NDA 214846/S-002

SUPPLEMENT APPROVAL

Myovant Sciences, GmbH
Attention: Lillian Justus, Pharm.D., R.Ph.
Senior Manager, Clinical Regulatory Affairs
2000 Sierra Point Parkway, 9th Floor
Brisbane, CA 94005

Dear Dr. Justus:

Please refer to your supplemental new drug application (sNDA) dated July 6, 2021, and your amendments, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Myfembree (relugolix, estradiol, and norethindrone acetate) tablets.

We acknowledge receipt of your major amendment dated May 4, 2022, which extended the goal date by three months.

This Prior Approval supplemental new drug application provides the following change for Myfembree: to expand the use for the management of moderate to severe pain associated with endometriosis.

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, Patient Package Insert), with the addition of any labeling changes in pending "Changes Being Effected" (CBE) supplements, as well as annual reportable changes not included in the enclosed labeling.

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

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 from publicly available labeling repositories.

Also within 14 days, amend all pending supplemental applications that include labeling changes for this NDA, including CBE supplements for which FDA has not yet issued an action letter, with the content of labeling [21 CFR 314.50(l)(1)(i)] in Microsoft Word format, that includes the changes approved in this supplemental application, as well as annual reportable changes. To facilitate review of your submission(s), provide a highlighted or marked-up copy that shows all changes, as well as a clean Microsoft Word version. The marked-up copy should provide appropriate annotations, including supplement number(s) and annual report date(s).

CARTON AND CONTAINER LABELING

We acknowledge your July 15, 2022, submission containing final printed carton and container labeling.

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

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 identify an unexpected serious risk of adverse pregnancy outcomes and potential exposure of the drug to breastfeeding infants.

[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.

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:

4312-1 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.

This PMR will be linked to the study under PMR 4038-4 and may be fulfilled by adding the indication of moderate to severe endometriosis associated pain (EAP) to the existing/planned pregnancy registry for relugolix-containing products indicated for heavy menstrual bleeding associated with uterine leiomyomas.

The timetable you submitted on July 27, 2022, states that you will conduct this study according to the following schedule and aligned with the milestone dates for the PMR 4038-4:

Final Protocol Submission:	10/2022
Interim Reports:	05/2023, 08/2025, 08/2027, 08/2029
Study Completion:	05/2031
Final Report Submission:	05/2032

4312-2 Conduct an additional pregnancy study that uses a different design from the Pregnancy Exposure Registry (for example, a retrospective cohort study in a 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.

This PMR will be linked to the study under PMR 4038-5 and may be fulfilled by adding the indication of moderate to severe EAP to the existing/planned pregnancy cohort

study for relugolix-containing products indicated for heavy menstrual bleeding associated with uterine leiomyomas.

The timetable you submitted on July 15, 2022, states that you will conduct this study according to the following schedule:

Draft Protocol Submission:	02/2023
Final Protocol Submission:	08/2023
Study Completion:	05/2027
Final Report Submission:	05/2028

4312-3 Conduct a milk-only lactation study in lactating women who have received relugolix using a validated assay to assess the concentrations of relugolix in breast milk.

The timetable you submitted on July 15, 2022, states that you will conduct this study according to the following schedule:

Draft Protocol Submission:	01/2023
Final Protocol Submission:	07/2023
Study Completion:	10/2024
Final Report Submission:	03/2025

Finally, we have determined that only a clinical trial (rather than a nonclinical or observational study) will be sufficient to assess a known serious risk of bone loss. Therefore, based on appropriate scientific data, FDA has determined that you are required to conduct the following trial:

4312-4 Conduct a prospective, open-label, single-arm clinical trial in premenopausal women with moderate to severe EAP to characterize changes in bone mineral density (BMD) after 48-months of Myfembree treatment. Ensure that post-treatment follow-up assessments at 12 months after treatment discontinuation are available from a minimum of 100 subjects.

The timetable you submitted on July 15, 2022, states that you will conduct this study according to the following schedule:

Draft Protocol Submission:	02/2023
Final Protocol Submission:	08/2023
Interim Report:	08/2026
Trial Completion:	08/2028
Final Report Submission:	08/2029

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 076642 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: **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.

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]

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[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.

[4] For the most recent version of a guidance, check the FDA guidance web page at https://www.fda.gov/media/128163/download.

You must submit final promotional materials and Prescribing Information, accompanied by a Form FDA 2253, at the time of initial dissemination or publication [21 CFR 314.81(b)(3)(i)]. Form FDA 2253 is available at FDA.gov.[5] Information and Instructions for completing the form can be found at FDA.gov.[6]

PATENT LISTING REQUIREMENTS

Pursuant to 21 CFR 314.53(d)(2) and 314.70(f), certain changes to an approved NDA submitted in a supplement require you to submit patent information for listing in the Orange Book upon approval of the supplement. You must submit the patent information required by 21 CFR 314.53(d)(2)(i)(A) through (C) and 314.53(d)(2)(ii)(A) and (C), as applicable, to FDA on Form FDA 3542 within 30 days after the date of approval of the supplement for the patent information to be timely filed (see 21 CFR 314.53(c)(2)(ii)). You also must ensure that any changes to your approved NDA that require the submission of a request to remove patent information from the Orange Book are submitted to FDA at the time of approval of the supplement pursuant to 21 CFR 314.53(d)(2)(ii)(B) and 314.53(f)(2)(iv).

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.
Acting 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
  - Patient Package Insert

[5] http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM083570.pdf
[6] http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM375154.pdf

- 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
08/05/2022 12:40:52 PM

AUDREY L GASSMAN
08/05/2022 12:56:06 PM