NDA 214846

NDA APPROVAL

Myovant Sciences, GmbH
Attention: Xiaoping Qi
Director, Clinical Regulatory Affairs
2000 Sierra Point Parkway, 9th Floor
Brisbane, CA 94005

Dear Ms. Qi:

Please refer to your new drug application (NDA) dated May 31, 2020, received June 1, 2020, and your amendments, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Myfembree (relugolix 40 mg, estradiol 1 mg, and norethindrone acetate 0.5 mg) tablets.

This new drug application provides for the use of Myfembree (relugolix, estradiol, and norethindrone acetate) tablets for the treatment of heavy menstrual bleeding associated with uterine fibroids.

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.

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.

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, Patient Package Insert) as well as annual reportable changes

[1] http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm

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.

CARTON AND CONTAINER LABELING

Submit final printed carton and container labeling that are identical to the enclosed carton and container labeling submitted on February 22, 2021, as soon as they are available, but no later that 30 days after they are printed. Please submit the 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 214846. Approval of this submission by FDA is not required before the labeling is used.

DATING PERIOD

Based on the stability data submitted to date, the expiry dating period for Myfembree (relugolix, estradiol, and norethindrone acetate) tablets shall be 24 months from the date of manufacture when stored at 15-30°C.

ADVISORY COMMITTEE

Your application for Myfembree was not referred to an FDA advisory committee because outside expertise was not necessary; there were no controversial issues that would benefit from advisory committee discussion.

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 studies requirement for this application because necessary studies are impossible or highly impracticable.

POSTMARKETING REQUIREMENTS UNDER 505(o)

[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.

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 a known serious risk of alopecia, evaluate a signal of serious risk of bone loss, or identify an unexpected serious risk of adverse pregnancy outcomes.

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 serious risks.

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

4038-1 A prospective observational study in premenopausal women to assess the incidence rate, time to onset, pattern, severity, and reversibility of alopecia using appropriate tools (physician/observer-reported outcomes and/or patient surveys) to capture timing, pattern, severity, and reversibility of alopecia cases. Evaluate a minimum of 50 alopecia cases.

The timetable you submitted on April 13, 2021, states that you will conduct this study according to the following schedule:

Draft Protocol Submission: 02/2022
Final Protocol Submission: 08/2022
Study Completion: 08/2027
Interim Study Report: 08/2025
Final Report Submission: 08/2028

4038-2 A cohort study to compare the incidence rate of alopecia in premenopausal women who experience heavy menstrual bleeding from uterine fibroids on relugolix-containing products with the incidence in an appropriate comparator population not treated with relugolix-containing products. If an electronic healthcare database is selected, conduct a validation study to validate an algorithm with an adequate positive predictive value (PPV) to identify alopecia, prior to initiating the comparative safety study. If an adequate PPV cannot be obtained,

conduct a prospective cohort study with primary data collection together with independent case adjudication.

The timetable you submitted on April 13, 2021, states that you will conduct this study according to the following schedule:

Draft Protocol Submission: 02/2022
Final Protocol Submission: 08/2022
Study Completion: 08/2027
Interim Study Report: 08/2026
Validation/Feasibility Report: 08/2024
Final Report Submission: 08/2028

4038-3 A prospective cohort study in premenopausal women with heavy menstrual bleeding from uterine fibroids to characterize changes in bone mineral density (BMD) as assessed by dual-energy X-ray absorptiometry (DXA) with long-term use of relugolix-containing products. Obtain BMD measurements at initiation of Myfembree and every 6 months over a 48-month treatment period. Determine mean percent change from baseline in BMD (with 95% confidence intervals) at the lumbar spine, total hip, and femoral neck for each timepoint. Include a categorical analysis of change from baseline in BMD, reporting the percentage of patients with various degrees of bone loss/gains.

Additionally, measure BMD every 6 months for at least 12 months post-treatment to characterize recovery of bone loss. For post-treatment BMD report: 1) mean change from baseline in BMD, and 2) percent recovery of bone loss for each anatomic site. Include power calculations with your statistical analysis plan. Capture fractures as an adverse event of special interest with information on how the fracture occurred and adjudicate these cases.

The timetable you submitted on April 13, 2021, states that you will conduct this study according to the following schedule:

Draft Protocol Submission: 02/2022
Final Protocol Submission: 08/2022
Study Completion: 08/2028
Interim Study Report: 08/2026
Final Report Submission: 08/2029

4038-4 Conduct a prospective pregnancy exposure registry that compares the maternal, fetal, and neonatal outcomes of women exposed to relugolix-containing products during pregnancy to those in an unexposed control

population. The registry should be designed to detect and record major and minor congenital malformations, spontaneous abortions, stillbirths, elective terminations, small for gestational age, preterm birth, and any adverse pregnancy outcomes. These outcomes will be assessed throughout pregnancy. Infant outcomes, including effects on postnatal growth and development, will be assessed through at least the infant's first year of life.

The timetable you submitted on April 13, 2021, states that you will conduct this study according to the following schedule:

Draft Protocol Submission:	11/2021
Final Protocol Submission:	05/2022
Study Completion:	05/2031
Interim Reports:	05/2023, 05/2025, 05/2027, and 05/2029
Final Report Submission:	05/2032

4038-5 Conduct an additional pregnancy study that uses a different design from the Pregnancy Exposure Registry (for example, a retrospective cohort study using claims or electronic medical record data or a case control study) to assess major congenital malformations, spontaneous abortions, stillbirths, and small for gestational age and preterm birth in premenopausal women exposed to relugolix-containing products during pregnancy compared to an unexposed pregnancy control population.

The timetable you submitted on April 13, 2021, states that you will conduct this study according to the following schedule:

Draft Protocol Submission,:	11/2021
Final Protocol Submission:	05/2022
Study Completion:	05/2027
Interim Report:	05/2026
Final Report Submission:	05/2028

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 protocol(s) to your IND 131161 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

[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.

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(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.

POSTMARKETING COMMITMENT SUBJECT TO REPORTING REQUIREMENTS UNDER SECTION 506B

We remind you of your postmarketing commitment under NDA 214621:

3962-1 Conduct a pharmacokinetic study to evaluate the effect of P-gp inhibitors when administered after relugolix to further inform dosing strategy. Submit the datasets with the final study report. The study results may inform product labeling.

The timetable you submitted on December 10, 2020, states that you will conduct this study according to the following schedule:

Final Protocol Submission:	06/2021
Study Completion:	01/2022
Final Report Submission:	04/2022

POSTMARKETING COMMITMENT NOT SUBJECT TO REPORTING REQUIREMENTS UNDER SECTION 506B

We remind you of your postmarketing commitment under NDA 214621:

3962-2 Submit test report for the currently ongoing study titled "The Zebrafish Extended One-Generation Reproduction Test" to support of the environmental risk assessment for relugolix.

The timetable you submitted on November 20, 2020, states that you will conduct this study according to the following schedule:

Final Report Submission: 08/2021

Submit clinical protocols to both INDs 131161 and 118736. Submit 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. 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).

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, Urology, Obstetrics and Reproductive Medicine
Office of New Drugs
Center for Drug Evaluation and Research

ENCLOSURES:

- Content of Labeling
  - Prescribing Information
  - Patient Package Insert
- 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
05/26/2021 12:16:39 PM

AUDREY L GASSMAN
05/26/2021 12:19:23 PM