NDA 213388

NDA APPROVAL

AbbVie Inc
Attention: Lakshmi Rebbapragada, M.S.
Associate Director, Regulatory Affairs
1 N. Waukegan Road
Dept. PA72/Bldg. AP30-4
North Chicago, IL 60064

Dear Ms. Rebbapragada:

Please refer to your new drug application (NDA) dated and received July 31, 2019, and your amendments, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Oriahnn (elagolix, estradiol and norethindrone acetate capsules; elagolix capsules) 300 mg, 1mg, and 0.5mg; 300 mg.

This new drug application provides for the use of Oriahnn (elagolix, estradiol and norethindrone acetate capsules; elagolix capsules) 300 mg, 1mg, and 0.5mg; 300 mg for the management of heavy menstrual bleeding associated with uterine leiomyomas (fibroids) in premenopausal women.

APPROVAL & LABELING

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.

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 FDA.gov.[1] Content of labeling must be identical to the enclosed labeling (text for the Prescribing Information and Medication Guide) as well as annual reportable changes not included in the enclosed labeling. 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.*[2]

The SPL will be accessible via publicly available labeling repositories.

[1] http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm
[2] We update guidances periodically. For the most recent version of a guidance, check the FDA Guidance Documents Database https://www.fda.gov/RegulatoryInformation/Guidances/default.htm.

CARTON AND CONTAINER LABELING

Submit final printed carton and container labeling that are identical to the enclosed carton and container labeling as soon as they are available, but no more than 30 days after they are printed. Please submit these labeling electronically according to the guidance for industry Providing Regulatory Submissions in Electronic Format — Certain Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications. For administrative purposes, designate this submission "Final Printed Carton and Container Labeling for approved NDA 213388." Approval of this submission by FDA is not required before the labeling is used.

WAIVER of ½ PAGE LENGTH REQUIREMENT FOR HIGHLIGHTS

We are waiving the requirements of 21 CFR 201.57(d)(8) regarding the length of Highlights of Prescribing Information. This waiver applies to all future supplements containing revised labeling unless we notify you otherwise.

ADVISORY COMMITTEE

Your application for Oriahnn was not referred to an FDA advisory committee because the application did not raise significant public health questions on the role of the drug in the diagnosis, cure, mitigation, treatment, or prevention of a disease.

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 this requirement for your application because this product does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients and is not likely to be used in a substantial number of pediatric patients.

POSTMARKETING REQUIREMENTS UNDER 505(o)

Section 505(o)(3) of the Federal Food, Drug, and Cosmetic Act (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 identify an unexpected serious risk of adverse pregnancy, maternal, and fetal/neonatal outcomes associated with exposure to Oriahnn or the risk of alopecia.

Furthermore, the active postmarket risk identification and analysis system as available under section 505(k)(3) of the FDCA will not be sufficient to assess these risks.

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

3837-1: *A prospective pregnancy registry to evaluate the adverse effects of elagolix-containing products, including Oriahnn, on pregnancy and maternal and fetal/neonatal outcomes.*

This PMR will be linked to the study under NDA 210450 PMR 3390-1.

The timetable you agreed to on May 7, 2020, states that you will conduct this study according to the following schedule:

Final Protocol Submission:	January 2019
Study Completion:	January 2029
Interim Reports:	January 2021, 2023, 2025, 2027
Final Report Submission:	January 2030

3837-2: *A retrospective cohort study in a claims-based database to evaluate the adverse effects of elagolix-containing products, including Oriahnn, on pregnancy-related outcomes.*

This PMR will be linked to the study under NDA 210450 PMR 3390-2.

The timetable you agreed to on May 7, 2020, states that you will conduct this study according to the following schedule:

Final Protocol Submission:	January 2019
Study Completion:	January 2024
Interim Report:	January 2023
Final Report Submission:	January 2025

3837-3: *A prospective observational study in premenopausal women receiving treatment with Oriahnn to assess the incidence rate, time to onset, pattern, extent, and reversibility of alopecia, as well as any racial/ethnic differences in developing alopecia. Physician/observer-reported outcome and/or patient survey should be developed and included in the PMR study to*

capture timing, pattern, extent, and reversibility of alopecia cases. The study shall evaluate 50 cases of alopecia.

The timetable you agreed to on May 28, 2020, states that you will conduct this study according to the following schedule:

Draft Protocol Submission:	February 2021
Final Protocol Submission:	August 2021
Interim Study Report:	August 2024
Study Completion:	August 2026
Final Report Submission:	August 2027

3837-4: *A cohort study to compare the incidence rate of alopecia in premenopausal women who initiate Oriahnn and an appropriate comparator population of women not treated with Oriahnn. The study should be powered to detect a 2-fold increase in the risk for alopecia with Oriahnn use. The study should also be powered for a subgroup analysis among African Americans who are treated with Oriahnn. If an electronic healthcare database is selected for the study, then conduct a validation study in the selected database to develop and validate an algorithm with a sufficient positive predictive value (PPV) to identify alopecia, prior to initiating the comparative safety study. If a sufficient PPV cannot be obtained, conduct a prospective cohort study with primary data collection with case adjudication.*

The timetable you agreed to on May 28, 2020, states that you will conduct this study according to the following schedule:

Draft Protocol Submission:	February 2021
Final Protocol Submission:	August 2021
Validation Report:	August 2023
Interim Report:	August 2025
Trial Completion:	August 2026
Final Report Submission:	December 2027

FDA considers the term *final* to mean that the applicant has submitted a protocol, the FDA review team has sent comments to the applicant, and the protocol has been revised as needed to meet the goal of the study or clinical trial.[3]

Submit clinical protocols to your IND 115528 with a cross-reference letter to this NDA. Submit nonclinical and chemistry, manufacturing, and controls protocols and all final report(s) 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:

[3] See the guidance for Industry *Postmarketing Studies and Clinical Trials—Implementation of Section 505(o)(3) of the Federal Food, Drug, and Cosmetic Act (October 2019).* https://www.fda.gov/RegulatoryInformation/Guidances/default.htm.

Required Postmarketing Protocol Under 505(o), Required Postmarketing Final Report Under 505(o), Required Postmarketing Correspondence Under 505(o). Submission of the protocol(s) 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.

PROMOTIONAL MATERIALS

You may request advisory comments on proposed introductory advertising and promotional labeling. For information about submitting promotional materials, see the final guidance for industry *Providing Regulatory Submissions in Electronic and Non-Electronic Format—Promotional Labeling and Advertising Materials for Human Prescription Drugs.*[4]

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 FDA.gov.[5] Information and Instructions for completing the form can be found at FDA.gov.[6]

[4] For the most recent version of a guidance, check the FDA guidance web page at https://www.fda.gov/media/128163/download.
[5] http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM083570.pdf
[6] http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM375154.pdf

REPORTING REQUIREMENTS

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

For a period of 3 years, submit as 15-Day alert reports, all initial and follow-up post-marketing adverse event reports of alopecia, bone mineral density decrease, elevated hepatic transaminases, depression/mood disorder, hormonally mediated malignancies, thromboembolic and vascular events, and pregnancy outcomes, from all post-marketing sources, including consumer reports, solicited reports, foreign reports, and clinical study reports. As part of the periodic safety reports, provide a summary analysis of the above-listed adverse events, from post-marketing reports, including clinical study reports and those published in the medical literature, as well as a cumulative summary of these events.

If you have any questions, call Maria Wasilik, Regulatory Project Manager, at 301-796-0567.

Sincerely,

{See appended electronic signature page}

Audrey Gassman, M.D.
Deputy Director
Division of Urology, Obstetrics, and Gynecology
Office of Rare Diseases, Pediatrics, Urologic and Reproductive Medicine
Center for Drug Evaluation and Research

ENCLOSURES:

- Content of Labeling
  - Prescribing Information
  - Medication Guide
- Carton and Container Labeling

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

MARIA R WASILIK
05/29/2020 09:43:18 AM

AUDREY L GASSMAN
05/29/2020 09:55:27 AM