CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

40326

ADMINISTRATIVE DOCUMENTS

REVIEW OF PROFESSIONAL LABELING
DIVISION OF LABELING AND PROGRAM SUPPORT
LABELING REVIEW BRANCH

ANDA Number: 40-326 **Date of Submission: August 13, 1998**

Applicant's Name: Mylan Pharmaceuticals

Established Name: Estradiol Tablets USP, 0.5 mg, 1 mg, and 2 mg

Labeling Deficiencies:

1. GENERAL COMMENTS:

   Please note that the reference listed drug product, Estrace®, is a scored tablet for all three strengths. We note that you describe your tablets as unscored in the HOW SUPPLIED section of the package insert. We refer you to CDER Manual of Policies and Procedures (MAPP 5223.2) for guidance. Please comment.

2. CONTAINER (100's and 500's)

   Satisfactory in draft.

3. PHYSICIAN INSERT

   a. DESCRIPTION

      i. Relocate the first sentence of paragraph two of this section to appear as the first sentence of paragraph one of this section.

      Each tablet, for oral administration, contains 0.5, 1, or 2 mg of micronized estradiol.

   b. PRECAUTIONS

      i. Include the following as the last subsection for this section:

      H. Pediatric Use: Safety and effectiveness in pediatric patients have not been established. Large and repeated doses of estrogen over an extended period of time have been shown to accelerate epiphyseal closure, resulting in

short adult stature if treatment is initiated before the completion of physiologic puberty in normally developing children. In patients in whom bone growth is not complete, periodic monitoring of boner maturation and effects on epiphyseal centers is recommended. Estrogen treatment of prepubertal children also induces premature breast development and vaginal cornification, and may potentially induce vaginal bleeding in girls. In boys, estrogen treatment may modify the normal pubertal process. All other physiological and adverse reactions shown to be associated with estrogen treatment of adults could potentially occur in the pediatric population, including thromboembolic disorders and growth stimulation of certain tumors. Therefore, estrogens should only be administered to pediatric patients when clearly indicated and the lowest effective dose should always be utilized.

4. PATIENT PACKAGE INSERT

a. Satisfactory in draft.

Please revise your labels and labeling, as instructed above, and submit 12 copies of final printed container labels for each strength and size, along with 12 copies of final printed insert labeling.

Please note that we reserve the right to request further changes in your labels and/or labeling based upon changes in the approved labeling of the listed drug or upon further review of the application prior to approval.

To facilitate review of your next submission, and in accordance with 21 CFR 314.94(a)(8)(iv), please provide a side-by-side comparison of your proposed labeling with your last submission with all differences annotated and explained.

/S/

Jerry Phillips
Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

RECORD OF TELEPHONE CONVERSATION

DATE: 3-23-99

PRODUCT NAME: Estradiol Tablets

ANDA NUMBER: 40-326

FIRM NAME: Mylan Pharmaceutical, Inc.

NAME AND TITLE OF PERSON WITH
WHOM CONVERSATION WAS HELD: Frank Sisto

PARTICIPANT(S) TELEPHONE: 304 - 599-2595
MINUTES OF CONVERSATION:

Telecon:
Mike Smela and M. Shaikh called Frank Sisto in order to request the firm to tighten the stability limits for both and Any Other Impurity from NMT % to NMT %. Mike Smela told him that he can tightened the limits based on the stability data - 3 months under accelerated conditions and 18 months at CRT. Mike told him that if it is okay with him, he can fax a telephone amendment, otherwise he can discuss the issue. Mike gave have him the fax number.

End of Conversation.

NAME OF OGD REPRESENTATIVE: Mike Smela/M. Shaikh /S/ 3/23/99

SIGNATURE OF OGD REPRESENTATIVE: /S/ 3/23/99

DIVISION/BRANCH: I/II