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<th><strong>Application Type</strong></th>
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<tr>
<td><strong>Application Number</strong></td>
<td>214846</td>
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<tr>
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<td><strong>Review Completion Date</strong></td>
<td>May 25, 2021</td>
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<tr>
<td><strong>Subject</strong></td>
<td>Evaluation of Need for a REMS</td>
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<tr>
<td><strong>Established Name</strong></td>
<td>Relugolix, estradiol, norethindrone acetate</td>
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<td><strong>Trade Name</strong></td>
<td>Myfembree</td>
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<td><strong>Name of Applicant</strong></td>
<td>Myovant Sciences, Inc.</td>
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<tr>
<td><strong>Therapeutic Class</strong></td>
<td>gonadotropin-releasing hormone (GnRH) receptor antagonist oral tablet</td>
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<td><strong>Formulation</strong></td>
<td>tablet</td>
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<tr>
<td><strong>Dosing Regimen</strong></td>
<td>relugolix 40 mg, estradiol 1 mg and norethindrone acetate 0.5 mg once daily</td>
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Executive Summary

This review evaluates whether a risk evaluation and mitigation strategy (REMS) for Myfembree (relugolix, estradiol, and norethindrone acetate) for oral use is necessary to ensure the benefits outweigh its risks. Myovant Sciences submitted a New Drug Application (NDA) 214846 for relugolix, estradiol and norethindrone acetate with the proposed indication for the treatment of heavy menstrual bleeding associated with uterine fibroids. Similar to other products in this class (estrogen and progestin combination products) Myfembree has the increased risk of thromboembolic disorders and vascular events. During the review of the application the indication was revised to the management of heavy menstrual bleeding associated with uterine leiomyomas (fibroids) in premenopausal women. The applicant did not submit a proposed REMS or risk management plan with this application.

The Division of Risk Management (DRM) has determined that a REMS is not needed to ensure the benefits of Myfembree outweigh its risks. Myfembree reduced heavy menstrual bleeding associated with fibroids in premenopausal women. Based on the clinical trials, the benefit-risk profile is acceptable and risk mitigation beyond labeling, which includes a Boxed Warning and Patient Package Insert (PPI), is not required. In general, because of the increased risk of thrombotic or thromboembolic disorders, including pulmonary embolism and deep vein thrombosis associated with other products in this class gynecologists and primary care physicians should be aware of these risks and familiar with how to manage them.

1 Introduction

This review evaluates whether a risk evaluation and mitigation strategy (REMS) for Myfembree (relugolix, estradiol, and norethindrone acetate) is necessary to ensure the benefits outweigh its risks. Myovant Sciences submitted a New Drug Application (NDA) with the proposed indication of heavy menstrual bleeding associated with uterine fibroids. This application is under review in the Division of Urology, Obstetrics and Gynecology (DUOG). The applicant did not submit a proposed REMS or risk management plan with this application.

2 Background

2.1 Product Information

Myfembree, a NME, 505(b)(2) application is a new combination of relugolix, a gonadotropin-releasing hormone (GnRH) receptor antagonist, estradiol, an estrogen, and norethindrone acetate, a progestin. Myfembree is proposed to be indicated for the treatment of heavy menstrual bleeding associated with uterine fibroids. During the review of the application, the indication was revised to the management of heavy menstrual bleeding associated with uterine leiomyomas (fibroids) in premenopausal women. Myfembree is proposed to be available as a fixed-dose, once daily, oral combination tablet containing relugolix 40 mg, estradiol 1 mg and norethindrone acetate 0.5 mg. Myfembree should be started as

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\(^a\) Section 505-1 (a) of the FD&C Act: FDAAA factor (F): Whether the drug is a new molecular entity
early as possible after the onset of menses but no later than 7 days after menses has started. The recommended total duration of treatment with Myfembree is 24 months.\textsuperscript{b} Myfembree has not been approved or marketed in the United States. Relugolix monotherapy 40 mg daily was approved in January 2019 in Japan for improvement of symptoms associated with uterine myoma.\textsuperscript{2} The drug has been marketed in Japan under the tradename Relumina since March 2019.

\textbf{2.2 Regulatory History}

The following is a summary of the regulatory history for NDA 214846 relevant to this review:

- 6/1/2020: New NDA received for Myfembree (relugolix, estradiol and norethindrone acetate) in treatment of heavy menstrual bleeding associated with uterine fibroids
- 11/16/2020: Mid-Cycle Communication meeting
- 12/18/2020: Orgovyx (relugolix) approved for the treatment of adult patients with advanced prostate cancer under NDA 214621
- 03/1/2021: Late-Cycle Meeting during which it was discussed no plan for a REMS
- 2/18/21: FDA sent IR to Myovant requesting clarification on clinical and statistical information for subjects with bone mineral density data
- 2/26/21: Myovant provided a response to the 2/18/21 IR which provided clarification to FDA’s request
- 3/17/21: FDA sent a general advice letter to Myovant pertaining to wording of boxed warning, bone mineral density language, and presentation along with the alopecia PMRs.

\textbf{3 Therapeutic Context and Treatment Options}

\textbf{3.1 Description of the Medical Condition}

Uterine fibroids, also known as uterine leiomyomas, are benign smooth muscle tumors that arise in three regions of the uterus (submucosal, intramural and subserosal). Uterine fibroids affect up to 70% of women by age 50 and an even higher proportion of African-American women across all age groups.\textsuperscript{c, 3} Symptoms occur in approximately 25-30% of women with fibroids. Submucosal and intramural types are more likely to be associated with heavy menstrual bleeding (usually defined as > 80 mL per menstrual cycle) which can lead to iron-deficiency anemia, pressure on adjacent organs, and back pain.\textsuperscript{d} The

\textsuperscript{b} Section 505-1 (a) of the FD&C Act: FDAAA factor (D): The expected or actual duration of treatment with the drug
\textsuperscript{c} Section 505-1 (a) of the FD&C Act: FDAAA factor (A): The estimated size of the population likely to use the drug involved
\textsuperscript{d} Section 505-1 (a) of the FD&C Act: FDAAA factor (B): The seriousness of the disease or condition that is to be treated with the drug.
etiology of fibroid development of uterine fibroids is not fully known. Genetics and hormonal effects play a role.\(^3\)

### 3.2 Description of Current Treatment Options

There are currently two FDA-approved medical therapies for fibroid-related bleeding issues: Lupron (leuprolide acetate) and Oriah (elagolix, estradiol and norethindrone acetate). Lupron (leuprolide acetate) is a GnRH agonist approved in 1995 for preoperative hematologic improvement of patients with anemia caused by uterine fibroids with concomitant iron therapy.\(^4\) Lupron is dosed as 3.75 mg monthly injections for three months or one 11.25 mg injection. Safety issues related to leuprolide acetate include loss of bone mineral density (BMD), embryo-fetal toxicity, hypersensitivity reactions, convulsions, and clinical depression. Oriah (elagolix, estradiol and norethindrone acetate) was approved in 2020 and is indicated in the management of heavy menstrual bleeding associated with uterine fibroids in premenopausal women.\(^5\) Oriah is a combination of the GnRH antagonist elagolix with an add-back therapy component consisting of estradiol and norethindrone acetate. The add-back therapy component is designed to reduce the bone loss and vasomotor symptoms associated with elagolix. Norethindrone acetate additionally helps to prevent endometrial hyperplasia and malignancies associated with excess estrogens. Safety issues related to this product include a boxed warning for thromboembolic disorders and vascular events. The Warnings & Precautions include bone loss, hormonally-sensitive malignancies, suicidal ideation, hepatic impairment/transaminase elevations, elevated blood pressure, gallbladder disease, change in menstrual bleeding, effects on carbohydrate metabolism, and alopecia. Based on current bone mineral density data, both of these products have a 2-year limitation of use. A REMS is not required for either of these treatments.

Definitive treatment for uterine fibroids is hysterectomy. Hysterectomy is typically performed abdominally either by laparotomy or laparoscopy. Vaginal hysterectomy with special coring techniques has also been used if fibroids are not excessive in size or for fibroids protruding into the endometrial cavity. Myomectomy procedures (abdominal and vaginal approaches) are usually performed in situations where uterine preservation is sought.

### 4 Benefit Assessment

The efficacy and safety of Myfembree to treat uterine fibroids in premenopausal women was derived from two Phase 3 studies [Study MVT-601-3001 (NCT03049735) and Study MVT-601-3002 (NCT03103087) comparing Myfembree versus placebo. Both trials were multicenter, double-masked, randomized, parallel-group, placebo-controlled studies. MVT-601-3001 and MVT-601-3002 enrolled 388 and 382 subjects, respectively, using a 1:1:1 randomization ratio to allocate patients to three study treatments:

- Relugolix 40 mg tablet co-administered orally with estradiol (E2) 1 mg and norethindrone acetate (NETA) 0.5 mg capsule (R+E2/NETA)
- Relugolix 40 mg tablet with E2/NETA placebo capsule orally for 12 weeks followed by relugolix 40 mg tablet co-administered orally with E2 1 mg and NETA 0.5 mg capsule for 12 weeks (R+delayed E2/NETA (delE2/NETA)]
- Relugolix placebo tablet co-administered orally with E2/NETA placebo capsule (placebo).
The primary endpoint for both studies was proportion of women in the relugolix/E2/NETA (R+E2/NETA) group compared with women in the placebo group who achieved menstrual blood loss volume of < 80 mL and at least a 50% reduction from baseline menstrual blood loss (MBL) volume over the last 35 days of treatment, as measured by the alkaline hematin method. Key secondary endpoints that were evaluated included those related to amenorrhea, percent change in MBL volume, and change in hemoglobin.

In the primary analyses for MVT-601-3001, the responder rate is 72.1% for R+E2/NETA and 16.8% for placebo resulting in a treatment difference (95% CI) of 55.3% (44.2%, 65.6%). For MVT-601-3002, the responder rate is 71.2% for R+E2/NETA and 14.7% for placebo resulting in a treatment difference (95% CI) of 56.5% (46.6%, 66.5%). Based on the clinical review, the secondary and sensitivity analyses all show similar robust findings and demonstrated the efficacy of R+E2/NETA in patients with heavy menstrual bleeding associated with uterine fibroids. The clinical reviewer concluded the results of both trials were highly consistent and establish substantial evidence of effectiveness for R+E2/NETA as a treatment for heavy menstrual bleeding associated with uterine fibroids in the target population.

5 Risk Assessment & Safe-Use Conditions

The safety assessment of Myfembree was primarily based on Study MVT-601-3001 (NCT03049735), Study MVT-601-3002 (NCT03103087), and Study MVT-601-3003. The primary safety population for this application is comprised of 634 subjects from Studies 3001 and 3002 who received at least one dose of R+E2/NETA. Discontinuation due to a treatment emergent adverse event (TEAE) occurred in 30/258 (11.6%) subjects in the pooled safety population for R+delE2/NETA and 10/254 (3.9%) subjects in the pooled safety population for R+E2/NETA compared to 11/256 (4.3%) for placebo. Treatment-emergent adverse events such as hypertension, alopecia, hot flush, decreased libido, menorrhagia, and irritability occurred in at least 2% of subjects in any treatment arm and at least 1% higher frequency in the R+E2/NETA arm than placebo arm for Trial MVT-601-3001 and MVT-601-3002 trial. No deaths occurred in Phase 3 studies.

The serious risk associated with relugolix of thromboembolic disorders and vascular events and bone loss are summarized in the section below.

5.1 Thromboembolic Disorders and Vascular Events

In the Phase 3 placebo-controlled clinical trials in 1066 women treated with MYFEMBREE for another indication, 2 thromboembolic events (DVT and PE) occurred in 1 woman with risk factors of obesity and a preceding knee injury and one case was reported for a woman treated with relugolix monotherapy in the postmarketing period.

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* Blood sample is added to an alkaline solution containing a non-ionic detergent, haemoglobin is converted to alkaline haematin which is a stable colour compound.
* Section 505-1 (a) of the FD&C Act: FDAAA factor (C): The expected benefit of the drug with respect to such disease or condition
Estrogen and progestin combinations, including the estradiol/norethindrone acetate component of Myfembree, increase the risk of thrombotic or thromboembolic disorders, including pulmonary embolism, deep vein thrombosis, stroke, and myocardial infarction, especially in women at high risk for these events. In general, the risk is greatest among women over 35 years of age who smoke, and women with uncontrolled hypertension, dyslipidemia, vascular disease, or obesity. Products containing estradiol in combination with norethindrone acetate, like Activella, contain a boxed warning regarding the risk of deep vein thrombosis (DVT), pulmonary embolism (PE), stroke and myocardial infarction (MI). Additionally, products like Oriahnn which contains a GnRh antagonist/E2/NETA combination product also includes a boxed warning regarding the risk of venous and arterial thrombotic or thromboembolic events. Based on the clinical review, a boxed warning will be required in the label to inform prescribers of the potential risk of thrombotic or thromboembolic disorders.

5.2 Bone Loss

In Phase 3 clinical trials, women treated with Myfembree for up to 52 weeks had a decline in lumbar spine BMD of 0.80%. After 52 weeks of treatment with R+E2/NETA, bone loss of at least 2% at the lumbar spine was observed for 36.4% of subjects. In comparison 25.8% of subjects from the uterine fibroid cohort of the observational study experienced ≥2% bone loss over 52 weeks of observation. Because the lumbar spine tends to be the most sensitive to reductions in estrogen levels, changes in BMD at this site will be included in product labeling. Given that bone loss occurs in a subset of women with 12 months of treatment and information on recovery is inadequate, considering the benefit-risk, we will require a Limitations of Use of 2 years. Additionally, the recommendation for BMD at baseline and periodically thereafter and a contraindication for use in women with known osteoporosis will also be included in product labeling. The approval letter will also include a postmarketing requirement to characterize bone loss with greater duration of treatment (4 years) and to characterize recovery of bone loss.

6 Expected Postmarket Use

The likely prescribers will be gynecologists and primary care physicians in the outpatient setting. In general, because of the increased risk of thrombotic or thromboembolic disorders, including pulmonary embolism and deep vein thrombosis associated with other products in this class gynecologists and primary care physicians should be aware of these risks and familiar with how to manage them.

7 Risk Management Activities Proposed by the Applicant

The Applicant did not propose any risk management activities for Myfembree beyond routine pharmacovigilance and labeling which includes a Patient Package Insert.

8 Discussion of Need for a REMS

The Clinical Reviewer recommends approval of Myfembree (relugolix, estradiol, and norethindrone acetate) on the basis of the efficacy and safety information currently available.
Uterine fibroids are associated with heavy menstrual bleeding which can lead to iron-deficiency anemia, pressure on adjacent organs, and back pain. There are currently two FDA-approved medical therapies for fibroid-related bleeding issues. The approved products are Lupron (leuprolide acetate) and a combination product, Oriahnn, that includes (elagolix, estradiol and norethindrone acetate).

Two trials demonstrate effectiveness of Myfembree to be administered orally for the management of heavy menstrual bleeding associated with uterine fibroids in premenopausal women. The results of both trials support a conclusion of superiority of R+E2/NETA over placebo. The secondary and sensitivity analyses all showed similar robust findings and demonstrated the efficacy of R+E2/NETA in patients with heavy menstrual bleeding associated with uterine fibroids.

In the clinical development program, the serious risk of thromboembolic disorders and vascular events was identified in patients treated with Myfembree. Estrogen and progestin combinations, including the estradiol/norethindrone acetate component of Myfembree increase the risk of thrombotic or thromboembolic disorders, including pulmonary embolism, deep vein thrombosis, stroke, and myocardial infarction. Similar products containing estradiol in combination with norethindrone acetate contain a boxed warning regarding these risks. A boxed warning will be required in the label to inform prescribers of the potential risk of thrombotic or thromboembolic disorders. Additionally, a Limitations of Use of 2 years and a recommendation in the Warnings & Precautions section for BMD at baseline and periodically thereafter along with a contraindication for use in women with known osteoporosis will also be included in product labeling.

Therefore, based on the available data and prescribing community’s likely familiarity with how to manage the serious risks that are associated with Myfembree given they are also a common risk of estrogen and progestin combination products, DRM is not recommending a REMS for Myfembree at this time.

9 Conclusion & Recommendations

Based on the available data, a REMS is not necessary to ensure the benefits outweigh the risks. The safety concern associated with Myfembree will be addressed in labeling which will include a Boxed Warning and PPI. In general, gynecologists and primary care physicians who prescribe Myfembree should be familiar with the risk of thromboembolic events that are associated with Myfembree and should be able to manage these risks. Should DUOG have any concerns or questions or if new safety information becomes available, please send a consult to the Division of Risk Management.

10 Appendices

10.1 REFERENCES

1 Myovant Sciences, Inc. US Prescribing Information for Myfembree (relugolix, estradiol, and norethindrone acetate) (May 4, 2021)

2 Clinical Overview for Myfembree (relugolix, estradiol, norethindrone acetate), May 5, 2021
3 (Pérez-López et al. 2014; Wise and Laughlin-Tommaso 2016)

4 Abbvie Endocrine Inc. US Prescribing Information for Lupron Depot (leuprolide acetate) (May 4, 2021)

5 Abbvie Endocrine Inc. US Prescribing Information for Oriahnn (elagolix, estradiol, and norethindrone acetate)


7 Myovant Sciences, Inc. Summary of Clinical Safety for Myfembree (relugolix, estradiol, and norethindrone acetate) (May 4, 2021)

8 Novo Nordisk Pharmaceuticals, Inc. US Prescribing Information for Activella (estradiol/norethindrone acetate) (May 4, 2021)
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