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RESEARCH**

*APPLICATION NUMBER:*

**208564Orig1s000**

**OTHER ACTION LETTERS**



NDA 208564

**COMPLETE RESPONSE**

TherapeuticsMD, Inc.  
Attention: Valerie Ahmuty  
Vice President, Regulatory Affairs  
6800 Broken Sound Parkway NW  
3<sup>rd</sup> Floor  
Boca Raton, FL 33487

Dear Ms. Ahmuty:

Please refer to your New Drug Application (NDA) dated and received July 7, 2016, and your amendments, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for estradiol vaginal insert, 4, 10, (b) (4)

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

**CLINICAL SAFETY**

1. Your application does not provide long-term endometrial safety data for the 4, 10, (b) (4) mcg estradiol vaginal inserts. Sufficient assessment of endometrial histology to support chronic use is critical to the safety evaluation of unopposed estrogen and to ensure adequate labeling for the safe use of your product. In making this determination, we have considered the following:
  - Treatment of moderate-to-severe dyspareunia, due to menopause, involves a chronic duration.
  - Unopposed estrogen use in a postmenopausal woman with a uterus increases the risk of endometrial hyperplasia/cancer.
  - 12-week safety data from Trial TXV14-01 are inadequate to assess long-term endometrial safety of your estradiol vaginal insert.

- Long-term endometrial safety data with your product are necessary to ensure its safe use.
  - Clinical practice allows the chronic treatment of local vaginal symptoms related to menopause, such as dyspareunia, with vaginally administered estrogen without opposing progestin therapy to mitigate the risk of endometrial hyperplasia and cancer in women with a uterus.
  - Proliferative changes of the endometrium were seen with your product in some women at 12 weeks of treatment compared to none on placebo. Based on these 12-week endometrial changes, it is unclear, without long-term data, whether your product could be used without an opposing progestin even if it is intended for local vaginal use.
    - Long-term endometrial safety information with your product in labeling is essential to guide prescribers' decisions regarding endometrial surveillance and the need for progestin therapy with the chronic use of your product in a woman with a uterus.
    - If long-term endometrial data are not reassuring and indicate that your product must be co-administered with a progestin for adequate endometrial protection, then the safety and efficacy of the co-administered drugs will need to be demonstrated.

2. The safety evaluation of your product is expected to quantify and characterize the general safety of the drug over a reasonable duration consistent with its intended chronic use. Such extended duration of exposure is needed to adequately characterize the pattern of drug-related adverse reactions over time or to detect adverse reactions that may occur only with a longer duration of treatment.

To address the aforementioned deficiencies, you will need to conduct and provide data from a long-term endometrial trial of sufficient size and duration to adequately characterize endometrial safety with your product. This trial should also collect and characterize the long-term general safety profile of your product. You are encouraged to request a meeting with us to discuss the details of such a trial.

## **PRESCRIBING INFORMATION**

We reserve comment on the proposed labeling until the application is otherwise adequate. We encourage you to review the labeling review resources on the [PLR Requirements for Prescribing Information](#) and [Pregnancy and Lactation Labeling Final Rule](#) websites, including regulations and related guidance documents and the Selected Requirements for Prescribing Information (SRPI) – a checklist of important format items from labeling regulations and guidances.

If you revise labeling, use the SRPI checklist to ensure that the prescribing information conforms with format items in regulations and guidances. Your response must include updated content of

labeling [21 CFR 314.50(l)(1)(i)] in structured product labeling (SPL) format as described at <http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm>

### **SAFETY UPDATE**

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/clinical trials for the proposed indication using the same format as in the original submission.
  - Present tabulations of the new safety data combined with the original application data.
  - Include tables that compare frequencies of adverse events in the original application 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 trial discontinuation by incorporating the drop-outs from the newly completed trials. Describe any new trends or patterns identified.
4. Provide case report forms and narrative summaries for each patient who died during a clinical trial or who did not complete a trial 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 application 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/product. Include an updated estimate of use for drug/product marketed in other countries.
8. Provide English translations of current approved foreign labeling not previously submitted.

### **ADDITIONAL COMMENTS**

We have the following comments/recommendations that are not approvability issues but should be addressed prior to or by the time of your NDA resubmission:

#### **Chemistry, Manufacturing, and Controls**

We remind you that the current USP includes a monograph for Estradiol Vaginal Inserts. We understand that the current USP monograph may not be a suitable public standard for your new drug product. However, there is an expectation that your product will conform to the compendial monograph requirements. Alternatively, deviations from the monograph requirements should be identified on your product labels. We recommend that you petition the USP with proposed revisions to the monograph in order to accommodate your new drug product. Please see the following link for more information about that USP process:  
<http://www.usp.org/usp-nf/pending-monographs>.

Specifically, we note differences in assay test method and acceptance criteria, the dissolution test method and acceptance criteria, and in the procedure for determining related substances.

The proposed analysis of estradiol-related compounds and degradation impurities by HPLC-MS may be acceptable for quality control purposes in the firm's laboratory but is currently unacceptable for regulatory purposes because the method does not work with a similar mass spectrometer in two different locations. It is therefore incumbent upon you to propose methods that are suitable for regulatory purposes.

With regard to the dissolution test method, we recommend that you perform dissolution method validation in accordance with US<1092>, The Dissolution Procedure: Development and Validation, and adopt appropriate acceptance criteria.

#### **Carton and Container Labeling**

When you resubmit, revise the draft carton and container labeling as follows:

Carton Labeling:

- a. There is insufficient differentiation between the strengths. This is because the colors used with the proprietary name and the logo (green, pink, and purple) are the primary colors used on the principal display panel and side panels. For example, the pink color used for the proprietary name is the same color used for the 4 mcg carton labeling. This use of color dilutes the impact of color differentiation and increases the risk for strength selection errors. The colors chosen should be unique to that strength and avoid overlap or similarity with the trade dress. Specifically, due to the prominence of pink, purple, and green throughout the trade dress, we recommend avoiding the use of these colors as a designation of strength to decrease the risk of dispensing errors.
- b. The dosage form is described as (b) (4), This is not the appropriate dosage form for the product. Revise the dosage form from (b) (4)

- to read “vaginal insert” on all labels and labeling to reflect the acceptable dosage form for this product.
- c. The established name lacks prominence commensurate with the proprietary name. Increase the prominence of the established name taking into account all pertinent factors including typography, layout, contrast, and other printing features in accordance with 21 CFR 201.10(g)(2).
  - d. The statement of strength is located away from the dosage form. We are concerned this important product strength information may be overlooked and lead to medication dispensing errors. Relocate the statement of strength to immediately follow the dosage form so it allows the reader immediate access to this information.

**Blister label:**

There is lack of drug-identifying information on the blister label in accordance with 21 CFR 201.10(i)(1) and per 21 CFR 201.17. Specifically, the blister label lacks important product information (e.g. proprietary and established name; product strength; lot or control number; expiration date [per USP]; and the name of the manufacturer, packer, or distributor). Furthermore, to help minimize confusion with the expiration date presentation, we recommend that you use a format similar to one of the following: MMMYYYY (e.g. JAN2017) or MMMDDYYYY (e.g., JAN012019)

**Proprietary Name**

The review of your proposed proprietary name has been terminated due to the deficiencies with the application as described in this letter. Resubmit the proposed proprietary name when you respond to the application deficiencies.

**OTHER**

Within one year after the date of this letter, you are required to resubmit or take other actions available under 21 CFR 314.110. If you do not take one of these actions, we may consider your lack of response a request to withdraw the application under 21 CFR 314.65. You may also request an extension of time in which to resubmit the application.

A resubmission must fully address all the deficiencies listed in this letter and should be clearly marked with "**RESUBMISSION**" in large font, bolded type at the beginning of the cover letter of the submission. The cover letter should clearly state that you consider this resubmission a complete response to the deficiencies outlined in this letter. A partial response to this letter will not be processed as a resubmission and will not start a new review cycle.

You may request a meeting or teleconference 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 draft FDA Guidance for Industry, “Formal Meetings Between the FDA and Sponsors or Applicants of PDUFA Products,” March 2015 at <http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm437431.pdf>.

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 Kim Shiley, R.N., B.S.N., Regulatory Project Manager, at (301) 796-2117.

Sincerely,

*{See appended electronic signature page}*

Christine Nguyen, M.D.  
Deputy Director for Safety  
Division of Bone, Reproductive, and Urologic Products  
Office of Drug Evaluation III  
Center for Drug Evaluation and Research

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
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/s/  
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CHRISTINE P NGUYEN  
05/05/2017