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APPLICATION NUMBER:

20-538/S-015

APPROVABLE LETTER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 20-538/S-012, S-014, S-015

Novartis Pharmaceuticals Corporation
Attention: Lynn Mellor
Associate Director, Drug Regulatory Affairs
59 Route 10
East Hanover, NJ 07936-1080

Dear Ms. Mellor:

Please refer to your supplemental new drug applications dated November 13, 2000, received November 15, 2000, resubmitted November 6, 2001, received November 8, 2001 (S-012); January 18, 2001, received January 19, 2001, (S-014), and January 22, 2001, received January 23, 2001, (S-015) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Vivelle-Dot™ (estradiol transdermal system) 0.025, 0.0375, 0.05, 0.075 and 0.1 mg/day.

We acknowledge receipt of your submissions dated: October 10, November 6, 8, 13, 15 and 16 (2), 2001 (S-012), January 18, February 12, March 7, October 1, November 6 (2), 8, 13, 15 and 16(2), 2001 (S-014) and January 22, February 12, May 18 and 25, July 17, October 1 and 16, November 6, 8, 13, 15, and November 16 (2), 2001 (S-015).

These supplemental new drug applications propose changes for the use of Vivelle-Dot™ as follows:

1. Revised labeling to incorporate safety information requested by the Agency in a letter dated August 10, 2000, (S-012),

2. Removal of the restrictive language, regarding vasomotor symptoms associated with the menopause, that some women taking the 0.0375 mg/day dosage may experience a delayed onset of efficacy and revision of the Clinical Pharmacology section of the Package Insert to be consistent with the FDA draft labeling guidance (S-014), and

3. Addition of the prevention of postmenopausal osteoporosis indication in at-risk patients for the 0.025 mg/day strength (S-015).

We have completed the review of these applications, as amended, and they are approvable. Before these applications may be approved, however, it will be necessary for you to submit draft labeling that incorporates the revisions in the enclosed Package Insert and Patient Information insert. Additions have been noted with underlining and deletions have been noted with ~~strikeouts.~~ Additional comments requiring response are in **14 pt bold face type**. A clean version copy has also been provided.

In addition, on the Physician Sample Box, the "Rx Only" statement should be moved to the main panel of the box.

Furthermore, all previous revisions as reflected in the most recently approved labeling must be included. To facilitate review of your submission, please provide a highlighted or marked-up copy that shows the changes that are being made.

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

Under 21 CFR 314.50(d)(5)(vi)(*b*), we request that you update your NDAs by submitting all safety information you now have regarding your new drugs. The safety update should include data from all nonclinical 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 supplemental applications, notify us of your intent to file amendments, or follow one of your other options under 21 CFR 314.110. In the absence of any such action FDA may proceed to withdraw the applications. 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.

This product may be considered to be misbranded under the Federal Food, Drug, and Cosmetic Act if it is marketed with these changes prior to approval of these supplemental applications.

If you have any questions, call Diane Moore, BS, Regulatory Project Manager, at (301) 827-4260.

Sincerely,

{See appended electronic signature page}

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

Enclosure:
Revised labeling

46 Page(s) Withheld

_____ § 552(b)(4) Trade Secret / Confidential

__X__ § 552(b)(4) Draft Labeling

_____ § 552(b)(5) Deliberative Process

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

/s/

Daniel A. Shames
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