

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:
20-655/S-008

APPROVAL LETTER



NDA 20-655/S-008

APPROVAL LETTER

Watson Laboratories, Inc.
Attention: Dorothy Frank, M.S., R.A.C.
Director, Regulatory Affairs
Research Park
417 Wakara Way
Salt Lake City, UT 84108

Dear Ms. Frank:

Please refer to your supplemental new drug application dated June 12, 2001, received June 13, 2001, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Alora (estradiol transdermal system) 0.025mg/day, 0.05mg/day, 0.075mg/day, and 0.1 mg/day.

We acknowledge receipt of your submissions dated November 19, 2001, and January 14 and 16, 2002. Your submission dated February 5, 2002, constituted a complete response to our January 18, 2002, action letter.

This supplement proposes the following changes: addition of a new indication, prevention of postmenopausal osteoporosis, and a new strength, 0.025 mg/day.

We have completed the review of this application, as amended, and have concluded that adequate information has been presented to demonstrate that the drug product is safe and effective for use as recommended in the agreed upon enclosed labeling text that reflects the minor editorial revisions provided to you by secured e-mail on April 5, 2002. These revisions are terms of the approval of this application.

Accordingly the application is approved effective on the date of this letter.

The final printed labeling (FPL) must be identical to, the enclosed labeling (text for the package insert, text for the patient package insert).

Please submit 20 paper copies of the FPL as soon as it is available, in no case more than 30 days after it is printed. Please mount individually ten of the copies on heavy-weight paper or similar material. Alternatively, you may submit the FPL electronically according to the guidance for industry titled *Providing Regulatory Submissions in Electronic Format – NDAs* (January 1999). For administrative purposes, this/these submission(s) should be designated "FPL for approved supplement NDA 20-655/S-008" Approval of this submission by FDA is not required before the labeling is used.

**APPEARS THIS WAY
ON ORIGINAL**

If you have any questions, call Dornette Spell-LeSane, NP-C, 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

**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/

Daniel A. Shames
4/5/02 02:20:45 PM

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We acknowledge receipt of your submissions dated January 14 and 16, 2002. Your submission of November 19, 2001, constituted a complete response to our November 16, 2001, action letter.

We also acknowledge receipt of your submission dated January 17, 2002. This submission has not been reviewed in the current review cycle. You may incorporate this submission by specific reference as part of your response to the deficiencies cited in this letter.

This supplement proposes the following changes: addition of a new indication, prevention of postmenopausal osteoporosis, and a new strength, 0.025 mg/day.

We have completed the review of this application, as amended, and it is approvable. Before this application may be approved, however, it will be necessary for you to address the following:

1. The table regarding vasomotor symptoms cannot be verified. To support Table 3, "Mean Change from Baseline in Frequency of Moderate-to-Severe Vasomotor Symptoms for Alora Compared to Placebo," submit the efficacy data from the placebo-controlled clinical trial (E94001). These data should be provided in SAS transport format according to the Guidance for Industry, entitled, "Providing Regulatory Submissions in Electronic Format-NDAs." Data should include values at baseline and weeks 4, 8 and 12, utilizing the last observation carried forward (LOCF) data imputation method. A data flag should be used to indicate any imputed value.
2. The graph provided by the Agency in figure 3 is an example of the presentation requested for that figure, "Mean % change in BMD from baseline at 1 and 2 years after initiation of therapy with placebo and Alora 0.025, 0.05 and 0.075 mg/day." A new graph using the corrected numbers in the completer and ITT populations should be generated.

In addition, it will be necessary for you to submit draft labeling for the drug. Revisions have been incorporated directly into the enclosed labeling (text for the package insert, text for the patient package insert). Additions have been noted with underlining, deletions have been noted as ~~strikeouts~~. Additional comments requiring response are in **14 pt bold face type**.

In addition, 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.

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

Within 10 days after the date of this letter, you are required to amend the supplemental application, notify us of your intent to file an amendment, 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 application. 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 this supplemental application.

If you have any questions, call Dornette Spell-LeSane, NP-C, 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

**APPEARS THIS WAY
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24 pages redacted from this section of
the approval package consisted of draft labeling



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Sincerely,

{See appended electronic signature page}

Daniel Shames, M.D.
Acting Director
Division of Reproductive and Urologic Drug Products
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Enclosure:
Revised Physician Insert
Revised Patient Package Insert

**APPEARS THIS WAY
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the approval package consisted of draft labeling

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7

pages of trade

secret and/or

confidential

commercial

information

24 pages redacted from this section of
the approval package consisted of draft labeling