



NDA 208564

NDA APPROVAL

TherapeuticsMD, Inc.
Attention: Christine Miller, Pharm.D.
Chief Regulatory and Quality Officer
6800 Broken Sound Parkway, N.W., 3rd Floor
Boca Raton, FL 33487

Dear Dr. Miller:

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 (FDCA) for IMVEXXY™ (estradiol vaginal inserts), 4 mcg and 10 mcg.

We acknowledge receipt of your amendment dated November 29, 2017, which constituted a complete response to our May 5, 2017, action letter.

This new drug application provides for the use of IMVEXXY™ (estradiol vaginal inserts), 4 mcg and 10 mcg for the treatment of moderate to severe dyspareunia, a symptom of vulvar and vaginal atrophy, due to menopause.

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

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, submit the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format using the FDA automated drug registration and listing system (eLIST), as described at <http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm>. Content of labeling must be identical to the enclosed labeling (text for the prescribing information, text for the patient package insert). Information on submitting SPL files using eLIST may be found in the guidance for industry *SPL Standard for Content of Labeling Technical Qs and As*, available at <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM072392.pdf>

The SPL will be accessible via publicly available labeling repositories.

CARTON AND IMMEDIATE CONTAINER LABELS

Submit final printed carton and immediate container labels that are identical to the enclosed carton and immediate container labels and identical to the carton and immediate container labels submitted on May 18, 2018, as soon as they are available, but no more than 30 days after they are printed. Please submit these labels electronically according to the guidance for industry titled *Providing Regulatory Submissions in Electronic Format — Certain Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications (May 2015, Revision 3)*. For administrative purposes, designate this submission “**Final Printed Carton and Container Labels for approved NDA 208564.**” Approval of this submission by FDA is not required before the labeling is used.

REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients (which includes new salts and new fixed combinations), new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication in pediatric patients unless this requirement is waived, deferred, or inapplicable.

We are waiving the pediatric study requirement for this application because necessary studies are impossible or highly impracticable, because this condition does not occur in the pediatric population.

POSTMARKETING REQUIREMENTS UNDER 505(o)

Section 505(o)(3) of the FDCA authorizes FDA to require holders of approved drug and biological product applications to conduct postmarketing studies and clinical trials for certain purposes, if FDA makes certain findings required by the statute.

We have determined that an analysis of spontaneous postmarketing adverse events reported under subsection 505(k)(1) of the FDCA will not be sufficient to assess the signal of a serious risk of endometrial cancer with long-term use of low-dose vaginal estrogen unopposed by a progestogen.

Furthermore, the new pharmacovigilance system that FDA is required to establish under section 505(k)(3) of the FDCA will not be sufficient to assess this serious risk.

Therefore, based on appropriate scientific data, FDA has determined that you are required to conduct the following study:

An observational study evaluating the risk of endometrial cancer in postmenopausal women with a uterus who use low-dose vaginal estrogen unopposed by a progestogen. The study should include safety data from the U.S. and other countries where your products are being prescribed to ensure sufficient study sample size. The proposed study data source(s), domestic and international, should 1) include vaginal estrogen users

across the entire postmenopausal age range, and 2) allow linkage to national cancer registries or adequate medication chart adjudication to confirm endometrial cancer cases. The median duration of follow-up should be at least 3 to 5 years after the first use of an unopposed vaginal estrogen product. Appropriate comparison groups should be selected to allow risk estimates for endometrial cancer. Wherever feasible, key baseline covariates, such as body mass index (BMI), smoking and family history of cancer, should be measured and controlled to reduce confounding.

Submit a proposal to address this requirement and timetable for draft protocol submission, final protocol submission, study completion, and submission of final report for the postmarketing requirement described above within 30 days from the date of this letter. Submit your proposal to your NDA and prominently identify the submission with the following wording in bold capital letters at the top of the first page of the submission: **REQUIRED POSTMARKETING CORRESPONDENCE UNDER 505(o).**

Submit clinical protocols to your IND 118439 with a cross-reference letter to this NDA. Submit nonclinical and chemistry, manufacturing, and controls protocols and all final reports to your NDA. Prominently identify the submission with the following wording in bold capital letters at the top of the first page of the submission, as appropriate: **Required Postmarketing Protocol Under 505(o), Required Postmarketing Final Report Under 505(o), Required Postmarketing Correspondence Under 505(o).**

Submission of the protocol for required postmarketing observational studies to your IND is for purposes of administrative tracking only. These studies do not constitute clinical investigations pursuant to 21 CFR 312.3(b) and therefore are not subject to the IND requirements under 21 CFR part 312 or FDA's regulations under 21 CFR parts 50 (Protection of Human Subjects) and 56 (Institutional Review Boards).

Section 505(o)(3)(E)(ii) of the FDCA requires you to report periodically on the status of any study or clinical trial required under this section. This section also requires you to periodically report to FDA on the status of any study or clinical trial otherwise undertaken to investigate a safety issue. Section 506B of the FDCA, as well as 21 CFR 314.81(b)(2)(vii) requires you to report annually on the status of any postmarketing commitments or required studies or clinical trials.

FDA will consider the submission of your annual report under section 506B and 21 CFR 314.81(b)(2)(vii) to satisfy the periodic reporting requirement under section 505(o)(3)(E)(ii) provided that you include the elements listed in 505(o) and 21 CFR 314.81(b)(2)(vii). We remind you that to comply with 505(o), your annual report must also include a report on the status of any study or clinical trial otherwise undertaken to investigate a safety issue. Failure to submit an annual report for studies or clinical trials required under 505(o) on the date required will be considered a violation of FDCA section 505(o)(3)(E)(ii) and could result in enforcement action.

POSTMARKETING COMMITMENTS NOT SUBJECT TO THE REPORTING REQUIREMENTS UNDER SECTION 506B

We remind you of your postmarketing commitments:

- #3407-1 Develop and validate a new regulatory method capable of detecting known and unknown estradiol-related impurities in the drug product.

The timetable you submitted on January 23, 2018, and discussed during an April 25, 2018, teleconference, states that you will conduct this study according to the following schedule:

Development Report Submission: June 2018
Study Completion: November 2018
Final Report Submission: November 2018

- #3407-2 Perform a revalidation of the dissolution method TxMD-003 in accordance with requirements of USP using one batch of each strength of the for-market formulations manufactured by the proposed commercial manufacturer.

The timetable you submitted on January 23, 2018, states that you will conduct this study according to the following schedule:

Development Report Submission: June 2018
Final Report Submission: Submitted in the first NDA Annual Report

Submit clinical protocols to your IND 118439 for this product. Submit nonclinical and chemistry, manufacturing, and controls protocols and all postmarketing final reports to this NDA. In addition, under 21 CFR 314.81(b)(2)(vii) and 314.81(b)(2)(viii) you should include a status summary of each commitment in your annual report to this NDA. The status summary should include expected summary completion and final report submission dates, any changes in plans since the last annual report, and, for clinical studies/trials, number of patients entered into each study/trial. All submissions, including supplements, relating to these postmarketing commitments should be prominently labeled **“Postmarketing Commitment Protocol,” “Postmarketing Commitment Final Report,” or “Postmarketing Commitment Correspondence.”**

PROMOTIONAL MATERIALS

You may request advisory comments on proposed introductory advertising and promotional labeling. To do so, submit, in triplicate, a cover letter requesting advisory comments, the proposed materials in draft or mock-up form with annotated references, and the prescribing information, Medication Guide, and patient PI (as applicable) to:

OPDP Regulatory Project Manager
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion
5901-B Ammendale Road
Beltsville, MD 20705-1266

Alternatively, you may submit a request for advisory comments electronically in eCTD format. For more information about submitting promotional materials in eCTD format, see the draft Guidance for Industry (available at: <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM443702.pdf>).

As required under 21 CFR 314.81(b)(3)(i), you must submit final promotional materials, and the prescribing information, at the time of initial dissemination or publication, accompanied by a Form FDA 2253. Form FDA 2253 is available at <http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM083570.pdf>. Information and Instructions for completing the form can be found at <http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM375154.pdf>. For more information about submission of promotional materials to the Office of Prescription Drug Promotion (OPDP), see <http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm>.

REPORTING REQUIREMENTS

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

Sincerely,

{See appended electronic signature page}

Christine P. 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

Enclosures:

Content of Labeling
Carton and Container Labeling

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

/s/

CHRISTINE P NGUYEN
05/29/2018