DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

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TRANSMITTED VIA FACSIMILE

Verne DeVries, Ph.D.
Assistant Vice President
Regulatory Affairs
Wyeth-Ayerst Laboratories
P.O. Box 8299
Philadelphia, PA 19101-8299

RE: NDA 20-151
Effexor (venlafaxine HCl) Tablets
MACMIS #4368

Dear Dr. DeVries:

Reference is made to Wyeth-Ayerst's (Wyeth) promotional materials for Effexor (venlafaxine HCl) Tablets that include journal advertisements directed to depressed patients with concomitant cardiovascular disease (i.e., "Broken hearts require special care"). These materials include, but are not limited to, promotional materials with the identification numbers 67332-00 and 67332-02. The Division of Drug Marketing, Advertising and Communications (DDMAC) has reviewed these promotional materials and finds them to be misleading and in violation of the Federal Food, Drug and Cosmetic Act.

Specifically, DDMAC objects to Wyeth's promotional materials because they imply that Effexor has been shown to be safe and effective in depressed patients with concomitant cardiovascular disease when, according to the approved product labeling (PI), Effexor has not been evaluated or used to any appreciable extent in patients with a recent history of myocardial infarction or unstable heart disease. In fact, patients with these diagnoses were systematically excluded from many clinical studies during the products pre-marketing testing. Further, Effexor been associated with sustained hypertension (see WARNINGS section of the PI). This adverse event was observed in patients without cardiovascular disease and has not been evaluated in the more vulnerable subpopulation already having cardiovascular disease. Thus, any promotional materials that target this subpopulation would be considered misleading.

DDMAC notes that, in these materials, Wyeth states or suggests that drug-drug interaction is a "critical concern" with depressed patients suffering from concomitant cardiovascular disease and presents Effexor as having minimal drug-

drug interactions with pharmaceuticals that utilize the cytochrome $P_{450}IID_6$ metabolism. This presentation is misleading because the scope of potential drug-drug interaction with cardiovascular pharmaceutical agents would be broader than those that utilize the cytochrome $P_{450}IID_6$ metabolism. Interactions of the pharmacological activity of these agents and, possibly, different sensitivities in this population is not known. Thus, it is misleading to conclude that Effexor is safe and effective in this subpopulation based on its affect on the cytochrome $P_{450}IID_6$ metabolism.

Finally, Wyeth claims that newly completed *in vivo* studies support the original *in vitro* studies (Drug Interactions subsection of the PI), implying that the new *in vivo* results now have demonstrated that there is clinical significance to the finding that Effexor is a weak inhibitor of the cytochrome $P_{450}IID_6$ metabolism. Such a claim is inconsistent with the PI and is considered misleading without adequate substantiation. If Wyeth has data demonstrating clinical significance, it should submit these data to the FDA in a labeling supplement.

Wyeth should immediately discontinue the use of these and other promotional materials for Effexor that contain similar presentations. Please respond to these comments in writing by July 10, 1997. This response should include a list of all violative promotional materials and Wyeth's methods for discontinuing their use.

If Wyeth has any questions or comments, please contact the undersigned by facsimile at (301) 594-6771, or at the Food and Drug Administration, HFD-040, Rm., 17B-20, 5600 Fishers Lane, Rockville, MD 20857. DDMAC reminds you that only written communications are considered official.

In all future correspondences regarding this particular matter, please refer to MACMIS ID# 4368 in addition to the NDA number.

Sincerely,

Lisa L. Stockbridge, Ph.D.
Regulatory Review Officer
Division of Drug Marketing,
Advertising and Communications