

MOR

REVIEW AND EVALUATION OF CLINICAL DATA

NDA: 20-990

SPONSOR: PFIZER, INC.

DRUG: ZOLOFT (sertraline HCl) ORAL CONCENTRATE

MATERIAL SUBMITTED: RESPONSE TO APPROVABLE LETTER

DATE SUBMITTED: 6/4/99

DATE RECEIVED: 6/7/99

MEDICAL REVIEWER: ANDREW MOSHOLDER, M.D.

Background: On April 15 1999, this Division issued an approvable letter for Zoloft concentrate (sertraline 20 mg per mL). This submission is the sponsor's response to the approvable letter. The sponsor has made a number of counter proposals for the labeling, which I will summarize here with my comments. The submission also contains chemistry information, which will be reviewed by the Chemistry review team.

Sponsor's labeling and counterproposals:

Under Description, the sponsor has added the percentage alcohol content, 12 percent, as requested in the approvable letter.

Under Clinical Pharmacology: the sponsor has slightly modified the bioavailability description concerning the concentrate. These changes will be reviewed by HFD-860.

Under Contraindications: here the sponsor has separated the existing MAOI contraindication from the new contraindication for concomitant Antabuse, which applies only to the oral concentrate. I see no difficulty with this.

The sponsor also added a statement that the predicted concentration of alcohol is one percent or less after the concentrate is diluted in appropriate liquid. I do not see the rationale for such a statement, since it is the amount of ethanol ingested, not the concentration, that is relevant. The sponsor has also omitted the term "high" with respect to the alcohol content, to which I have no objection as long as the contraindication is clear.

Under Information for patients: the sponsor has again omitted the term "high" with respect to the alcohol content, and added the predicted alcohol concentration after dilution. My previous comments on these changes apply here also.

The sponsor has now omitted the advisory about the dropper containing latex, a cautionary statement directed at individuals with latex allergy. I believe this statement should be restored. There is growing recognition of the public health importance of latex sensitivity, and allergic reactions have been reported to a variety of medical products and household items (for review see Landwehr and Boguliewicz, *J Pediatr* 1996;128(3):305-12). The sponsor's argument is that the existing regulation under 21 CFR 801.437 requiring labeling for devices that contain latex does not apply. Although it may be true that this specific regulation does not apply, in my opinion there would seem to be every reason to inform patients (or those dispensing the medication) that the dropper assembly contains latex, given the high prevalence of latex allergy.

Under Drug Interactions, for the sumatriptan drug interaction the sponsor has added citalopram to the list of SSRIs, and I have no objection to this.

Under Adverse Reactions, the sponsor has taken this opportunity to correct some errors in the incidence of the adverse dropouts for the panic disorder clinical trials. Table 3 listing the most common adverse events associated with dropout has been revised to reflect correct incidence figures in the Panic Disorder column. The sponsor supplied an accompanying appendix table at the end of this submission to document the revisions. The new figures appear to be correct based on the appendix table, with the exception of nervousness, for which the incidence of dropout should be 2% instead of 0%.

Also under Adverse Reactions, the sponsor has included the requested language concerning sexual dysfunction, with a few minor changes. With respect to ejaculation failure, the sponsor has added a notation that this was primarily delayed ejaculation. I have no reason to dispute this, although no supporting information was provided. The sponsor has also added a statement that untowards sexual experiences were generally well tolerated, apparently because relatively few patients discontinued. In my view, the conclusion that sexual dysfunction was well tolerated is a speculative judgement and should be deleted. Also, the sponsor has slightly modified the statement concerning priapism to reflect the fact that priapism has been reported with all SSRIs. I have no objection to this, especially in view of the recent evaluation of priapism by OPDRA (see memo dated 7/23/99).

Under Overdosage, the sponsor has incorporated the requested labeling changes.

Under Dosage and Administration, the sponsor has deleted the previous statement concerning latex sensitivity, and in my opinion this should be restored, as noted above. The sponsor has also added the description of the predicted alcohol concentration after dilution, and as before, I do not think this is necessary.

Conclusions and Recommendations: With the few exceptions noted above, I believe that the sponsor's labeling is appropriate, and from a clinical standpoint, the application may be approved. The major points where I differ with the sponsor are that the latex warning should be restored, and the statement that sexual dysfunctions were well tolerated should be deleted.

IS/ 8/11/99

Andrew Mosholder, M.D.
Medical Officer, HFD-120

8-11-99

I agree with above recommendations.
Let's try to resolve differences
in labeling by preparing
a counter-proposal, with
proposed comments explaining our
objections language & plan on copying
to sponsor.

NDA 20-990
Div file
HFD-120 Laughren, David, Mosholder, Klein

IS/

MEMORANDUM

DATE: April 15, 1999

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

TO: File, NDA 20-990

SUBJECT: Approvable Memo for NDA 20-990, for Zoloft Oral Solution

This NDA for Zoloft oral concentrate was submitted on 4/15/98 by Pfizer Pharmaceuticals. A bioequivalence study comparing the performance of the concentrate to the approved immediate release tablets serves as the basis for concluding that the concentrate is approvable.

There is one point, however, that I believe needs to be addressed for the record.

In a review dated 10/13/98, Dr. Jacqueline A. O'Shaughnessy of the Division of Scientific Investigations includes the following comment in her conclusions:

"It is our opinion that conclusions drawn from Protocol 050-028 [the definitive bioequivalence study] should take into consideration that the accuracy of the reported sertraline concentrations could not be confirmed since the firm failed to (1) document the preparation of standards and QCs and (2) verify the amount of sertraline weighed for the preparation of stock solutions."

Because this appeared to call into question the validity of the study on which any action would be based, I phoned Dr. O'Shaughnessy and asked for further clarification about the nature of her concerns.

In an e-mail to me dated 4/9/99, she noted that while the accuracy of the plasma concentrations could not be confirmed (based on the lack of documentation of the preparation of the standards), in her view this would not effect the comparisons of plasma levels between concentrate and standard, given that whatever inaccuracies might exist with regard to a determination of absolute plasma levels would "cancel out" each other.

I discussed this with Dr. Seevers, chemistry team leader. He thought this seemed reasonable, as long as the plasma levels from both the concentrate and tablet periods were analyzed based on a run calibrated with the same standard (standard from the same lot).

In a fax dated 4/14/99 from the sponsor, we have received assurance that the standard for all assays was prepared from the same lot, and that all study samples were analyzed between 8/3/94-8/22/94. I have discussed this with Dr. Seevers, who feels that these data

are reassuring, and that the results Protocol 050-028 can be considered reliable. I agree, as does Dr. Sahajwalla, of OCPB.

Accordingly, I will issue the attached Approvable letter.

/S/

Russell Katz, M.D.

APPROVED THIS WAY
ON ORIGINAL

Cc:
NDA 20-990
HFD-120
HFD-120/Katz/Laughren/Seevers/Mosholder/Klein/David
HFD-860/Sahajwalla

APPROVED THIS WAY
ON ORIGINAL

REVIEW AND EVALUATION OF CLINICAL DATA

NDA: 20-990

SPONSOR: PFIZER

DRUG: Sertraline HCl (Zoloft) Oral Solution 20 mg/ml

MATERIAL SUBMITTED: ORIGINAL NDA SUBMISSION

DATE SUBMITTED: 4/15/98

USER FEE DUE DATE: 4/16/99 -

MEDICAL OFFICER: Andrew Mosholder, M.D.

1. Background

Zoloft is marketed as 25, 50, and 100 mg tablets. The current labeling recommends a maximum dose of 200 mg daily, giving once a day. The smallest recommended dose is 25 mg, for pediatric patients and initial treatment in panic disorder patients.

This NDA provides for sertraline oral concentrate 20 mg per mL. According to the draft labeling, the concentrate should be diluted in a suitable beverage prior to administration. It will be supplied in bottles of 60 mL, containing 1200 mg of sertraline. The solution contains 12 percent ethanol, as well as glycerin, menthol, and BHT. I will discuss implications of the alcohol content below.

In this application, the sponsor has included the relevant chemistry, manufacturing, and controls information, along with reports from three in vivo bioequivalence and bioavailability studies.

2. Labeling

The sponsor's draft labeling contains additions under the Description, Dosage and Administration and How Supplied sections. Because the dropper contains

I note that the label on the box and on the bottle states that the solution contains 12 percent alcohol, but that the ethanol content is not stated in the sponsor's draft labeling except under Dosage and Administration. Please refer to the Chemistry review by Dr. Klein for additional comments on the labeling. Dr. Klein notes that this concentrate is classified as a flammable liquid.

2. In vivo studies

Please refer to the biopharmaceutics review by Dr. Sekar for full details. I will comment here on the safety findings.

Study 050-027: This was an open label crossover pharmacokinetic study, comparing the 100 mg marketed tablet to 100 mg as the concentrate, in single oral doses. A total of 12 healthy subjects participated. Subjects received the drug fasted. Pharmacokinetic results showed that the point estimate for AUC and C_{max} were somewhat higher for the liquid than for the tablet, with the difference in C_{max} being statistically significant. The confidence limit values did not permit the formulations to be declared bioequivalent. With respect to safety findings, no subjects discontinued the study due to adverse events, and there were no serious adverse events. The overall pattern of the adverse events did not

differ markedly between two formulations, although with such a small sample these data are inconclusive.

Study 0500-028: This was a single dose, open label, crossover study comparing 100 mg of sertraline administered as the marketed tablet or as solution; essentially, this was a reproduction of protocol 050-027 with a larger sample (n=20 healthy adult volunteers). Note that after auditing by the Division of Scientific Investigations (DSI), data for some subjects was deemed unacceptable, resulting in a usable sample of 16 subjects. The pharmacokinetic results, based on the smaller sample of 16 subjects, showed that the mean AUC was 818 ng.h/ml with the solution and 713 ng.hr/ml for the tablet, a difference which was statistically significant. Similarly, the mean Cmax was 34 ng per ml with the solution and 28 ng per ml with the tablet, a difference which was also statistically significant. The confidence limits derived from these data did not permit the two formulations to be declared bioequivalent by the usual criteria. In respect to safety findings, no subjects discontinued the study due to adverse events, and there were no serious adverse events. Side effects which occurred in more than 2 subjects included nausea, diarrhea, nervousness, vomiting, dizziness, and headache. The incidence of adverse events by treatment appeared similar with the exception of nervousness, reported by 8 subjects with the solution and 4 with the tablet. The small sample size notwithstanding, there were no striking differences in the adverse event profiles by treatment.

Study 050-029: This was a three way crossover study comparing the bioavailability of 100 mg sertraline given as the concentrate with the subjects fasting, as the concentrate with the subjects fed, and as a capsule not marketed in the U.S. with the subjects fasted. Twenty subjects entered the study. Two subjects discontinued for adverse events after the concentrate-fed condition (one for vomiting and one for a vasovagal episode). Two other subjects experienced vasovagal episodes but did not discontinue (the specific treatment associated with these events was not reported). The analysis excluding data questioned by DSI showed a slight increase in AUC in the fed state, which did not reach statistical significance.

Conclusions regarding the in vivo studies:

1. Recognizing that these were small studies involving only single doses, there was no data to suggest that the oral solution is associated with a unique pattern of adverse drug reactions.
2. The modest differences in Cmax and AUC noted above, while not permitting the oral concentrate and the solution to be considered bioequivalent by the usual rules, are not likely to be of clinical consequence given the wide therapeutic index for sertraline, and the fact that there is considerable inter-individual variation in pharmacokinetic parameters. No dosage adjustment is required to account for the modest increase in bioavailability with the liquid over the tablets.

3. Ethanol content

The fact that this formulation is 12% ethanol has certain clinical ramifications. First, the concentrate should be contraindicated with disulfiram (Antabuse). Secondly, it may be asked if this concentration of ethanol is excessive, being roughly equivalent to 24 proof for an alcoholic beverage.

Under 21 CFR 328.10, over the counter drug products may not contain more than 5% ethanol if labeled for use by pediatric patients aged 6-12 (as Zoloft is). The maximum content for adult drug products sold over the counter is 10%. It is my impression, however, that there are no corresponding limits set by the agency for ethanol content in prescription drug products.

A report by the Committee on Drugs of the American Academy of Pediatrics (Pediatrics 1984: 73(3), 405-407, provides some guidelines and a method for estimating the achievable blood ethanol concentration in pediatric patients receiving formulations containing ethanol. According to their estimates, for a formulation containing 12.5% ethanol (approximating this drug product), a potentially lethal ethanol dose for a toddler weighing 12 kg would be 365 ml. This would be roughly six bottles of Zoloft concentrate (equivalent to 7200 mg of sertraline). Thus acute ethanol toxicity is not likely to be a great concern should the drug product get into the hands of a very young child, according to this estimation.

Also, according to the same source, the dose of drug product containing 12.5 % ethanol required to produce a blood alcohol content of 25 mg/dL would be 32 ml for a 6 year old child weighing 21 kg.¹ (In these units, 80 or 100 mg/dL is frequently the legal definition of intoxication).

Thus, the ethanol content of this drug product is not likely to represent a hazard clinically.

4. Additional chemistry issues

The sponsor has been sent a letter regarding a variety of chemistry deficiencies (dated 2/11/99). Among these are a request for clarification that the closures are child resistant and a request for more information on the concentrate's apparent reactivity when in contact with stainless steel.

APPEAR THIS WAY
ON ORIGINAL

¹ The following is a more complete method for estimating these effects, using the method from the same source cited previously.

Assuming that a lethal dose of ethanol is 3 g/kg or 3.8 ml/kg, a lethal dose for a 12 kg child would be 12 kg x 3.8 ml/kg = 45.6 ml. For a 12% solution,
 $0.12x = 45.6 \text{ ml}$
 $x = 380 \text{ ml}$

There is also the issue of what blood ethanol concentrations may be anticipated for a child using this drug product. Assuming a worse case scenario, consider a child of 6 years old taking the maximum dose of 200 mg/d (=10 ml/d). Taking 21 kg as the weight of a 6 year old, and assuming complete absorption and no clearance to estimate the C_{max}, the expected C_{max} may be estimated from the volume of distribution for ethanol (V_d=0.6 L/kg). Thus, with the density of ethanol = 0.789 g/ml,

$10 \text{ ml} \times 0.12 = 1.2 \text{ ml ethanol} \times (0.789 \text{ g/ml}) = 947 \text{ mg ethanol}$
 $V_d = 0.6 \text{ L/kg} \times 21 \text{ kg} = 12.6 \text{ L}$
 $C_{\text{max}} = 945 \text{ mg}/12.6 \text{ L} = 75 \text{ mg/L} = 7.5 \text{ mg/dL}$

Conclusions and Recommendations:

1. This NDA may be approved from a clinical standpoint. The differences in pharmacokinetic parameters between the concentrate and the tablet formulations, while beyond the limits for bioequivalence, are not likely to have a clinical impact.
2. The labeling should state that the alcohol content is 12% not only under Dosage and Administration, but also under Description and How Supplied.
3. The labeling should indicate that Antabuse is contraindicated with Zoloft concentrate. This should be under Contraindications and also under Dosage and Administration.

/S/

3/5/99

Andrew Mosholder, M.D.
Medical Officer, HFD-120

APPROVED BY
ON ORIGINAL

NDA 20-990
Div file
HFD-120 Laughren/David/Mosholder/SeEVERS/Klein
HFD-860 Sahajwalla/Sekar

3-8-99

I agree that there are no clinical concerns that would preclude the approvability of this NDA.

/S/