DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

TRANSMITTED BY FACSIMILE

Robert Essner
Chairman and Chief Executive Officer
Wyeth Pharmaceuticals Inc.
P.O. Box 8299
Philadelphia, PA 19101-8299

RE: NDA # 20-699
Effexor XR® (venlafaxine HCl) Tablets
MACMIS # 15394

WARNING LETTER

Dear Mr. Essner:

The Division of Drug Marketing, Advertising, and Communications (DDMAC) of the U.S. Food and Drug Administration (FDA) has reviewed a professional journal ad submitted by Wyeth Pharmaceuticals Inc. (Wyeth) for Effexor XR® (venlafaxine HCl) Tablets (Effexor XR) under cover of Form FDA-2253. The journal ad is misleading because it overstates the efficacy of Effexor XR, makes unsubstantiated superiority claims, in addition to other unsubstantiated claims, and minimizes the risks associated with the use of Effexor XR. Therefore, the piece misbrands the drug in violation of the Federal Food, Drug, and Cosmetic Act (Act), 21 U.S.C. § 352(n) and FDA implementing regulations, 21 CFR 202.1(e)(6)(i) & (6)(ii); (e)(7)(i). These violations are concerning from a public health perspective because they suggest that Effexor XR is safer and more effective than has been demonstrated.

Background

According to its FDA approved product labeling (PI)[1], Effexor XR is indicated, among other things, for the treatment of major depressive disorder.

Effexor XR use is associated with a number of serious risks. The PI for Effexor XR includes a black box warning regarding suicidality in children and

[1] The PI submitted with the promotional piece is dated August, 2006. The most recent PI is dated September 20, 2007. The current PI includes additional Warnings and Precautions, such as suicidality in young adults, anxiety and insomnia, activation of mania/hypomania, and interstitial lung disease and eosinophilic pneumonia.

adolescents. Furthermore, there are numerous warnings associated with Effexor XR use, including clinical worsening and suicide risk, the need to screen patients for bipolar disorder, the potential for interactions with monoamine oxidase inhibitors, serotonin syndrome, sustained hypertension, and mydriasis. The PI for Effexor XR also contains precautions concerning discontinuation of Effexor XR, insomnia and nervousness, changes in weight, changes in height, changes in appetite, activation of mania/hypomania, hyponatremia, seizures, abnormal bleeding, serum cholesterol elevation, and use in patients with concomitant illness.

Overstatement of Efficacy/Unsubstantiated Superiority Claim

The journal ad claims that "In an open-label study of patients who failed previous antidepressant treatment, nearly **60%** achieved remission when changed to EFFEXOR XR" (emphasis original). This claim is misleading because it suggests that Effexor XR is more effective than has been demonstrated by substantial evidence or substantial clinical experience. In addition, by implying that Effexor XR can successfully treat patients who have not responded to other antidepressant treatments, the claim misleadingly suggests that Effexor XR is superior to other antidepressant treatments when this has not been demonstrated by substantial evidence or substantial clinical experience.

The cited reference[2] is a randomized, open-label, multi-center study of 3097 subjects with two treatment arms (Effexor XR and conventional antidepressants). For several reasons, the cited reference for the claim fails to support the magnitude of the claimed 60% response rate as well as any conclusion that Effexor XR is superior to alternatives. First, the study was an open-label (non-blinded) study, which is not an appropriate study design to evaluate subjective endpoints, such as those measured by the Hamilton Rating Scale for Depression (HAM-D), because it fails to minimize potential bias. Blinding is intended to minimize potential biases resulting from differences in management, treatment, or assessment of patients, or interpretation of results that could arise as a result of subject or investigator knowledge of the assigned treatment.[3] Thus, because the study was not blinded, the comparison between Effexor XR and standard treatment is not an unbiased comparison, and the 7.8% difference (59.3% vs. 51.5% for Effexor XR and conventional antidepressants, respectively), while nominally statistically significant in this very large study (over 3000 patients), cannot be relied upon as substantial evidence or substantial clinical experience.

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[2] Baldomero EB, Ubago JG, Cercos CL, et al. Venlafaxine extended release versus conventional antidepressants in the remission of depressive disorders after previous antidepressant failure. ARGOS study. *Depress Anxiety* 2005,22:68-76.

[3] Guidance for Industry E 10 Choice of Control Group and Related Issues in Clinical Trials, at 4, http://www.fda.gov/cder/guidance/4155fnl.pdf.

Second, because placebo responses are substantial in depression studies and the study lacked a placebo group, the 60% remission rate is misleadingly high. Without a placebo control group, there is no way to determine the actual effect size of the drug. Based on experience with placebo-controlled trials, the placebo-subtracted response rate for Effexor XR would almost certainly be well below 60%.

Finally, the study provides no information about whether Effexor XR is superior to failed therapy because study subjects were not randomized to their previously failed therapy. Because improvement in depression can occur over time, subjects in the Effexor XR arm of the study who responded well to treatment might have responded just as well had they continued on the previously failed therapy.

Other claims in the ad cite no supporting references but add to the misleading implication discussed above, that Effexor XR is more effective than other antidepressants. For example, the claims:

- "Still depressed?

  ☑ Anxiety, insomnia, low energy
  ☑ Currently on an SSRI
  ☑ Still suffering,"

  "It may be time to make a change,"

- "Break the Cycle with EFFEXOR XR," and

- "The change they deserve."

contribute to the impression that patients who have failed previous antidepressant therapy can expect improvement when switching to Effexor XR when this has not been demonstrated by substantial evidence or substantial clinical experience.

Overstatement of Efficacy

The journal ad additionally overstates Effexor XR's effectiveness when it claims, "In the **PRE**VEN**T**™ study, the probability of preventing a new episode of depression was **92%** with EFFEXOR XR in maintenance year 2 vs. 55% with placebo" (emphasis original). This claim misleadingly overstates the probability of preventing a new episode of depression with Effexor XR in maintenance year 2 because it is based on a study that is inadequate to support this claim. Specifically, by selecting only patients who responded to Effexor XR to continue to the next phase of treatment, and by failing to properly account for potential recurrent depressive episodes in those patients who discontinued Effexor XR, the study design is biased in favor of Effexor XR treatment.

The study cited[4] in support of this claim is a randomized, multicenter, double-blind, study (n=1096) comparing Effexor XR with placebo. The study followed patients through 4 different time periods: a 10-week acute period, a 6-month continuation period, an initial 12-month maintenance period (maintenance year 1), and a second 12-month maintenance period (maintenance year 2). At the end of each period (acute, continuation, maintenance year 1), patients were only considered eligible for inclusion in the next period if they were still responding to the drug. Patients also dropped out of the study during each of the periods for other reasons (e.g., adverse events). At the start of each maintenance period, the remaining patients who still showed a response to Effexor XR were re-randomized to Effexor XR or placebo. Thus, of the 164 patients randomized to Effexor XR at the beginning of the maintenance phase, only 31 (19%) had completed Effexor XR treatment at the end of maintenance year 2. Because a high percentage of Effexor XR patients were either re-randomized to placebo or were discontinued from the study before entering maintenance year 2, additional new episodes of depression that may have occurred had those patients participated in maintenance year 2 on Effexor XR were not recorded. Therefore, this study is not adequate to support this claim, and this claim misleadingly overstates the efficacy of Effexor XR. We note that the flawed study design is partially presented as a footnote in the journal ad:

> A randomized, multicenter, double-blind, placebo-controlled study (N=1096). This trial included an acute, a continuation, and 2 one-year maintenance phases. At the start of each of the 2 maintenance phases, EFFEXOR XR responders were re-randomized to either EFFEXOR XR or placebo. The primary end point was time to recurrence of depression.

However, the disclosure of the study design is insufficient to mitigate the misleading presentation.

Unsubstantiated Claim/Overstatement of Efficacy/Minimization of Risk

The journal ad claims, “More than **12** years of clinical experience and over **20** million patients treated with EFFEXOR/EFFEXOR XR" (emphasis original). It is misleading to claim that over 20 million patients have been treated with Effexor/Effexor XR based on the referenced data because the calculations used do not reflect the number of “unique” patients. For example, the calculation used for total patients included patients who discontinued and then restarted therapy with Effexor/Effexor XR during the 12 year period. The claim is also misleading because it was based, in part, on an estimate of daily average consumption that used year 2001 data for years 1997 through 2000, a limitation that is acknowledged in the reference that Wyeth cited in support of the claim. Therefore, it is misleading to imply that “over 20 million” is an accurate reflection of the number of unique patients treated with Effexor/Effexor XR. Because economic models show that people use market share information, such as the number of patients treated,

[4] Data on file, Wyeth Pharmaceuticals Inc.

to infer quality,[5] falsely inflating the number of people treated with Effexor XR may mislead consumers and healthcare providers into inferring greater efficacy and safety than would be warranted by the actual numbers.

Conclusion and Requested Action

For the reasons discussed above, the promotional piece misbrands Effexor XR in violation of the Act, 21 U.S.C. § 352(n), and FDA implementing regulations, 21 CFR 202.1(e)(6)(i) & (6)(ii); (e)(7)(i).

DDMAC requests that Wyeth immediately cease the dissemination of violative promotional materials for Effexor XR such as those described above. Please submit a written response to this letter on or before December 21, 2007, stating whether you intend to comply with this request, listing all violative promotional materials for Effexor XR that are the same as, or similar to, those described above, and explaining your plan for discontinuing use of such materials. Because the violations described above are serious, we request, further, that your submission include a comprehensive plan of action to disseminate truthful, non-misleading, and complete corrective messages about the issues discussed in this letter to the audience(s) that received the violative promotional materials. Please direct your response to me at the Food and Drug Administration, Center for Drug Evaluation and Research, Division of Drug Marketing, Advertising, and Communications, 5901-B Ammendale Road, Beltsville, MD 20705-1266, or facsimile at 301-796-9878. In all future correspondence regarding this matter, please refer to MACMIS # 15394 in addition to the NDA number. We remind you that only written communications are considered official.

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 XR comply with each applicable requirement of the Act and FDA implementing regulations. Failure to correct the violations discussed above may result in FDA regulatory action, including seizure or injunction, without further notice.

Sincerely,

{See appended electronic signature page}

Thomas Abrams, R.Ph., M.B.A.
Director
Division of Drug Marketing,
Advertising, and Communications

[5] *See, e.g.*, Ramon Caminal & Xavier Vives, *Why Market Shares Matter: An Information-Based Theory*, 27 Rand J. Econ. 221 (1996).

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/s/

Thomas Abrams

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