CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 19-839/S-035
20-990/S-003

ADMINISTRATIVE DOCUMENTS
CORRESPONDENCE

Zoloft®
(sertraline hydrochloride)
Tablets and Oral Concentrate
Long-Term PTSD

TABLE OF CONTENTS

NDA/EFFICACY SUPPLEMENT ACTION PACKAGE CHECKLIST

NDA 19-839 /SE 8 - 035

Drug Zoloft (sertraline HCl) Applicant Pfizer

RPM Hemenway Phone 4-5535

☑ 505(b)(1)
☐ 505(b)(2) Reference listed drug _____

☐ Fast Track ☐ Rolling Review Review priority: ☑ S ☐ P

Pivotal IND(s) _____

Application classifications:
Chem Class _____
Other (e.g., orphan, OTC) _____

PDUFA Goal Dates:
Primary _____
Secondary _____

Arrange package in the following order:

Indicate N/A (not applicable), X (completed), or add a comment.

GENERAL INFORMATION:

- User Fee Information: ☑ User Fee Paid
  ☐ User Fee Waiver (attach waiver notification letter)
  ☐ User Fee Exemption

- Action Letter..... ☑ AP ☐ AE ☐ NA

- Labeling & Labels
  FDA revised labeling and reviews..... _____
  Original proposed labeling (package insert, patient package insert) ..... ✓
  Other labeling in class (most recent 3) or class labeling..... _____
  Has DDMAC reviewed the labeling? ..... ☐ Yes (include review) ☑ No
  Immediate container and carton labels ..... _____
  Nomenclature review..... _____

- Application Integrity Policy (AIP) ☐ Applicant is on the AIP. This application ☐ is ☑ is not on the AIP.
  Exception for review (Center Director's memo)..... _____
  OC Clearance for approval..... _____

Continued ⇨

- Status of advertising (if AP action) ☐ Reviewed (for Subpart H – attach review) ☑ Materials requested in AP letter

- Post-marketing Commitments
  - Agency request for Phase 4 Commitments.....
  - Copy of Applicant's commitments .....

- Was Press Office notified of action (for approval action only)?..... ☐ Yes ☑ No
  - Copy of Press Release or Talk Paper.....

- Patent
  - Information [505(b)(1)] .....
  - Patent Certification [505(b)(2)].....
  - Copy of notification to patent holder [21 CFR 314.50 (i)(4)].....

- Exclusivity Summary ..... ✓

- Debarment Statement .....

- Financial Disclosure
  - No disclosable information .....
  - Disclosable information – indicate where review is located .....

- Correspondence/Memoranda/Faxes ..... ✓

- Minutes of Meetings .....
  - Date of EOP2 Meeting _____
  - Date of pre NDA Meeting _____
  - Date of pre-AP Safety Conference _____

- Advisory Committee Meeting .....
  - Date of Meeting .....
  - Questions considered by the committee .....
  - Minutes or 48-hour alert or pertinent section of transcript .....

- Federal Register Notices, DESI documents .....

CLINICAL INFORMATION:

Indicate N/A (not applicable), X (completed), or add a comment.

- Summary memoranda (e.g., Office Director's memo, Division Director's memo, Group Leader's memo) ..... ✓

- Clinical review(s) and memoranda ..... ✓

Continued ⇨

- Safety Update review(s) ..... _____

- Pediatric Information
  ☐ Waiver/partial waiver (Indicate location of rationale for waiver) ☐ Deferred
  Pediatric Page..... _____
  ☐ Pediatric Exclusivity requested? ☐ Denied ☐ Granted ☐ Not Applicable

- Statistical review(s) and memoranda ..... ✓

- Biopharmaceutical review(s) and memoranda..... _____

- Abuse Liability review(s) ..... _____
  Recommendation for scheduling ..... _____

- Microbiology (efficacy) review(s) and memoranda ..... _____

- DSI Audits ..... _____
  ☐Clinical studies ☐ bioequivalence studies ..... _____

CMC INFORMATION: **Indicate N/A (not applicable), X (completed), or add a comment.**

- CMC review(s) and memoranda ..... _____

- Statistics review(s) and memoranda regarding dissolution and/or stability ..... _____

- DMF review(s) ..... _____

- Environmental Assessment review/FONSI/Categorical exemption ..... _____

- Micro (validation of sterilization) review(s) and memoranda ..... _____

- Facilities Inspection (include EES report)
  Date completed _____ ..... ☐ Acceptable ☐ Not Acceptable

- Methods Validation ..... ☐ Completed ☐ Not Completed

PRECLINICAL PHARM/TOX INFORMATION: **Indicate N/A (not applicable), X (completed), or add a comment.**

- Pharm/Tox review(s) and memoranda ..... _____

- Memo from DSI regarding GLP inspection (if any) ..... _____

Continued ⇨

- Statistical review(s) of carcinogenicity studies ..... _____
- CAC/ECAC report ..... _____

EXCLUSIVITY SUMMARY for NDA # 19-839/S-035 & 20-990/S-003

Trade Name Zoloft Generic Name sertraline HCl

Applicant Name Pfizer Pharm HFD- 120

Approval Date

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.)? SE8

   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?

_____ ____

_____

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

YES /___/ NO /_X_/

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

2. Has a product with the same active ingredient(s), dosage form, strength, route of administration, and dosing schedule previously been approved by FDA for the same use? (Rx to OTC) Switches should be answered No - Please indicate as such).

YES /_ __/ NO /X_/

If yes, NDA # 19-839 Drug Name Zoloft

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

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

YES /___/ NO /_X_/

IF THE ANSWER TO QUESTION 3 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9 (even if a study was required for the upgrade).

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

1. Single active ingredient product.

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

YES /_X__/ NO /__/

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

NDA # 19-839 Zoloft

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 9. IF "YES," GO TO PART III.

PART III: <u>THREE-YEAR EXCLUSIVITY FOR NDA'S AND SUPPLEMENTS</u>

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

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

YES /_X__/ NO /___/

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

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

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

   (a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES /_X__/ NO /___/

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval **AND GO DIRECTLY TO SIGNATURE BLOCK ON Page 9:**

_____

_____

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

YES /___/ NO /_X__/

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

YES /___/ NO /___/

If yes, explain: _____

_____

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES /___/ NO /_X__/

If yes, explain: _____

_____

(c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

Investigation #1, Study # Study 672

Investigation #2, Study # Study 703

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 #__, Study # Study 672

Investigation #__, Study # Study 703

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 # _ [redacted] _/	NO /___/ Explain: _____
	_____
	_____
Investigation #2	
IND # [redacted] /	NO /___/ Explain: _____
	_____
	_____

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

Investigation #1	
YES /__/ Explain _____	NO /___/ Explain _____
_____	_____
_____	_____

Investigation #2	
YES /__/ Explain _____	NO /___/ Explain _____
_____	_____
_____	_____

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

YES /___/ NO /_X_/

If yes, explain: _____

_____

_____

/S/

Signature of Preparer

Date 7/31/01

Title: Regulatory Health Project Manager

/S/

Signature of Office of Division Director

8/8/01

Date

cc:
Archival NDA

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

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

APPEARS THIS WAY
ON ORIGINAL

MEMORANDUM

DATE: March 22, 2001

FROM: Division Director
Division of Neuropharmacological Drug Products/HFD-120

TO: File, NDA 19-839/S-035 & NDA 20-990/S-003

SUBJECT: Action Memo for NDA 19-839/S-035 & NDA 20-990/S-003, for the use of Zoloft (sertraline HCl) tablets and oral concentrate for use as long-term treatment of patients with Post Traumatic Stress Disorder (PTSD)

Zoloft (sertraline HCl), a selective serotonin re-uptake inhibitor, approved for several indications, has recently been approved (12/7/99) for the treatment of patients with Post Traumatic Stress Disorder (PTSD). The original approval was based on the results of 2 "positive" controlled trials which were 12 weeks in duration (2 other controlled trials were not positive).

On 5/31/00, Pfizer Pharmaceuticals, Inc. submitted the 2 supplemental NDAs described here for the long-term use of patients with PTSD. The applications contain a report of a single-controlled trial, in which patients who responded to treatment in a 24 week open label phase were randomized to sertraline or placebo for an additional 28 weeks.

The applications have been reviewed by Dr. Earl Hearst, medical officer in the division (review dated 1/12/01), Dr. John Lawrence, statistician (review dated 1/8/01), and Dr. Tom Laughren, Psychiatric Drugs Team Leader (memo dated 2/3/01). The review team recommends that the application be judged Approvable, with recommended changes in the product labeling.

I agree. The study clearly indicates the effectiveness of sertraline in the long-term treatment of patients with PTSD. I believe, though, that there are a few points that require some minor clarification.

The primary endpoints as described in the protocol were 1) the time to relapse and the rate of relapse, and 2) the time to relapse or discontinuation due to insufficient clinical response and the rate of relapse or discontinuation due to insufficient response. It is not clear, in the reviews, what the distinction between 1) and 2) is, especially since one of the mandatory criteria that define relapse is the requirement that, in the clinician's opinion, the patient's condition had significantly worsened. Further, Dr. Hearst refers several times to an additional category of patients, those who suffered an acute exacerbation of their condition. It is not clear how an acute exacerbation differs from a relapse.

I have asked Dr. Hearst for clarification of these issues. He informs me that these categories were created by the sponsor, and has given me their definitions of each. For the record, they are:

1) **Relapse**: as defined by the reviews; patients must meet 2 criteria defined by scores on 2 different measurement instruments, and, as noted above, the investigator must conclude that the patient's condition had significantly worsened. Critically, these criteria were required to have been met on at least 2 consecutive visits.
2) **Discontinuation due to insufficient response**: patients "...who discontinued the study after worsening of clinical symptoms but before the two consecutive visits required to satisfy the definition of relapse.". Therefore, these patients, included in group 2 as defined in the preceding section for analysis purposes, were patients who met either relapse criteria or this definition of discontinuation due to insufficient response. I cannot tell from the documents available to me at this time whether patients who met this latter definition **must** have met relapse criteria at one visit and then were discontinued by the investigator, or whether any patient discontinued by the investigator based on his or her clinical judgment, but not necessarily meeting relapse criteria at a visit, were included in this group.
3) **Acute exacerbation**: This group included patients who met relapse criteria or those who met the criterion for discontinuation due to insufficient response or those who met relapse criteria for the first time at the last visit.

As Dr. Hearst points out, no adjustments for multiple comparisons were made; there are, in effect, 4 primary outcome measures. As it turns out, all 4 of these comparisons are highly statistically significant, and 3 of the 4 would still reach significance if the required alpha level was maximally adjusted (.05/4 or 0.0125). However, the p-value for one of the 4 primary contrasts, Rate of Relapse, was 0.0166, which, technically, would fail a strict Bonferroni adjustment of the alpha level (0.0125). However, given the clear, robust pattern of responses, including the highly statistically significant treatment differences on many of the secondary outcomes, and the strict, perhaps overly conservative, Bonferroni adjustment described, the outcome on the Rate of Relapse poses no regulatory problem.

Finally, I note my concerns, expressed in my Approval memo for the original PTSD approval (12/6/00), that there were no "positive" findings in men in the 2 studies upon which we based the original approval (there were also no positive responses in men in the other studies as well). It was not clear whether or not this was related to the nature of the trauma suffered by men as compared to that suffered by women (one "negative" study was performed at the VA, and predominantly included men whose trauma was war-related) or to some other unknown reason(s), although it did not appear to be a question of inadequate power.

In any event, various analyses of secondary endpoints in this trial (see Dr. Hearst's review, pages 16-17, and Dr. Lawrence's review, page 7), demonstrate that there was an effect of treatment in both men and women. While the reviews do not specifically describe the results by sex for the primary outcomes, I suspect that the numbers of primary events were too small to make any reasonable statements about response by sex.

There were no new safety issues identified.

For the reasons stated above, I will issue the attached Approvable letter with appended draft labeling.

Russell Katz, M.D.

/s/

Russell Katz
3/22/01 11:52:28 AM
MEDICAL OFFICER

APPEARS THIS WAY
ON ORIGINAL

MEMORANDUM

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

DATE: February 3, 2001

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

SUBJECT: Recommendation for Approvable Action for
Zoloft tablets (sertraline) for the longer-term treatment of Posttraumatic Stress Disorder (PTSD)

TO: File NDA 19-839/S-035 and NDA 20-990/S-003
[Note: This overview should be filed with the 5-31-00 original submission.]

1.0 BACKGROUND

Sertraline is a selective serotonin reuptake inhibitor currently approved and marketed for depression, OCD, panic disorder, and posttraumatic stress disorder (PTSD) in an immediate release tablet, i.e., Zoloft (NDA 19-839, originally approved for depression 12-30-91; subsequent approvals for OCD on 10-25-96, panic disorder 7-8-97, and PTSD 12-7-99). S-035 provides data in support of a new claim for this same Zoloft tablet in the treatment of Posttraumatic Stress Disorder (PTSD) in a dose range of 50-200 mg/day.

We did not have any meetings or correspondence with Pfizer regarding their program for obtaining longer-term efficacy data for the PTSD indication.

Since the proposal is to use the currently approved Zoloft immediate release tablets for this expanded population, there was no need for chemistry, pharmacology, or biopharmaceutic reviews of this supplement. The focus was on clinical data. The primary review of the efficacy and safety data was done by Earl Hearst, M.D., from the clinical group. John Lawrence, Ph.D., from the Division of Biometrics, also reviewed the efficacy data.

The studies supporting this supplement were conducted under [redacted] he original supplement for this expanded indication (S-035) was submitted 5-31-00.

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

2.0 CHEMISTRY

As Zoloft tablets are already marketed, there were no CMC issues requiring review for this supplement.

3.0 PHARMACOLOGY

As Zoloft tablets are already marketed, there were no pharm/tox issues requiring review for this supplement.

4.0 BIOPHARMACEUTICS

As Zoloft tablets are already marketed, there were no biopharmaceutics issues requiring review for this supplement.

5.0 CLINICAL DATA

5.1 Efficacy Data

5.1.1 Overview of Studies Pertinent to Efficacy

Results from 2 studies were submitted in support of this claim for longer-term efficacy of sertraline in PTSD. 672 was a 24-week, open label study involving 252 patients who had completed either of 2 12-week double blind PTSD "feeder" studies. Of 139 patients who completed the 24 weeks of study 672 and were considered "responders," 96 were randomized to study 703, a double-blind, parallel group discontinuation trial. "Response" in study 672 was defined as: (1) CGI-I of 1 (very much improved) or 2 (much improved); and (2) a decrease in the CAPS-2 score by > 30% compared to baseline of the initial double-blind feeder study.

Study 703 was conducted at 24 sites. 46 patients were randomized to their same dose of sertraline in study 672 and 50 were randomized to placebo. Assessments during the up to 28 weeks of followup in

study 703 included (1) the Clinician-Administered PTSD Scale Part 2 (CAPS-2), (2) the Impact of Event Scale (IES), and (3) the CGI (both severity and improvement). The primary outcomes specified for study 703 were (1) time to relapse and rate of relapse, and (2) time to relapse or discontinuation due to insufficient clinical response, and rate of relapse or discontinuation due to insufficient clinical response. Relapse was defined as all of the following conditions being met on 2 consecutive visits: (1) CGI-I ≥ 3; (2) CAPS-2 score increased by $\geq 30\%$ and by ≥ 15 points relative to baseline at the start of study 703; (3) the investigator judged the patients condition to be significantly worsened. Discontinuation for insufficient clinical response was not further defined; apparently, this was a subjective judgement on the part of each investigator.

For the "relapse" analyses, patients who left for other reasons were censored. Kaplan-Meier estimates were used for determining the probability of remaining in the study for 28 weeks. The logrank test was used for testing statistical significance of time to relapse. Relapse rates, i.e., the proportions of patients in each treatment group who relapsed, were compared using Fisher's exact test. Similar analyses were done for relapse or discontinuation due to insufficient clinical response.

Patients in study 703 were roughly 2/3 female, mostly Caucasian, and the mean age was roughly 43 years.

The probability of remaining relapse free for 28 weeks was:

Sertraline-0.9474 Placebo-0.6989 Logrank p-value 0.007

Note: Most of the relapses occurred relatively early.

The probability of remaining free of relapse or discontinuation due to insufficient clinical response. for 28 weeks was:

Sertraline-0.8194 Placebo-0.5125 Logrank p-value 0.002

The effect was roughly comparable in males and females.

5.1.3 Conclusions Regarding Efficacy Data

Study 703 demonstrated a benefit of sertraline over placebo for the maintenance of response in patients with PTSD who demonstrated a response during an initial 24-week open label treatment period and were then observed for relapse during a 28-week followup period.

5.2 Safety Data

Dr. Hearst's safety review of this supplement was based on 252 patients who received sertraline in study 672 and 46 who received sertraline in study 703. Sertraline completers in study 703 were receiving mean doses of 134 mg/day in weeks 27-28. There were no unexpected safety findings among these patients, and no basis for changes in the labeling for Zoloft from the standpoint of safety.

5.3 Clinical Sections of Labeling

We have modified the language in the 3 sections of labeling in which the sponsor has proposed changes, i.e., Clinical Trials, Indications, and Dosage and Administration.

6.0 WORLD LITERATURE

The sponsor reported finding no published literature pertinent specifically to the long-term efficacy of sertraline in PTSD.

7.0 FOREIGN REGULATORY ACTIONS

To my knowledge, Zoloft is not approved for the longer-term treatment of PTSD anywhere at this time.

8.0 PSYCHOPHARMACOLOGICAL DRUGS ADVISORY COMMITTEE (PDAC) MEETING

As noted, we did not take this supplement to the Psychopharmacological Drugs Advisory Committee (PDAC).

9.0 DSI INSPECTIONS

DSI does not routinely inspect investigative sites for supplements, and did not in this case. Nevertheless, data from one investigator, [redacted] were excluded from the analyses due to a determination of scientific misconduct by [redacted]

10.0 LABELING AND APPROVABLE LETTER

10.1 Labeling Attached to Approvable Package

Our proposed labeling for this new claim is included in the approvable letter.

10.2 Foreign Labeling

To my knowledge, Zoloft is not approved for the longer-term treatment of PTSD anywhere at this time.

10.3 Approvable Letter

The approvable letter includes our proposed labeling for this supplement.

11.0 CONCLUSIONS AND RECOMMENDATIONS

I believe that Pfizer has submitted sufficient data to support the conclusion that Zoloft tablets are effective and acceptably safe in the longer-term treatment of PTSD. I recommend that we issue the attached approvable letter with our proposed labeling language for this expanded claim.

APPEARS THIS WAY
ON ORIGINAL

cc:
Orig NDA 19-839/S-035 & NDA 20-990/S-003
HFD-120
HFD-120/TLaughren/RKatz/EHearst/AMHomonnay

DOC: ———

APPEARS THIS WAY
ON ORIGINAL

/s/

Thomas Laughren
2/3/01 09:55:53 AM
MEDICAL OFFICER

APPEARS THIS WAY
ON ORIGINAL