CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 20-151/S-017/S-018
20-699/S-015/S-016

APPROVABLE LETTER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 20-151/S-017, S-018
NDA 20-699/S-015, S-016

Wyeth-Ayerst Research
Attention: Kenneth R. Bonk
Associate Director
Worldwide Regulatory Affairs
P.O. Box 8299
Philadelphia, PA 19101-8299

Dear Mr. Bonk:

Please refer to your supplemental new drug applications dated May 5, 2000, May 18, 2000, and May 19, 2000, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Effexor Tablets and Effexor XR Capsules.

These supplemental new drug applications propose the use of Effexor Tablets and Effexor XR Capsules for the prevention of recurrence of depression and for the prevention of relapse of depression.

We have completed the review of these applications, and they are approvable. Before these applications may be approved, however, it will be necessary for you to submit final printed labeling revised as follows:

Under **CLINICAL PHARMACOLOGY, Clinical Trials,**

> [The following should be inserted as the final two paragraphs in this subsection (for Effexor XR, these would be the final two paragraphs under the Depression subheading). While we appreciate the importance of trying to better characterize the course of depressive illness and to develop a consistent language for describing improvement and worsening with treatment, we do not feel that the field has reached a level of consensus in this effort to justify incorporating your proposed distinctions into labeling at this time. In particular, we do not feel that there is yet sufficient agreement on the distinction between continuation and maintenance treatment, and between relapse and recurrence, to introduce these concepts into labeling. In terms of describing these longer-term trials and their outcomes in labeling, we feel the important issues are how long patients were treated during the initial open treatment periods during which response criteria were met and how long patients were observed for relapse during the double blind phase. Until there is greater consensus, we feel it is most useful to keep to the facts of each trial, using concepts that can be quantitatively defined for each trial. These concepts include response and relapse, where response is defined as the criteria that must be met for entry into the phase of observation for relapse and relapse is defined as the criteria

for worsening to declare that a patient is no longer a responder. We prefer at this time to use the term maintenance treatment to characterize all sustained treatment beyond the period of acute treatment and stabilization, i.e., beyond the point at which patients are randomized for observation of relapse.]

In one longer-term study, outpatients meeting DSM-IV criteria for major depressive disorder who had responded during an 8-week open trial on Effexor XR (75, 150, or 225 mg, qAM) were randomized to continuation of their same Effexor XR dose or to placebo, for up to 26 weeks of observation for relapse. Response during the open phase was defined as a CGI Severity score of ≤ 3 and a HAMD-21 total score of ≤ 10 at the day 56 evaluation. Relapse during the double-blind phase was defined as follows: (1) a reappearance of major depressive disorder as defined by DSM-IV criteria and a CGI Severity score of ≥ 4 (moderately ill), or (2) 2 consecutive CGI Severity scores of ≥ 4, or (3) a final CGI Severity score of ≥ 4 for any patient who withdrew from the study for any reason. Patients receiving continued Effexor XR treatment experienced significantly lower relapse rates over the subsequent 26 weeks compared to those receiving placebo.

In a second longer-term trial, outpatients meeting DSM-III-R criteria for major depressive disorder, recurrent type, who had responded (HAMD-21 total score ≤ 12 at the day 56 evaluation) and continued to be improved [defined as the following criteria being met for days 56 through 180: (1) no HAMD-21 total score ≥ 20, (2) no more than 2 HAMD-21 total scores > 10, and (3) no single CGI severity score ≥ 4 (moderately ill)] during an initial 26 weeks of treatment on Effexor (100-200 mg/day, on a bid schedule) were randomized to continuation of their same Effexor dose or to placebo. The follow-up period to observe patients for relapse, defined as a CGI Severity score of ≥ 4, was for up to 52 weeks. Patients receiving continued Effexor treatment experienced significantly lower relapse rates over the subsequent 52 weeks compared to those receiving placebo.

Under **INDICATIONS AND USAGE**

[Since we disagree with the distinction between continuation and maintenance treatment, and between relapse and recurrence, we have not made your proposed changes in this section. Rather, we ask that you add the following paragraph as a replacement to the currently approved last paragraph in this section. For Effexor XR, this will be the last paragraph under the Depression subheading.]

The efficacy of Effexor XR in maintaining an antidepressant response for up to 26 weeks following 8 weeks of acute treatment was demonstrated in a placebo-controlled trial. The efficacy of Effexor in maintaining an antidepressant response in patients with recurrent depression who had responded and continued to be improved during an initial 26 weeks of treatment and were then followed for a period of up to 52 weeks was demonstrated in a second placebo-controlled tria. ——————— Nevertheless, the physician who elects to use Effexor /Effexor XR for extended periods should periodically re-evaluate the long-term usefulness of the drug for the individual patient.

Under **DOSAGE AND ADMINISTRATION, Maintenance Treatment**

[Since we disagree with the distinction between continuation and maintenance treatment, we have not made most of your proposed changes in this section. Rather, we have simply added a brief description of the two longer-term trials.]

Maintenance Treatment

It is generally agreed that acute episodes of depression require several months or longer of sustained pharmacological therapy beyond response to the acute episode. In one study, in which patients responding during 8 weeks of acute treatment with Effexor XR were assigned randomly to placebo or to the same dose of Effexor XR (75, 150, or 225 mg/day, qAM) during 26 weeks of maintenance treatment as they had received during the acute stabilization phase, longer-term efficacy was demonstrated. A second longer-term study has demonstrated the efficacy of Effexor in maintaining an antidepressant response in patients with recurrent depression who had responded and continued to be improved during an initial 26 weeks of treatment and were then randomly assigned to placebo or to Effexor for a period of up to 52 weeks on the same dose (100-200 mg/day, on a bid schedule)(see Clinical Trials under Clinical Pharmacology). Based on these limited data, it is not known whether or not the dose of Effexor / Effexor XR 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.

Under **ADVERSE REACTIONS, Other Events Observed during the Premarketing Evaluation of Venlafaxine**

[We do not object to the addition of the new terms you have proposed.]

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.

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 (to each application), ten of which individually mounted on heavy weight paper or similar material.

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 have any questions, call Melaine Shin, R.Ph., Regulatory Management Officer, at (301) 594-5793.

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

ATTACHMENT 13

64 page(s) of revised draft labeling has been redacted from this portion of the review.