**Comments to Guidance**

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

**Re: Docket No. 98D-0834**
**Draft Guidance for Industry on Labeling for Noncontraceptive Estrogen Drug Products for the Treatment of Vasomotor Symptoms and Vulvar and Vaginal Atrophy Symptoms –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; Availability**
**Comments to Guidance**

Dear Sir/Madam,

We agree with the Agency that prescribing physicians and patients should be warned about the potential for increased risks associated with the use of estrogen drug products as reflected by the large scale WHI substudy. We also agree with the Agency that such information should be highlighted in the prescribing information of each product adding to the awareness of physicians and patients. However, there are sufficient differences among the various estrogen products to suggest that classifying them in one category modeled after Prempro (the only hormone combination product used in the substudy) is not appropriate.

Prempro contains a large number of estrogen components, the exact identity of which has not been completely characterized. The contribution of each of these components to the overall efficacy and safety of Prempro has also not been determined. In fact, the Agency has cited these reasons as the basis for not approving a synthetic generic version of Premarin. As also stated in a previous memorandum from CDER[1] ".....all estrogens do not exert their effects in a uniform manner with respect to different target tissues, i.e., one estrogen can be more active than another in a specific tissue or organ such as breast, uterus, or bone. These differences may be due to variable pharmacokinetics, tissue metabolism, tissue specific receptor factors, or additional reasons." Accordingly, the effects on non-reproductive tissue may be different for one product compared to another and safety information for one product may not be generalizable to every other product in the class.

[1] Availability of a Synthetic Generic Version of Premarin", memorandum from Director/CDER to Douglas L. Sporn, Director, Office of Generic Drugs, May 5, 1997.

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It is noteworthy that safety concerns with specific products have not usually led to the extrapolation of findings from the one product to the entire class. For example, the market withdrawal of Rezulin® (troglitazone) due to serious safety issues did not lead to either the withdrawal of or even to the inclusion of black box warnings for either Rosiglitazone or Pioglitazone, but risk information based on troglitazone was included in the PRECAUTION Section (Hepatic Effects) of the two products' labeling.

While we agree that safety information derived from the WHI substudy should be highlighted in a product's prescribing information, it should be additional as appropriate to the product's specific information. For example, only Prempro should include the Women's Health Initiative Study in the CLINICAL STUDIES Section as this section should provide useful information to prescribing physicians that is relevant only to the particular product. Since the WHI substudy investigated only one specific hormone combination which has different potency and safety profiles than other products in its class, the inclusion of the WHI substudy in the CLINICAL STUDIES Section of all estrogen drug products will not add any value to the information provided and may only confuse prescribing physicians.

Similarly, the ADVERSE REACTIONS section should emphasize adverse reactions that are specific to the particular drug (observed during clinical trials and postmarketing experience), rather than those of the entire class. The class labeling part of the ADVERSE REACTIONS section should focus on those reactions observed for the drug class that have not necessarily been observed for the specific drug. Other approaches for presentation of adverse events (such as all adverse events observed for a particular drug, plus an exhaustive list of class adverse events as recommended in the labeling guidance) could result in a lengthy and redundant ADVERSE REACTIONS section. Emphasis of drug-specific adverse reactions in the ADVERSE REACTIONS section would also lead to more consistency between this labeling guidance and the guidances on adverse events reporting[2,3]. The latter guidances state that adverse events listed as occurring with a class of drugs but not specifically mentioned for a particular drug are considered unexpected, and should be reported.

In conclusion, it is our recommendation that the labeling guidance for noncontraceptive estrogen drug products be revised so that the labeling information for each product emphasizes the product's true and specific properties, while highlighting the warnings and risks associated with the entire class.

Sincerely,

NOVO NORDISK PHARMACEUTICALS, INC.

Barry Reit, Ph.D.
Vice President, Regulatory Affairs and Quality Assurance

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[2] Guideline for Postmarketing Reporting of Adverse Drug Experiences (Docket No. 85D-0249) March 1992.

[3] Guidance for Industry – Postmarketing Safety Reporting for Human Drug and Biological Products Including Vaccines – March 2001