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APPLICATION NUMBER:

214846Orig1s000

OTHER REVIEW(S)

Clinical Inspection Summary

Date	April 15, 2021
From	Ling Yang, M.D., Ph.D., FAAFP Min Lu, M.D., M.P.H., Team Leader Kassa Ayalew, M.D., M.P.H., Branch Chief Good Clinical Practice Assessment Branch (GCPAB) Division of Clinical Compliance Evaluation (DCCE) Office of Scientific Investigations (OSI)
To	Jennifer Lawrence, M.D., Clinical Reviewer Linda Jaffe, M.D., Clinical Reviewer Gerald Willett, M.D., Clinical Team Leader Maria Wasilik, Regulatory Project Manager Division of Urology, Obstetrics and Gynecology (DUOG)
NDA #	214846
Applicant	Myovant Sciences GmbH
Drug	MYFEMBREE (relugolix, estradiol, norethindrone acetate)
NME (Yes/No)	Yes
Review Priority	Standard
Proposed Indication(s)	Treatment of heavy menstrual bleeding associated with uterine fibroids
Consultation Request Date	July 15, 2020
Summary Goal Date	May 01, 2021
Action Goal Date	May 27, 2021
PDUFA Date	June 01, 2021

I. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

Clinical data from Studies MVT-601-3001, MVT-601-3002 and MVT-601-3003 were submitted to the Agency in support of this New Drug Application (NDA) for MYFEMBREE (relugolix, estradiol, norethindrone acetate) oral tablets for the proposed indication. Four clinical investigators (CIs): Drs. Roberta Venturella (Site 3094; Study MVT-601-3001), Nelson Uzquiano (Site 1123; Studies MVT-601-3001 & MVT-601-3003), Gregory Michael Swor (Site 1023; Studies MVT-601-3002 & MVT-601-3003) and Lydie Hazan (Site 1077; Study MVT-601-3002) were selected for clinical inspections.

The ongoing COVID-19 global pandemic has significantly limited the Office of Regulatory Affairs (ORA)'s ability to conduct onsite Good Clinical Practice (GCP) inspections, particularly in the foreign countries. Following discussions between the OSI and the Division of Urology, Obstetrics and Gynecology (DUOG), a decision was made that assessment of the application could proceed without GCP inspections if any clinical site was not possible before the action due date. At this time, following guidelines to protect the health, safety, and welfare of FDA employees and study staff, and with repeated evaluations of the current situation and mission-critical priorities, the planned inspection of Dr. Roberta Venturella (Site 3094; Study MVT-601-3001) in Italy has been cancelled.

The three domestic inspections verified the sponsor Myovant Sciences GmbH (Myovant) submitted clinical data with source records at the CI sites. Based on the results of these CI inspections, Studies MVT-601-3001, MVT-601-3002 and MVT-601-3003 appear to have been conducted adequately, and the data generated by these sites and submitted by the sponsor appear acceptable in support of the respective indication.

II. BACKGROUND

Myovant submitted NDA 214846 for MYFEMBREE (relugolix, estradiol, norethindrone acetate) 40 mg/1 mg/0.5 mg oral tablets on 05/29/2020. The proposed indication is the treatment of heavy menstrual bleeding associated with uterine fibroids.

Data from two pivotal Phase 3 studies (MVT-601-3001 and MVT-601-3002) and one Phase 3 long-term extension study (MVT-601-3003) were submitted to support the approval of the product.

Study MVT-601-3001

Study MVT-601-3001 was a randomized, double-blind, placebo-controlled, Phase 3 study to evaluate the efficacy and safety of once daily oral relugolix 40 mg co-administered with estradiol (E2) 1 mg and norethindrone acetate (NETA) 0.5 mg for 24 weeks in women with heavy menstrual bleeding associated with uterine fibroids. The primary study objective was to determine the benefit of relugolix/E2/NETA combination therapy once a day compared with placebo for 24 weeks for the proposed indication. The primary efficacy endpoint was the proportion of women in the treatment group vs the placebo group who achieved a menstrual blood loss (MBL) volume of < 80 mL and at least a 50% reduction from baseline MBL volume over the last 35 days of treatment, as measured by the alkaline hematin method.

Eligible subjects were randomized at 1:1:1 ratio to Group A relugolix/E2/NETA once daily for 24 weeks; or Group B relugolix monotherapy once daily for 12 weeks followed by relugolix/E2/NETA once daily for 12 weeks; or Group C placebo for 24 weeks. Subjects attended visits monthly. Standardized feminine products were provided for use during the study and used feminine products were collected for assessment of blood loss. Subjects completed daily electronic diaries (eDiaries) to capture compliance with study treatment, menstrual bleeding, use of feminine products for menstrual bleeding, uterine fibroid-associated pain by the numerical rating scale, and use of pain medication to treat pain caused by uterine fibroids. Baseline bone mineral density (BMD) with dual-energy x-ray absorptiometry (DEXA) was assessed at the Screening, Week 12, and 24 visits. A transvaginal ultrasound and endometrial biopsy were performed at Week 24 to assess uterine and fibroid volumes. Blood samples for complete blood counts and blood chemistry were collected monthly. Safety was assessed throughout the study and quality-of-life questionnaires were completed at the study site throughout the study. Subjects who completed the study and met all eligibility criteria were offered the opportunity to enroll in the extension study (MVT-601-3003). Subjects not enrolled into the extension study had a follow-up visit 30 days after the last dose of study treatment.

The study screened a total of 2279 subjects and enrolled 388 subjects in 80 study sites in North America, Brazil, Italy, Poland, South Africa, and the United Kingdom. The first subject was screened on March 07, 2017, and the last subject completed the study on December 01, 2019.

Study MVT-601-3002

Study MVT-601-3002 was a Phase 3, randomized, double-blind, placebo-controlled study to evaluate relugolix co-administered with and without E2/NETA in women with heavy menstrual bleeding associated with uterine fibroids. The primary study objective was to determine the benefit of relugolix 40 mg once daily co-administered with E2 1 mg/NETA 0.5 mg compared with placebo for 24 weeks for the proposed indication. The primary efficacy endpoint was the proportion of women in the relugolix/E2/NETA group vs the placebo group who achieved an MBL volume of < 80 mL and at least a 50% reduction from baseline MBL volume over the last 35 days of treatment, as measured by the alkaline hematin method.

Eligible subjects were randomized at 1:1:1 ratio to Group A relugolix/E2/NETA once daily for 24 weeks; or Group B relugolix 40 mg monotherapy once daily for 12 weeks followed by relugolix/E2/NETA once daily for 12 weeks; or Group C placebo for 24 weeks. Subjects attended visits monthly. Subjects were provided standardized feminine products for use during the study and used feminine products were collected for assessment of blood loss. Subjects completed daily eDiaries to capture compliance with study treatment, menstrual bleeding, use of feminine products for menstrual bleeding, uterine fibroid-associated pain by the numerical rating scale, and use of pain medication to treat pain caused by uterine fibroids. BMD with DEXA was assessed at the Screening, Week 12, and 24 visits. A transvaginal ultrasound with endometrial biopsy was performed at Week 24. Subjects who completed the study and met all eligibility criteria were offered the opportunity to enroll in the extension study (MVT-601-3003). Subjects not enrolled into the extension study had a follow-up visit 30 days after the last dose of study treatment.

The study screened a total of 2899 subjects and enrolled 382 subjects in 99 study sites in North America, Belgium, Brazil, Chile, Czech Republic, Hungary, Poland, and South Africa. The first subject was screened on May 03, 2017 and the last subject completed the study on July 10, 2019.

Of note, the sponsor informed the FDA in 06/2020 that Site #1152 in Poland was pre-closed on 02/25-26/2020 for “multiple observations of GCP noncompliance” and the root cause was “multiple study coordinator changes at the site and inadequate monitoring resources given the relatively high enrollment rate at this site”. The sponsor stated that “patient safety was not considered jeopardized”. Due to the current COVID 19 pandemic and local restrictions, full data audit of the pre-closed foreign Site #1152 in Poland is not feasible. OSI recommends that data generated from Site #1152 be excluded in the per protocol analysis because the study was not conducted at the site per the protocol. The recommendations were communicated to the DUOG on 03/04/2021.

Study MVT-601-3003

Study MVT-601-3003 was a multinational, Phase 3, open-label, single-arm, long-term efficacy and safety extension study that enrolled eligible subjects who completed Study MVT-601-3001 or MVT-601-3002. The primary study objective was to evaluate the long-term efficacy of relugolix/E2/NETA once daily for up to 52 weeks for subjects who previously completed a 24-week treatment period in Study MVT-601-3001 or MVT-601-3002, on heavy menstrual bleeding associated with uterine fibroids. The primary efficacy endpoint was the proportion of women who achieved or maintained an MBL volume < 80 mL and at least a 50% reduction from parent study baseline to the last 35 days of treatment, as measured by the alkaline hematin method.

Eligible subjects were treated with relugolix 40 mg/E2 1 mg/NETA 0.5 mg orally once daily for up to 52 weeks (including treatment of the previous 24 weeks). A BMD by DEXA was assessed at the Week 36 visit and Week 52/Early Termination visit.

The study enrolled 477 subjects in 149 study sites in the US, Belgium, Brazil, Chile, Czech Republic, Hungary, Italy, Poland, and South Africa. The first subject was enrolled on December 05, 2017 and the last subject completed the study on January 24, 2020.

Rationale for Site Selection
Four CIs: Drs. Roberta Venturella (Site 3094; Study MVT-601-3001), Nelson Uzquiano (Site 1123; Studies MVT-601-3001 & MVT-601-3003), Gregory Michael Swor (Site 1023; Studies MVT-601-3002 & MVT-601-3003) and Lydie Hazan (Site 1077; Study MVT-601-3002) were requested for clinical inspection in support of the application. These sites were selected based on enrolling a high number of subjects to the study treatment arms that may have an impact in the review division's clinical decision-making process.

III. RESULTS

1. Dr. Nelson Uzquiano, Site 1123

14990 Northwest Freeway
Houston, Texas 77040

This CI was inspected on 08/17- 09/11/2020 as a data audit for Studies MVT 601-3001 and MVT 601-3003. This was the initial inspection for Dr. Uzquiano.

For Study MVT 601-3001, the study site screened a total of 45 subjects, enrolled 12 subjects, with 10 subjects completed the study. All source records were reviewed for all 12 enrolled subjects and 10 (30%) of the 33 screen failure subjects.

For Study MVT 601-3003, the study site enrolled all of the 10 subjects who completed Study MVT 601-3001, and all 10 subjects completed the study. All source records of all 10 subjects were reviewed.

Source records reviewed during the inspection included the study protocol and amendments, Informed Consent Forms (ICFs), documentation of eligibility criteria and enrollment logs, medical records [including monitoring logs, laboratory tests, ECGs, DEXA reports, adverse events (AEs)], investigation product (IP) accountability records, visit data, certified copies of electronic Case Report Forms (eCRFs) and electronic data capture (EDC), protocol deviations and related regulatory documents [e.g., institutional review board (IRB) approvals and communications, staff training logs, monitoring logs, financial disclosures and delegation of authority].

The inspection found adequate source documentation for inspected study subjects, with no significant deficiencies reported. The submitted data were verifiable with source records at the study site. The primary efficacy data source was not verified because the primary endpoint MBL was analyzed and read by the central lab. The site's documentation of the collection of subjects'

sanitary products and shipping records for samples to the third-party laboratory were verified. There was no evidence of underreporting of AEs or SAEs.

At the end of the inspection, a Form 483 (Inspectional Observations) was issued for failure to conduct an investigation in accordance with the signed statement of investigator and investigational plan.

Specifically, the Clinical Investigator did not personally supervise this investigation as follows:

1. Subject # (b) (6) (Study #3001) had an "abnormal ECG, possibly significant-flat T waves" on (b) (6) at Week 12. A follow-up by a cardiologist was recommended by the CI, but no follow-up or evaluation of the abnormal ECG was done. This subject's ECG remained abnormal through Week 52 (extension study - Study #3003) and no cardiac evaluation of this abnormal finding was done. The subject's final physical was not signed by the CI until (b) (6).

   Reviewer's Comment: The abnormal EKG was reported as an AE in the submission. There were no actions taken nor change of the IP use because of the AE. The CI responded to Form 483 on 09/30/2020 that a cardiologist appointment for evaluation was made for the subject, who failed to follow. The subject had no cardiac symptoms throughout the study.

2. Subject # (b) (6) (Study #3001) had an abnormal ECG of "possibly significant - prolonged QTcF > 450 ms" on (b) (6) as documented on the source records. This abnormal ECG was not signed by the CI until (b) (6) and was not reported as an AE.

   Reviewer's Comments: A review of the submission identified that an AE of prolonged mQRS complex was reported on (b) (6) for the subject. The AE did not resolve until the study completion and did not lead to any intervention or interruption of the IP use. Thus, the abnormal EKG on (b) (6) can be considered as unresolved AE of that previously reported AE on (b) (6).

3. Subject # (b) (6) (Study #3001) had a BP of 89/56 mmHg on (b) (6) at Week 8. This abnormal result was not evaluated by the CI or reported as an AE.

   Reviewer's Comment: the CI responded to Form 483 on 09/30/2020 that the subject's baseline BP was 95/66 mmHg and the BP of 89/56 mmHg was within the normal range of the subject that did not meet the criteria of an AE. Per the study protocol, this incidence does not meet the definition of AE, as the subject had no signs or symptoms, had no intervention or required interruption or IP discontinuation.

Other items discussed were:

1) Study MVT-601-3001: A mix-up of IP kit was dispensed to Subject # (b) (6) on (b) (6) at Week 28. This episode was reported to the IRB.
2) Study MVT-601-3003: Subject # (b) (6) was dispensed three kits instead of two as designated.

Reviewer's Comments: Subject # (b) (6) 's dispense issue was not reported as a protocol deviation in the submission, while Subject # (b) (6) 's dispense issue was reported as a protocol deviation.

In general, this clinical site appeared to be in compliance with GCP except the observations noted above. These observations appear unlikely to have significant impacts on the overall efficacy and safety results.

2. Dr. Gregory Michael Swor, Site 1023
1617 South Tuttle Ave. Suite 1A
Sarasota, FL 34239

This CI was inspected on 12/14-18/2020 as a data audit for Study MVT 601-3002 and MVT 601-3003. This was the first inspection for Dr. Swor.

For Study MVT 601-3002, the site screened a total of 59 subjects, enrolled 9 subjects, with 8 subjects completed the study. The first subject was enrolled on 06/13/2017 and the last subject's last follow-up visit was on 03/12/2019. All source records of all 9 enrolled subjects were reviewed.

For Study MVT 601-3003, the site enrolled all 8 subjects who completed Study MVT 601-3002, with 7 subjects completed the study. The first subject was enrolled on 02/14/2018 and the last subject's last follow-up visit was on 09/17/2019. All source records of all 8 enrolled subjects were reviewed.

Source records reviewed during the inspection included study protocol and amendments, ICFs, documentation of eligibility criteria and enrollment logs, medical records (including monitoring logs, visit reports, laboratory tests, DEXA scans and EKG readings, AEs, concomitant medication use), IP accountability records, paper source documents, EDC, eCRFs, protocol deviations, sponsor audit and monitoring logs and related regulatory documents (e.g., IRB approvals and communications, staff training records, financial disclosures and delegation of authority).

The inspection found adequate source documentation for the study subjects, with no significant deficiencies reported. The submitted data were verifiable with source records at the study site. The primary efficacy endpoint was not verified because the primary endpoint MBL was analyzed and read by the central lab, although the site's documentation of collection of subjects' sanitary products and shipping records for samples to the central lab were verified. There was no evidence of underreporting of AEs.

At the end of the inspection, a Form 483, Inspectional Observations, was not issued. Discussed items were:

1) Study MVT-601-3002:
   a. Baseline pharmacogenomic laboratory samples for five subjects' (Subjects # (b) (6)) were not collected.
   b. Subject # (b) (6) 's baseline quality of life questionnaires were not completed.
   c. Subject # 's Week 12 DEXA scan was not completed.
   d. Subject # 's ECG for Week 2 was not completed.

2) Study MVT-601-3003: Subject # (b) (6) 's Week 8 subject diary was not completed.

Reviewer's Comments: Except for the missing DEXA scan for subject (b) (6), all of the above identified issues were not reported as protocol deviations in the submission, that should be reported.

In general, this clinical site appeared to be in compliance with good clinical practice (GCP) except the items noted above. These findings appear unlikely to have significant impacts on the overall efficacy and safety results.

3. Dr. Lydie Hazan, Site 1077
5800 Wilshire Blvd.
Los Angeles, CA 90036

This CI was inspected on 10/19-23/2020 as a data audit for Study MVT 601-3002. This was the fourth inspection for Dr. Hazan (inspections in 04/2010--VAI; 09/2012--NAI and 02/2015--VAI). Previously identified inspection issues were out of window subjects' visits, lab supply issues, and missed procedures.

The study site screened a total of 99 subjects, enrolled 12 subjects, with 10 subjects completed the study. The first subject was enrolled on 08/17/2017 and the last subject's last follow-up visit was on 04/01/2019. All source records of all 12 enrolled subjects were reviewed.

Source records reviewed during the inspection included the ICFs, documentation of eligibility criteria, study protocol and amendments, medical records (including monitoring logs, visit reports, laboratory tests, DEXA scans and EKG readings, AEs, concomitant medication use), IP accountability records, subject eDiaries, EDC, eCRFs, protocol deviations, sponsor audit and monitoring logs and related regulatory documents (e.g., IRB approvals and communications, staff training records, financial disclosures and delegation of authority).

The inspection found adequate source documentation for inspected study subjects, with no significant deficiencies reported. The submitted data were verifiable with source records at the study site. The primary efficacy data source was not verified because the primary endpoint MBL was analyzed and read by the central lab. The site's documentation of the collection of subjects' sanitary products and shipping records for samples to the third-party laboratory were verified. There was no evidence of underreporting of AEs.

At the end of the inspection, a Form 483, Inspectional Observations, was not issued. Discussed items included the following:

1) Expired open urine test dipstick supplies were intermingled with laboratory supplies, although the CI stated "in-date" urine analysis sticks were used.

2) Subject # (b) (6) withdrew the ICF after the Week 24 visit and did not complete all required tests. The Subject was listed as "completed" in the submission.

Reviewer's Comment: Subject # (b) (6) *should be listed as "withdrawn".*

3) Protocol deviations: Transvaginal ultrasounds (TVUs) were not documented on the CRFs for Subjects # (b) (6) and # (b) (6) at Week 24, although the CI provided documentation that those were performed.

Reviewer's Comments: Subject # (b) (6) *'s missing TVU at Week 24 was not reported as protocol deviation, but Subject #* (b) (6) *'s missing TVU at Week 24 was reported in the submission.*

In general, this clinical site appeared to be in compliance with GCP except the items noted above. These findings appear unlikely to have significant impacts on the overall efficacy and safety results.

{See appended electronic signature page}

Ling Yang, M.D., Ph.D.
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

CONCURRENCE:

{See appended electronic signature page}

Min Lu, M.D., M.P.H.
Team Leader
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

CONCURRENCE: {See appended electronic signature page}

Kassa Ayalew, M.D., M.P.H
Branch Chief
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

CC:

Central Doc. Rm.\NDA 214846
DUOG\Deputy Division Director\Audrey Gassman
DUOG\CDTL\Gerald Willett
DUOG\Reviewer\Jennifer Lawrence
DUOG\Reviewer\Linda Jaffe
DUOG\Project Manager\Maria Wasilik
OSI\DCCE\Division Director\Ni Khin
OSI\DCCE\GCPAB\Branch Chief\Kassa Ayalew
OSI\DCCE\GCPAB\Team Leader\Min Lu
OSI\DCCE\GCPAB\Reviewer\Ling Yang
OSI\DCCE\Program Analysts\Yolanda Patague

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/s/

LING YANG
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MIN LU
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KASSA AYALEW
04/15/2021 04:18:35 PM

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Medical Policy

PATIENT LABELING REVIEW

Date:	March 31, 2021
To:	Maria Wasilik Regulatory Project Manager **Division of Urology, Obstetrics and Gynecology (DUOG)**
Through:	LaShawn Griffiths, MSHS-PH, BSN, RN Associate Director for Patient Labeling **Division of Medical Policy Programs (DMPP)**
From:	Sharon W. Williams, MSN, BSN, RN Senior Patient Labeling Reviewer **Division of Medical Policy Programs (DMPP)**
	Elvy Varghese, PharmD. Regulatory Review Officer **Office of Prescription Drug Promotion (OPDP)**
Subject:	Review of Patient Labeling: Patient Package Insert (PPI)
Drug Name (established name):	MYFEMBREE (relugolix, estradiol and norethindrone acetate)
Dosage Form and Route:	tablet, for oral use
Application Type/Number:	NDA 214846
Applicant:	Myovant Sciences

1 INTRODUCTION

On May 29, 2020, Myovant Sciences submitted for the Agency's review an original New Drug Application (NDA) 21486 for MYFEMBREE (relugolix/estradiol/norethindrone acetate) tablet, for oral use indicated as a treatment of heavy menstrual bleeding associated with uterine fibroids.

This collaborative review is written by the Division of Medical Policy Programs (DMPP) and the Office of Prescription Drug Promoiton (OPDP) in response to a request by the Division of Urology, Obstetrics and Gynecology (DUOG)) on October 28, 2020 to review the Applicant's proposed Patient Package Insert (PPI) for MYFEMBREE (relugolix/estradiol/norethindrone acetate) tablet, for oral use.

2 MATERIAL REVIEWED

- Draft MYFEMBREE (relugolix/estradiol/norethindrone acetate) PPI received on May 29, 2020, and received by DMPP and OPDP on March 18, 2021.
- Draft MYFEMBREE (relugolix/estradiol/norethindrone acetate) Prescribing Information received on May 29, 2020, and received by DMPP and OPDP on March 18, 2021.
- Approved ORIAHNN (elagolix/estradiol/norethindrone acetate) MG dated May 29, 2020.

3 REVIEW METHODS

To enhance patient comprehension, materials should be written at a 6th to 8th grade reading level, and have a reading ease score of at least 60%. A reading ease score of 60% corresponds to an 8th grade reading level.

Additionally, in 2008 the American Society of Consultant Pharmacists Foundation (ASCP) in collaboration with the American Foundation for the Blind (AFB) published *Guidelines for Prescription Labeling and Consumer Medication Information for People with Vision Loss*. The ASCP and AFB recommended using fonts such as Verdana, Arial or APHont to make medical information more accessible for patients with vision loss.

In our collaborative review of the PPI we:

- simplified wording and clarified concepts where possible
- ensured that the PPI is consistent with the Prescribing Information (PI)
- removed unnecessary or redundant information
- ensured that the PPI is free of promotional language or suggested revisions to ensure that it is free of promotional language
- ensured that the PPI meets the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)

4 CONCLUSIONS

The PPI is acceptable with our recommended changes.

5 RECOMMENDATIONS

- Please send these comments to the Applicant and copy DMPP and OPDP on the correspondence.
- Our review of the PPI is appended to this memorandum. Consult DMPP and OPDP regarding any additional revisions made to the PI to determine if corresponding revisions need to be made to the PPI.

Please let us know if you have any questions.

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/s/

SHARON W WILLIAMS
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ELVY M VARGHESE
03/31/2021 04:22:52 PM

LASHAWN M GRIFFITHS
03/31/2021 04:25:32 PM

FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion

****Pre-decisional Agency Information****

Memorandum

Date: March 23, 2021

To: Maria Wasilik
Regulatory Project Manager
Division of Urology, Obstetrics and Gynecology (DUOG)

From: Jina Kwak
Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

CC: Matthew Falter
Team Leader, OPDP

Subject: OPDP Labeling Comments for MYFEMBREE® (relugolix, estradiol, and norethindrone acetate) tablets, for oral use

NDA: 214846

In response to DUOG consult request dated October 28, 2020, OPDP has reviewed the proposed product labeling (PI), Patient Package Insert (PPI) and carton/container labeling MYFEMBREE® (relugolix, estradiol, and norethindrone acetate) tablets, for oral use (Myfembree).

Labeling: OPDP's comments on the proposed labeling are based on the draft labeling received by electronic mail from DUOG (Maria Wasilik) on March 18, 2021 are provided below.

A combined OPDP and Division of Medical Policy Programs (DMPP) review will be completed, and comments on the proposed Medication Guide will be sent under separate cover.

Carton and Container Labeling: OPDP has reviewed the attached proposed carton and container labeling submitted by the Sponsor to the electronic document room on February 22, 2021 and we do not have any comments.

Thank you for your consult. If you have any questions, please contact Jina Kwak: 301-796-4809 or Jina.kwak@fda.hhs.gov

16 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

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/s/

JINA KWAK
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FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH
DIVISION OF ANESTHESIOLOGY, ADDICTION MEDICINE, AND PAIN MEDICINE
10903 New Hampshire Ave, Silver Spring, MD 20993
Tel: (301) 796-2280

Consult Response

TO:	Jenifer Lawrence, MD Medical Officer Division of Urology, Obstetrics and Gynecology (DUOG) OND, CDER
FROM:	Timothy Jiang, MD, PhD Medical Officer Division of Anesthesiology, Addiction Medicine and Pain Medicine (DAAP)
THROUGH:	Emily Deng, MD, MPH Clinical Team Leader DAAP Joette Meyer, Pharm D Acting Associate Director for Pain Medicine DAAP Silvana Borges, MD Acting Deputy Division Director DAAP Rigoberto Roca, MD Division Director DAAP
SUBJECT:	Consult Response
SOURCE DOCUMENT:	Consult Request and Submissions to NDA 214846
DATE of REQUEST:	January 29, 2021
DATE of RESPONSE:	Stamp

Executive Summary

Relugolix is an orally active, nonpeptide, gonadotropin-releasing hormone (GnRH) receptor antagonist being developed in combination with estradiol (E2) and norethindrone acetate (NETA) (relugolix combination therapy) for the treatment of heavy menstrual bleeding associated with uterine fibroids. The fixed-dose combination (FDC) tablet (MYFENBREE) contains 40 mg of relugolix, 1 mg of E2, and 0.5 mg of NETA (relugolix/E2/NETA [40 mg/1 mg/0.5 mg]) to deliver relugolix combination therapy in a single tablet to be taken once daily for the proposed indication of the treatment of heavy menstrual bleeding associated with uterine fibroids.

The Applicant conducted two randomized, double-blind, placebo-controlled 24-week Phase 3 studies in women with heavy menstrual bleeding associated with uterine fibroids (MVT-601-3001 and MVT-601-3002) to support the indication. An extension (MVT-601-3003) to these studies was conducted to evaluate the long-term efficacy and safety of relugolix combination therapy. The two pivotal protocols and pertinent results are summarized in Appendix.

The protocol specified key pain-related secondary endpoint is proportion of women who achieved a maximum NRS score ≤ 1 for uterine fibroids associated pain over the last 35 days of treatment in the subset of women with a maximum pain score ≥ 4 during the 35 days prior to randomization. DAAP has not been previously consulted for the pivotal Phase 3 clinical protocol review during the pre-NDA stage.

(b) (4)

[redacted]

DAAP Response

We defer to review Division to determine if the Applicant has provided substantial evidence of effectiveness to support the proposed indication for the treatment of heavy menstrual bleeding associated with uterine fibroids. We acknowledge that the Applicant is not seeking a pain indicatio (b) (4) [redacted]

The protocol specified pain-related secondary endpoint of "proportion of women who achieved a maximum NRS score ≤ 1 for uterine fibroids associated pain over the last 35 days of treatment in the subset of women with a maximum pain score ≥ 4 during the 35 days prior to randomization" doesn't capture the clinically meaningful pain intensity change for the treatment of pain associated with uterine fibroids. We acknowledge that the pain associated with uterine fibroids is a chronic intermittent pain in which the severity of pain is correlated with heavy menstrual bleeding. However, one single maximum NRS value at baseline and at the end of treatment as landmarks are not adequate to capture the change in intensity of chronic, intermittent pain, which may wax and wane daily over a time period. For example, the women with a maximum pain score ≥ 4 during the 35 days prior to randomization may also have had a maximum pain score NRS score ≤ 1 on one or more of the other 35 days prior to randomization. Similarly, women who achieved a maximum NRS score ≤ 1 for uterine fibroids associated pain over

the last 35 days of treatment may have had a maximum pain score ≥ 4 at the end of treatment. Alternatively, women who achieved a maximum NRS score ≤ 1 for uterine fibroids associated pain prior to the randomization may have had a maximum pain score ≥ 4 as well at the end of treatment.

For the landmark analysis (i.e., change from the baseline), we recommend that the baseline pain intensity score be defined as an average of all available daily maximum pain scores over menstrual bleeding period in the last 35 days prior to randomization, and the end of treatment landmark be defined as an average of all available daily maximum pain scores over menstrual bleeding period in the last 35 days of treatment. If a responder analysis is used, the percent decrease in pain intensity should be clinically meaningful for the patient population. We acknowledge that a 30% decrease in pain intensity, (b) (4), is generally considered to be a clinically meaningful change in other chronic pain models. Additional analyses should include a plot of the monthly change from baseline in the average maximum pain intensity score during the time of menstrual bleeding over the entire double-blind treatment period.

It is important to take into consideration the use of rescue analgesics as additional outcome measures when assessing pain endpoints. The proportion of patients using rescue analgesic medication as well as the frequency and amount used should be documented. A broad spectrum of analgesics was used as concomitant medication in the two pivotal studies. Both studies failed to identify the specific rescue medications, the dosage and quantity of rescue use. In addition, the studies failed to specify pain intensity criteria pain for when a rescue medication should be administered, and the timing of pain in relation to the allowed rescue medication use. Rescue medication should be used in a manner that does not interfere with pain assessments. For example, pain could be assessed just before the administration of rescue medication and these data carried over to the next scheduled assessment time.

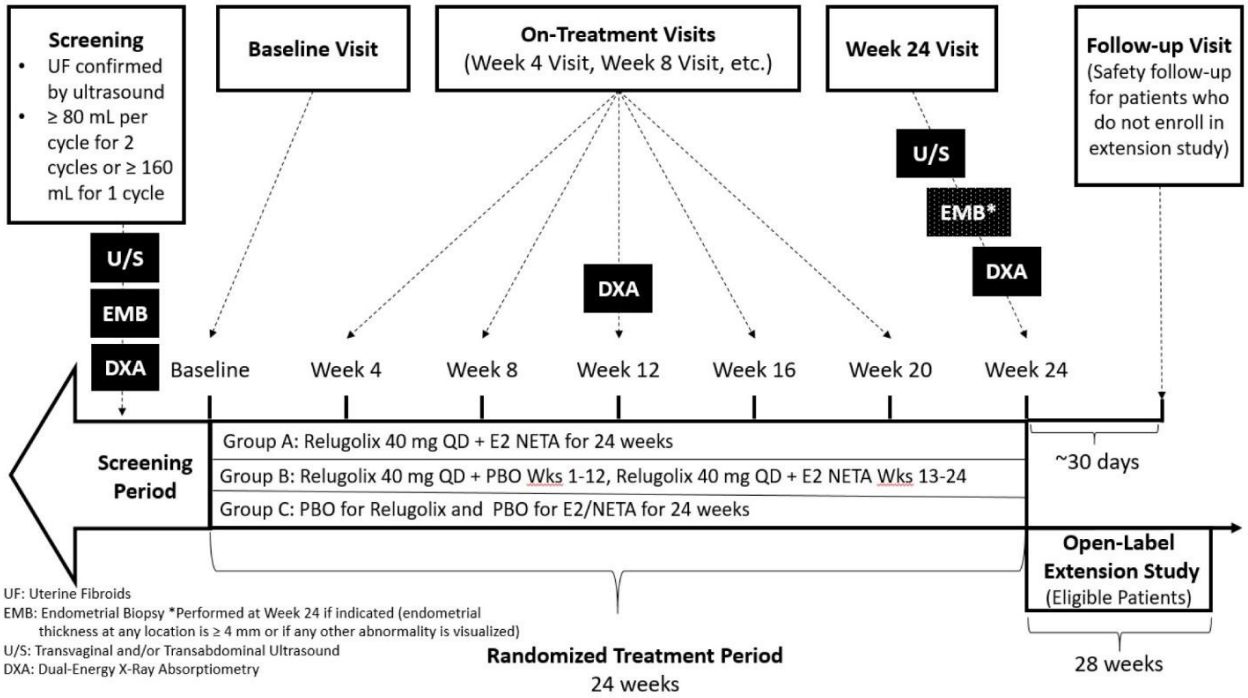
Lastly, the inclusion criteria for both pivotal Phase 3 studies didn't include a minimal pain intensity score at baseline. A subgroup analysis in women with a maximum pain score ≥ 4 during the 35 days prior to randomization is not valid, from a statistical perspective, if randomization was not stratified by baseline pain intensity score.

Appendix
Study MVT-601-3001 and MVT-601-3002
Relevant features of the two protocols with the same study design are summarized as followings:

Study Title:
An International Phase 3 Randomized, Double-Blind, Placebo-Controlled Efficacy and Safety Study to Evaluate relugolix Co-Administered with and without Low-Dose Estradiol and Norethindrone Acetate in Women with Heavy Menstrual Bleeding Associated with Uterine Fibroids

Primary Objective:
To determine the benefit of relugolix 40 mg once a day co-administered with estradiol (E2) 1 mg and norethindrone acetate (NETA) 0.5 mg compared with placebo for 24 weeks on heavy menstrual bleeding associated with uterine fibroids.

Methods:
Both studies were international Phase 3, randomized, double-blind, placebo-controlled study to evaluate the efficacy and safety of oral relugolix 40 mg once a day co-administered with E2 1 mg and NETA 0.5 mg for 24 weeks. The study scheme for both studies are summarized by the Sponsor as follows:



Source: Applicant's submission

Patients completed daily electronic diaries (eDiaries) that captured compliance with study treatment, menstrual bleeding, use of feminine products for menstrual bleeding, uterine fibroid-associated pain by the numerical rating scale (NRS), and use of pain medication to treat pain caused by uterine fibroids.

Study Populations:
For MVT-601-3001, a total of 388 patients were randomized with 128 randomized to relugolix + E2/NETA, 132 randomized to relugolix + delayed E2/NETA, and 128 randomized to placebo. For, MVT-601-3002, a total of 382 patients were randomized: with 126 randomized to relugolix + E2/NETA, 127 randomized to relugolix + delayed E2/NETA, and 129 randomized to placebo.

Key Inclusion Criteria:

- Premenopausal female aged 18 to 50 years old (inclusive)
- Had regularly-occurring menstrual periods of ≤ 14 days duration with a cycle of 21 to 38 days from the start of one menstrual period until the start of the next, by patient history for at least three months prior to the screening 1 visit;
- Had a diagnosis of uterine fibroids that was confirmed by a transvaginal ultrasound performed during the screening period; at least one uterine fibroid had to be verified by a central reader to meet at least one of the following criteria
    - Subserosal, intramural, or < 50% intracavitary submucosal fibroid with a diameter ≥ 2 cm (longest diameter), or
    - Multiple small fibroids with a total uterine volume of ≥ 130 cm3
- Had heavy menstrual bleeding associated with uterine fibroids as evidenced by an MBL volume of ≥ 160 mL during 1 cycle or ≥ 80 mL per cycle for 2 menstrual cycles as measured by the alkaline hematin method during the screening period.

Reviewer's comments:
Pain intensity is not one of the inclusion criteria.

Key Exclusion Criteria:

- Had transvaginal and/or transabdominal ultrasound during the screening period demonstrating pathology other than uterine fibroids that could have been responsible for or contributing to the patient's heavy menstrual bleeding, such as uterine or cervical polyps ≥ 2.0 cm, large simple ovarian cyst > 4.0 cm, endometrioma(s) > 4.0 cm, or any other clinically significant gynecological disorder determined by the investigator to require further evaluation and/or treatment during the study
- Had known rapidly enlarging uterine fibroids in the opinion of the investigator;
- Had undergone myomectomy, ultrasound-guided laparoscopic radiofrequency ablation, or any other surgical procedure for fibroids, uterine artery embolization, magnetic resonance-guided focused ultrasound for fibroids, as well as endometrial

ablation for abnormal uterine bleeding within 6 months prior to the screening 1 visit;
- Had a weight that exceeded the weight limit of the DXA scanner or had a condition that precluded an adequate DXA measurement at the lumbar spine and proximal femur (eg, bilateral hip replacement or spinal hardware in the lumbar spine);
- Had a baseline BMD z-score < -2.0 at spine, total hip, or femoral neck;

Analgesics Use:
From the Screening 1 visit to the Week 24 (or early termination) visit, the recommended analgesics for uterine-fibroid associated pain were as follows:
First-line: ibuprofen
Second-line: non-ibuprofen non-steroidal anti-inflammatory drug or acetaminophen
Third-line: opioid or opioid-acetaminophen combination
Fourth-line: investigator discretion

Reviewer's comments:
A broad spectrum of analgesics could be used as concomitant medication. None of those analgesics is clearly defined as a rescue.

Efficacy:
Primary efficacy endpoint
Proportion of women in the relugolix + E2/NETA group versus the placebo group who achieved an MBL volume of < 80 mL and at least a 50% reduction from baseline MBL volume over the last 35 days of treatment

Key pain-related secondary endpoint with multiplicity adjusted
Proportion of women who achieved a maximum NRS score ≤ 1 for uterine fibroids associated pain over the last 35 days of treatment in the subset of women with a maximum pain score ≥ 4 during the 35 days prior to randomization.

Pertinent Results
Demographics of the two studies are summarized as below:

TABLE 1 SUMMARY OF SELECTED BASELINE CHARACTERISTICS ACROSS PHASE 3 RELUGOLIX COMBINATION THERAPY STUDIES (MITT POPULATION)

Study No.	MVT-601-3001	MVT-601-3002	MVT-601-3003
N	387	381	476
MBL volume (mL)[a]	229.1 (156.6)	228.5 (152.2)	234.33 (161.753)
N	387	381	476
Hgb concentration (g/dL)	11.25 (1.531)	11.16 (1.556)	11.22 (1.538)
N	385	376	NA
Maximum NRS score	5.4 (3.24)	5.6 (3.07)	NA

Maximum NRS score by severity: N (%)			
NRS < 4	117 (30.2%)	96 (25.2%)	123 (25.8%)
NRS ≥ 4	268 (69.3.%)	280 (73.5%)	350 (73.5%)
Missing	2 (0.5%)	4 (1.3%)	3 (0.6%)
N	384	375	476
BPD scale score	68.90 (22.115)	70.89 (21.312)	70.80 (20.067)
UFS-QoL symptom severity score	58.6 (20.87)	60.3 (20.81)	60.09 (19.806)
UFS-QoL total score [b, c]	36.5 (21.01)	37.2 (21.82)	35.90 (20.639)
PGA for function[d]: N(%)			
No limitation	32 (8.3%)	27 (7.1%)	29 (6.1%)
Mild to extreme limitation	268 (69.3%)	300 (78.7%)	365 (76.7%)
Missing	87 (22.5%)	54 (14.2%)	82 (17.2%)
N	385	381	474
Index uterine fibroid volume (cm^3)[e]	79.32 (132.414)	75.56 (136.224)	81.57 (136.996)
N	386	381	476
Uterine volume (cm^3)	416.28 (362.299)	399.52 (372.555)	409.24 (347.615)

Applicant's submission

The mean maximal NRS scores within the last 35 days prior to study entry ranged from 5.4 to 5.6 across studies during the time prior to randomization; across studies approximately 70% of patients reported maximum NRS ≥ 4 at baseline (as no minimal NRS is required in inclusion criteria).

A summary of concomitant medications for the two studies are provided as below by the Sponsor:

TABLE 2 SUMMARY OF CONCOMITANT MEDICATIONS REPORTED IN > 5% OF PATIENTS IN ANY TREATMENT GROUP (MVT-601-3001)

Preferred Term	Relugolix + E2/NETA (N = 128)	Relugolix + Delayed E2/NETA (N = 132)	Placebo (N = 127)	Total (N = 387)
IBUPROFEN	76 (59.4%)	74 (56.1%)	92 (72.4%)	242 (62.5%)
FERROUS SULFATE	36 (28.1%)	39 (29.5%)	32 (25.2%)	107 (27.6%)
PARACETAMOL	23 (18.0%)	26 (19.7%)	26 (20.5%)	75 (19.4%)
IRON	22 (17.2%)	20 (15.2%)	18 (14.2%)	60 (15.5%)
HYDROCHLOROTHIAZIDE	13 (10.2%)	6 (4.5%)	9 (7.1%)	28 (7.2%)
COLECALCIFEROL	13 (10.2%)	13 (9.8%)	15 (11.8%)	41 (10.6%)
VITAMINS NOS	11 (8.6%)	13 (9.8%)	22 (17.3%)	46 (11.9%)
LISINOPRIL	9 (7.0%)	1 (0.8%)	4 (3.1%)	14 (3.6%)

VITAMIN D NOS	9 (7.0%)	23 (17.4%)	19 (15.0%)	51 (13.2%)
ASCORBIC ACID	8 (6.3%)	5 (3.8%)	5 (3.9%)	18 (4.7%)
NAPROXEN SODIUM	8 (6.3%)	8 (6.1%)	10 (7.9%)	26 (6.7%)
PHENTERMINE	7 (5.5%)	2 (1.5%)	3 (2.4%)	12 (3.1%)
FERRIC SODIUM GLUCONATE COMPLEX	7 (5.5%)	2 (1.5%)	5 (3.9%)	14 (3.6%)
NAPROXEN	6 (4.7%)	9 (6.8%)	15 (11.8%)	30 (7.8%)
AZITHROMYCIN	4 (3.1%)	7 (5.3%)	4 (3.1%)	15 (3.9%)
AMOXICILLIN	2 (1.6%)	3 (2.3%)	8 (6.3%)	13 (3.4%)
CALCIUM CARBONATE	2 (1.6%)	5 (3.8%)	7 (5.5%)	14 (3.6%)
FLUTICASONE PROPIONATE	2 (1.6%)	7 (5.3%)	3 (2.4%)	12 (3.1%)
CIPROFLOXACIN	2 (1.6%)	8 (6.1%)	2 (1.6%)	12 (3.1%)

Source: Applicant's submission

In MVT-601-3001, ibuprofen and naproxen were reported more in the subjects taking study drug than that of placebo, however, paracetamol was distributed evenly between the treatment and placebo.

TABLE 3 SUMMARY OF CONCOMITANT MEDICATIONS REPORTED IN > 5% OF PATIENTS IN ANY TREATMENT GROUP (MVT-601-3002)

Preferred Term	Relugolix + E2/NETA (N = 126)	Relugolix + Delayed E2/NETA (N = 126)	Placebo (N = 129)	Total (N = 381)
IBUPROFEN	80 (63.5%)	76 (60.3%)	81 (62.8%)	237 (62.2%)
FERROUS SULFATE	35 (27.8%)	28 (22.2%)	35 (27.1%)	98 (25.7%)
IRON	25 (19.8%)	24 (19.0%)	23 (17.8%)	72 (18.9%)
PARACETAMOL	22 (17.5%)	23 (18.3%)	32 (24.8%)	77 (20.2%)
VITAMIN D NOS	16 (12.7%)	13 (10.3%)	15 (11.6%)	44 (11.5%)
VITAMINS NOS	13 (10.3%)	16 (12.7%)	16 (12.4%)	45 (11.8%)
COLECALCIFEROL	10 (7.9%)	17 (13.5%)	12 (9.3%)	39 (10.2%)
NAPROXEN	9 (7.1%)	8 (6.3%)	7 (5.4%)	24 (6.3%)
TRAMADOL	7 (5.6%)	2 (1.6%)	4 (3.1%)	13 (3.4%)
LORATADINE	7 (5.6%)	3 (2.4%)	4 (3.1%)	14 (3.7%)
NAPROXEN SODIUM	7 (5.6%)	4 (3.2%)	5 (3.9%)	16 (4.2%)
HYDROCHLOROTHIAZIDE	7 (5.6%)	7 (5.6%)	7 (5.4%)	21 (5.5%)
OMEPRAZOLE	6 (4.8%)	8 (6.3%)	6 (4.7%)	20 (5.2%)
VITAMIN B12 NOS	3 (2.4%)	7 (5.6%)	11 (8.5%)	21 (5.5%)
METRONIDAZOLE	1 (0.8%)	2 (1.6%)	7 (5.4%)	10 (2.6%)

Source: Applicant's submission

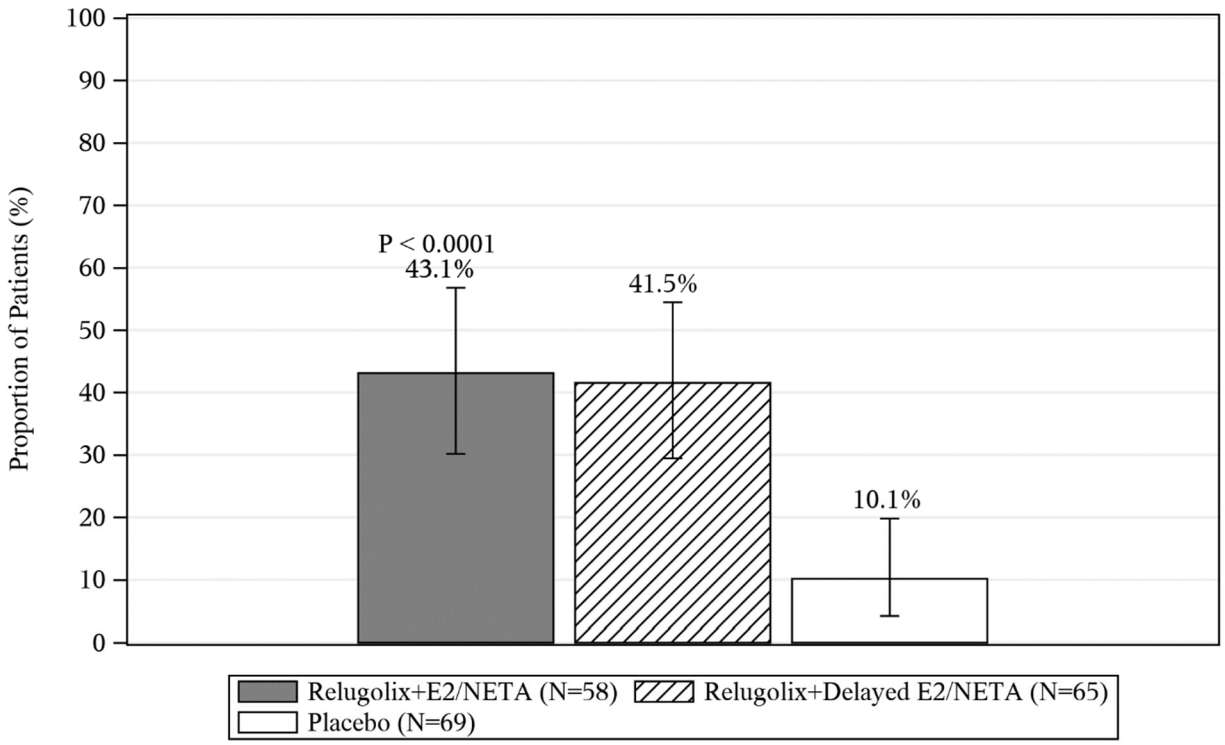
In MVT-601-3002, there is no clear pattern of less analgesics use in the treatment arm than the placebo arm.

Pain-related results

One of the seven key secondary efficacy endpoints with multiplicity adjustment is *Proportion of women who achieved a maximum NRS score ≤ 1 for uterine fibroids associated pain over the last 35 days of treatment in the subset of women with a maximum pain score ≥ 4 during the 35 days prior to randomization.*

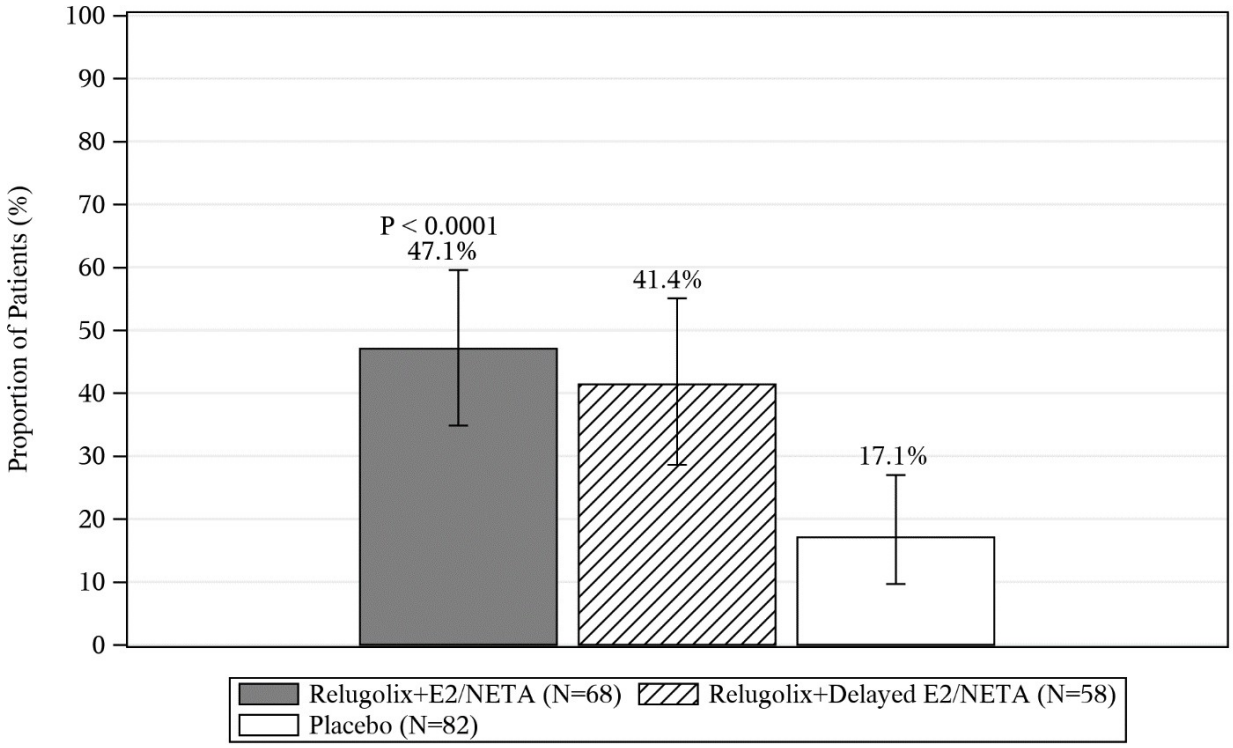
In the pain-evaluable population (ie, those women reporting maximum NRS pain scores ≥ 4 [moderate to severe pain] during the 35 days prior to randomization and who had at least 28 days of NRS scores recorded in their eDiary over the last 35 days of treatment), 43 % and 47% of women in the relugolix + E2/NETA group achieved NRS ≤ 1 (minimal to no pain) over the last 35 days of treatment, compared with 10 % and 17% of women in the placebo group (p< 0.0001), in MVT-601-3001 and MVT-601-3002 respectively as figures below:

FIGURE 1 PROPORTION OF PATIENTS WITH A MAXIMUM NRS SCORE ≤ 1 DURING THE LAST 35 DAYS OF TREATMENT IN A SUBSET OF PAIN EVALUABLE PATIENTS (MVT-601-3001)



Source: Applicant's submission

FIGURE 2 PROPORTION OF PATIENTS WITH MAXIMUM NRS SCORE ≤ 1 DURING THE LAST 35 DAYS OF TREATMENT IN A SUBSET OF PAIN EVALUABLE PATIENTS (MVT-601-3002)



Source: Applicant's submission

Reviewer's comments:

One single maximum NRS value at baseline and landmark can't adequately capture the pain intensity of chronic pain, which may wax and wane daily. In addition, to establish analgesic efficacy, DAAP prefers pain intensity change from landmark to baseline, rather than, responder analysis.

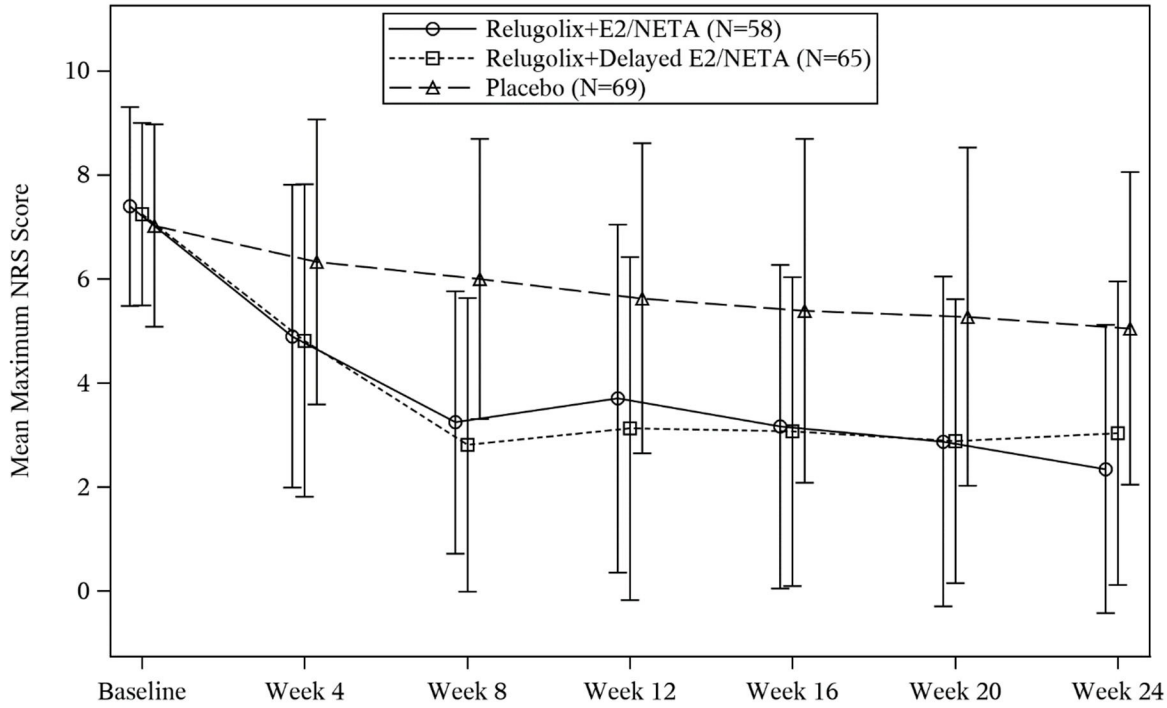
Additional Analyses of Pain

Additional analyses of pain include, mean maximum monthly pain scores, the percentage of patients with a 30% reduction from baseline in NRS score, and pain NRS during bleeding days (dysmenorrhea) and non-bleeding days (nonmenstrual pain), which all seem to favor the study drug in terms in the pain reduction population. Furthermore, changes in analgesic use also were analyzed for both pivotal studies, both menstrual and nonmenstrual, with relugolix combination therapy relative to placebo, were associated with reductions in the use of analgesics for both studies. The additional analyses are summarized as follows:

Mean maximum monthly pain scores

The Mean maximum monthly pain scores for the two pivotal studies are presented in the figures below:

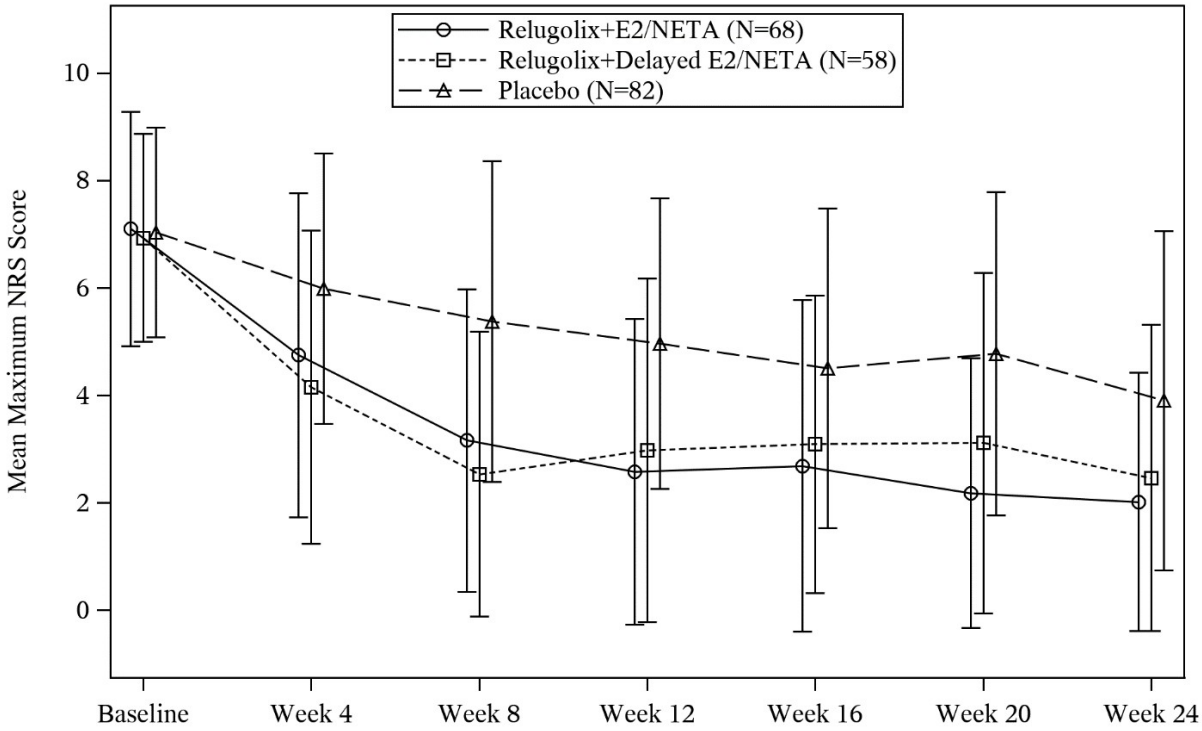
FIGURE 3 MEAN MAXIMUM MONTHLY PAIN SCORE OVER TIME FOR PATIENTS WITH MAXIMUM NRS ≥ 4 AT BASELINE (MVT-601-3001)



Source: Applicant's submission

At baseline, mean maximum NRS pain scores in the pain evaluable population were similar across treatment groups ranging from 7.0 in the placebo group to 7.4 in the relugolix + E2/NETA group. The mean maximum NRS pain score at each visit was calculated as the average of maximum NRS scores observed from the individual patients over the period from previous visit to the corresponding time point. In the relugolix + E2/NETA group, mean maximum NRS pain scores decreased with increasing duration of study drug exposure, from severe pain (7.4) at baseline to mild pain (2.3) at Week 24. While mean maximum NRS pain scores decreased in the placebo group throughout the study, from severe pain (7.0) at baseline to moderate pain (5.0) at Week 24, the decreases observed in the relugolix + E2/NETA group were greater than those in the placebo group.

FIGURE 4 MEAN MAXIMUM MONTHLY PAIN SCORE OVER TIME FOR PATIENTS WITH MAXIMUM NRS ≥ 4 AT BASELINE (MVT-601-3002)



Source: Applicant's submission

At baseline, mean maximum NRS pain scores in patients with a maximum NRS score ≥ 4 at baseline were similar across treatment groups ranging from 6.9 in the relugolix + delayed E2/NETA group to 7.1 in the relugolix + E2/NETA group. The mean maximum NRS pain score at each visit was calculated as the average of maximum NRS scores observed from the individual patients over the period from previous visit to the corresponding timepoint. In the relugolix + E2/NETA group, mean maximum NRS pain scores decreased with increasing duration of study drug exposure, from severe pain (7.1) at baseline to mild pain (2.0) at Week 24. While mean maximum NRS pain scores decreased in the placebo group throughout the study, from severe pain (7.0) at baseline to moderate pain (3.9) at Week 24, the decreases observed in the relugolix + E2/NETA group were greater than those in the placebo group.

Percentage of patients with a 30% reduction from baseline in NRS score
In the subset of pain evaluable patients of Study MVT-601-3001, a higher proportion of patients in the relugolix + E2/NETA group achieved a ≥ 30% reduction in NRS score for uterine fibroid-associated pain from baseline to the last 35 days of treatment (72.41%) when compared with patients in the placebo group (39.13%).

In the subset of pain evaluable patients of Study MVT-601-3002, in the same trend of MVT-601-3001, a higher proportion of patients in the relugolix + E2/NETA group achieved a ≥ 30% reduction in NRS score for uterine fibroid-associated pain from baseline to the last 35 days of treatment (70.59%) when compared with patients in the placebo group (41.46%).

Reviewer's comments:
While 30% reduction in NRS score is generally considered as clinically meaningful, it is not clear how the baseline and the landmark pain intensity is captured.

Pain Analyses by Bleeding and Non-Bleeding Days
To further characterize patients' experiences with uterine fibroid-associated pain, the proportions of patients with a maximum NRS pain score ≤ 1 during the last 35 days of treatment, assessed during bleeding and non-bleeding days, were evaluated in the pain evaluable patients.

The proportion of dysmenorrhea-evaluable patients and non-menstrual pain evaluable patients (maximum NRS pain score ≥ 4 on a bleeding day at baseline) who achieved a maximum NRS pain score ≤ 1 during bleeding days in the last 35 days of treatment was higher in the relugolix + E2/NETA group when compared with the placebo group for both studies.

Analgesic Use
For MVT-601-3001, in the dysmenorrhea-evaluable population, a similar proportion of women used medication to treat uterine fibroid pain in the relugolix + E2/NETA and placebo groups (analgesic use on 32.8% and 34.1% of bleeding days, respectively) at baseline, At Week 24/EOT, patients in the relugolix + E2/NETA group used pain medication less often (6.6% of bleeding days) compared with women in the placebo group (26.4% of bleeding days).

For MVT-601-3002, at baseline, in the dysmenorrhea-evaluable population, a similar proportion of women used medication to treat uterine fibroid pain in the relugolix + E2/NETA and placebo groups (38.6% and 35.3% of bleeding days, respectively). Whereas, at Week 24/EOT, patients in the relugolix + E2/NETA group used pain medication less often (7.7% of bleeding days) compared with women in the placebo group (24.7% of bleeding days).

In the non-menstrual pain evaluable population, analgesic use follows the similar trend as in the dysmenorrhea-evaluable population according the Sponsor.

Reviewer's comments:

These analyses are not clinically meaningful as the protocols failed to identify what type and amount of analgesics used in the studies.

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/

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Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research | Office of Surveillance and Epidemiology (OSE)

Feasibility of ARIA to Evaluate the Association between Myfembree Use and Risks of Pregnancy, Maternal, and Fetal/Neonatal Outcomes

Date:	March 2, 2021
Reviewer:	Wei Liu, PhD, MSc Division of Epidemiology II
Team Leader (acting):	Wei Liu, PhD, MSc Division of Epidemiology II
Division Director:	CAPT David Moeny, RPh, MPH, USPHS Division of Epidemiology II
OPE Director:	Judith Zander, MD
FDA Sentinel Team Lead:	Michael D. Nguyen, MD
OSE Deputy Director:	Robert Ball, MD, MPH, ScM
Subject:	Feasibility of ARIA to evaluate the association between Myfembree use and risks of pregnancy, maternal, and fetal/neonatal outcomes
Drug Name(s):	Myfembree (relugolix/estradiol/norethindrone acetate)
Application Type/Number:	NDA 214846
Applicant/sponsor:	Myovant
OSE RCM #:	2020-1119

EXECUTIVE SUMMARY *(place "X" in appropriate boxes)*

Memo type	
-Initial	
-Interim	
-Final	X
Source of safety concern	
-Peri-approval	X
-Post-approval	
Is ARIA sufficient to help characterize the safety concern?	
-Yes	
-No	X
If "No", please identify the area(s) of concern.	
-Surveillance or Study Population	
-Exposure	
-Outcome(s) of Interest	
-Covariate(s) of Interest	
-Surveillance Design/Analytic Tools	X

A. General ARIA Sufficiency Template

1. BACKGROUND INFORMATION

1.1. Medical Product

Myfembree® is a combination oral product containing the gonadotropin-releasing hormone (GnRH) receptor antagonist relugolix 40 mg, estradiol 1 mg, and norethindrone acetate 0.5 mg. The applicant seeks to market Myfembree (hereafter referred to as R+E2/NETA) for the treatment of heavy menstrual bleeding associated with uterine fibroids in premenopausal women. Two 6-month, randomized, placebo-controlled, double-blinded, phase-3 clinical trials showed that the primary efficacy endpoints (e.g., the proportion of women whose menstrual blood loss [MBL] was less than 80 mL and the proportion of women with at least 50% reduction in MBL volume) were met successfully.

1.2. Describe the Safety Concern

Relugolix can suppress ovarian estradiol production. Although all clinical trial participants of relugolix were asked to use nonhormonal contraception, a total of 27 pregnancies were still reported in clinical development program of relugolix.[a] Among these, 11 women became pregnant during treatment with relugolix (as monotherapy or in combination with E2/NETA or with delayed E2/NETA), 1 woman became pregnant prior to initiating treatment with relugolix (inadvertent early pregnancy exposure to relugolix), 4 women became pregnant after completing treatment with relugolix, 10 women were in the placebo group, and 1 woman was a participant of the randomized withdrawal study. No cases of major congenital malformations were reported resulting from maternal exposure to relugolix during pregnancy.

Of the 11 pregnancies in women who became pregnant during treatment with relugolix, four resulted in live birth (three full term, one premature), one resulted in missed abortion, three remain ongoing, and three are of unknown status/lost to follow-up. The one pregnancy with conception prior to initiation of treatment resulted in a live birth at full term. Of the four pregnancies in women who became pregnant after completing treatment with relugolix, two resulted in live birth (one full term, one premature), one resulted in missed abortion, and one remains ongoing. Of the 10 pregnancies in women who were in a placebo group, 4 resulted in live birth (all full term), 2 resulted in induced abortion, 2 remain ongoing, and 2 are of unknown status/lost to follow-up.

Exposure to Myfembree early in pregnancy may increase the risk of early pregnancy loss. Thus, Myfembree is contraindicated in women who are pregnant. However, it is expected that pregnancies will occur in women who use Myfembree, given the drug's

[a] Myfembree® 120-Day Safety Update Report. Module 5.3.5.1 of EDR.

proposed indication (management of heavy menstrual bleeding associated with uterine fibroids) and target population (premenopausal women).

In July 2018, the FDA approved elagolix (Orilissa®), another oral GnRH receptor antagonist, indicated for the management of moderate to severe pain associated with endometriosis. Subsequently in May 2020, the FDA approved Oriahnn®, an oral combination of elagolix, estradiol, and norethindrone acetate, for the management of heavy menstrual bleeding associated with uterine fibroids in premenopausal women. Prior to the approval of both Orilissa and Oriahnn, Division of Epidemiology (DEPI) filed active risk identification and analysis (ARIA) memorandums, both of which concluded that the ARIA analytic tools were insufficient to support the proposed post-marketing pregnancy outcome (i.e., signal detection) study because data mining methods such as TreeScan have not been tested for birth defects and other pregnant outcomes (Wei Liu. OSE RCM # 2017-2302 and #2020-826). Hence, upon approval of Orilissa/Oriahnn, FDA required the sponsor to conduct postmarketing studies including a prospective pregnancy registry study and a pharmacoepidemiology database surveillance study to evaluate the effects of elagolix-containing medication on pregnancies, maternal, and fetal/neonatal outcomes. Postmarketing requirements (PMR) for Orilissa/Oriahnn used broad inclusion criteria, such that they can enroll women receiving elagolix-containing medication regardless of indication (e.g., elagolix with or without add-back therapy).

Other FDA approved GnRH agonists (e.g., lupron, buserelin, triptorelin) and GnRH antagonists (e.g., ganirelix, cetrorelix) are previously categorized as FDA Pregnancy X drugs (i.e., fetal abnormalities are demonstrated in animal or human studies and the risks involved in use of the drug in pregnant women outweigh potential benefits) and are contraindicated in women who are or may become pregnant.[b]

Hormonal contraception containing E2 and/or NETA have been widely used. To date, no data suggests that these products are associated with increased risk of adverse pregnancy outcomes. Therefore, the additional components in the combination product do not raise any new safety concerns.

1.3. FDAAA Purpose (per Section 505(o)(3)(B))

Purpose (place an "X" in the appropriate boxes; more than one may be chosen)	
Assess a known serious risk	
Assess signals of serious risk	
Identify unexpected serious risk when available data indicate potential for serious risk	X

[b] Under the new PLLR rule, the sponsors are required to update the product label by removing pregnancy category classification and provide updated and accurate recommendations for labeling subsections 8.1-8.3. The new recommendations should reflect an integrated assessment of known risks relevant to pregnancy, lactation and infertility based on available information/data (e.g., from published literature, relevant cases reported in the drug pharmacovigilance database, ongoing/closed pregnancy registry).

2. REVIEW QUESTIONS

2.1. Why is pregnancy safety a safety concern for this product? Check all that apply.

☐ Specific FDA-approved indication in pregnant women exists and exposure is expected
☐ No approved indication, but practitioners may use product off-label in pregnant women
☒ No approved indication, but there is the potential for inadvertent exposure before a pregnancy is recognized
☒ No approved indication, but use in women of child bearing age is a general concern

2.2. Regulatory Goal

☒ Signal detection – Nonspecific safety concern with no prerequisite level of statistical precision and certainty
☐ *Signal refinement of specific outcome(s)* – Important safety concern needing moderate level of statistical precision and certainty.
☐ *Signal evaluation of specific outcome(s)* – Important safety concern needing highest level of statistical precision and certainty (e.g., chart review).

2.3. What type of analysis or study design is being considered or requested along with ARIA? Check all that apply.

☒ Pregnancy registry with internal comparison group
☐ Pregnancy registry with external comparison group
☐ Enhanced pharmacovigilance (i.e., passive surveillance enhanced by with additional actions)
☒ Electronic database study with chart review
☐ Electronic database study without chart review
☐ Other, please specify: *Click here to enter text.*

2.4. Which are the major areas where ARIA not sufficient, and what would be needed to make ARIA sufficient?

☐ Study Population
☐ Exposures
☐ Outcomes
☐ Covariates
☒ Analytical Tools

For any checked boxes above, please describe briefly:

Analytical tool:

ARIA analytic tools are not sufficient to assess the regulatory question of interest because data mining methods have not been tested for birth defects and other pregnancy outcomes.

2.5. Please include the proposed PMR language in the approval letter.

The PMRs to be issued for the combined product R+E2/NETA (Myfembree) are as follows:

Based on appropriate scientific data, FDA has determined that you are required to conduct the following studies and trial:

PMR #1: Conduct a Pregnancy Exposure Registry, a prospective, registry based observational exposure cohort study, that compares the maternal, fetal, and infant outcomes of women exposed to relugolix plus E2/NETA during pregnancy to 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 other 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 first year of life.

PMR #2: 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 women exposed to relugolix plus E2/NETA during pregnancy compared to an unexposed disease-matched control population.

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ROBERT BALL
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DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Division of Pediatric and Maternal Health
Office of New Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Silver Spring, MD 20993
Tel 301-796-2200
FAX 301-796-9744

Division of Pediatric and Maternal Health Review

Date: February 9, 2021 **Date consulted:** January 27, 2021

From: Miriam Dinatale, DO, Team Leader, Maternal Health
Division of Pediatric and Maternal Health (DPMH)

Through: Lynne P. Yao, MD, OND, Division Director, DPMH

To: Division of Urology, Obstetrics and Gynecology (DUOG)

Drug: Myfembree (relugolix, estradiol, and norethindrone) tablets

NDA: 214846

Applicant: Myovant

Subject: Evaluation of post-marketing requirements (PMRs)

Proposed Indication: For the treatment of heavy menstrual bleeding associated with uterine fibroids

Materials Reviewed:

- DPMH consult request dated January 27, 2021, DARRTS reference ID 4683300
- Applicant's submitted background package and proposed labeling for NDA 214846

Consult Question: "We are requesting PMRs for pregnancy outcomes and have two draft initial proposals."

INTRODUCTION AND BACKGROUND

On May 29, 2020, Myovant submitted an 505(b)(2) original NDA for Myfembree **(**relugolix, estradiol, and norethindrone) tablets for the proposed indication of the treatment of heavy menstrual bleeding associated with uterine fibroids. The relugolix component is a new molecular entity while estradiol and norethindrone are approved drugs.

On January 27, 2021, DUOG consulted DPMH to assist with PMR language for two proposed pregnancy safety studies. DUOG reviewed the applicant's proposed labeling language and recommends a pregnancy contraindication based on findings from animal studies, the drug's mechanism of action, and potential for Myfembree to cause early pregnancy loss.

Regulatory History

Relugolix (Relumina) was approved as monotherapy to improve the symptoms of uterine myoma in Japan in January 2019. The new NDA for Myfembree includes a three-drug combination of relugolix, estradiol and norethindrone.

Drug Characteristics[1]

- Mechanism of Action:
    - Relugolix is a non-peptide GnRH receptor antagonist that competitively binds to pituitary GnRH receptors, thereby reducing the release of luteinizing hormone (LH) and follicle-stimulating hormone (FSH), and consequently, the production of estrogen, the corpus luteum, and secretion of progesterone.
    - Estradiol acts by binding to nuclear receptors that are expressed in estrogen-responsive tissues. As a component of MYFEMBREE, the addition of exogenous estradiol may reduce the increase in bone resorption and resultant bone loss that can occur due to a decrease in circulating estrogen from relugolix alone.
    - Progestins, such as norethindrone, act by binding to nuclear receptors that are expressed in progesterone-responsive tissues. As a component of MYFEMBREE, norethindrone may protect the uterus from the potential adverse endometrial effects of unopposed estrogen.
- Dose and administration:40mg/1mg/0.5mg fixed dose combination tablet. One tablet is taken once daily and started (b) (4) the onset of menstrual bleeding.
- Bioavailability for relugolix: 11.6%
- Half-life: 61.5 hours (relugolix), 16.6 hours (estradiol), 10.9 hours (norethindrone)
- Molecular weight: 623.63 Daltons (relugolix), (b) (4) Daltons (estradiol), 340.5 Daltons (norethindrone)
- Adverse reactions: thromboembolic disease, liver disease

[1] Applicant's proposed labeling for Myfembree with input from the DUOG Review Team

REVIEW

PREGNANCY

Uterine Fibroids and Pregnancy[2,3]

The prevalence of uterine fibroids is 4.5 to 68.6% depending on the study population and diagnostic methods used. Fibroids occur in 70% of black women or at a 2 to 3-fold higher risk compared to Caucasian women. Older age, pre-menopause, hypertension, and family history of uterine fibroids increase the risk of uterine fibroids in women.

Medical therapy to reduce heavy menstrual bleeding includes hormonal contraceptives, tranexamic acid, and nonsteroidal anti-inflammatory drugs. Gonadotropin-releasing hormone agonists or selective progesterone receptor modulators are an option for patients who need symptom relief preoperatively or who are approaching menopause. Surgical treatment includes hysterectomy, myomectomy, uterine artery embolization, and magnetic resonance-guided focused ultrasound surgery.

Nonclinical Experience[4]

In an embryo-fetal development study, oral administration of relugolix to pregnant rabbits during the period of organogenesis (Days 6 to 18 of gestation) resulted in abortion, total litter loss, or decreased number of live fetuses at a dose of 9 mg/kg/day (about half the human exposure at the maximum recommended human dose (MRHD) of 40 mg daily, based on AUC). No treatment related malformations were observed in surviving fetuses. No treatment related effects were observed at 3 mg/kg/day (about 0.1-fold the MRHD) or lower. The binding affinity of relugolix for rabbit GnRH receptors is unknown.

In a similar embryo-fetal development study, oral administration of relugolix to pregnant rats during the period of organogenesis (Days 6 to 17 of gestation) did not affect pregnancy status or fetal endpoints at doses up to 1000 mg/kg/day (300 times the MRHD), a dose at which maternal toxicity (decreased body weight gain and food consumption) was observed. A no adverse effect level (NOAEL) for maternal toxicity was 200 mg/kg/day (86 times the MRHD). In rats, the binding affinity of relugolix for GnRH receptors is more than 1000-fold less than in humans, and this study represents an assessment of non-pharmacological targets of relugolix during pregnancy. No treatment related malformations were observed up to 1000 mg/kg/day.

In a pre- and postnatal developmental study in pregnant and lactating rats, oral administration of relugolix to rats during late pregnancy and lactation (Day 6 of gestation to Day 20 of lactation) had no effects on pre- and postnatal development at doses up to 1000 mg/kg/day (300 times th e MRHD), a dose in which maternal toxicity was observed (effects on body weight gain). A NOAEL for maternal toxicity was 100 mg/kg/day (34 times the MRHD.)

Review of Pharmacovigilance Database

The applicant searched their safety database of all completed and ongoing clinical trials using a cut-off date of July 7, 2020. The applicant identified 27 pregnancies. Of these pregnancies, 10 included patients in the placebo group. The following are outcomes of the remaining 17 patients:

[2] Stewart et al. Epidemiology of uterine fibroids: a systematic review. BJOG. 2017. 124(10): 1501-1512.

[3] De La Cruz, M and Buchanan E. Uterine Fibroids: Diagnosis and Treatment. Am Fam Physician. 2017. 95(2): 100-107.

[4] Applicant's proposed labeling for relugolix, estradiol, and norethindrone with DUOG Nonclinical input.

- 11 patients exposed to relugolix during pregnancy.
  - 4 live births (3 full term, one premature neonate)
  - 1 missed abortion
  - 3 ongoing pregnancies
  - 3 lost-to-follow-up
- 1 patient exposed to relugolix prior to start of study. The patient had a live birth that was full term.
- 4 patients became pregnant after completing treatment with relugolix. There were two live births (1 full term and 1 preterm), one missed abortion, one pregnancy was ongoing.
- 1 patient became pregnant while in the randomized withdrawal study (while receiving blinded therapy relugolix combination or placebo.)

The applicant concluded that no safety signals were identified for the pregnancies exposed to relugolix.

DATA REVIEW

DPMH conducted a review of literature regarding relugolix and pregnancy and lactation[5] in PubMed and regarding lactation in LactMed[6] and *Medications and Mother's Milk*[7]. There is no published information on the use of relugolix in pregnant or lactating women.

DISCUSSION AND CONCLUSIONS

Pregnancy

Uterine fibroids are a common condition among females of reproductive potential. In clinical trials with relugolix, there were a total of 11 pregnancies that were exposed to relugolix. Although labeling language will include a pregnancy contraindication, GnRH antagonists can suppress the production of sex hormones that lead to ovulation; therefore, females who take Myfembree may experience amenorrhea or a reduction in the amount, intensity, or duration of menstrual bleeding, which may delay the ability to recognize the occurrence of a pregnancy. Given the anticipated use of relugolix, estradiol (E2), and norethindrone (NETA) in females of reproductive potential who may become pregnant, post-marketing studies are essential. DPMH agrees with DUOG's plan to issues PMRs for both a pregnancy registry study and complementary study.

Lactation

Relugolix is present in rat milk. There is no information about the presence of relugolix in human milk. Detectable amounts of estrogen and progestin have been identified in the breast milk of women receiving estrogen plus progestin therapy and can reduce milk production in breastfeeding females. DPMH discussed a PMR for a clinical lactation study with the DUOG clinical team who noted that the patients who will be using Myfembree will likely not be pregnant or in the postpartum period; therefore, a clinical lactation study would not be warranted in this patient population. If the product gets approved for a supplemental indication, such as

[5] DPMH PLLR Review for Repatha. Christos Mastroyannis MD. June 4, 2015. DARRTS Reference ID 3786269
[6] LactMed. https://www.ncbi nlm nih.gov/books/NBK500751/. Accessed 1/14/2021.
[7] https://www.halesmeds.com/monographs/62131?q=evolucumab. Accessed 1/14/2021.

(b) (4) DUOG noted that they would reconsider a PMR for a clinical lactation study. DPMH agreed with DUOG's plan.

DPMH RECOMMENDATIONS FOR POSTMARKETING REQUIREMENTS (PMR)

DPMH recommends the following PMR language:

1. For the pregnancy exposure registry, the PMR description should include the following: Conduct a Pregnancy Exposure Registry, a prospective, registry based observational exposure cohort study, that compares the maternal, fetal, and infant outcomes of women exposed to relugolix plus E2/NETA during pregnancy to 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 other 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 first year of life.

2. For the complementary study, DPMH recommends the following PMR language: 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 women exposed to relugolix plus E2/NETA during pregnancy compared to an unexposed control population.

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/s/

MIRIAM C DINATALE
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LYNNE P YAO
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MEMORANDUM

REVIEW OF REVISED LABEL AND LABELING
Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

Date of This Memorandum:	January 29, 2021
Requesting Office or Division:	Division of Urology, Obstetrics, and Gynecology (DUOG)
Application Type and Number:	NDA 214846
Product Name and Strength:	Myfembree (relugolix/estradiol/norethindrone acetate) tablets, 40 mg/1 mg/0.5 mg
Applicant/Sponsor Name:	Myovant Sciences GmbH (Myovant)
OSE RCM #:	2020-1121-2
DMEPA Safety Evaluator:	Denise V. Baugh, PharmD, BCPS
DMEPA (Acting) Team Leader:	Celeste Karpow, PharmD, MPH

1 PURPOSE OF MEMORANDUM

The Applicant submitted a revised container label received on January 21, 2021 for Myfembree. The Division of Urology, Obstetrics, and Gynecology (DUOG) requested that we review the revised container label for Myfembree (Appendix B) to determine if it is acceptable from a medication error perspective. The revisions are in response to recommendations that we made during a previous label and labeling review.[a]

2 ASSESSMENT

We previously recommended that the expiration date format on the container label align with what is recommended by the Agency. In response to our information request (Appendix A), Myovant stated that the expiration date format as proposed, 'DD-MMM-YYYY', includes the key elements which they believe should minimize confusion and reduce the risk for deteriorated drug medication errors.

[a] Baugh D. Label and Labeling Review for Myfembree (NDA 214846). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2021 DEC 10. RCM No.: 2020-1121-1.

Upon further review, although the date (DD) and year (YYYY) of the proposed expiration date do not align with what is recommended by the Agency, we find it acceptable from a medication error perspective.

3 CONCLUSION

The Applicant considered our recommendations and we have no additional recommendations at this time.

APPENDIX A. MYOVANT'S RESPONSE RECEIVED JANUARY 21, 2021 TO OUR DECEMBER 18, 2020 INFORMATION REQUEST: \\CDSESUB1\evsprod\nda214846\0026\m1\us\rsp-cmc-ir-dated-18-dec-2020.pdf

APPENDIX B. IMAGE OF CONTAINER LABEL RECEIVED ON JANUARY 21, 2021

Container labels

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/s/

DENISE V BAUGH
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CELESTE A KARPOW
01/29/2021 07:21:24 PM

Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research | Office of Surveillance and Epidemiology (OSE)
Epidemiology: ARIA Sufficiency Templates
Version: 2018-01-24

Date:	12/18/2020
Reviewer(s):	Wei Liu, PhD, MSc Division of Epidemiology II
Team Leader:	Wei Liu, PhD, MSc (Acting) Division of Epidemiology II
Division Director:	CAPT David Moeny, RPh, MPH, USPHS Division of Epidemiology II
OPE Director:	Judith Zander, MD
FDA Sentinel Team Lead:	Michael D. Nguyen, MD
OSE Deputy Director:	Robert Ball, MD, MPH, ScM
Subject:	Sufficiency assessment of ARIA to evaluate the risk for alopecia with Myfembree use
Drug Name(s):	Myfembree (relugolix/estradiol/norethindrone acetate)
Application Type/Number:	NDA 214846
Applicant/sponsor:	Myovant
OSE RCM #:	2020-1119

EXECUTIVE SUMMARY *(place "X" in appropriate boxes)*

Memo type	
-Initial	
-Interim	
-Final	X
Source of safety concern	
-Peri-approval	X
-Post-approval	
Is ARIA sufficient to help characterize the safety concern?	
-Yes	
-No	X
If "No", please identify the area(s) of concern.	
-Surveillance or Study Population	
-Exposure	
-Outcome(s) of Interest	X
-Covariate(s) of Interest	
-Surveillance Design/Analytic Tools	X

A. General ARIA Sufficiency Template

1. BACKGROUND INFORMATION

1.1. Medical Product

Myfembree® is a combination oral product containing the gonadotropin-releasing hormone (GnRH) receptor antagonist relugolix 40 mg, estradiol 1 mg, and norethindrone acetate 0.5 mg. The applicant seeks to market Myfembree (hereafter referred to as R+E2/NETA) for the treatment of heavy menstrual bleeding associated with uterine fibroids in premenopausal women. Two 6-month, randomized, placebo-controlled, double-blinded, Phase-3 clinical trials showed that the primary efficacy endpoints (e.g., the proportion of women whose menstrual blood loss [MBL] was less than 80 mL and the proportion of women with at least 50% reduction in MBL volume) were met successfully.

1.2. Describe the Safety Concern

In pre-approval trials of Myfembree, there was an imbalance in the number of cases of alopecia in the R+E2/NETA group compared to the placebo group. The incidence of alopecia was 3.5% with R+E2/NETA *versus* 0.8% with placebo (alopecia was reported for 9 and 2 patients in R+E2/NETA *versus* placebo group, respectively). No pattern of alopecia (e.g., hair loss or hair thinning) can be characterized from the clinical trial data because of the small number of adverse event cases reported in the approval trials. One patient who reported to have experienced alopecia in the R+E2/NETA group was assessed as grade 2, and the remaining events occurred in either treatment arm were assessed as grade 1.[a] Alopecia occurred within 9-148 days of R+E2/NETA treatment initiation. Seven subjects in the R+E2/NETA group were potentially irreversible as they did not experience resolution of alopecia during the studies. The other two cases in the R+E2/NETA group had their symptoms resolved by the end of the study.

There is no confirmed biological mechanism for R+E2/NETA and alopecia. However, hormonal disruption owing to GnRH antagonist inhibition of the release of luteinizing hormone and follicle stimulating hormone may be a possible cause of alopecia. For R+E2/NETA, the level of safety concern is high given the targeted population (premenopausal women) and potential for long-term use. The Division of Urology, Obstetrics and Gynecology (DUOG) plans to label the risk for alopecia in the Warnings and Precautions section of product label and intends to request a postmarketing requirement (PMR) study in premenopausal women to assess the incidence rate, time to onset, pattern, extent and reversibility of alopecia with R+E2/NETA use. Clinical characterization of the safety outcome is critical as no such information is available

[a] Grade 1 = hair loss of <50% of normal for that individual that is not obvious from a distance but only on close inspection; a different hair style may be required to cover the hair loss, but it does not require a wig or hair piece to camouflage. Grade 2 = hair loss of ≥50% normal for that individual that is readily apparent to others; a wig or hair piece is necessary if the patient desires to completely camouflage the hair loss.

from clinical trials. This additional information will enable informed decision-making for physicians and patients based on the benefit-risk profile (i.e. significant reduction of bleeding due to uterine fibroids vs. potential irreversible alopecia among premenopausal women, both having a substantial impact on quality of life).

FDA approved Oriahnn®, another GnRH receptor antagonist with low-dose combined hormone therapy (Elagolix 300 mg, E2 1 mg, and NETA 0.5 mg) for the management of heavy menstrual bleeding with uterine fibroids in premenopausal women in May 2020. In Phase-3 trials of Oriahnn, the incidence of alopecia was 3.5% in Elagolix+E2/NETA group *versus* 1% in the placebo group. About 1/3 of alopecia cases (n=24) were potentially irreversible as the adverse events had not resolved at the end of the study. Most adverse events occurred within 3 to 7 months of Elagolix+E2/NETA treatment. There was one severe alopecia case, three moderate cases and 11 mild cases in the Elagolix+E2/NETA arm.

1.3. FDAAA Purpose (per Section 505(o)(3)(B))

- Please ensure that the selected purpose is consistent with the other PMR documents in DARRTS

Purpose (place an "X" in the appropriate boxes; more than one may be chosen)	
Assess a known serious risk	X
Assess signals of serious risk	
Identify unexpected serious risk when available data indicate potential for serious risk	

1.4. Statement of Purpose

The purposes of this PMR are two-fold:

a) To assess the incidence, time to onset, pattern, severity, and reversibility of alopecia in premenopausal women receiving treatment with Myfembree.
b) To compare the incidence rate of alopecia in premenopausal women who initiate Myfembree and an appropriate comparator population of women not treated with Myfembree. This study should be powered to detect a 2-fold increase in the risk for alopecia with Myfembree use. A RR=2 is generally considered clinically significant for the exposure-outcome association under study.

1.5. Effect Size of Interest or Estimated Sample Size Desired

The ARIA administrative claims data are insufficient to address Objective #1 stated above, because claims data have limited granularity to describe the key clinical features of alopecia including pattern, severity, and disease course (including reversibility) of alopecia.

For Objective #1, sample size sufficiency should be appraised with reference to the desired level of precision in estimates of incidence of alopecia. Sample size sufficiency should also be justified by taking into consideration the full spectrum and variation of other clinical endpoints under investigation (time to onset, pattern, severity, and reversibility), pragmatic issues such as frequency of interview/self-report, and non-response rate.

The coprimary outcome (Objective #2), incidence rate of alopecia, was used to ascertain required sample size estimates. The sample size estimation used data based on the incidence rate of alopecia from preapproval trials described above. An incidence rate of 8 per 1,000 person-years among subjects in the reference group was assumed. Further assuming type I error of 0.05, power of 80%, and 1:1 propensity score matching, approximately 2,708 subjects/group is required (i.e., total required number of alopecia events is 65) are needed in order to rule out a two-fold increased risk of alopecia comparing R+E2/NETA with the control drug.[b] Thus, it seems reasonable to expect that the ARIA administrative claims databases will contain sufficient number of users that will exceed the sample size requirement for the goal of assessing Objective #2.

2. SURVEILLANCE OR DESIRED STUDY POPULATION

2.1 Population

Women with heavy menstrual bleeding due to uterine fibroids, including those treated with R+E2/NETA, and women treated with a comparator drug.

2.2 Is ARIA sufficient to assess the intended population?

Yes

3 EXPOSURES

3.1 Treatment Exposure(s)

Women with heavy menstrual bleeding associated with uterine fibroids who use R+E2/NETA.

3.2 Comparator Exposure(s)

Women with heavy menstrual bleeding associated with uterine fibroids who do not use R+E2/NETA.

3.3 Is ARIA sufficient to identify the exposure of interest?

Yes.

4 OUTCOME(S)

4.1 Outcomes of Interest

Alopecia, hair loss and hair thinning.

[b] Based on Schoenfeld formula, R package for power/sample size calculation.

4.2 Is ARIA sufficient to assess the outcome of interest?

No. there is no validated claims-based algorithm for alopecia. The PMR study aims to identify the pattern and reversibility of alopecia cases, which will require prospective follow-up to collect such information among R+E2/NETA users. Medical chart review and/or physician and/or patient survey data may be used to characterize the safety outcome of interest.

5 COVARIATES

5.1 Covariates of Interest

Various factors could cause hair loss, including thyroid disorders, diabetes, or lupus. Certain medicines or have chemotherapy for cancer may also lead to hair loss. Other causes are stress, a low protein diet, family history, or poor nutrition, scalp infection, scalp psoriasis, sexually transmitted infection, polycystic ovary syndrome, and hormonal imbalance (e.g., discontinuing birth control pills).

5.2 Is ARIA sufficient to assess the covariates of interest?

Skipped given the response in Section 4.

6 SURVEILLANCE DESIGN / ANALYTIC TOOLS

6.1 Surveillance or Study Design

A prospective observational study with medical chart review or patient survey.

6.1.1 Is ARIA sufficient with respect to the design/analytic tools available to assess the question of interest?

No. Chart review and/or patient survey are not possible in the ARIA system.

7 NEXT STEPS

Division of Urology, Obstetrics, and Gynecology (DUOG) is planning to inform the applicant that two prospective observational studies (e.g., a 2-pronged approach) will be required as PMR. The rationale for 2 studies is as follows. A prospective study with primary data collection with patient reported outcomes (PROs) is able to produce more valid results than a study conducted using secondary data in providing the required clinical granularity of alopecia, but it is expected that the applicant will have difficulty in recruiting sufficient numbers of women given that the response rate might be low for PROs (i.e., collected via repeated patient surveys/self-reports). Therefore, a comparative safety analyses that may use electronic healthcare data would provide the required sample size to evaluate this relatively rare outcome. Finally, the applicant is being encouraged to utilize hybrid designs to enhance study variable collection through primary and secondary data linkage (e.g., claims data linked with patient reported outcomes, electronic medical records, or other real-time healthcare data).

PMR #1: A prospective observational study in premenopausal women receiving treatment with Myfembree to assess the incidence rate, time to onset, pattern, extent,

and reversibility of 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.

PMR #2: A cohort study to compare the incidence rate of alopecia in premenopausal women who initiate Myfembree and an appropriate comparator population of women not treated with Myfembree. The study should be powered to detect a 2-fold increase in the risk of alopecia with Myfembree use. 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.

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JUDITH W ZANDER
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MICHAEL D NGUYEN
12/18/2020 01:48:54 PM

ROBERT BALL
12/18/2020 01:52:10 PM

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology Review (OSE)
Office of Pharmacovigilance and Epidemiology (OPE)

Epidemiology: Review of E2-NETA (b) (4)

Date:	December 16, 2020
Reviewer:	Wei Liu, Ph.D., MSc Division of Epidemiology II
Team Leader:	Wei Liu, Ph.D., MSc (Acting) Division of Epidemiology II
Deputy Director:	Efe Eworuke, Ph.D. (Acting) Division of Epidemiology II
Subject:	(b) (4)
Drug Name(s):	Myfembree (relugolix/estradiol/norethindrone acetate, 40mg/1mg/0.5mg)
Submission Numbers:	NDA 214846
Applicant:	Myovant Sciences
OSE RCM #:	2020-1119

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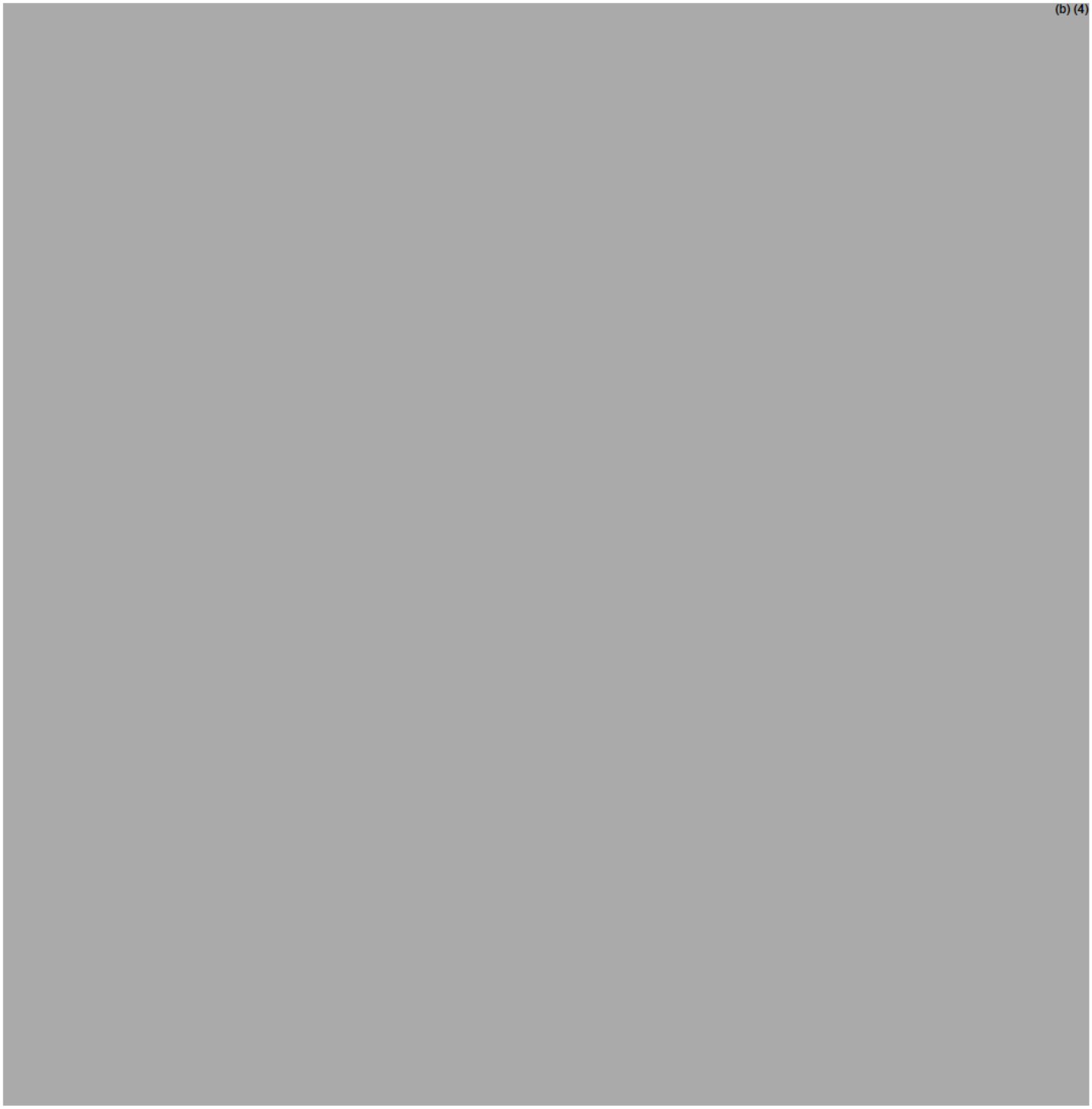

5 CONCLUSION

Both combined oral contraceptives and combined oral postmenopausal hormone therapies are associated with a small but clinically relevant risk of both venous and arterial thrombosis. Although results of this study suggest no indication of an increased cardiovascular risk associated with 1mg E2 and 0.5mg NETA (b) (4) .

6 RECOMMENDATION TO DUOG

In DEPI's view, a boxed warning about the increased risk of thromboembolic disorders and vascular events should be included in the product labeling for relugolix combination therapy. (b) (4) .

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MEMORANDUM

REVIEW OF REVISED LABEL AND LABELING
Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

Date of This Memorandum:	December 10, 2020
Requesting Office or Division:	Division of Urology, Obstetrics, and Gynecology (DUOG)
Application Type and Number:	NDA 214846
Product Name and Strength:	Myfembree (relugolix/estradiol/norethindrone acetate) tablets 40 mg/1 mg/0.5 mg
Applicant/Sponsor Name:	Myovant Sciences GmbH (Myovant)
OSE RCM #:	2020-1121-1
DMEPA Safety Evaluator:	Denise V. Baugh, PharmD, BCPS
DMEPA Team Leader:	Briana Rider, PharmD, CPPS

1 PURPOSE OF MEMORANDUM

The Applicant submitted revised container label received on December 1, 2020 for Myfembree. The Division of Urology, Obstetrics, and Gynecology (DUOG) requested that we review the revised container label for Myfembree (Appendix A) to determine if it is acceptable from a medication error perspective. The revisions are in response to recommendations that we made during a previous label and labeling review.[a]

2 CONCLUSION

The Applicant implemented our previous recommendations. However, the proposed expiration date format (i.e., DD MMM YYYY) does not align with the format recommended by the Agency.

3 RECOMMENDATIONS FOR MYOVANT SCIENCES GMBH

We recommend the following be implemented prior to approval of this NDA:

A. We note that the expiration date is expressed as 'DD MMM YYYY' which does not align with the format recommended by the Agency. The Drug Supply Chain Security Act

[a] Baugh D. Label and Labeling Review for Myfembree (NDA 214846). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2020 OCT 15. RCM No.: 2020-1121.

(DSCSA) guidance on product identifiers[b] recommends that the expiration date appear in YYYY-MM-DD format if only numerical characters are used or in YYYY-MMM-DD if alphabetical characters are used to represent the month. Consider revising the expiration date format to align with one of the FDA recommended formats.

[b] The draft guidance is available from: https://www.fda.gov/ucm/groups/fdagov-public/@fdagov-drugs-gen/documents/document/ucm621044.pdf

APPENDIX A. IMAGES OF LABEL AND LABELING RECEIVED ON DECEMBER 1, 2020

Container label

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/s/

DENISE V BAUGH
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BRIANA B RIDER
12/10/2020 03:20:15 PM

LABEL, LABELING, AND PACKAGING REVIEW
Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

*** This document contains proprietary information that cannot be released to the public***

Date of This Review:	October 15, 2020
Requesting Office or Division:	Division of Urology, Obstetrics, and Gynecology (DUOG)
Application Type and Number:	NDA 214846
Product Name and Strength:	Myfembree (relugolix/estradiol/norethindrone acetate) tablets 40 mg/1 mg/0.5 mg
Product Type:	Multi-Ingredient Product
Rx or OTC:	Prescription (Rx)
Applicant/Sponsor Name:	Myovant Sciences GmbH (Myovant)
FDA Received Date:	June 1, 2020 and August 26, 2020
OSE RCM #:	2020-1121
DMEPA Safety Evaluator:	Denise V. Baugh, PharmD, BCPS
DMEPA Team Leader:	Briana Rider, PharmD, CPPS

1 REASON FOR REVIEW

As part of the approval process for Myfembree (relugolix/estradiol/norethindrone acetate) tablets, the Division of Urology, Obstetrics, and Gynecology (DUOG) requested that we review the proposed Myfembree prescribing information (PI) and container label for areas of vulnerability that may lead to medication errors.

2 MATERIALS REVIEWED

Table 1. Materials Considered for this Label and Labeling Review

Material Reviewed	Appendix Section (for Methods and Results)
Product Information/Prescribing Information	A
Previous DMEPA Reviews	B
ISMP Newsletters*	C – N/A
FDA Adverse Event Reporting System (FAERS)*	D – N/A
Other	E – N/A
Labels and Labeling	F

N/A=not applicable for this review
*We do not typically search FAERS or ISMP Newsletters for our label and labeling reviews unless we are aware of medication errors through our routine post-market safety surveillance

3 FINDINGS AND RECOMMENDATIONS

Tables 2 and 3 below include the identified medication error issues with the submitted prescribing information (PI) and container label, our rationale for concern, and the proposed recommendation to minimize the risk for medication error.

Table 2. Identified Issues and Recommendations for Division of Urology, Obstetrics, and Gynecology (DUOG)

	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
Highlights of Prescribing Information (HPI)			
1.	The dosage statement within the 'Dosage and Administration' section of the HPI does not include the route of administration (i.e., oral).	May pose risk of wrong route of administration errors.	We recommend revising the statement "One tablet to be taken once daily" to read: "One tablet to be taken orally once daily".
Full Prescribing Information – Section 16 How Supplied/Storage and Handling			

Table 2. Identified Issues and Recommendations for Division of Urology, Obstetrics, and Gynecology (DUOG)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
1.	The NDC numbers are denoted by placeholders (i.e., XXXX-XXXX-XX) in Section 16.1 (How Supplied).	We are unable to assess the NDC numbers from a medication safety perspective.	Replace the placeholder (i.e., XXXX-XXXX-XX) with the appropriate NDC number for the proposed product.
Full Prescribing Information – Section 17 Patient Counseling			
1.	The Dosage and Administration section (Section 2) of the Prescribing Information (PI) recommends that the administration of Myfembree be initiated (b) (4) the onset of menstrual bleeding. However, this information is not included in the Patient Counseling Information section (Section 17) of the PI.	Inappropriate treatment initiation may increase the risk of irregular and/or heavy menstrual bleeding.	Consider adding 'begin taking Myfembree (b) (4) the onset of menstrual bleeding' to the 'Dosage and Administration' subsection within Section 17 of the PI.

Table 3. Identified Issues and Recommendations for Myovant Sciences GmbH (entire table to be conveyed to Applicant)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
Container Label			
1.	The net quantity and usual dosage statement are presented in (b) (4) on the principal display panel (PDP).	The presentation of the net quantity and dosage statement (b) (4) competes in prominence with more critical information such as the proprietary and established name, active ingredients, and strength on the PDP.	Ensure the proprietary name, established names and strength are the most prominent information on the PDP.
2.	The established name does not include the finished dosage form.	This presentation is inconsistent with the	Revise the established name to include the dosage form (i.e., tablets).

Table 3. Identified Issues and Recommendations for Myovant Sciences GmbH (entire table to be conveyed to Applicant)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
		presentation for drug products[a].	
3.	The established name is expressed with strengths between each active ingredient (i.e., relugolix 40 mg/estradiol 1 mg/norethindrone acetate 0.5 mg).	The active ingredients should be expressed without any intervening written, printed, or graphic matter between them.	Remove the strengths from the established name and position the product strength below the established name on the principal display panel.
4.	The usual dosage statement is located on the principal display panel (PDP) (i.e., Usual dosage – One tablet daily) and on the side panel (i.e., See package insert for Full Prescribing Information).	This presentation is redundant and competes with critical drug information on the PDP such as the proprietary and established names, and strength.	Remove the usual dosage statement from the PDP.
5.	The usual dosage statement – (b) (4) can be improved.	To ensure consistency with the physician labeling rule (PLR) formatted Prescribing Information.	Revise the statement (b) (4) to read 'Dosage: See Prescribing Information.'
6.	The container label lacks a placeholder for the lot number and expiration date.	The lot number and expiration date are required on the container label per 21 CFR 201.10(i)(1) and 21 CFR 211.137, respectively.	Revise the container label to indicate where the lot number and expiration date will appear. Ensure the lot number is clearly differentiated from the expiration date. Additionally, identify the expiration date format you intend to use. FDA recommends that the human-readable expiration date on the drug package label include a year, month, and non-zero day. FDA

[a] Guidance for Industry: Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors. Food and Drug Administration. 2013. Available from http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM349009.pdf

Table 3. Identified Issues and Recommendations for Myovant Sciences GmbH (entire table to be conveyed to Applicant)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
			recommends that the expiration date appear in YYYY-MM-DD format if only numerical characters are used or in YYYY-MMM-DD if alphabetical characters are used to represent the month. If there are space limitations on the drug package, the human-readable text may include only a year and month, to be expressed as: YYYY-MM if only numerical characters are used or YYYY-MMM if alphabetical characters are used to represent the month. FDA recommends that a hyphen or a space be used to separate the portions of the expiration date.
7.	We note the presence of the placeholder "NDC FPO" on the container label.	It is unclear whether this placeholder is for a linear barcode. A linear barcode is required on the immediate container label per 21 CFR 201.25(c)(2).	Ensure the container label contains a linear barcode that contains, at a minimum, the appropriate National Drug Code (NDC) number.
8.	We note the presence of the unvarnished area for 'variable text for serialization'.	As currently presented, there is no placeholder for a product identifier. In September 2018, FDA released draft guidance on product identifiers required under the Drug Supply Chain Security Act (DSCSA).[b] The Act requires manufacturers and re-packagers, respectively, to affix or imprint a product identifier to each package and homogenous case of a	We recommend that you review the draft guidance. If you determine that the product identifier requirements apply to your product's labeling, we request you add a placeholder for the human-readable and machine-readable (2-D data matrix barcode) product identifier to the carton labeling. The DSCSA guidance on product identifiers recommends the format of the human-readable

[b] The draft guidance is available from: https://www.fda.gov/ucm/groups/fdagov-public/@fdagov-drugs-gen/documents/document/ucm621044.pdf

Table 3. Identified Issues and Recommendations for Myovant Sciences GmbH (entire table to be conveyed to Applicant)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
		product intended to be introduced in a transaction in(to) commerce beginning November 27, 2017, and November 27, 2018, respectively.	portion be located near the 2D data matrix barcode as follows: NDC: [insert NDC] Serial: [insert serial number] LOT: [insert lot number] EXP: [insert expiration date]
9.	We note the NDC number is denoted as 72974-000-00.	It is unclear whether '000' and '00' are placeholders for the product code and package code, respectively.	Please confirm the NDC number for the intend to market product.

4 CONCLUSION

Our evaluation of the proposed Myfembree prescribing information (PI) and container label identified areas of vulnerability that may lead to medication errors. Above, we have provided recommendations in Table 2 for the Division and Table 3 for the Applicant. We ask that the Division convey Table 3 in its entirety to Myovant Sciences GmbH so that recommendations are implemented prior to approval of this NDA.

APPENDICES: METHODS & RESULTS FOR EACH MATERIAL REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 4 presents relevant product information for Myfembree that Myovant Sciences GmbH (Myovant) submitted on August 26, 2020.

Table 4. Relevant Product Information for Myfembree	
Initial Approval Date	N/A
Active Ingredient	relugolix/estradiol/norethindrone acetate
Indication	Treatment of heavy menstrual bleeding associated with uterine fibroids
Route of Administration	oral
Dosage Form	tablet
Strength	40 mg/1 mg/0.5 mg
Dose and Frequency	One tablet once daily
How Supplied	28 count, child resistant cap HDPE bottle
Storage	15˚C to 30˚C (59˚F to 86˚F)

APPENDIX B. PREVIOUS DMEPA REVIEWS

On September 15, 2020, we searched for previous DMEPA reviews relevant to this current review using the terms, 'Myfembree', '214846' and 'relugolix'. Our search identified no previous reviews.

APPENDIX F. LABELS AND LABELING

F.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,[c] along with post-market medication error data, we reviewed the following Myfembree labels and labeling submitted by Myovant Sciences GmbH.

- Container label(s) received on June 1, 2020
- Prescribing Information (Image not shown) received on August 26, 2020, available from: \\CDSESUB1\evsprod\nda214846\0006\m1\us\m1-14-1-3-draft-labeling-text-clean.docx.

F.2 Label and Labeling Images

Container label

[c] Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

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/s/

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M E M O R A N D U M

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: 8/3/2020

TO: Division of Urology, Obstetrics, and Gynecology (DUOG)
Office of Rare Diseases, Pediatrics, Urology and Reproductive Medicine (ORPURM)

FROM: Division of New Drug Study Integrity (DNDSI)
Office of Study Integrity and Surveillance (OSIS)

SUBJECT: **Decline to conduct an on-site inspection**

RE: NDA 214846

The Division of New Drug Study Integrity (DNDSI) within the Office of Study Integrity and Surveillance (OSIS) determined that an inspection is not warranted at this time for the sites listed below. The rationale for this decision is noted below.

Rationale

The clinical inspection was conducted in Febuary 2018 and the analytical inspection was conducted in (b) (4), which falls within the surveillance interval. The inspections were conducted under the following submissions: Non-Responsive.

The final classification for the inspections was No Action Indicated (NAI).

Therefore, based on the rationale provided above, inspections are not warranted at this time.

Inspection Sites

Facility Type	Facility Name	Facility Address
Clinical	Clinical Pharmacology of Miami, LLC.	550 West 84th Street, Miami, FL
Analytical	(b) (4)	

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