ENDEAVOR
PHARMACEUTICALS

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April 4, 2003

Dockets Management Branch (HFA-305)
Food and Drug Administration
5630 Fishers Lane
Room 1061
Rockville, Maryland 20852

RE: Docket No. 98D-0834: Proposed Labeling Guidance - Comments

To Whom It May Concern:

Reference is made to the Agency's request for comments regarding the January, 2003, Labeling Guidance for Noncontraceptive Estrogen Drug Products for the Treatment of Vasomotor Symptoms and Vulvar and Vaginal Atrophy Symptoms – Prescribing Information for Health Care Providers and Patient Labeling. We appreciate this opportunity to respond.

INTRODUCTION

Decades of clinical experience and use by millions of women have established estrogen therapy as the gold-standard treatment for relief of vasomotor symptoms associated with menopause. As the only FDA-approved therapy for relief of such symptoms, this is an important consideration given the changing demographics with more women experiencing or approaching menopause than ever before. Class labeling for these products must accurately and fairly portray the benefits and risks associated with their use.

OVERVIEW

The labeling guidance, as currently proposed, is somewhat misleading when applied to estrogen-only products. The extensive extrapolation of WHI study data to estrogen-only therapies is inconsistent with relevant information pertaining to the relief of vulvar and vaginal atrophy and vasomotor symptoms associated with menopause. The liberal interpretation of these data may preclude use of estrogen therapies by some women who would benefit by them. Specific quotes from the proposed labeling guidance, where

applicable, are provided (in bold type) below. Endeavor's commentary, supported by key opinion leaders and literature references, and labeling recommendations are arranged according to the following topics:

- Applicability of findings from the discontinued Estrogen-Progestin Therapy (EPT) arm (Prempro™) of the Women's Health Initiative study to class labeling for Estrogen Therapy (ET) products
  - Fundamental differences between ET and EPT/Hormone Therapy (HT)
  - Fundamental differences between synthetically-derived *conjugated estrogens* (CE) and *conjugated equine estrogens* (CEE)
  - Comparison of medroxyprogesterone (MPA) to other progestins
  - Importance of risk/benefit ratio to indicated population
- Impact of liberal WHI study inclusion criteria, including subject age variability and pre-existing medical conditions

DISCUSSION

Applicability of findings from the discontinued Estrogen-Progestin Therapy (Prempro™) of the Women's Health Initiative study to class labeling for Estrogen Therapy products

Fundamental differences between ET and EPT

Draft Guidance: PAGE 2, LINES 60-69: **"The Women's Health Initiative (WHI) study reported increased risks of myocardial infarction, stroke, invasive breast cancer, pulmonary emboli, and deep vein thrombosis in postmenopausal women during 5 years of treatment with conjugated equine estrogens (CE 0.625 mg) combined with medroxyprogesterone acetate (MPA 2.5 mg) relative to placebo. Other doses of conjugated estrogens with medroxyprogesterone and other combinations of estrogens and progestins were not studied in the WHI and, in the absence of comparable data, these risks should be assumed to be similar. Because of these risks, estrogens with or without progestins should be prescribed at the lowest effective doses and for the shortest duration consistent with treatment goals and risks for the individual woman."**

Response:

- The majority of the proposed black box warnings for increased cardiovascular and cancer risks stem from the WHI study, a study involving only one product, an estrogen/progestin combination product. To extend the WHI findings to all products (much less to estrogen-only products) is unfounded. These results are not consistent with the substantial base of data, the majority of which are based on therapies other than Prempro™. For example (as referenced from N Engl J Med 1991; 325:756-62)[1], the ten-year follow-up from the Nurses' Health Study concludes "Current estrogen use is associated with a reduction in the incidence of coronary heart disease as well as in mortality from cardiovascular disease, but it is not associated with any change in the risk of stroke." This report was issued almost 5 years prior to the introduction of Prempro™ to the US market, and, therefore, represents experience with other therapies.

- It is premature to apply the effects of this one study to the entire class of ET and EPT, as the ET arm of the WHI study is in progress. The ET arm of WHI continues because no equivalent increase in risk has emerged; as such, ET and EPT should not be treated similarly in clinical evaluations, or addressed as such in class labeling guidance.

- The July 20, 2002, British Medical Journal[2] article entitled *Hormone Replacement Therapy: Findings of women's health initiative trial need not alarm users* states: "Given the biological effects of estrogen on the cardiovascular system, the lack of benefit on coronary heart disease is surprising---but these findings apply only to this particular hormone replacement therapy regimen, and other coronary heart disease studies of this hormone replacement therapy have not shown benefit." The article also states "But the metabolic effects of different regimens are clearly different, and this is most likely to have an impact on their cardiovascular effects."

- The aforementioned British Medical Journal[2] article further states "It is most unhelpful that this point about different estrogens and progestogens was not appreciated by the recent recommendations of the Committee for Safety of Medicines and the Medicines Control Agency, which were inappropriate with respect to cardiovascular disease. Particularly for coronary heart disease, the dose (and possibly type) of estrogen and the type of progestogen may be crucial."

- The March 15, 2003, Cancer[3] journal article entitled: *Hormone Replacement Therapy Containing Progestins and Given Continuously Increases Breast Carcinoma Risk in Sweden* discusses outcomes from a population-based cohort of 2,950 women interviewed during 1990-1992 to determine whether there are any differences in breast carcinoma risks according to different types and duration of HRT use. The journal article states "Progestin-containing preparations used continuously are the most hazardous to women." "These data indicate that estrogen-only therapy is a rather safe therapy with little breast carcinoma risk. If there is a need for HRT containing progestins, as in women with intact uterine tissue, an attractive alternative would be to use a more androgenic progestin combination..." The article also states "The results of the...investigation confirm a high risk for breast carcinoma after at least 4 years of HRT use, especially for progestin-containing preparations." ..."The greatest hazard appears to be for continuous combined therapy, whereas combined sequential therapy shows an intermediate risk and estradiol-only preparations are not associated with a significantly increased risk. These results may help physicians to better tailor therapy to avoid breast carcinoma." These data are consistent with the WHI EPT results, the Nurses' Health Study database, and with the fact that the estrogen-only arm of the WHI study is continuing.

- Estrogen alone and estrogen/progestin combination products are different drugs with different pharmacological profiles. This is best exemplified by the fact that

it is well known that estrogen therapy induces endometrial cancer in some patients. Estrogen/progestin therapy inhibits this induction and has an incidence of endometrial cancer equal to or less than that of untreated populations. Estrogen and estrogen/progestin combination products require independent clinical trials and independent registration applications to obtain FDA approval. The data released from WHI to date focus upon EPT (i.e., CEE in combination with MPA).

- Robert L. Barbieri, MD, Chief, Department of Obstetrics and Gynecology, Brigham and Women's Hospital, Boston, Massachusetts, and Editor-in-Chief of the OBG Management Journal[4] states the "Agency's position that the findings of WHI should be extended to all estrogen preparations whether or not they contain progestin is shaky scientifically. After all the mere fact that the estrogen-only arm of the WHI continues implies that it is associated with a pattern of benefits and risks superior to that of the estrogen-progestin arm."

- Robert Jaffe, MD, Fredd Gellert Professor of Reproductive Medicine and Biology, University of California, San Francisco, President of the Hormone Foundation, and member of the Endocrine Society's Council of the Endocrine and Hormone Society stated at the NIH Office of Research on Women's Health workshop, October 23-24, 2002, "It is only this estrogen and this progestin that's implicated. Actions are very complex, multiple receptors and organ specificity govern the relationships between these responses."

- Janet Woodcock, MD, Director of CDER, noted in her presentation at the NIH Office of Research on Women's Health workshop, October 23-24, 2002, it is "not possible to establish dose toxicity findings to other products" since WHI defines risks for only one estrogen-progestin product.

Fundamental differences between synthetically-derived conjugated estrogens (CE) and conjugated equine estrogens (CEE)

Draft Guidance: Lines 51-53: **"There is no evidence that "natural" estrogens present a different endometrial risk profile than synthetic estrogens at equivalent estrogen doses."**

Response:

- Natural is an ambiguous term with many potential meanings. In the absence of comparable data, and for accuracy and fairness, we suggest the following statement, "It is unknown whether the rate of endometrial carcinomas varies between types of estrogens."

- The guidance does not address the fact that the estrogen component of the combination product investigated in WHI was derived from equine urine sources (i.e., conjugated equine estrogens); it is unfair to compare this with synthetically-derived estrogens that are unique and treated as new chemical entities in the drug approval process. Reference to the WHI study treatment arm should include "conjugated equine estrogens" (instead of "conjugated estrogens"), and "CEE" (instead of "CE"). It is neither fair nor appropriate to differentiate these terms in

only some sections of the labeling. Estrogen alone and estrogen/progestin combination products are different drugs with different pharmacological profiles. This is best exemplified by the fact that it is well known that estrogen therapy induces endometrial cancer in some patients. Estrogen/progestin therapy inhibits this induction and has an incidence of endometrial cancer equal to or less than that of untreated populations. Estrogen and estrogen/progestin combination products require independent clinical trials and independent registration applications to obtain FDA approval. The data released from WHI to date focus upon EPT (i.e., CEE in combination with MPA).

- The proposed class labeling guidance neglects to differentiate combination products from estrogen-only products. Such differentiation is key to proper interpretation of study results provided for the drug of interest, as opposed to results from the WHI study.

Comparison of medroxyprogesterone (MPA) to other progestins

Draft Guidance: PAGE 2, LINES 64-67: **"Other doses of conjugated estrogens with medroxyprogesterone and other combination of estrogens and progestins were not studied in the WHI and, in the absence of comparable data, these risks should be assumed to be similar."**

Response:

- The guidance uses a "broad" approach to treat all estrogen and estrogen/progestin products the same, based upon the less-than-favorable results from the Prempro™ study arm. If this logic is applied in reverse, the positive effects associated with the WHI study treatment would automatically be included in labeling for the class (i.e., indications for treatment of osteoporosis/bone fracture and reduction in colon cancer). Hypothetically, had the results from WHI been positive regarding the effect on cardiovascular disease, would the Agency have proposed class (including estrogen-only products) labeling accommodating an indication for prevention of cardiovascular disease?

- The aforementioned British Medical Journal[1] states "The findings may not be the same for types of hormone replacement therapy other than those used in (the WHI) trial, or for lower doses of the regimen that was used---a point that is acknowledged by the authors of the study."

- MPA is known to be the most proliferative progestin on breast tissue. There are other progestins that are more androgenic and more protective of the breast.

- According to the NAMS Position Statement published in Menopause[5], Vol. 10, 2003 "In animal studies, cyclic high-dose MPA (equivalent to 10 mg/day in humans) and continuous low-dose MPA (equivalent to 2.5 mg/day in humans) diminished the beneficial effect of CEE on acetylcholine-induced coronary vascular dilation. However, the addition of nomegestrol acetate to ET did not reverse the beneficial effects of 17β-estradiol on vascular dilation, indicating that

different progestins exert different effects. In another study, coronary artery vasospasm was avoided with the combination of 17β-estradiol plus progesterone but not with 17β-estradiol plus MPA."

- In the 1995 PEPI trial "good" cholesterol levels increased more in women treated with ET compared to those in the EPT arm, indicating that MPA has negative cardiovascular effects. According to the January 18, 1995, Journal of the American Medical Association[6] (Vol. 273, No. 3) article "Estrogen alone or in combination with a progestin improved lipoproteins and lowers fibrinogen levels without detectable effects on post-challenge insulin or blood pressure. Unopposed estrogen is the optimal regimen for elevation of HDL-C, but the high rate of endometrial hyperplasia restricts use to women without a uterus."

- According to the Climacteric[7] journal (2002;5:332-340) article entitled: *Combined hormone replacement therapy and risk of breast cancer in a French cohort study of 3175 women,* "MPA is a synthetic progestin that may be different from progesterone or other progestins in its effects on breast tissues. According to surgical breast biopsies performed in postmenopausal women, the breast epithelial cell mitotic activity increases during treatment with oral CEE, and even more so during HRT combining oral CEE and MPA."

Importance of risk/benefit ratio to indicated population

- Drug package inserts should clarify the intended use of the drug and any associated risks. The addition of WHI study-related information to the extent proposed is specific to Prempro™. Information not specific to the drug of interest is confusing to the health care professional.

- The aforementioned Cancer[3] article states "The authors previously reported an increased risk of breast carcinoma with longer duration of hormone replacement therapy (HRT) use. It is unclear if different types of HRT confer different risks."

- Since the estrogen-only arm of the WHI study is ongoing, and because no equivalent increase in risk has emerged, risks associated with Prempro™ should not be applied to estrogen-only products.

- The Climacteric[8] journal (2002;5:341-350) article entitled: *Differing effects of low-dose estrogen-progestin therapy and pravastatin in postmenopausal hypercholesterolemic women* states "Low-dose estrogen alleviates vasomotor symptoms, protects against bone loss, and is associated with fewer side-effects such as mastalgia and irregular bleeding. Hence, the prescription of low-dose therapy is increasing."

Impact of liberal WHI study inclusion criteria, including subject age variability and pre-existing medical conditions

Draft Guidance: **[Table inserted between lines 247 and 248 and accompanying paragraphs (lines 231 – 247 and lines 257-263)]**

Response:

- Line 242: We endorse the Agency's proposed wording "The CE-only substudy is continuing and results have not been reported." This is a fair and accurate statement and helps to provide important balance.

- The proposed table addresses CE/MPA exclusively. As such, it is more relevant to combination estrogen/progestin products. It is much less relevant to estrogen-only products. Even so, an adaptation to other combination products constitutes a liberal interpretation, as there is no evidence to suggest other progestins or other such combination products will yield a similar safety profile.

- Lines 231-247: The paragraphs preceding the table adequately discuss the results of WHI associated with the combination therapy treatment arm; a separate table is not necessary. The adverse events observed in WHI are appropriately addressed in the WARNINGS section (coronary heart disease (lines 320–350), venous thromboembolism (lines 354-366), breast cancer (lines 391–412) subsections) of the proposed labeling guidance.

- Inclusion of the WHI table may lead the reader to conclude the package insert is intended for Prempro™.

- The phrase on line 247: "...average follow-up of 5.2 years..." is misleading. This does not accurately fully communicate the cumulative time participants were exposed to HRT. Specifically, WHI study participants were enrolled in the study for 5.2 years. Prior to enrollment, they were not HRT naïve. As such, total exposure to HRT is longer than the 5.2 years stated in the labeling guidance. Furthermore, the present wording may be interpreted that these events occurred upon follow-up evaluation 5.2 years after study drug was discontinued, incorrectly implying a lingering safety concern well after therapy was discontinued.

- A statement regarding the liberal inclusion criteria in the WHI "all-comers" study, including previous medical history and the wide age range and average and mean ages of study participants, should be included for accuracy and perspective. The study included patients for whom estrogen was essentially contraindicated.

- The proposed guidance does not clarify that the women studied in WHI were not reflective of the population typically needing treatment for VMS or VVA, nor was the purpose of WHI to study effectiveness for these well-established

indications. According to the May 8, 2003, (pre-publication) New England Journal of Medicine[9] article "It is important to note that the WHI was not designed to test the effect of hormone therapy on vasomotor or other menopausal symptoms. The majority of women enrolled in the WHI did not have menopausal symptoms. Among the 12 percent of women who did report moderate-to-severe vasomotor symptoms at baseline, the symptoms were unlikely to be very bothersome, since the women were willing to be randomly assigned to placebo. In the subgroup, hormone therapy improved vasomotor symptoms and reduced sleep disturbance. Multiple other randomized trials among younger women with hot flashes have shown that systemic estrogen therapy is highly effective in relieving vasomotor symptoms, reducing both the severity and the frequency of hot flashes by about 80 percent and thereby improving the quality of life." This is particularly relevant, considering the labeling guidance is specifically intended for "...the treatment of vasomotor symptoms and vulvar and vaginal atrophy symptoms....".

- The results of WHI are not directly applicable to younger women. Two-thirds of the WHI study participants were in the 60-70 year age group, (10+ years post-menopause) rather than at menopause, when women generally begin hormone therapy.

- WHI was intended to be a study of women without heart disease. However, a number of the participants were known to have underlying heart disease. It is well-established that a percentage of women over the age of 60 have undiagnosed heart disease. Since 2/3 of the study population was over 60, this predisposes them to higher rates of undiagnosed heart disease, and could skew the data.

- Women with prior thromboembolic events were admitted to the WHI study. Underlying hypertension or other pre-existing conditions could influence study outcomes. Thirty-six percent of the subjects in the EPT arm of the WHI study had hypertension and 4% were diabetics. Typical practice would not prescribe HT to women with these pre-existing conditions.

- Jacques Rossouw, MD, of NHLBI, noted during the NIH Office of Research on Women's Health workshop, October 23-24, 2002, that the effects attributed to estrogen from progestin must be distinguished. Cardiovascular profiles of women with hysterectomies differ from those of non-hysterectomized women.

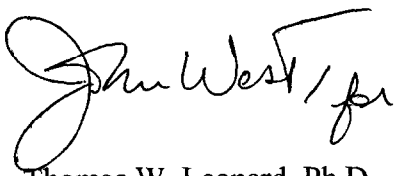
- WHI inadequately blinded the study participants. Forty-four percent of the patients in the WHI study were aware of their treatment due to breakthrough bleeding. Once inadvertently unblinded, participants may have had a greater tendency to report adverse events.

CONCLUSION

Global application of the WHI study findings regarding estrogens combined with medroxyprogesterone in the class labeling to other combination products, much less estrogen-alone products, is misleading and inappropriate. The proposed draft guidance does not provide fair balance to all ET and EPT products by omitting positive study outcomes, while mandating inclusion of extensive negative findings from WHI and not placing such findings in perspective. Overwhelming consensus of opinion leaders at the NIH Office of Research on Women's Health workshop, October 23-24, 2002, regarding generalization of WHI data was that these data are not applicable to all other products in the class. Furthermore, the medical community has embraced lower dose, shorter duration estrogen and estrogen/progestin therapy in the post-WHI environment. When applied to the intended patient population, it is reasonable to infer that these treatment trends will minimize the likelihood for WHI study safety-related issues to occur.

We appreciate your consideration and this opportunity to comment. Endeavor welcomes this and any other ways we may assist the Agency's efforts to finalize the labeling guidance.

Sincerely,



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Enclosures

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