CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-788

APPROVABLE LETTER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-788

COMPLETE RESPONSE

Duramed Research, Inc
Attention: Charlene Bruno
Senior Manager, Regulatory Affairs
One Belmont Avenue, 11th Floor
Bala Cynwyd, PA 19004

Dear Ms. Bruno:

Please refer to your new drug application (NDA) dated June 25, 2004, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for synthetic conjugated estrogens, A vaginal cream, 0.625 mg/g.

We also acknowledge receipt of your submissions dated March 12, April 21, June 12, July 29, September 9, 10, 11 and 12, 2008.

The March 12, 2008, amendment constituted a complete response to our April 25, 2005, action letter.

We have completed the review of your application, as amended, and have determined that we cannot approve this application in its present form. We have described below our reasons for this action and, where possible, our recommendations to address these issues.

1. Labeling remains unresolved. Because we have failed to come to agreement on the labeling, we will continue discussions based on the version you sent to us this morning. In addition, revised carton and container labeling should be submitted when we have agreed on a mutually acceptable proprietary name.

2. The details pertaining to your postmarketing commitment have not been finalized. We acknowledge your intention to conduct a study to evaluate lower exposure of synthetic conjugated estrogens, A vaginal cream that might prove effective for the treatment of vulvovaginal atrophy associated with menopause. We will continue discussion of this commitment based on the letter you sent to us this morning. In addition, propose a timeframe for protocol submission, study start, and final report submission.

When you respond to the above deficiencies, include a safety update as described at 21 CFR 314.50(d)(5)(vi)(*b*). The safety update should include data from all nonclinical and clinical studies/trials 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 updated exposure information for the clinical studies/trials (e.g., number of subjects, person time).

7. Provide a summary of worldwide experience on the safety of this drug. Include an updated estimate of use for drug marketed in other countries.

8. Provide English translations of current approved foreign labeling not previously submitted.

Within one year after the date of this letter, you are required to resubmit or take one of the other actions available under 21 CFR 314.110. If you do not take one of these actions, we will consider your lack of response a request to withdraw the application under 21 CFR 314.65. A resubmission must fully address all the deficiencies listed. A partial response to this letter will not be processed as a resubmission and will not start a new review cycle.

Under 21 CFR 314.102(d), you may request a meeting or telephone conference with us to discuss what steps you need to take before the application may be approved. If you wish to have such a meeting, submit your meeting request as described in the FDA Guidance for Industry *Formal Meetings With Sponsors and Applicants for PDUFA Products*, February, 2000 (http://www.fda.gov/cder/guidance/2125fnl.htm).

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, R.Ph., Sr. Regulatory Health Project Manager, at (301) 796-0948.

Sincerely,

{See appended electronic signature page}

George Benson, M.D.
Deputy Director
Division of Reproductive and Urologic Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

APPEARS THIS WAY
ON ORIGINAL

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

/s/

George Benson
9/12/2008 05:00:24 PM

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-788

Duramed Pharmaceuticals Inc.
Attention: Patricia Thomas
Director, Regulatory Affairs
One Bala Plaza, Suite 324
Bala Cynwyd, PA 19004-1401

Dear Ms. Thomas:

Please refer to your new drug application (NDA) dated June 25, 2004, received June 25, 2004, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for synthetic conjugated estrogens, A vaginal cream 0.625 mg/g.

We acknowledge receipt of your submissions dated November 1, 3, 23, December 16 and 20, 2004, February 10, 16, 25 and March 4, 10, 17 and 23, 2005.

We have completed our review and have found the information presented is inadequate. Therefore, the application is not approvable under section 505(d) of the Act and 21 CFR 314.125(b). The deficiencies are summarized as follows:

1. Effectiveness has not been established because in the single phase 3 study, Study DP3-2002-002, neither the twice weekly nor the daily dosing regimens of synthetic conjugated estrogens, A vaginal cream achieved statistical significance compared to placebo at week 12 for the co-primary endpoint "subject self-assessment of most bothersome vulvar and vaginal atrophy symptom at baseline."

2. Labeling remains unresolved.

The following is needed to address these deficiencies:

1. Submission of the results of an adequate and well-controlled clinical trial that establishes the effectiveness of synthetic conjugated estrogens, A vaginal cream in the treatment of vulvar and vaginal atrophy by demonstrating a statistically significant improvement compared to placebo in all 3 of the co-primary endpoints described in the draft Guidance for Industry "Estrogen and Estrogen/Progestin Drug Products to Treat Vasmotor Symptoms and Vulvar and Vaginal Atrophy Symptoms - Recommendations for Clinical Evaluation (January 2003)" at week 12 relative to baseline.

2. Submission of proposed revised draft labeling that incorporates the results of the clinical trial that addresses the first deficiency.

When you respond to the above deficiencies, 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.

Within 10 days after the date of this letter, you are required to amend the application(s), notify us of your intent to file (an) amendment(s), or follow one of your other options under 21 CFR 314.120. If you do not follow one of these options, we will consider your lack of response a request to withdraw the application(s) 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 the Division of Reproductive and Urologic Drug Products 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, contact George Lyght, R.Ph., Regulatory Project Manager, at (301) 827-4260.

Sincerely,

{See appended electronic signature page}

Donna Griebel, M.D.
Deputy Division Director
Division of Reproductive and Urologic Drug Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

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/s/

Donna Griebel
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