



TRANSMITTED BY FACSIMILE

Carole S. Ben-Maimon, M.D.
President and Chief Operating Officer
Duramed Pharmaceuticals, Inc.
One Belmont Avenue
11th Floor
Bala Cynwyd, PA 19004

Re: NDA # 20-992
Cenestin[®] (synthetic conjugated estrogens, A) Tablets
MACMIS ID # 13589

WARNING LETTER

Dear Dr. Ben-Maimon:

The Division of Drug Marketing, Advertising, and Communications (DDMAC) has reviewed a professional journal advertisement (ad) [BRC05519] for Cenestin[®] (synthetic conjugated estrogens, A) Tablets submitted by Duramed Pharmaceuticals, Inc. (Duramed) under cover of Form FDA 2253. The ad is false or misleading because it omits material risk information, minimizes risks associated with Cenestin therapy, and presents unsubstantiated implied superiority claims. Therefore, the ad misbrands the drug within the meaning of the Federal Food, Drug, and Cosmetic Act (the Act) and FDA implementing regulations. 21 U.S.C. §§ 352(n); 321(n); 21 CFR 202.1(e)(5)(i), (iii); (e)(6)(i), (xx); (e)(7)(viii). This ad is concerning from a public health perspective because it suggests that Cenestin is safer than has been demonstrated by substantial evidence or substantial clinical experience.

Background

According to the Indications and Usage section of the approved product labeling (PI), the 0.45 mg, 0.625 mg, 0.9 mg, and 1.25 mg doses of Cenestin are indicated for the "Treatment of moderate to severe vasomotor symptoms associated with the menopause." The 0.3 mg dose of Cenestin is indicated for the "Treatment of moderate to severe symptoms of vulvar and vaginal atrophy associated with the menopause. When prescribing solely for the treatment of symptoms of vulvar and vaginal atrophy, topical vaginal products should be considered."

The PI for Cenestin contains numerous important contraindications, warnings, precautions, and adverse events. Most importantly, the labeling contains a Boxed Warning which states (emphasis in original):

ESTROGENS INCREASE THE RISK OF ENDOMETRIAL CANCER

Close clinical surveillance of all women taking estrogens is important. Adequate diagnostic measures, including endometrial sampling when indicated, should be undertaken to rule out malignancy in all cases of undiagnosed persistent or recurring abnormal vaginal bleeding. There is no evidence that the use of “natural” estrogens results in a different endometrial risk profile than synthetic estrogens at equivalent estrogen doses. (See **WARNINGS, Malignant neoplasms, *Endometrial cancer.***)

CARDIOVASCULAR AND OTHER RISKS

Estrogens with or without progestins should not be used for the prevention of cardiovascular disease. (See **WARNINGS, Cardiovascular disorders.**)

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 (50 to 79 years of age) during 5 years of treatment with oral conjugated equine estrogens (CE 0.625 mg) combined with medroxyprogesterone acetate (MPA 2.5 mg) relative to placebo (See **CLINICAL PHARMACOLOGY, Clinical Studies.**)

The Women's Health Initiative Memory Study (WHIMS), a substudy of WHI, reported increased risk of developing probable dementia in postmenopausal women 65 years of age or older during 4 years of treatment with oral conjugated estrogens plus medroxyprogesterone acetate relative to placebo. It is unknown whether this finding applies to younger postmenopausal women. (See **CLINICAL PHARMACOLOGY, Clinical Studies.**)

Other doses of oral conjugated estrogens with medroxyprogesterone acetate, and other combinations and dosage forms of estrogens and progestins were not studied in the WHI clinical trials 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.

In addition, the labeling contains the following contraindication (in pertinent part):

Cenestin should not be used in women with any of the following conditions: ...

6. Liver dysfunction or disease.

Omission of Risk Information

The ad misleadingly fails to reveal facts that are material in light of representations made with respect to consequences that may result from the use of the drug as recommended or suggested in the materials. For example, the ad fails to reveal the following important risk information from the Boxed Warning:

The Women's Health Initiative Memory Study (WHIMS), a substudy of WHI, reported increased risk of developing probable dementia in postmenopausal women 65 years of age or older during 4 years of treatment with oral conjugated estrogens plus medroxyprogesterone acetate relative to placebo. It is unknown whether this finding applies to younger postmenopausal women.

Although the ad includes the statement that "Estrogens should not be used for the prevention of cardiovascular disease or dementia," this statement fails to reveal the fact that there is an increased risk of dementia associated with estrogen use.

Additionally, the ad is misleading because it fails to reveal an important contraindication; specifically, the ad fails to reveal that Cenestin should not be used in women with liver dysfunction or disease.

Minimization of Risk

The ad is misleading because it minimizes the risk of endometrial cancer in women with intact uteri associated with Cenestin therapy, thereby suggesting that the drug is safer than has been demonstrated by substantial evidence or substantial clinical experience. Specifically, the ad includes the claim "In women with intact uteri, use of estrogen without progestin **may** increase the risk of endometrial cancer" (emphasis added). This statement is inconsistent with the Boxed Warning of the PI and with the Warnings section of the PI, which states "The reported endometrial cancer risk among unopposed estrogen users is about 2- to 12-fold greater than in non-users, and appears dependent on duration of treatment and on estrogen dose."

Furthermore, the ad is misleading because it minimizes the risks associated with Cenestin by presenting required information relating to side effects or contraindications by means of a general term for a group in place of disclosing each specific side effect and contraindication. Specifically, the ad includes the claim "Due to the increased risk of **cardiovascular** and **thromboembolic** events...estrogen ... should be prescribed at the lowest effective dose for the shortest duration" (emphasis added). The terms "cardiovascular" and "thromboembolic" are inadequate to describe the conditions listed in the Boxed Warning of the PI, specifically, "[M]yocardial infarction, stroke ... pulmonary emboli, and deep vein thrombosis...."

We note that the problems above are magnified because the ad fails to present risk information with a prominence and readability reasonably comparable with the presentation of information relating to the effectiveness of Cenestin. See 21 CFR 202.1(e)(7)(viii).

Unsubstantiated Implied Superiority Claims

The ad is misleading because it suggests that Cenestin is superior to other estrogen formulations (patch or tablet) when this has not been demonstrated by substantial evidence or substantial clinical experience. Specifically, the ad includes the following claims (emphasis in original):

- *Because all menopausal women are not alike...* [presented in conjunction with a graphic of a female-shaped cookie cutter]
CENESTIN[®] helps you treat them as individuals.
CENESTIN therapy offers distinct patient benefits...
 - Consistent estrogen release¹⁻³
 - Plant-derived formulation
 - Effective 0.45 mg low starting dose
- Choose **Cenestin[®]** ... *For consistent release.*

The totality of these claims and presentations misleadingly suggests that Cenestin confers a therapeutic benefit greater than other estrogen formulations, when this has not been demonstrated by substantial evidence or substantial clinical experience. For example, the claims and graphic in the ad (e.g., “Cenestin[®] helps you treat them as individuals,” “Because all menopausal women are not alike,” female-shaped cookie cutter) misleadingly suggest that Cenestin is a targeted therapy that is superior to other estrogen formulations in that it confers unique therapeutic benefits to each individual receiving the drug, when this has not been demonstrated by substantial evidence or substantial clinical experience.

Additionally, the claims above indicate that Cenestin “offers distinct patient benefits,” because of “consistent estrogen release.” However, FDA is not aware of any studies demonstrating that the absorption and dissolution characteristics of Cenestin offer any distinct patient benefits or that the consistent release of hormone over time conveys any clinically significant advantage. If you have such studies, please submit them to FDA. Moreover, the oral administration of Cenestin tablets does not provide “consistent estrogen release” but rather provides slow release of estrogens over several hours with distinct maximum and minimum concentration (C_{max} and C_{min}) profiles typical of orally administered estrogen drug products. Thus, these claims are false and misleading.

Furthermore, the claims above indicate that Cenestin “offers distinct patient benefits,” because it is a “plant-derived formulation.” It should be noted that Cenestin is a synthetic rather than a natural estrogen, despite being a plant-derived formulation. FDA is not aware of any evidence, in general, that the use of “plant-derived” estrogens results in a different risk profile than the use of natural or synthetic estrogens of equivalent estrogen dose. Regarding endometrial risks, however, the PI specifically states, “There is no evidence that the use of ‘natural’ estrogens results in a different endometrial risk profile than synthetic estrogens at equivalent estrogen doses.” Thus, the fact that Cenestin’s formulation is “plant-derived” does not offer “distinct patient benefits.”

Finally, the claims above misleadingly suggest that Cenestin “offers distinct patient benefits” because it is available in a low 0.45 mg dose. However, at least one drug for the treatment of moderate to severe vasomotor symptoms associated with the menopause, Premarin[®], is available in a lower starting dose (0.3 mg).

Conclusion and Requested Action

The ad omits and minimizes risk information, and makes unsubstantiated implied superiority claims in violation of the Act and FDA's implementing regulations. 21 U.S.C. §§ 352(n); 321(n); 21 CFR 202.1(e)(5)(i), (iii); (e)(6)(i), (xx); (e)(7)(viii).

DDMAC requests that Duramed immediately cease the dissemination of violative promotional materials for Cenestin such as those described above. Please submit a written response to this letter on or before January 19, 2006, stating whether you intend to comply with this request, listing all violative promotional materials for Cenestin such as those described above, and explaining your plan for discontinuing use of such materials. Because the violations described above are serious, we request, further, that your submission include a plan of action to disseminate truthful, non-misleading, and complete corrective messages about the issues discussed in this letter to the audience(s) that received the violative promotional materials. Please direct your response to me at the Food and Drug Administration, Division of Drug Marketing, Advertising, and Communications, 5901-B Ammendale Road, Beltsville, MD 20705, facsimile at (301) 796-9877. In all future correspondence regarding this matter, please refer to MACMIS ID # 13589 in addition to the NDA number. We remind you that only written communications are considered official.

The violations discussed in this letter do not necessarily constitute an exhaustive list. It is your responsibility to ensure that your promotional materials for Cenestin[®] comply with each applicable requirement of the Act and FDA implementing regulations.

Failure to correct the violations discussed above may result in FDA regulatory action, including seizure or injunction, without further notice.

Sincerely,

{See appended electronic signature page}

Thomas Abrams, RPh, MBA
Director
Division of Drug Marketing,
Advertising, and Communications

**This is a representation of an electronic record that was signed electronically and
this page is the manifestation of the electronic signature.**

/s/

Thomas Abrams

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