Ajari, L.J., "Withdrawal reaction after sertraline discontinuation," Am. J. Psychiatry, 151:3, 450-1, 1994.

The withdrawal reaction in a 46-yo F following discontinuation of sertraline was described. A regimen of sertraline was initiated and increased to 150 mg/day over 4 weeks. During the next 3 weeks the dose was reduced to 100 mg/day. Lithium potentiation was attempted but was not successful. Following another 2 weeks on sertraline (100 mg/day) alone, the dose was abruptly discontinued. Two days later, patient reported fatigue, severe abdominal cramps, and distention, insomnia, increased dreaming, slight shortness of breath, impairment of short-term memory, and influenza-like symptoms consisting of general aching, chills without fever, headache, and sore eyes. All these symptoms quickly remitted when sertraline 25 mg/day was restarted. To discontinue sertraline treatment, a taper, maintaining each dose level for 2-3 weeks, was started. The taper sequence was as follows: 25 mg on 2 days out of every 3, 12.5 mg each day, 12.5 mg on 2 days out of every 3, 12.5 mg every other day, and 12.5 mg once every 3 days. Patient reported the same withdrawal symptoms returned to a milder degree, $1^1/_2$ days after each dose reduction. Patient was finally able to stop sertraline treatment and be symptom free 14 weeks after first attempting to discontinue. Fluoxetine does not appear to result in a withdrawal syndrome after abrupt discontinuation, possibly because of its long half-life and active metabolite. Sertraline's half-life of 1 day is shorter, and it might allow a potential withdrawal reaction to be revealed. One metabolite of sertraline does block the reuptake of serotonin, and it might prevent withdrawal by extending the biologic half-life of sertraline. However, the metabolite has been inactive in animal models measuring antidepressant action, and its clinical significance is unclear.

Rapport, D. J. and Calabrese, J. R., "Tolerance to fluoxetine," J. Clin. Psychopharmacol., 13(5), 361, 1993.

Drug tolerance is defined as the progressive diminution of efficacy resulting from continued administration. To this time, there are no reports of it developing with any of the selective serotonin uptake inhibitors (SSRI). There is growing consensus among clinicians that tolerance to the SSRIs occasionally occurs in a

small subgroup of patients with long-standing refractory major depression. First tolerance developed to one SSRI (fluoxetine). Dose was tapered and then discontinued. After 1-week washout, symptoms of melancholia were unchanged. Sertraline (50 mg/day) was begun. Within 1 week, this resulted in a partial response. The dose was then increased to 100 mg/day, but over the next 3 weeks, mood deteriorated in response to job stress. Dose was then increased to 200 mg/day, and 3 weeks later, a full remission resulted. Dose was eventually decreased. Alternate SSRIs may override the development of tolerance as long as this degenerative process is limited and the system maintains a minimum capacity to respond.

Nunes, E.V., Donovan, S.J., Brady, R., Quitkin, F.M., "Evaluation and treatment of mood and anxiety disorders in opioid-dependent patients," J. Psychoactive Drugs, 26(2), 147-153, 1994.

If tricyclics are ineffective or poorly tolerated, the SSRIs are a good alternative. SSRIs have fewer side effects, are less sedating, and have no abuse potential. They are highly effective in nonaddict populations, but have only begun to be studied in opioid-dependent patients. Sertraline is recommended for opioid dependent patients because it has a short half life and minimal tendency to impair the metabolism of other drugs. The most serious side effect of SSRIs is jitteriness, which occurs shortly after beginning the medication and may be mistaken for worsening depression or anxiety. Sertraline is an effective alternative if imipramine fails, SARIS are probably effective against social phobia, and again sertraline would be the first choice.

Markel, H., Lee, A., Holmes, R.D. and Domino, E.F., "LSD flashback syndrome exacerbated by selective serotonin reuptake inhibitor antidepressants in adolescents," J. Pediatrics, 125(5), 817-9, 1994.

Two adolescents with a long history of abuse of LSD and symptoms consistent with major depressive disorder, on initiation of antidepressant therapy with selective serotonin reuptake inhibitor agents, had the new onset or worsening of LSD flashback syndrome. The similarity in neuroreceptor physiology for both LSD and serotonin suggests that the LSD flashback syndrome may be induced by these drugs in patients with a history of LSD abuse.

There was a worsening or new onset of an LSD flashback syndrome on initiation of antidepressant therapy with selective serotonin reuptake inhibitor agents (sertraline & paroxetine).

LSD increases serotonin levels in the brain. It has specific

binding affinities for the 5-HT1 and 5-HT-2 receptors in rat and mouse brain. LSD in the rodent mimics serotonin in producing inhibition at both presynaptic and postsynaptic sites. May 14, 1997 strongly inhibits serotonergic neuron firing by binding to presynaptic autoreceptors on the soma or dendrites. Another possible mechanism that might explain the relationship of LSD abuse, treatment with SSRI agents, and the exacerbation of the flashback syndrome would be increased stimulation of 5-HT1 and 5-HT2 receptor sites, resulting from blockade of serotonin reuptake and an increased concentration of serotonin in the CNS, yielding LSD-like flashbacks. Great care is needed in eliciting a complete substance abuse history in patients with depression, especially when one is treating adolescents. Patients with history of LSD use should be warned that flashback or hallucinatory episodes are possible and to approach such agents with caution.

Sponsor's Proposed Label:

Physical and Psychological Dependence - "In human and animal studies, ZOLOFT has not demonstrated potential for abuse and there is no evidence that it causes either tolerance or physical or 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 positive subjective effects indicative of abuse potential. In contrast, subjects rated both alprazolam and d-amphetamine significantly greater than placebo on measures of drug liking, euphoria, and abuse potential. ZOLOFT did not produce either the stimulation and anxiety associated with d-amphetamine or the sedation and psychomotor impairment associated with alprazolam. ZOLOFT does not function as a positive reinforcer in rhesus monkeys trained to self-administer cocaine, nor does it substitute as a discriminative stimulus for either d-amphetamine or pentobarbital in rhesus monkeys. There are no reports of ZOLOFT abuse or diversion for non-prescription use. 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 misuse or abuse (e.g., development of tolerance, incrementation of dose, drug-seeking behavior)."

RECOMMENDATION - REVIEWER COMMENTS on proposed language (in bold, below):

Physical and Psychological Dependence -

SENTENCE #1:

"In human and animal studies, ZOLOFT has not demonstrated potential for abuse and there is no evidence that it causes either tolerance or physical or psychological dependence.

> **In human & animal studies, Zoloft does not demonstrate stimulant and or barbiturate-like (depressant) abuse potential. Published literature data suggests that actual physical dependence does occur, however, with long term treatment with Zoloft. A withdrawal syndrome has been described and is characterized by fatigue, severe abdominal cramps, and distention, insomnia, increased dreaming, slight shortness of breath, impairment of short-term memory, and influenza-like symptoms consisting of general aching, chills without fever, headache, and sore eyes (Louie et al., 1994). Also, it has been reported that individuals who had previously taken LSD, experienced flashbacks after taking SARIS (Markel et al., 1994). There is also an indication of tolerance development (Rapport et al., 1993).**

SENTENCE #2:

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 positive subjective effects indicative of abuse potential. In contrast, subjects rated both alprazolam and d-amphetamine significantly greater than placebo on measures of drug liking, euphoria, and abuse potential. ZOLOFT did not produce either the stimulation and anxiety associated with d-amphetamine or the sedation and psychomotor impairment associated with alprazolam.

> **The clinical study was clearly flawed. Because the patient population consisted of drug users, care must be given in extrapolating the results of this study to a non-drug abusing population. Euphoria was reported as a common adverse drug reaction, despite the fact that it was not measured by the ARCI/MBG scale. Many concomitant drugs were taken, including 60% reported use of Cannabis during period of study. Also, there was a very large reporting of placebo responses during**

study. Also, very large standard deviations were reported.

SENTENCE #3:

ZOLOFT does not function as a positive reinforcer in rhesus monkeys trained to self-administer cocaine, nor does it substitute as a discriminative stimulus for either d-amphetamine or pentobarbital in rhesus monkeys.

This is basically true. At a dose (0.4 mg/kg/injection) that is 8.3 folds lower than the recommended daily dose (200 mg/day or 3.3 mg/kg/day), sertraline did not maintain self-administration behavior. In the drug discrimination study, sertraline at doses up to 9.7 folds higher than the recommended daily dose did not generalize to d-amphetamine or pentobarbital cue. However, one monkey at high doses generalized to d-amphetamine cue. However, sertraline was not compared with drugs which are pharmacologically similar. The drug's hallucinogenic response, and information relative to its dependence production have not been addressed. The clinical relevance of this part is questionable. Therefore we recommend this sentence be deleted.

SENTENCE #4:

There are no reports of ZOLOFT abuse or diversion for non-prescription use.

DAWN reports include many suicides, as well as dependence, recreational use and other psychic reasons for using drug that resulted in ER admissions. The ER mentions in DAWN for Zoloft include 141 mentions in the 6 to 12 year age group. This compares with 132 ER mentions for Prozac during the same time period. MedWatch reports include: Withdrawal, hallucination, tolerance, drug dependence, few cases of euphoria. Withdrawal, suicide, and intentional overdose were major ones. A withdrawal syndrome was reported as well for infants.

We recommend that a sentence be included, with a statement of the number of reports, the source of the data, and significance with adequate warning.

SENTENCE #5:

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 misuse or abuse (e.g., development of tolerance, incrementation of dose, drug-seeking behavior)."

This is an adequate statement, but we recommend deletion of the opening phrase "As with any CNS active drug, however," and that the sentence begin with Physicians.

REVIEWERS' PROPOSED LABELING:

In human & animal studies, ZOLOFT does not demonstrate stimulant and or barbiturate-like (depressant) abuse potential. Published literature data suggests that actual physical dependence does occur with long term treatment with ZOLOFT. The withdrawal syndrome has is characterized by fatigue, severe abdominal cramps, and distention, insomnia, increased dreaming, slight shortness of breath, impairment of short-term memory, and influenza-like symptoms consisting of general aching, chills without fever, headache, and sore eyes (Louie *et al.*, 1994). Also, it has been reported that individuals who had previously taken LSD, experienced flashbacks after taking other serotonergic agents (Markel *et al.*, 1994). There is also an indication of tolerance development (Rapport *et al.*, 1993). There have been 117,707 ER mentions for ZOLOFT from 1993 to 1995. These mentions included many suicides or suicide attempts (13,748), as well as dependence (396), recreational use (253), and other psychic effects (2,130). MedWatch has reported cases of withdrawal (312), suicide (136), hallucination (109), tolerance (31), and a few cases of drug dependence (13) and euphoria (18). Use of ZOLOFT in pregnant females should be used with caution, as a withdrawal syndrome in newborns has been reported. Physicians should carefully evaluate patients for history of drug abuse and follow such patients closely, observing them for signs of misuse or abuse (e.g. development of tolerance, incrementation of doses, drug-seeking behavior). ZOLOFT should not be prescribed to patients with a history of hallucinogen abuse (such as LSD).