DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

TRANSMITTED BY FACSIMILE

Tracy Rockney
Director, Worldwide Regulatory Affairs
Wyeth Pharmaceuticals
PO Box 8299
Philadelphia, PA 19101

RE: NDA # 20-699, 20-151
Effexor® XR (venlafaxine hydrochloride) Extended Release Capsules
Effexor® (venlafaxine hydrochloride) Tablets
MACMIS # 11135

Dear Ms. Rockney:

The Division of Drug Marketing, Advertising, and Communications (DDMAC) has reviewed a patient case study mailer (ID # 82263-00), a journal advertisement (ID # 100812-01), a reprint carrier (ID # 82210-00), and a radio advertisement (ID # 103488-00) for Effexor® XR (venlafaxine hydrochloride) Extended Release Capsules and Effexor® (venlafaxine hydrochloride) Tablets submitted by Wyeth Pharmaceuticals (Wyeth) under cover of Form FDA 2253. These materials are false or misleading with respect to the effectiveness and safety of Effexor XR in violation of the Federal Food, Drug, and Cosmetic Act (Act) (21 U.S.C. 352(a) & (n)) and FDA implementing regulations (21 CFR 202.1(e)(1) & (e)(3)(ii)).

Background

According to the approved product labeling (PI), Effexor XR is indicated for the treatment of (among other things) major depressive disorder. The PI states, further:

> The efficacy of Effexor XR in the treatment of major depressive disorder was established in 8- and 12-week controlled trials of outpatients whose diagnoses corresponded most closely to the DSM-III-R or DSM-IV category of major depressive disorder (see **Clinical Trials**).
>
> A major depressive episode (DSM-IV) implies a prominent and relatively persistent (nearly every day for at least 2 weeks) depressed mood or the loss of interest or pleasure in nearly all activities, representing a change from previous functioning, and includes the presence of at least five of the following nine symptoms during the same two-week period: depressed mood, markedly diminished interest or pleasure in usual activities, significant change in weight and/or appetite, insomnia or hypersomnia, psychomotor agitation or retardation,

> increased fatigue, feelings of guilt or worthlessness, slowed thinking or impaired concentration, a suicide attempt or suicidal ideation.

The PI also describes the following commonly observed adverse events for Effexor XR:

> Note in particular the following adverse events that occurred in at least 5% of the Effexor XR patients and at a rate at least twice that of the placebo group for all placebo-controlled trials for the major depressive disorder (Table 3): Abnormal ejaculation, gastrointestinal complaints (nausea, dry mouth, and anorexia), CNS complaints (dizziness, somnolence, and abnormal dreams), and sweating. In the two U.S. placebo-controlled trials, the following additional events occurred in at least 5% of Effexor XR-treated patients (n=192) and at a rate at least twice that of the placebo group: Abnormalities of sexual function (impotence in men, anorgasmia in women, and libido decreased), gastrointestinal complaints (constipation and flatulence), CNS complaints (insomnia, nervousness, and tremor), problems of special senses (abnormal vision), cardiovascular effects (hypertension and vasodilation), and yawning.

EFFEXOR XR is an SNRI (serotonin and norepinephrine reuptake inhibitor). According to the PI, preclinical studies have shown that venlafaxine and its active metabolite, O-desmethylvenlafaxine (ODV), are potent inhibitors of neuronal serotonin and norepinephrine reuptake and weak inhibitors of dopamine reuptake. Several other FDA-approved prescription drugs, many of which are indicated in the treatment of depression, also inhibit neuronal serotonin. These drugs, which include citalopram hydrochloride, paroxetine hydrochloride, fluoxetine hydrochloride, and sertraline hydrochloride, are commonly referred to as selective serotonin reuptake inhibitors, or SSRIs.

Unsubstantiated Superiority Claims

The mailer, the journal advertisement, and the reprint carrier include statements comparing Effexor XR to SSRIs. For example:

- "EFFEXOR XR / EFFEXOR helped approximately 1/3 more patients achieve remission of symptoms" (mailer)
- "[A]pproximately 1/3 more patients got their life back" (journal advertisement)
- "Significant Efficacy of EFFEXOR® XR (venlafaxine HCl) vs. SSRIs" (reprint carrier)
- "Approximately 1/3 more patients reached remission with Effexor XR / Effexor" (reprint carrier)

These materials thus claim that Effexor XR/Effexor is more effective than SSRIs when this has not been demonstrated by substantial evidence or substantial clinical experience. The meta-analysis cited in the materials is not sufficient to support this claim, for the following reasons:

1. The meta-analysis does not include studies comparing Effexor XR to citalopram or sertraline, and only two studies used paroxetine, one of which showed no difference from Effexor XR. Furthermore, the analysis included a study comparing venlafaxine to fluvoxamine, a drug that has not been demonstrated to be effective in depression. Thus, the meta-analysis is essentially a

comparison of venlafaxine to fluoxetine. It, therefore, fails to support the claim that Effexor XR is superior to all SSRIs.

2. The meta-analysis is potentially biased, because none of the studies excluded patients who had failed to respond to SSRIs. Thus, it is possible that any advantage observed for venlafaxine was driven by a subgroup of patients who had previously failed trials of SSRIs. This limitation was noted by the authors of the meta-analysis, and is widely recognized (e.g., ICH E-10: *Choice of Control Group in Clinical Trials*).

3. The authors obtained the results of their meta-analysis through multiple analyses of the data from the underlying trials. To be significant, the results must be of a greater statistical power, which was not met.

For these reasons, the cited meta-analysis does not constitute substantial evidence or provide substantial clinical experience demonstrating that Effexor XR/Effexor is more effective than SSRIs, as the materials claim. FDA is not aware of any other data or information to support the superiority claim.

Other Misleading Claims

The radio advertisement fails to include specific indications for use of the drug for purposes claimed in the advertisement (21 CFR 202.1(e)(3)(ii)). Specifically, the advertisement fails to communicate important characteristics necessary to distinguish between major depressive disorder and variations of normal daily functioning.

The advertisement begins with an announcer asking the rhetorical questions: "Hey you, listening to the radio…how're you feeling these days? Okay? Not Bad? Come on, is that where you want to be? When was the last time you did something you once looked forward to doing? You know, symptoms of depression could be holding you back." The follow-up announcer statements fail to clarify characteristics of depression that profoundly affect daily functioning, including depressed mood, markedly diminished interest or pleasure in usual activities, significant change in weight or appetite, insomnia or hypersomnia, feelings of guilt or worthlessness and suicidal ideation.

The broad questions in the radio advertisement followed by the statement answering "You know, symptoms of depression could be holding you back" combine to suggest that the illness of depression can be equated with feelings of low energy or lack of interest in daily activities. However, these statements fail to convey the serious nature of major depressive disorder and to sufficiently communicate the intensity of the distress suffered and to thereby distinguish "symptoms of depression" from variations of normal daily functioning. By failing to draw a clear distinction between major depressive disorder and normal periodic feelings of low interest or low energy, the advertisement broadens the indication for Effexor XR.

The radio advertisement also fails to include information relating to the major side effects and contraindications of EFFEXOR XR, as required by 21 CFR 202.1(e)(1). The advertisement includes some risk information, but does not mention other risks associated with use of the drug in treating major depressive disorder, including sexual side effects, dry mouth, abnormal dreams, and sweating.

Conclusion and Requested Action

For the reasons discussed above, the mailer, journal advertisement, reprint carrier, and radio advertisement misbrand Effexor and Effexor XR under section 502(a) and (n) of the Act, 21 U.S.C. 352(a) & (n), and FDA implementing regulations, 21 CFR 202.1(e)(1) and (e)(3)(ii).

DDMAC requests that Wyeth immediately cease the dissemination of promotional materials for Effexor and Effexor XR that contain violations the same as or similar to those described above. Please submit a written response to this letter on or before April 1, 2004, describing your intent to comply with this request, listing all promotional materials for Effexor and Effexor XR that contain violations the same as or similar to those described above, and explaining your plan for discontinuing use of such materials. Please direct your response to me at the Food and Drug Administration, Division of Drug Marketing, Advertising, and Communications, HFD-42, Room 8B-45, 5600 Fishers Lane, Rockville, Maryland 20857, facsimile at (301) 594-6771. In all future correspondence regarding this matter, please refer to MACMIS # 11135 and NDA # 20-699. We remind you that only written communications are considered official.

If you choose to disseminate revised promotional materials, DDMAC is willing to assist you in assuring that your revised materials are in compliance with applicable provisions of the Act and of FDA regulations by reviewing the revisions before dissemination. There are different ways of revising your materials to address the issues identified in this letter. Wyeth could, for example, correct the issue with unsubstantiated superiority claims by providing substantial evidence or substantial clinical experience. Alternatively, Wyeth could choose to omit the claims from promotion entirely. To address the inadequate communication of the indication in the radio advertisement, Wyeth could delete the references to symptoms that may be confused with normal functioning and either simply state that Effexor XR is indicated to treat major depression, a serious medical condition that has symptoms more severe than everyday feelings of low mood; or alternatively, include in the advertisement a description of the essential features of major depressive disorder (e.g., "A prominent and relatively persistent (every day for at least 2 weeks) depressed mood or loss of interest or pleasure in nearly all activities (as well as several other possible symptoms), to such an extent that symptoms profoundly interfere with daily functioning"). Finally, to address the risk information issue for the radio advertisement, Wyeth could revise the list of common side effects to be consistent with the most common side effects in the PI (i.e., sexual side effects, nausea, dry mouth, anorexia, dizziness, somnolence, abnormal dreams, and sweating).

The violations discussed in this letter do not necessarily constitute an exhaustive list. It is your responsibility to ensure that your promotional materials for Effexor and Effexor XR comply with each applicable requirement of the Act and FDA implementing regulations.

Sincerely,

{See appended electronic signature page}

Rebecca Williams, PharmD
Group Leader
Division of Drug Marketing,
Advertising, and Communications

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

/s/

Rebecca Williams

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