Guidance for Industry

Estrogen and Estrogen/Progestin Drug Products to Treat Vasomotor Symptoms and Vulvar and Vaginal Atrophy Symptoms — Recommendations for Clinical Evaluation

DRAFT GUIDANCE

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For questions on the content of the draft document contact Margaret Kober at 301-827-4243

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)

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The Division of Drug Information (HFD-240)
Center for Drug Evaluation and Research
5600 Fishers Lane
Rockville, MD 20857
(Tel) 301-827-4573
Internet at http://www.fda.gov/cder/guidance/index.htm

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D. Monitoring

We recommend that:

- All subjects who have a uterus undergo an endometrial biopsy at end-of-study.
- Any new findings noted during the conduct of the study or during the end-of-study physical examination (including findings related to the breast) receive careful and appropriate evaluation and be monitored until there is complete clinical resolution of any diagnosed condition.
- Sponsors provide plans for monitoring and/or reducing the risk of adverse endometrial effects in women who have a uterus.
- Safety assessments of lipids and of carbohydrate and coagulation parameters (antithrombin III, factor V Leiden, protein-C and protein-S) be conducted.
- Serum levels of the parent compounds and metabolites be measured.

E. Primary Endpoints

For the treatment of moderate to severe vasomotor symptoms, we recommend the following co-primary endpoints:

- Mean change in frequency of moderate to severe vasomotor symptoms from baseline to week 4
- Mean change in frequency of moderate to severe vasomotor symptoms from baseline to week 12
- Mean change in severity of moderate to severe vasomotor symptoms from baseline to week 4
- Mean change in severity of moderate to severe vasomotor symptoms from baseline to week 12

For the treatment of moderate to severe symptoms of vulvar and vaginal atrophy, we recommend the following co-primary endpoints.

- Mean change from baseline to week 12 in the moderate to severe symptom that has been identified by the patient as being the most bothersome to her
- Mean change from baseline to week 12 in vaginal pH
- Mean change from baseline to week 12 in vaginal maturation index (parabasal and superficial cells)

F. Study Analysis

For estrogen alone products intended to treat moderate to severe vasomotor symptoms, we recommend that the primary efficacy analyses show a clinically and a statistically significant