

CENTER FOR DRUG EVALUATION AND RESEARCH

APPROVAL PACKAGE FOR:

APPLICATION NUMBER

NDA 21-443

Approval Letter(s)



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-443

Duramed Pharmaceuticals,
Subsidiary of Barr Pharmaceuticals, Inc.
Attention: Joseph Carrado, M.Sc., R.Ph.
Senior Director, Regulatory Affairs
One Bala Plaza, Suite 324
Bala Cynwyd, PA 19004

Dear Mr. Carrado:

Please refer to your new drug application (NDA) dated March 21, 2002, received March 22, 2002, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Enjuvia™ (synthetic conjugated estrogens, B) 0.625 mg and 1.25 mg tablets.

We acknowledge receipt of your submissions dated August 13, 2003, March 9, and May 5, 2004. The March 9, 2004 submission constitutes a complete response to our April 22, 2003 action letter.

This new drug application provides for the use of Enjuvia™ (synthetic conjugated estrogens, B) 0.625 mg and 1.25 mg tablets for the treatment of moderate to severe vasomotor symptoms associated with the menopause.

We completed our review of this application, as amended. It is approved, effective on the date of this letter, for use as recommended in the agreed-upon labeling text.

The final printed labeling (FPL) must be identical to the enclosed labeling (package insert and patient package insert) and the immediate container and carton labels submitted May 5, 2004. Marketing the product with FPL that is not identical to the approved labeling text may render the product misbranded and an unapproved new drug.

Please submit an electronic version of the FPL according to the guidance for industry titled *Providing Regulatory Submissions in Electronic Format - NDA*. Alternatively, you may submit 20 paper copies of the FPL as soon as it is available but no more than 30 days after it is printed. Individually mount 15 of the copies on heavy-weight paper or similar material. For administrative purposes, designate this submission "FPL for approved NDA 21-443." Approval of this submission by FDA is not required before the labeling is used.

All applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred. We are waiving the pediatric study requirement for this application.

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In addition, submit three copies of the introductory promotional materials that you propose to use for this product. Submit all proposed materials in draft or mock-up form, not final print. Send one copy to this division and two copies of both the promotional materials and the package insert directly to:

Division of Drug Marketing, Advertising,
and Communications, HFD-42
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

If you have any questions, call George Lyght, R.Ph., Regulatory Project Manager, at (301) 827-4260.

Sincerely,

{See appended electronic signature page}

Daniel Shames, M.D.
Director
Division of Reproductive and Urologic Drug
Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

Enclosure: Physician Insert and Patient Package Insert.

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/s/

Daniel A. Shames
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Approvable Letter (s)



NDA 21-443

Endeavor Pharmaceuticals
Attention: John West
127 Racine Drive
Wilmington, NC 28403

Dear Mr. West:

Please refer to your new drug application (NDA) dated March 21, 2002, received March 22, 2002, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for EnjuviaTM (synthetic conjugated estrogens, B) 0.625 mg and 1.25 mg tablets.

We also acknowledge receipt of your submissions dated May 2, 3, 17, June 21, 27, July 10, 17, August 30, September 27, October 4, 10, 23, November 18, December 5, 19, and 23, 2002, January 17, February 11, 12, 28, March 20, 24, 27, April 1, and 7, and 21, 2003. These submissions were reviewed for this action.

We completed our review of this application, as amended, and it is approvable for marketing of Enjuvia 0.625 mg and 1.25 mg tablets. Before this application may be approved, however, it will be necessary for you to submit draft labeling that incorporates the revisions to the package insert, patient package insert, carton, bottle, and blister labels sent to you on April 17, 2003.

If additional information relating to the safety or effectiveness of this drug becomes available, revision of the labeling may be required.

When you respond to the above deficiency, include a safety update as described at 21 CFR 314.50(d)(5)(vi)(b). The safety update should include data from all non-clinical and clinical studies of the drug under consideration regardless of indication, dosage form, or dose level.

1. Describe in detail any significant changes or findings in the safety profile.
2. When assembling the sections describing discontinuations due to adverse events, serious adverse events, and common adverse events, incorporate new safety data as follows:
 - Present new safety data from the studies for the proposed indication using the same format as the original NDA submission.
 - Present tabulations of the new safety data combined with the original NDA data.
 - Include tables that compare frequencies of adverse events in the original NDA with the retabulated frequencies described in the bullet above.
 - For indications other than the proposed indication, provide separate tables for the frequencies of adverse events occurring in clinical trials.

3. Present a retabulation of the reasons for premature study discontinuation by incorporating the drop-outs from the newly completed studies. Describe any new trends or patterns identified.
4. Provide case report forms and narrative summaries for each patient who died during a clinical study or who did not complete a study because of an adverse event. In addition, provide narrative summaries for serious adverse events.
5. Describe any information that suggests a substantial change in the incidence of common, but less serious, adverse events between the new data and the original NDA data.
6. Provide a summary of worldwide experience on the safety of this drug. Include an updated estimate of use for drug marketed in other countries.
7. Provide English translations of current approved foreign labeling not previously submitted.

In addition, submit three copies of the introductory promotional materials that you propose to use for this product. Submit all proposed materials in draft or mock-up form, not final print. Send one copy to this division and two copies of both the promotional materials and the package insert(s) directly to:

Division of Drug Marketing, Advertising, and Communications, HFD-42
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

Within 10 days after the date of this letter, you are required to amend this application, notify us of your intent to file an amendment, or follow one of your other options under 21 CFR 314.110. If you do not follow one of these options, we will consider your lack of response a request to withdraw the application under 21 CFR 314.65. Any amendment should respond to all the deficiencies listed. We will not process a partial reply as a major amendment nor will the review clock be reactivated until all deficiencies have been addressed.

Under 21 CFR 314.102(d), you may request an informal meeting or telephone conference with this division to discuss what steps need to be taken before the application may be approved.

The drug product may not be legally marketed until you have been notified in writing that this application is approved.

If you have any questions, call George Lyght, Regulatory Project Manager, at (301) 827-4260.

Sincerely,

{See appended electronic signature page}

Daniel Shames, M.D.
Director
Division of Reproductive and Urologic Drug
Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

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/s/

Daniel A. Shames
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