

## DEPARTMENT OF HEALTH AND HUMAN SERVICES

### Food and Drug Administration

[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### Draft Guidance for Industry on Labeling for Noncontraceptive Estrogen Drug Products for the Treatment of Vasomotor Symptoms and Vulvar and Vaginal Atrophy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

**AGENCY:** Food and Drug Administration, HHS.

**ACTION:** Notice.

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**SUMMARY:** The Food and Drug Administration (FDA) is announcing the availability of a draft guidance for industry entitled “Labeling Guidance for Noncontraceptive Estrogen Drug Products for the Treatment of Vasomotor Symptoms and Vulvar and Vaginal Atrophy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.” The draft guidance is intended to assist applicants in developing labeling for new drug applications for such drug products. This is the second draft of the guidance, which initially issued in September 1999.

**DATES:** Submit written or electronic comments on the draft guidance by [*insert date 60 days after date of publication in the **Federal Register***]. General comments on agency guidance documents are welcome at any time.

**ADDRESSES:** Submit written requests for single copies of the draft guidance to the Division of Drug Information (HFD–240), Center for Drug Evaluation and Research, Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857. Send one self-addressed adhesive label to assist that office in processing

your requests. Submit written comments on the draft guidance to the Dockets Management Branch (HFA-305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852. Submit electronic comments to <http://www.fda.gov/dockets/ecomments>. See the **SUPPLEMENTARY INFORMATION** section for electronic access to the draft guidance document.

**FOR FURTHER INFORMATION CONTACT:** Margaret Kober, Center for Drug Evaluation and Research (HFD-580), Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857, 301-827-4243.

**SUPPLEMENTARY INFORMATION:**

**I. Background**

FDA is announcing the availability of a draft guidance for industry entitled “Labeling Guidance for Noncontraceptive Estrogen Drug Products for the Treatment of Vasomotor Symptoms and Vulvar and Vaginal Atrophy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.” The draft guidance describes the recommended labeling for health care providers and patient instructions for inclusion in new drug applications (NDAs). A draft of this guidance was first issued in September 1999 (64 FR 52100). However, on September 10, 2002, the agency withdrew the draft guidance (67 FR 57432), pending consideration of the results from the National Institutes of Health (NIH) Women’s Health Initiative (WHI).<sup>1</sup> This second draft reflects the agency’s thinking after considering the results of the WHI substudy.

In the WHI substudy, postmenopausal women who took conjugated estrogen 0.625 milligram (mg) combined with medroxyprogesterone acetate 2.5 mg had higher risks of several serious adverse events relative to those women

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<sup>1</sup> The results of the NIH Women’s Health Initiative trial were reported in the *Journal of the American Medical Association*, 288: 321-333, 2002.

who took placebo. Conjugated estrogens alone also increased the rates of cardiovascular disease compared to placebo. Other doses of conjugated estrogens and medroxyprogesterone acetate and other combinations of estrogens and progestins were not studied in the WHI. However, in the absence of comparable data, the risks of serious adverse events should be assumed to be similar because other studies show that estrogens and progestins are associated with these types of events.

This second draft of the guidance reflects several changes. For example, the draft guidance provides specific labeling recommendations for two indications (moderate to severe vasomotor symptoms and moderate to severe symptoms of vulvar and vaginal atrophy). It refers sponsors to the appropriate review divisions for guidance on labeling products to treat other indications. In addition, the guidance recommends that the following additions be made to the labeling for noncontraceptive estrogen drug products for the treatment of vasomotor symptoms and symptoms of vulvar and vaginal atrophy:

- New information to the boxed warning;
- Information from the WHI, including a statement that, although only a single dose and type of estrogen and progestin were studied in the WHI, risks for serious adverse events should be assumed to be similar for other estrogens and progestins until data show otherwise;
- A statement recommending that use of estrogens should be at the lowest doses and for the shortest duration in hopes of minimizing risks;
- A revised indication for the treatment of vulvar and vaginal atrophy in women who have moderate to severe symptoms so that benefits from drug therapy may outweigh risks; and

- Information from the WHI on cardiovascular and cancer risks as well as other information from the WHI and other studies.

Finally, the new draft updates other information in the label based on current scientific studies.

This level 1 draft guidance is being issued consistent with FDA's good guidance practices regulation (21 CFR 10.115). The draft guidance represents the agency's current thinking on labeling for noncontraceptive estrogen drug products for the treatment of vasomotor symptoms and vulvar and vaginal atrophy symptoms. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. An alternative approach may be used if such approach satisfies the requirements of the applicable statutes and regulations.

## **II. Comments**

Interested persons may submit to the Dockets Management Branch (see **ADDRESSES**) written or electronic comments regarding the draft guidance. Submit a single copy of electronic comments to <http://www.fda.gov/dockets/ecomments> or two hard copies of any written comments, except that individuals may submit one hard copy. Comments are to be identified with the docket number found in brackets in the heading of this document. The draft guidance and received comments may be seen in the Dockets Management Branch between 9 a.m. and 4 p.m., Monday through Friday.

**III. Electronic Access**

Persons with access to the Internet may obtain the document at either <http://www.fda.gov/cder/guidance/index.htm> or <http://www.fda.gov/ohrms/dockets/default.htm>.

Dated: January 23, 2003.

**Margaret M. Dotzel,**

*Assistant Commissioner for Policy.*

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