

MEMORANDUM

DATE: December 6, 1999

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

TO: File, NDA 19-839/S-026

SUBJECT: Action Memo for NDA 19-839/S-026, for the use of Zoloft (sertraline) in patients with Post Traumatic Stress Disorder (PTSD)

On 10/7/98, Pfizer Inc. submitted supplement 026 for the use of Zoloft (sertraline hydrochloride) in patients with post-traumatic stress disorder (PTSD). In support of this claim, the sponsor submitted the results of 4 placebo controlled trials adequate by design to address the question of Zoloft's effectiveness for this indication.

The safety and effectiveness data have been reviewed by Dr. Hearst of the Division (review dated 6/8/99) and the efficacy data have been reviewed by Dr. Smith of Biometrics (review dated 9/27/99).

Dr. Laughren, Team Leader of the Psychiatric Drugs Group, has written a memo (10/19/99) in which he reviews the relevant data and discusses the issues of potential concern in the application. Specifically, these issues were:

- 1) Only 2 of the trials yielded results that reached statistical significance for their primary outcomes. One of the 2 trials that did not yield a statistically significant result enrolled patients similar to those enrolled in the 2 "positive" trials (these trials enrolled patients from a general community population whose precipitating traumatic events were typically physical/sexual trauma); the fourth study enrolled VA patients exclusively, whose primary traumatic event was typically war related.
- 2) In the 2 "positive" trials, the effects seemed to arise only from the women enrolled in the trials.
- 3) There was concern that the results seen on the primary outcome measures (scales which purported to assess PTSD specific symptomatology but that did have items that assessed depressive symptoms) could have been accounted for by the known antidepressant effect of Zoloft, given that depression was a fairly common co-morbid diagnosis in these patients.

As noted by Dr. Laughren, the Psychopharmacological Drugs Advisory Committee discussed this application at a meeting on 10/8/99. They recommended, by a vote of 6-1, that the supplement should be approved. There was in-depth discussion of all of the points of concern described above.

I will briefly comment on each of these areas.

- 1) As noted by Dr. Laughren, it is not uncommon, in the development program of effective psychotropic drugs, that several adequate and well controlled trials may not yield results that are statistically significant. The reasons for this are usually not clear; that is the case here, in my view. In particular, however, the non-positive results in the VA study raise the question of the ability of patients whose primary traumatic event(s) were war-related to respond to this treatment. As Dr. Laughren points out, this outcome is apparently consistent with other studies reported in the literature which apparently also show that these patients do not respond to available therapies to which other patients (patients with other precipitating traumatic events) respond. This raises interesting questions about the disorder (for example, do the war-related trauma patients simply represent the most severe, and therefore treatment refractory, patients with PTSD, or do they suffer from a disorder that, although clinically similar to the disorder suffered by patients with other precipitating traumatic events, is fundamentally different from it). However, interesting though these questions are, there is nothing in the data in this supplement that addresses them definitively, and, more important, the evidence that the sponsor has submitted certainly meets the test for substantial evidence of effectiveness.
- 2) Again, as noted by Dr. Laughren, the effect of the treatment appears to come essentially completely from women (see the table on Page 7 of his memo). The reason for this is not well understood at this time. One could imagine that sex is confounded with specific traumatic event (in the VA study, most patients were men), but this was not true for the 2 studies that were "positive" (in these 2 studies, men did not seem to have systematically different types of traumatic events compared to the women in these studies, although there were relatively few men in these studies). The difference did also not seem to be related to any systematic differences in kinetics between the sexes.

I find the difference in outcomes between the sexes intriguing. An examination of this outcome reveals an almost complete lack of treatment effect in men; there are essentially no numerical trends in favor of the drug, suggesting that the lack of statistical significance in men was not related to inadequate power, but that men and women may respond fundamentally differently to this treatment. Again, the application does not provide definitive information on this point.

There was considerable discussion at the Advisory Committee meeting on this point. No definitive understanding of the phenomenon emerged from that discussion, but the committee did generally agree that the drug should not be specifically indicated for use in women (although there was not unanimity on this point). I agree that such a limitation should not be imposed at this time; as Dr. Laughren noted at the meeting, limiting the indication to a specific sub-group identified by post hoc analyses (even one as "natural" as sex) is treacherous business, and should not be done lightly. However, I do believe that this is an issue that warrants further exploration (apparently, the sponsor has at least one additional study on-going that may address this question, and we await its completion and the submission of the results).

- 3) Depression is common in patients with PTSD (about 57% of the patients in the 2 positive studies had a diagnosis of depression at baseline). This gave rise to concern that the effects seen on the presumed "PTSD specific" outcome measures were related to sertraline's known anti-depressant effect. As noted by Dr. Laughren, however, analyses which examined the strata of patients defined by presence or absence of pre-existing depression showed statistically significant between treatment differences in both strata. In addition, the analyses performed by Drs. Hearst and Smith, although somewhat arbitrary in its choice of depression "improvers" and "non-improvers", also seems to support an effect of sertraline on the symptoms of PTSD independent of its anti-depressant effects. Finally, an analysis of those items of the scales used that are expected to measure symptoms that are truly specific to PTSD (intrusions) and do not overlap with items that might also be expected to detect an antidepressant effect also show an effect of sertraline. As discussed by Dr. Laughren, though, (page 6 of his memo), the between treatment comparisons on the intrusion items on the 2 scales only reach nominal significance in one study when the results are pooled; in the second study, the results when pooled almost reach nominal significance. I agree with Dr. Laughren that the lack of nominal significance for the individual studies is most likely related to the inadequate power to find such a difference.

I have reviewed the labeling that accompanies this package; this labeling has been negotiated between the review team and the sponsor, and both have agreed to it. I agree that the labeling is acceptable. It contains not only PTSD specific changes in various sections, but also changes in other sections (Clinical Pharmacology, Adverse Reactions, Overdosage) that are the result of data submitted in various supplements in response to various Agency requests (the review of the studies in renal and hepatic impaired patients is in the file for NDA 20-990, for the use of sertraline concentrate).

APPEARS THIS WAY
ON ORIGINAL

ACTION

The sponsor has submitted substantial evidence of effectiveness for Zoloft as a treatment for patients with Post Traumatic Stress Disorder. Specifically, given that this is the first application to be submitted for this indication, all other relevant aspects of the protocol and development program are acceptable (e.g., the population enrolled, the outcome measures used in the trials, the duration of the studies). As such, I will issue the attached Approval letter.

APPEARS THIS WAY
ON ORIGINAL

/S/

Russell Katz, M.D.

Cc:
NDA 19-839/S-026
HFD-120
HFD-120/Katz/Laughren/Hearst/Homanny
HFD-710-Smith/Jin

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: October 19, 1999

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

SUBJECT: Recommendation for Approval Action for
Zoloft tablets (sertraline) for the treatment of Posttraumatic Stress Disorder (PTSD)

TO: File NDA 19-839/S-026
[Note: This overview should be filed with the 10-7-98
original submission.]

1.0 BACKGROUND

Sertraline is a selective serotonin reuptake inhibitor currently approved and marketed for depression, OCD, and panic disorder 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 and panic disorder 7-8-97). S-026 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.

It should be noted that, at the current time, there are no drugs specifically approved in the US for the treatment of PTSD. However, PTSD has long been recognized by the psychiatric community as a legitimate psychiatric disorder and is listed in DSM-IV. Nevertheless, given the symptom overlap between patients with PTSD and those with various depressive disorders, one of the concerns identified early in the development of this new indication for Zoloft was how this overlap would be sorted out in making a judgement regarding the specific benefit of this product in PTSD.

While we did not have a formal end-of-phase 2 meeting with the sponsor during the development of this indication, we did communicate with them by letter regarding study design and overall development plans.

We met with the sponsor on 10-9-97 for a preNDA meeting, and again, one issue was our concern about the symptom overlap of PTSD with various depressive disorders. We also provided technical advice about the submission of the NDA.

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. David Smith, Ph.D., from the Division of Biometrics, also reviewed the efficacy data.

The studies supporting this supplement were conducted under IND [redacted] The original supplement for this expanded indication (S-026) was submitted 10-7-98.

We took this supplement to the Psychopharmacological Drugs Advisory Committee (PDAC) on 10-8-99. The committee voted 6 to 1 in favor of Zoloft being shown to be effective for PTSD, and 7 to 0 in favor of it being shown to be safe for treatment of this new indication.

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.

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5.0 CLINICAL DATA

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ON ORIGINAL

5.1 Efficacy Data

5.1.1 Overview of Studies Pertinent to Efficacy

Our review of efficacy was based on the results of 4 multicenter, double-blind, randomized, parallel group, 12-week, flexible dose, placebo-controlled trials (640, 641, 671, 682) in adult outpatients meeting DSM-III-R criteria for PTSD. These were all 2-arm trials, with patients assigned to sertraline receiving an initial dose of 25 mg/day (all dosing qd, PM or AM), with increase to 50 mg by the end of week 1. Thereafter, patients were titrated, on the basis of tolerability and efficacy, within a range of 50-200 mg/day. Dose changes were in increments of 50-mg per week.

Patients were screened using the SCID to establish the diagnosis of PTSD and exclude other axis I disorders as primary diagnoses. Protocols 640 & 641 were identical, as were 671 & 682. The only important difference between the 2 sets of studies was the length of placebo washout, with a 1-week washout for 640, 641 and 2 weeks for 671, 682. All studies were conducted at US sites. Subjects must have had a Clinician-Administered PTSD Scale Part 2 (CAPS-2) baseline score of at least 50 to be entered.

Primary efficacy assessments at each visit were: the CAPS-2, the Impact of Event (IES) scale, and the CGI. The identified primary outcome measures for these studies were change from baseline for three of these measures (CAPS-2 total score, IES total score, and CGI-S), and the raw score at endpoint for CGI-I. Importantly, patients were also assessed on the HAMD. The CAPS-2 has a total of 30 items (rated by clinicians), with each item being rated on a scale of 0 to 4 for both frequency and intensity. However, for the purpose of assessing change in treatment trials, the focus is on the first 17 items that map directly to the 17 items in the DSM-IV criteria for PTSD. That was the case for Pfizer's PTSD program as well, so the CAPS-2 total scores for these 17 items, again with frequency and intensity rated separately, ranges from 0 to 136. The IES total score (self rating) ranges from [redacted] (15 items with ratings on 0, 1, 3, or 5 on each). The CGI ranges from 1-7 for both severity and improvement.

The statistical model was ANCOVA with terms for treatment, site, Rx-by-site, and baseline score was the covariate (except for CGI-I). Analyses were done on the datasets for all patients randomized and who also received at least 1 dose of assigned treatment and who were assessed for efficacy at baseline and at least 1 followup time.

Four additional trials were ongoing at the time of submission, including (1) 672, a 24-wk open extension for 671 & 682; (2) 703, a 28-wk relapse prevention trial for responders in 672; (3) 005, a nonUS RCT; and (4) 001, also a nonUS RCT.

5.1.2 Summary of Study Results

5.1.2.1 Demographic and Illness Characteristics

- Patients were predominantly female in 3 of the studies (640:78%; 671:73%; 682:75%), and predominantly male in the 4th study (641:20% female), which was conducted in VA hospitals.
- Patients were predominantly caucasian in all 4 studies.
- Mean ages ranged from 37 to 46 across the 4 studies.
- These patients were in general chronically ill with PTSD, with mean durations of illness ranging from 11 to 18 years.
- The predominant trauma for the patients in the 3 nonVA studies was physical or sexual assault.
- Mean total scores on the CAPS-2 (first 17 items) at baseline ranged from [] across the groups in the 4 studies.
- Although patients with other axis I disorders as a primary diagnosis were excluded, axis I disorders were permitted as secondary diagnoses, and depression was a very common secondary diagnosis, occurring in proportions ranging from [] of study-subjects across the 4 studies. Anxiety was the second most common comorbid psychiatric condition, occurring in proportions ranging from 14% to 27% of study subjects across the 4 studies.

5.1.2.2 Completion Rates

Proportions of the intent-to-treat samples (all patients randomized who received at least 1 dose of assigned treatment and at least 1 postbaseline efficacy assessment) who completed to the 12-week endpoint across the 4 studies were as follows:

<u>Study</u>	<u>Sertraline</u>	<u>Placebo</u>
640	73/98(75%)	74/104(71%)
641	62/84(74%)	69/82(84%)
671	64/93(69%)	67/90(74%)
682	72/94(77%)	71/94(76%)

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5.1.2.3 Sertraline Doses

The mean sertraline doses (for weeks 11 & 12) for completers were as follows:

<u>Study</u>	<u>Dose</u>
640	146 mg/day
641	156 mg/day
671	151 mg/day
682	156 mg/day

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5.1.2.4 Efficacy Results

Summary results (LOCF at the 12 week endpoint) for the 4 primary endpoints for the 4 studies are provided in appendix Table 1. This table summarizes the outcomes for the study samples overall; results broken out according to gender and improvement on depression will be provided subsequently.

Table 1 reveals the following:—

In the LOCF analyses for studies 640 and 671, sertraline is favored over placebo on essentially all primary endpoints; the only exception is IES for study 671, where the p-value just misses nominal significance at 0.07. For study 640, while none of the OC analyses at week 12 reach statistical significance for sertraline over placebo, the p-values are close for CAPS-2 and CGI-I (0.066 & 0.065, respectively), and the effects (drug/placebo differences) are about the same size as in the LOCF analyses; Dr. Smith attributes this loss of statistical significance to diminished power, and I agree. For study 671, all of the OC analyses at week 12 reach statistical significance for sertraline over placebo, except for CGI-I, for which the p-value is 0.062; and again, the effect sizes for all outcomes in the OC analyses are consistent with those seen in the LOCF analyses.

In the LOCF analyses for studies 641 and 682, there is not even a hint of a difference between sertraline and placebo, except for IES in study 682, where placebo is superior to sertraline ($p=0.017$). In study 641, there is dramatically less change from baseline for both sertraline and placebo than was seen in the other 3 studies, with no difference between these treatment groups. This was the VA study, and this result may reflect the very chronic and refractory PTSD found in that setting. In fact, this finding is consistent with published studies of drug treatment of PTSD in veteran populations. In study 682, the placebo effect was somewhat larger than that seen in the 2 positive studies, while the sertraline effect was somewhat less. In any case, there was no sertraline/placebo difference observed, except for that noted above, and this study is also negative.

5.1.3 Comment on Other Findings in the Efficacy Analyses for Sertraline in PTSD

Results for PTSD Clusters

The 17 items from the CAPS-2 comprising the total score for this primary outcome map directly to items in the DSM-IV criteria for PTSD, and these are divided into 3 clusters that define PTSD:

- (1) re-experiencing/intrusion:
intrusive thoughts

- psychological distress
- flashbacks
- distressing dreams
- (2) avoidance/numbing:
 - avoiding thoughts of trauma
 - avoiding places
 - amnesia
 - diminished interest
 - feelings of detachment
 - restricted affect
 - foreshortened future
- (3) hyperarousal.
 - difficulty falling/staying asleep
 - difficulty concentrating
 - irritability/anger
 - hypervigilance
 - exaggerated startle
 - physiological reactivity

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While there is considerable overlap between items typically on depression rating scales and the items on both the avoidance/numbing and hyperarousal clusters, the re-experiencing/intrusion cluster appears to be reasonably specific to PTSD.

The sponsor presented the individual results for these 3 clusters for both positive studies (640 and 671) and also the pooled results for these clusters for these 2 studies. The p-values (sertraline vs placebo) for these clusters are as follows:

<u>CAPS-2 Cluster</u>	<u>640</u>	<u>671</u>	<u>640/671</u>
Re-experiencing/Intrusion	0.30	0.14	0.06
Avoidance/Numbing	0.02	0.02	<0.001
Hyperarousal	0.12	0.03	0.007

For the IES, there was also a sorting of items into clusters, i.e., re-experiencing/intrusion and avoidance/numbing, and the p-values for these 2 clusters were as follows:

<u>IES Cluster</u>	<u>640</u>	<u>671</u>	<u>640/671</u>
Re-experiencing/Intrusion	0.03	0.16	0.02
Avoidance/Numbing	0.05	0.09	0.004

While these results are not as strong for the one cluster of the CAPS-2 that appears to be relatively specific to PTSD as for the other 2 clusters, there is reasonable support for an effect of sertraline on the re-experiencing/intrusion item, at least for the pooled analysis. The studies were not individually powered to detect differences on clusters.

Interaction Between Gender and Effectiveness

In the 2 positive studies, there was evidence of an interaction for gender, as follows:

Gender Interaction for Pool of 2 Positive Studies (640 & 671)							
Outcome	Women			Men			Inter- action p-value
	Change from BL		p-value	Change from BL		p-value	
	Sert.	Placebo		Sert.	Placebo		
(N)	152	139		39	55		
CAPS-2	-34	-23	0.0001	-29	-29	0.99	0.04
IES	-18	-13	0.001	-16	-15	0.80	0.16
CGI-I	2	3	0.0001	2	3	0.34	0.22
HAMD	-8	-5	0.005	-6	-7	0.69	0.09

The male sample was roughly 1/3 the size of the female sample, and that may have accounted for some of the failure to find statistically significant differences among the male patients, e.g., for the CGI-I. However, the effect sizes also revealed the differences between the 2 genders, especially for the CAPS-2 and IES totals, and also, importantly, for the HAMD; for all 3, there were essentially no drug/placebo differences in the males. An examination for the individual study data revealed that this gender interaction was apparent for both studies individually as well. While there is no clear explanation for this difference, one possible factor is the type trauma; physical and/or sexual assault was a more common trauma for women with PTSD than men with this disorder.

Depression as a Potential Confounder

As noted, even before receiving this supplement, we alerted the sponsor to our concerns about potential confounding by the presence of depression and the antidepressant effects of sertraline. In this section, I will summarize analyses done both by the sponsor and by Drs. Smith and Hearst to explore for such confounding.

The sponsor conducted several analyses to look for differences in PTSD responses based on presence or absence of depression at baseline.

In one of these analyses, women from a pool of the 2 positive studies were subgrouped based on those with and without a comorbid diagnosis of depression at baseline. The results were as follows:

Subgroup Analysis Based on Presence or Absence of Comorbid Depression for Pool of Women from 2 Positive Studies (640 & 671)						
Outcome	No Comorbid Depression			Comorbid Depression		
	Change from BL		p-value	Change from BL		p-value
	Sert.	Placebo		Sert.	Placebo	
(N)	85	80		67	59	
CAPS-2	-33	-22	0.005	-39	-25	0.002
IES	-17	-13	0.031	-21	-14	0.010
CGI-I	2.3	3.0	0.001	2.4	3.0	0.018

This analysis demonstrated that, whether or not comorbid depression was present at baseline, an approximately equal (and significant) effect was seen for sertraline on PTSD outcomes.

Given the overlap in symptoms on the HAMD and various instruments used to assess PTSD, the sponsor also looked at correlations between change from baseline in the HAMD and change from baseline in various total and cluster scores for PTSD measures. Not surprisingly, strong correlations were noted. However, they were strong for both sertraline and placebo patients, suggesting that the correlation is not related specifically to a sertraline effect. It is important to note that whether or not patients met criteria for clinical depression at baseline, they had higher than normal depression scores on the HAMD at baseline (about 24 for those designated as having comorbid depression and about 19 for those without). It is also important to note that a designation of clinical depression is based on a clinician's judgement, not on a quantitative rating on an instrument like the HAMD. The data showing a positive correlation between changes in the HAMD and changes in PTSD measures should not, in my view, be considered support for the hypothesis that it is the antidepressant effects of sertraline that are the basis for the apparent specific improvements on the PTSD measures. It would not be surprising that mood is improving in someone whose PTSD is improving, and that might be viewed more as a secondary effect than a primary effect. In fact, it would not be surprising to see a positive correlation between responses on the HAMD and responses on other disease specific measures, even for nonpsychiatric disorders, since it would be expected that mood would improve with improvement in whatever primary disease is being treated.

An alternative approach was used by Drs. Smith and Hearst to explore for confounding. They subgrouped patients on the basis of whether or not they had improved on a measure of depression and then looked at the PTSD responses in these different subgroups. They hypothesized that whether or not a patient improves on depressive symptoms should not influence the patient's responsiveness on PTSD measures, providing these outcomes are independent. They defined improvers and non-improvers in terms of how much their HAMDs changed from baseline to endpoint, taking into consideration what the HAMD was at baseline. Based on this subgrouping,

the p-values for the sertraline/placebo differences for key PTSD outcomes for the pooled data for the 2 positive studies (640 & 671) are as follows:

<u>Outcome</u>	<u>Depression Non-Improvers</u>	<u>Depression Improvers</u>
CAPS-2	0.11	0.07
IES	0.06	0.64
CGI-S	0.06	0.20

These data for the measures identified as primary outcomes in these trials suggest there is either no difference in the PTSD response on the basis of this subgrouping, or perhaps an advantage for depression non-improvers. One possible effect of this subgrouping is to separate out the placebo responders, i.e., those subjects with prominent changes on all measures (PTSD and HAMD), regardless of treatment assignment. In any case, these findings tend to provide support for the independence of the PTSD response from an antidepressant response, in my view.

Drs. Smith and Hearst also provided a series of similar analyses using a classification of patients as depression improvers or non-improvers based on the HAMD depressed mood item. These analyses yield similar results as for the subgroupings based in HAMD responses, and thus, again tend to support an independence of the PTSD response from the antidepressant response.

Evidence Bearing on the Question of Dose/Response for Efficacy

All 4 studies in the development program involved flexible dosing in a range of 50-200 mg/day, and thus, provided no evidence pertinent to the issue of dose response. The mean doses for completers to 12 weeks in the two positive studies were 146 and 151 mg/day, respectively, but these findings are not interpretable regarding dose response since patients in such trials are generally pushed to the higher end of the permitted dose range, regardless of need. Thus the most one can say about dosing for PTSD is that there was evidence of response for patients dosed within a range of 50-200 mg/day.

Size of Treatment Effect

It is difficult to clinically interpret the effect sizes on the measures observed for the 2 positive studies in terms of differences between drug and placebo in change from baseline. For the CAPS-2 total score, mean baseline scores ranged from [redacted] and sertraline patients had decreases to mean scores of roughly 42, compared to decreases to about 50 for placebo patients. As is the case for other psychiatric indications, the mean score after treatment was still within a range that would leave many patients considered clinically ill. Another way of looking at the treatment effect is to classify patients as responders/nonresponders. A definition of response as a rating on the CGI-I of 1 (very much improved) or 2 (much improved) yielded the following results for the 2 positive studies:

<u>Studies</u>	<u>% Responders</u>	
	<u>Sertraline</u>	<u>Placebo</u>
640	74%	54%
671	61%	42%

These results, while not striking, are consistent with what we often observe in psychotropic treatment trials and they suggest to me a clinically relevant treatment effect.

Duration of Treatment

The two positive studies provide evidence of effectiveness for patients dosed up to 12 weeks. The only study in the development program capable of addressing effectiveness beyond 12 weeks is study 703. However, the results from that study have not yet been submitted.

5.1.3 Conclusions Regarding Efficacy Data

The sponsor has, in my view, provided sufficient evidence to support the claim of a beneficial effect of Zoloft in the treatment of PTSD. Two of the 3 studies in PTSD patients in the general population were able to distinguish sertraline from placebo, albeit only in women with this disorder. Nevertheless, studies 640 & 671 were positive overall, and the failure to find an effect in men with this disorder is something that can be noted in labeling. There was considerable discussion of this issue at the PDAC meeting, and it was clearly also the committee's view that the claim should be for PTSD overall, with the gender finding described in Clinical Trials. Regarding the number of positive trials, it is not uncommon for drug trials in psychiatric disorders to fail, and so the finding of 1 failure among 3 studies is not uncharacteristic. The failure of the VA study is apparently consistent with similar studies in this population, and can be discounted.

A major review concern was whether or not the effect of sertraline in this disorder can be considered a specific effect or is simply another demonstration of sertraline's antidepressant properties. While this question can be approached in several ways, I find 2 pieces of evidence supportive of a specific effect: (1) a benefit was demonstrated for the re-experiencing/intrusion cluster of both the CAPS-2 and IES, and I consider that cluster reasonably specific to PTSD; (2) whether or not patients were clinically depressed at baseline, it was possible to demonstrate an effect on PTSD measures. In my view, these results are perhaps the most persuasive in favor of a specific benefit, in the sense that patients not diagnosed with depression, and therefore not candidates for treatment with Zoloft according to FDA approved labeling, were, nevertheless, demonstrated to benefit from such treatment with improvement on measures of PTSD. I am less persuaded that the correlation of responses on the HAM-D and PTSD measures is a reasonable basis for denying a specific claim for this disorder, and in fact, the analyses of Drs. Smith and Hearst subgrouping patients into depression improvers and nonimprovers actually provided support for the view that the PTSD effect is independent of the antidepressant effect. This issue also had considerable discussion at the PDAC meeting, and the committee's view was that an independent PTSD effect had been demonstrated.

The issue of longer-term efficacy cannot be addressed until we have received and reviewed the results of study 703. In addition, since PTSD is also a disorder found in the pediatric population and, once approved for this indication, Zoloft will likely be used in pediatric patients, we will recommend adequate and well-controlled trials of Zoloft in this population as well. The PDAC strongly endorsed the need for pediatric studies in this disorder.

5.2 Safety Data

Dr. Hearst's safety review of S-026 was based on an integrated database consisting of a pooling of safety data for the four 12-week studies. In addition, any serious events reported in from 4 ongoing PTSD studies were included in this supplement. The cut-off date for safety data was 2-26-98. There was no safety update.

Overall, 374 patients were exposed to sertraline in the sponsor's development program for PTSD (i.e., in the 4 completed studies). The demographic characteristics and the dosing information for these patients were previously described.

Given our prior knowledge of the risks associated with sertraline use in the same dose range utilized in this program, the focus in the safety review was on any differences between the recognized safety profile for this drug in its approved indications from that observed in the PTSD population.

5.2.2 Overview of Adverse Event Profile for Zoloft in PTSD

Overall, the adverse events profile for sertraline in these PTSD trials was comparable to that observed in patients with depression, OCD, and panic disorder receiving this drug.

5.2.3 Conclusions Regarding Safety of Zoloft in PTSD

There were no new safety findings to suggest a substantially different safety profile for Zoloft in PTSD compared to that observed for the other 3 approved indications, and no basis for substantial changes in the labeling for Zoloft from the standpoint of safety.

5.3 Clinical Sections of Labeling

Following the 10-8-99 PDAC meeting, we negotiated with the sponsor regarding labeling and were able to reach agreement on 10-18-99. The only points of disagreement were with the description of the clinical trials and the Indications and Usage statement.

6.0 WORLD LITERATURE

Dr. Hearst reviewed the sponsor's reports on the published literature for sertraline in PTSD included in the NDA and did not discover any previously unrecognized important safety concerns for this drug.

7.0 FOREIGN REGULATORY ACTIONS

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

8.0 PSYCHOPHARMACOLOGICAL DRUGS ADVISORY COMMITTEE (PDAC) MEETING

As noted, we took this supplement to the Psychopharmacological Drugs Advisory Committee (PDAC) on 10-8-99. The committee voted 6 to 1 in favor of Zoloft being shown to be effective for PTSD, and 7 to 0 in favor of it being shown to be safe for treatment of this new indication.

9.0 DSI INSPECTIONS

Although DSI does not routinely inspect investigative sites for supplements, and did not in this case, none of the listed investigators for these trials was recognized as having had compliance problems in the past.

10.0 LABELING AND APPROVAL LETTER

10.1 Final Labeling Attached to Approval Package

The mutually agreed upon final labeling is attached to the approval letter.

10.2 Foreign Labeling

Zoloft is not approved for PTSD anywhere at this time.

10.3 Approval Letter

The approval letter includes final labeling and requests for additional studies of Zoloft in PTSD, in particular, (1) a report on study 703, the completed relapse prevention trial, and (2) studies of PTSD in pediatric populations with this disorder.

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 treatment of PTSD. I recommend that we issue the attached approval letter with the mutually agreed upon final labeling and the above noted requests.

APPEARS THIS WAY
ON ORIGINAL

cc:

Orig NDA 19-839/S-026

HFD-120

HFD-120/TLaughren/RKatz/EHearst/AMHomonnay

DOC: MEMZPTSD.API

<p align="center">Table 1 Summary of Efficacy Results (LOCF) for 4 Studies of Sertraline in PTSD</p>					
Study	Variable	Baseline ¹	Sertraline ²	Placebo ²	P-Value ³
640	CAPS-2	74	-33.0	-26.2	0.043
	IES	39	-19.2	-14.1	0.018
	CGI-S	4.6	-1.3	-1.0	0.037
	CGI-I	-	2.3	2.8	0.014
641	CAPS-2	73	-13.1	-15.4	0.587
	IES	42	-8.7	-8.1	0.799
	CGI-S	4.6	-0.5	-0.6	0.468
	CGI-I	-	3.0	3.0	0.879
671	CAPS-2	76	-33.0	-23.2	0.016
	IES	37	-16.2	-12.1	0.071
	CGI-S	4.6	-1.2	-0.8	0.012
	CGI-I	-	2.5	3.0	0.016
682	CAPS-2	72	-27.4	-27.9	0.896
	IES	39	-13.6	-19.7	0.017
	CGI-S	4.5	-1.0	-0.9	0.798
	CGI-I	-	2.6	2.6	0.891

- 1 Mean score at baseline (both groups combined) for CAPS-2, IES, and CGI-S.
- 2 Mean change from baseline to endpoint for CAPS-2, IES, and CGI-S; mean raw score at endpoint for CGI-I.
- 3 Sertraline vs Placebo, 2-sided.

APPEARS THIS WAY
ON ORIGINAL