CENTER FOR DRUG EVALUATION AND RESEARCH

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

APPROVABLE LETTER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 19-839/S-035
NDA 20-990/S-003

Pfizer Pharmaceuticals, Inc.
Attention: Andy Clair
Regulatory Affairs Division
235 East 42nd Street
New York, NY 10017-5755

Dear Mr. Clair:

Please refer to your supplemental new drug applications dated May 31, 2000, received June 1, 2000, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Zoloft® (sertraline HCl) Tablets and Zoloft® (sertraline HCl) Oral Concentrate.

We acknowledge receipt of your submissions dated August 17 and September 22, 2000; and February 16, 2001.

These supplemental new drug applications provides for the use of Zoloft® (sertraline HCl) Tablets and Zoloft® (sertraline HCl) Oral Concentrate for the long-term treatment of posttraumatic stress disorder.

We have completed the review of these applications, as amended, and they are approvable. Before these applications may be approved, however, it will be necessary for you to address the following:

LABELING

We have made revisions to the 3 sections of labeling for which you have proposed language. Our proposed revisions for these 3 sections are as follows:

Under **CLINICAL PHARMACOLOGY, Clinical Trials, PTSD:**

[The following paragraph should be inserted as the fourth and final paragraph in this subsection.]

In a longer-term study, patients meeting DSM-III-R criteria for PTSD who had responded during a 24-week open trial on Zoloft 50-200 mg/day (n=96) were randomized to continuation of Zoloft or to placebo for up to 28 weeks of observation for relapse. Response during the open phase was defined as a CGI-Improvement score of 1 (very much improved) or 2 (much improved), and a decrease in the CAPS-2 score of > 30% compared to baseline. Relapse during the double-blind phase was defined as the following conditions being met on two consecutive visits: (1) CGI-I $\geq$ 3; (2) CAPS-2 score increased by $\geq$ 30% and by $\geq$ 15 points relative to baseline; and (3) worsening of the patient's condition in the investigator's judgement. Patients receiving continued Zoloft treatment experienced significantly lower relapse rates over the subsequent 28 weeks compared to those receiving placebo. This pattern was demonstrated in both male and female subjects.

Under **INDICATIONS AND USAGE, PTSD:**

[The following paragraph should be inserted as the fourth and final paragraph in this subsection.]

The efficacy of Zoloft in maintaining a response in patients with PTSD for up to 28 weeks following 24 weeks of initial open-label treatment was demonstrated in a placebo-controlled trial. Nevertheless, the physician who elects to use Zoloft for extended periods should periodically re-evaluate the long-term usefulness of the drug for the individual patient (see Clinical Trials under Clinical Pharmacology).

Under **DOSAGE AND ADMINISTRATION, Maintenance Treatment:**

[The following three paragraphs should be inserted to replace the current language in this subsection. We have made several changes to bring this subsection into consistency with what has now become standard language.]

Depression It is generally agreed that acute episodes of depression require several months or longer of sustained pharmacological therapy beyond response to the acute episode. Systematic evaluation of Zoloft has demonstrated that its antidepressant efficacy is maintained for periods of up to 44 weeks following 8 weeks of initial treatment at a dose of 50-200 mg/day. (see Clinical Trials under Clinical Pharmacology). Based on these limited data, it is unknown whether or not the dose of Zoloft needed for maintenance treatment is identical to the dose needed to achieve an initial response. Patients should be periodically reassessed to determine the need for maintenance treatment and the appropriate dose for such treatment.

Posttraumatic Stress Disorder It is generally agreed that PTSD requires several months or longer of sustained pharmacological therapy beyond response to initial treatment. Systematic evaluation of Zoloft has demonstrated that its efficacy in PTSD is maintained for periods of up to 28 weeks following 24 weeks of initial treatment at a dose of 50-200 mg/day (see Clinical Trials under Clinical Pharmacology). Based on these limited data, it is unknown whether or not the dose of Zoloft needed for maintenance treatment is identical to the dose needed to achieve an initial response. Patients should be periodically reassessed to determine the need for maintenance treatment and the appropriate dose for such treatment.

Obsessive-Compulsive Disorder and Panic Disorder Although the efficacy of Zoloft beyond 10-12 weeks of dosing for OCD and Panic Disorder has not been systematically demonstrated in controlled trials, both are chronic conditions, and it is reasonable to consider continuation of a responding patient. Dosage adjustments may be needed to maintain the patient on the lowest effective dosage and patients should be periodically reassessed to determine the need for continued treatment.

In addition, all previous revisions as reflected in the most recently approved labeling must be included. To facilitate review of your submission, please provide a highlighted or marked-up copy that shows the changes that are being made.

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

Within 10 days after the date of this letter, you are required to amend the supplemental applications, notify us of your intent to file amendments, or follow one of your other options under 21 CFR 314.110. In the absence of any such action FDA may proceed to withdraw the applications. Any amendment should respond to all the deficiencies listed. We will not process a partial reply as a major amendment nor will the review clock be reactivated until all deficiencies have been addressed.

These products may be considered to be misbranded under the Federal Food, Drug, and Cosmetic Act if they are marketed with these changes prior to approval of these supplemental applications.

If you should have any questions, please call Ms. Anna Marie Homonnay, R.Ph., Regulatory Project Manager, at (301) 594-5535.

Sincerely,

{See appended electronic signature page}

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

APPEARS THIS WAY
ON ORIGINAL

/s/

Russell Katz
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CENTER FOR DRUG EVALUATION AND RESEARCH

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

APPROVAL LETTER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
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Pfizer Pharmaceuticals, Inc.
Attention: Andrew Clair, Ph.D.
Regulatory Affairs Division
235 East 42nd Street
New York, NY 10017-5755

Dear Dr. Clair:

Please refer to your supplemental new drug applications dated May 31, 2000, received June 1, 2000, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Zoloft® (sertraline hydrochloride) Tablets and Oral Concentrate.

We acknowledge receipt of your submission dated May 25, 2001 (draft labeling). Your submission of May 25, 2001 constituted a complete response to our March 22, 2001 action letter.

These supplemental new drug applications provide for the use of Zoloft® (sertraline hydrochloride) for the long-term treatment of posttraumatic stress disorder.

We have completed the review of these supplemental applications, as amended, and have concluded that adequate information has been presented to demonstrate that the drug products are safe and effective for use as recommended in the agreed upon labeling text dated May 25, 2001. Accordingly, these supplemental applications are approved effective on the date of this letter.

The final printed labeling (FPL) must be identical, to the submitted draft labeling (package insert submitted May 25, 2001).

Please submit the copies of final printed labeling (FPL) electronically to each application according to the guidance for industry titled *Providing Regulatory Submissions in Electronic Format - NDA* (January 1999). Alternatively, you may submit 20 paper copies of the FPL as soon as it is available but no more than 30 days after it is printed. Please individually mount ten of the copies on heavy-weight paper or similar material. For administrative purposes, these submissions should be designated "FPL for approved supplement NDA 19-839/S-035, 20-990/S-003." Approval of these submissions by FDA is not required before the labeling is used.

In addition, please submit three copies of the introductory promotional materials that you propose to use for these products. 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 materials and the package inserts directly to:

Division of Drug Marketing, Advertising, and Communications, HFD-42
Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20857

If a letter communicating important information about this drug product (i.e., a "Dear Health Care Professional" letter) is issued to physicians and others responsible for patient care, we request that you submit a copy of the letter to this NDA and a copy to the following address:

MEDWATCH, HF-2
FDA
5600 Fishers Lane
Rockville, MD 20857

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 should have any questions, please call Ms. Anna Marie Homonnay, R.Ph., Regulatory Health Project Manager, at (301) 594-5535.

Sincerely,

{See appended electronic signature page}

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

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Russell Katz
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APPEARS THIS WAY
ON ORIGINAL