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Reimbursement Recommendation

Relugolix-Estradiol–Norethindrone Acetate (Myfembree)

Indication: Management of heavy menstrual bleeding associated with uterine fibroids in premenopausal women

Sponsor: Knight Therapeutics Inc.

Final recommendation: Reimburse with conditions

Summary

What Is the Reimbursement Recommendation for Myfembree?

Canada's Drug Agency (CDA-AMC) recommends that Myfembree should be reimbursed by public drug plans for the treatment of heavy menstrual bleeding (HMB) from uterine fibroids (UFs) in patients in the premenopausal stage if certain conditions are met.

Which Patients Are Eligible for Coverage?

Myfembree should only be covered to treat patients who are aged 18 years or older who have HMB from UFs and who have not reached menopause.

What Are the Conditions for Reimbursement?

Myfembree should only be reimbursed if prescribed by clinicians with expertise in diagnosing and managing UFs and the cost is not more than the least costly regimen of leuprolide acetate with or without add-back therapy (hormonal therapy to reduce negative side effects). When first prescribed, Myfembree should be reimbursed for 6 months, after which response to treatment should be assessed. The drug should not be reimbursed if used in combination with a gonadotropin-releasing hormone agonist or antagonist, upon successful surgery or medical procedure to treat UFs, pregnancy, menopause, or if significant bone loss occurs.

Why Did CDA-AMC Make This Recommendation?

- Evidence from 2 clinical trials demonstrated that more patients receiving Myfembree experienced a meaningful reduction in menstrual blood loss after being on treatment for 6 months compared to patients receiving placebo.
- More patients receiving Myfembree had an improvement in anemia, pain, and health-related quality of life (HRQoL) compared to patients receiving placebo.
- Myfembree may meet patients' need for a treatment that improves symptoms (e.g., bleeding and pain) and HRQoL; however, it is unclear if patients on the medication are able to avoid surgery over the long term.
- Based on the CDA-AMC assessment of the health economic evidence, Myfembree does not represent good value to the health care system at the public list price. Canadian Drug Expert Committee (CDEC) determined there is not enough evidence to justify a greater cost for Myfembree compared with the least costly regimen of leuprolide acetate with or without add-back.

Summary

- Based on public list prices, Myfembree is estimated to cost the public drug plans approximately $7.6 million over the next 3 years.

Additional Information

What Is HMB From UFs?

UFs are noncancerous growths located in and around the uterus that can cause large amounts of blood loss during menstrual periods. People with UFs may also experience other symptoms that affect HRQoL, such as pain, abdominal bloating, low iron levels, and tiredness, and may also be less likely to become pregnant. UFs are estimated to occur in approximately 5.5% of females aged 15 to 49 years in Canada.

Unmet Needs in HMB From UFs

Patients experiencing HMB from UFs need other effective treatment options that reduce symptoms (e.g., bleeding and pain) and improve low iron levels and HRQoL. Patients are also looking for treatments with acceptable side effects that allow patients to avoid or delay surgery or medical procedures and avoid 3-month dosage commitments.

How Much Does Myfembree Cost?

Treatment with Myfembree is expected to cost approximately $3,285 per patient per year.

Recommendation

The Canada's Drug Agency (CDA-AMC) Canadian Drug Expert Committee (CDEC) recommends that relugolix-estradiol–norethindrone acetate (RGX-E2-NETA) be reimbursed for the management of heavy menstrual bleeding (HMB) associated with uterine fibroids (UFs) in patients in the premenopausal stage only if the conditions listed in Table 1 are met.

Rationale for the Recommendation

In 2 phase III, double-blind, randomized controlled trials (RCTs) in patients aged 18 to 50 years who were in the premenopausal stage with a confirmed diagnosis of UFs and HMB (the LIBERTY 1 and LIBERTY 2 trials), once-daily RGX-E2-NETA (relugolix 40 mg, estradiol 1 mg, and norethindrone acetate 0.5 mg) was associated with statistically significant and clinically meaningful improvements compared to placebo for the primary end point. This end point was the proportion of patients with treatment response, defined as having a menstrual blood loss (MBL) volume of less than 80 mL and a 50% or greater reduction in MBL volume from baseline over the last 35 days of treatment as measured by the alkaline hematin method. At week 24, the difference between the RGX-E2-NETA group and the placebo group was 54.5% (95% confidence interval [CI], 44.3% to 64.7%; $P < 0.0001$) in the LIBERTY 1 trial and 56.5% (95% CI, 46.6% to 66.5%; $P < 0.0001$) in the LIBERTY 2 trial. Furthermore, RGX-E2-NETA was associated with improvements compared with placebo in other clinically relevant outcomes, such as anemia (based on a subset of patients who had a hemoglobin of 10.5 g/dL or lower at baseline with a meaningful increase in hemoglobin concentration), UF-associated pain (based on a subset of patients who had a maximum numerical rating scale [NRS] score of 4 points or greater prior to randomization with an improvement in UF-associated pain on the NRS), and health-related quality of life (HRQoL) (as measured using the Uterine Fibroid Symptom Quality of Life [UFS-QOL]). Results for these supportive outcomes were less certain due to risk of bias, a lack of published minimal important differences, and missing data.

There was a lack of comparative evidence between RGX-E2-NETA and other treatments for UF-associated HMB. As such, the sponsor submitted a network meta-analysis (NMA) comparing RGX-E2-NETA and leuprolide acetate (LA) without add-back therapy (hormonal therapy to reduce negative side effects) for the treatment of HMB associated with UFs in people in the premenopausal stage for review. However, LA is prescribed with add-back therapy in Canada; therefore, the results of the NMA were minimally informative regarding how relevant treatments for HMB compare. Additional limitations with the evidence included the lack of information for anemia and pain outcomes and harms relating to bone mineral density (BMD), which is a concern when using gonadotropin-releasing hormones (GnRHs). Other issues included imprecision in the effect estimates and key assumptions for NMAs that could not be satisfied. Thus, CDEC could not draw firm conclusions on the comparative efficacy and safety of RGX-E2-NETA.

Patient input received for this review noted that there is a need for safe and effective treatments that improve symptoms (e.g., bleeding and pain) and HRQoL with simpler regimens that allow patients to avoid surgery

and 3-month dosage commitments. Based on the results from the LIBERTY 1 and LIBERTY 2 trials, RGX-E2-NETA may address patient-important outcomes of symptom and HRQoL improvement.

At the sponsor-submitted price for RGX-E2-NETA and publicly listed price for LA with or without add-back, RGX-E2-NETA was less costly than LA with or without add-back. There is a lack of evidence comparing RGX-E2-NETA with LA with add-back and uncertainty in the direction of treatment effect compared to LA without add-back due to limitations in the sponsor's NMA, so the total drug cost of RGX-E2-NETA should not exceed the total drug cost of LA with or without add-back.

Table 1: Reimbursement Conditions and Reasons

Reimbursement condition	Reason	Implementation guidance
Initiation		
1. Patients in the premenopausal stage and aged 18 years or older with confirmed UFs and HMB.	The LIBERTY 1 and LIBERTY 2 trials enrolled patients aged 18 to 50 years in the premenopausal stage with confirmed UF-associated HMB. The clinical expert consulted for this review stated that adult patients in the premenopausal stage (without an upper age restriction) could receive RGX-E2-NETA for the management of HMB associated with UFs. Based on the sponsor-submitted indirect evidence of a comparison with leuprolide acetate, RGX-E2-NETA is expected to occupy a similar place in therapy.	In practice, HMB due to UFs is identified through clinical assessment as abnormal uterine bleeding that interferes with a patient's HRQoL and activities of daily living rather than a specific MBL volume quantified using the alkaline hematin method as is used in clinical trials. The clinical expert noted that RGX-E2-NETA could be a treatment option once a diagnosis of UFs with HMB is confirmed and it is expected that the drug will be used to complement and facilitate less-invasive medical procedures and surgical approaches. In practice, a diagnosis of UFs is confirmed via imaging. The Society of Obstetricians and Gynaecologists of Canada clinical practice guidelines for abnormal uterine bleeding in women in the premenopausal stage note that nonhormonal drugs and hormonal drugs (e.g., combined hormonal contraceptives, progestins, depot medroxyprogesterone acetate, and levonorgestrel-releasing intrauterine systems) can be used to treat HMB.
2. The maximum duration of initial authorization is 6 months.	The primary end point of the LIBERTY 1 and LIBERTY 2 trials (MBL volume response) was assessed at 6 months.	—
Renewal		
3. For renewal after initial authorization, the physician must provide proof of clinical response, defined as reduction in MBL volume, reduction in pain, improvement in hemoglobin	The LIBERTY 1 and LIBERTY 2 trials assessed outcomes for MBL volume response by the alkaline hematin method, UF-associated pain by NRS score, hemoglobin levels, and HRQoL using the UFS-QOL. In addition, reduction in MBL volume and pain and improvement	—

Reimbursement condition	Reason	Implementation guidance
(in patients with anemia), or improvement in HRQoL.	in anemia and HRQoL are important to patients.	
4. The physician must provide proof of maintenance of a reduction in MBL volume, reduction in pain, improvement in hemoglobin (in patients with anemia), or improvement in HRQoL from baseline every 6 months for subsequent authorization.	This is meant to ensure that only those patients whose HMB associated with UFs is responding to treatment with RGX-E2-NETA are continuing to receive treatment.	—
Discontinuation		
5. Reimbursement for RGX-E2-NETA should be discontinued upon occurrence of any of the following: successful surgery or procedure, plans for pregnancy, menopause, or a meaningful decline in BMD.	According to the clinical expert, RGX-E2-NETA should be discontinued upon successful surgery or procedure, plans for pregnancy, menopause, a meaningful decline in BMD, or intolerable adverse effects.	The Health Canada product monograph recommends that assessment of BMD by DXA be performed at baseline and that periodic DXA be performed during treatment. The product monograph also states that use of RGX-E2-NETA should be limited to 24 months due to the risk of continued bone loss, which may not be reversible. In the clinical development program for RGX-E2-NETA, 3% bone loss was noted as being clinically meaningful in the trials.
Prescribing		
6. RGX-E2-NETA should be prescribed by clinicians with expertise in diagnosing and managing UFs (e.g., obstetrician-gynecologist).	This is meant to ensure that RGX-E2-NETA is prescribed for appropriate patients and that adverse effects are managed in an optimized and timely manner.	—
7. RGX-E2-NETA should not be used in combination with another gonadotropin-releasing hormone agonist or antagonist.	In the LIBERTY 1 and LIBERTY 2 trials, the use of hypothalamic-pituitary-gonadal axis medications was prohibited.	—
Pricing		
8. RGX-E2-NETA should be negotiated so that it does not exceed the drug program cost of treatment with the least costly regimen of leuprolide acetate with or without add-back that is reimbursed for the treatment of HMB associated with UFs in patients in the premenopausal stage.	Indirect evidence comparing RGX-E2-NETA to leuprolide acetate without add-back was inconclusive, and evidence comparing RGX-E2-NETA to leuprolide acetate with add-back was not presented. As such, there is insufficient evidence to justify a cost premium for RGX-E2-NETA over the least expensive regimen of leuprolide acetate with or without add-back reimbursed for the treatment of HMB associated with UFs in patients in the premenopausal stage.	—

BMD = bone mineral density; DXA = dual-energy X-ray absorptiometry; HMB = heavy menstrual bleeding; HRQoL = health-related quality of life; MBL = menstrual blood loss; NRS = numerical rating scale; RGX-E2-NETA = relugolix-estradiol–norethindrone acetate; UF = uterine fibroid; UFS-QOL = Uterine Fibroid Symptom Quality of Life.

Discussion Points

- **Unmet needs:** Based on patient group input, there is a need for treatments that allow patients to prepare for surgery and mitigate the risks associated with surgery (e.g., significant blood loss). The committee noted that, based on the opinion of the clinical expert consulted for this review, RGX-E2-NETA may result in a clinically important increase in the number of patients who experience improvement in anemia compared to placebo. Patient group input also indicated a need for treatments for patients who are ineligible for or do not wish to undergo surgeries or procedures. There is no evidence from the LIBERTY trial program to assess the impact of RGX-E2-NETA on avoiding future surgeries or procedures.
- **GRADE assessment:** Input from patients with UF-associated HMB identified a need for treatments that improve symptoms, such as bleeding and pain. Based on the LIBERTY 1 and LIBERTY 2 trials, RGX-E2-NETA results in a clinically important increase in the proportion of patients who had a MBL volume response and may result in a clinically important increase in the proportion of patients who experienced improvement in anemia or improvement in pain compared with placebo. The certainty of evidence was low for both anemia and pain outcomes because results were based on subpopulations (putting the results at increased risk of bias) and because the lower bound of the 95% CI for the between-group difference was consistent with an effect that would not be considered clinically important for patients. The committee noted that, in practice, treatment is focused on a reduction in MBL volume that the patient is satisfied with and for hemoglobin levels to improve such that the HMB and anemia no longer affect the patient's HRQoL or activities of daily living.
- **HRQoL:** Patients also noted a desire for treatments that improve HRQoL. Evidence from the studies showed that RGX-E2-NETA likely results in a clinically important increase in UFS-QOL symptom severity and HRQoL total scores compared with placebo. The committee discussed that although missing outcome data and a lack of published minimal important differences introduced some uncertainty in the evidence, the results suggested a clinically meaningful improvement based on clinical expert opinion.
- **Persistence of treatment effect:** The committee reviewed the longer-term evidence from the extension studies (the LIBERTY EXTENSION and LIBERTY RWS studies) that suggested treatment effects were maintained for reduced MBL volume and patient-reported symptom severity and improved HRQoL (up to 104 weeks total treatment) and anemia based on hemoglobin levels (up to 52 weeks total treatment). There were limitations with the study designs, a large number of discontinuations, and a potential selection bias for patients who respond to and tolerate the drug that increase the uncertainty of the longer-term results.
- **Comparison to LA:** Based on the sponsor-submitted indirect treatment comparison, LA is a relevant comparator to RGX-E2-NETA. LA is associated with treatment-initiation flare ups, a long discontinuation process, and an increased risk of irreversible BMD loss and it may be less convenient to patients because it is an intramuscular injection. Input from patients and clinicians noted a need for treatments that avoid these issues. The committee noted that it is unclear if RGX-E2-NETA meets all these needs because symptom flare was not assessed in the LIBERTY studies. It is an oral

medication without titration; therefore, discontinuation can occur at any time. The Health Canada product monograph recommends limiting use of RGX-E2-NETA to 24 months due to the risk of continued bone loss that may be irreversible. The oral route of administration of RGX-E2-NETA as a once-daily combined pill may be more convenient for patients than other therapies for UFs, such as those that use an injection.

- **Indirect comparison:** The committee discussed the sponsor-submitted NMA that included LA without add-back therapy. The results were inconclusive due to imprecision that showed either treatment could be favoured for reduction in MBL volume and UFS-QOL outcomes. Additionally, patient-important outcomes for improving anemia and UF-associated pain were not captured in the NMA. The committee also noted that there was an absence of data for RGX-E2-NETA versus LA with add-back therapy, which is how the comparator is prescribed in Canada. According to the sponsor, LA with add-back therapy could not be included because an indirect comparison was infeasible based on the available evidence. As such, the committee agreed that definitive conclusions on the treatment effect of RGX-E2-NETA relative to LA with add-back therapy could not be made.
- **Place in therapy:** The sponsor-submitted NMA only compared RGX-E2-NETA and LA for UFs. Therefore, CDEC noted that in the absence of comparative evidence for RGX-E2-NETA versus other treatments, RGX-E2-NETA would occupy the same place in therapy as LA. The committee also discussed the place in therapy for RGX-E2-NETA and noted that, in practice, most patients would likely have already tried other therapies, including hormonal therapies, to manage HMB associated with UFs before receiving RGX-E2-NETA. In the LIBERTY 1 and LIBERTY 2 trials, 92.2% and 91.4% of patients, respectively, received at least 1 medication before enrolment in the studies; however, CDEC noted that it was not clear if these treatments were used to manage HMB or UFs.

Background

UFs, also known as myomas or leiomyomas, are benign neoplasms of uterine smooth muscle and are the most common tumours in females. UFs are typically diagnosed in people who are between menarche and menopause. The main risk factors are early menarche, late onset of menopause, African ancestry, and history of no childbirth. A common symptom is abnormal uterine bleeding, particularly HMB, which is reported by 50% to 80% of patients with symptomatic UFs in surveys and trials. Infertility, abdominal bloating, constipation, increased urinary frequency, incontinence, dyspareunia, anemia, and fatigue are among other symptoms that can affect HRQoL. For research purposes, HMB is defined as more than 80 mL of blood loss during each menstrual cycle, based on the direct measurement of MBL via the alkaline hematin method. However, from a clinical practice point of view, it is defined as a volume that interferes with a patient's HRQoL, including physical, social, and emotional aspects. Prevalence estimates of UFs vary widely and have been estimated to be 5.5% based on females aged 15 to 49 years in Canada who self-reported having physician-diagnosed UFs.

According to the literature and the clinical expert consulted for this review, the overall goals of treatment are to reduce menstrual bleeding, allow for activities of daily living, increase hemoglobin levels, address pain

and bulk symptoms, and improve HRQoL. The clinical expert also noted that reducing the size of UFs can allow for less-invasive surgery, a delay or reduction in the need for surgery, symptom management until menopause (when symptoms tend to alleviate), and reduced impact of UFs on fertility.

Treatment can include surgical, procedural, and pharmacological options; the choice of treatment depends on the clinical presentation (symptoms, severity, size, and location of UFs), patient's age, and patient's goals (i.e., to preserve fertility and/or the uterus). First-line pharmacological options include combined estrogen-progestin contraceptives, progestin-releasing intrauterine system, and tranexamic acid; however, HMB is often inadequately controlled with these drugs alone. For HMB that responds inadequately to first-line treatments, GnRH antagonists and agonists are used in combination with or without hormonal add-back therapy (used to mitigate hypoestrogenic side effects and protect the endometrium). GnRH agonists (e.g., LA) are often used as preoperative therapy (i.e., short-term for approximately 3 to 6 months) with concomitant iron therapy to reduce the size of UFs and improve anemia before surgery. GnRH agonists are associated with an initial flare effect (symptom exacerbation) that is not seen with GnRH antagonists and once the drug is stopped, UF regrowth often occurs within 3 months. Uterine artery embolization is used to address HMB and bulk symptoms. However, it does not remove UFs and is associated with ovarian dysfunction and the need for reintervention. Hysteroscopic resection or myomectomy of submucosal UFs have been associated with high blood loss and UF recurrence. Hysterectomy is the only definitive treatment for UFs. Due to its association with significant morbidity and mortality, it is a last-line option for patients who have persistent symptoms, despite other treatments.

RGX-E2-NETA has been approved by Health Canada in women in the premenopausal stage for the management of HMB associated with UFs and for the management of moderate to severe pain associated with endometriosis. RGX-E2-NETA is a nonpeptide GnRH receptor antagonist, an estrogen, and a progestin, available as relugolix 40 mg, estradiol 1 mg, and norethindrone acetate 0.5 mg. The recommended dosage in the product monograph is 1 tablet daily. The monograph also states that use of the drug should be limited to 24 months due to the risk of continued bone loss that may not be reversible.

Sources of Information Used by the Committee

To make its recommendation, the committee considered the following information:

- a review of 2 pivotal RCTs in females aged 18 to 50 years with a diagnosis of UFs and HMB associated with UFs, 2 open-label extension (OLE) studies, and 1 indirect treatment comparison
- patients' perspectives gathered by 1 patient group, CANFib
- input from public drug plans that participate in the reimbursement review process
- one clinical specialist with expertise diagnosing and treating patients with HMB associated with UFs
- a review of the pharmacoeconomic model and report submitted by the sponsor.

Perspectives of Patients, Clinicians, and Drug Programs

Patient Group Input

This section was prepared by the review team based on the input provided by patient groups.

CDA-AMC received 1 patient group input submission from CANFib. The organization provides a forum for females in Canada with UFs to discuss their symptoms, talk to peers, find out more about UFs, discuss navigation of the Canadian medical system while learning more about the treatments and medications approved by Health Canada for UFs. CANFib also works with Canadian pharmaceutical outreach, researchers, insurance companies, and specialists to push for new ideas that become future treatments and solutions.

CANFib conducted a survey in 2023, and respondents included 315 females with UFs. The patient group noted that 59% of the respondents had to wait between 7 months to more than 13 months to visit their health care provider. Based on the survey results, a new symptom or a current medication that was not working were the top reasons to return to the specialist. Additionally, pain was the top reason (n = 266) for seeking medical help, followed by excessive bleeding (n = 249); these symptoms led 73% of the respondents to take at least 2 days off work per month. CANFib explained that 261 respondents reported consulting the internet for information on UF relief; 84% of those who consulted medical professionals felt they left the consultation still “uninformed” about the condition and 86% felt they were not given the full list of Health Canada–approved treatments and medications. CANFib highlighted that the top reason to return to the specialist was ineffectiveness of the medications and because of the long wait time from diagnosis to treatment and the long wait time for appointments, more options and earlier treatment will benefit patients and reduce the need for follow-up visits and surgery.

CANFib also conducted group call discussions with 32 females with UFs who had experience with RGX-E2-NETA. Of these respondents, 31 reported being “very happy” and 1 reported feeling “indifferent” about the results of RGX-E2-NETA on symptoms. Two of the 32 females with UFs were able to work again. Of the 32 respondents, 2 had access to RGX-E2-NETA by extended insurance coverage and 30 had to pay out of pocket for the medication; 3 of the respondents said they could or would continue to afford the medication for even a notable period. CANFib added that RGX-E2-NETA enabled the females in the discussion group to lead a full life, be with family, care for children and/or older parents, show up at work, and function without the debilitating pain, heavy blood loss, or ongoing depression.

CANFib explained that, based on member discussions, most females reported primary symptoms of heavy bleeding and pain; lost time at work, inability to function within a family unit, lack of social life or professional life, and eventual depression are also common events. The discussion group described the constant need for open access to a bathroom at work or at home, and how their relationships suffer under the immense pressure of feeling as though they must carry on as if they do not have any symptoms.

Regarding experiences with currently available treatments, CANFib noted that there are a number of treatments and medications used to treat UFs, yet there is no cure other than surgical hysterectomy. According to the group, desirable outcomes include having access to an effective treatment that does not

require 3-month dosage commitments, regaining confidence, and being able to have a family, social, and professional life.

This patient group submission also included comments from the incoming Society of Obstetricians and Gynecologists of Canada president and endorsement from The Women's Health Coalition.

Input From the Clinical Expert Consulted for This Review

According to the clinical expert consulted for this review, patients seek new therapies that adequately and rapidly relieve symptoms without adverse effects, improve HRQoL, are simpler to administer, and have a treatment effect with rapid onset of action and quick resolution upon discontinuation.

Based on input from the clinical expert, first-line treatment of abnormal uterine bleeding includes nonsteroidal anti-inflammatory drugs, hormonal contraceptives (including progestins and levonorgestrel intrauterine systems), tranexamic acid, and iron repletion as further investigations take place to identify the cause of the abnormal uterine bleeding. Once a diagnosis of UFs (with HMB) is confirmed, RGX-E2-NETA would be a treatment option depending on the symptoms, severity, and location of the UFs, absence of endometrial pathology, and the patient's goals. The clinical expert expects that RGX-E2-NETA will be used in practice to complement and facilitate less-invasive medical procedures and surgical approaches, such as hysteroscopic procedures and fertility-preserving surgical approaches. As per the expert, RGX-E2-NETA may be used as a bridge treatment in patients who plan to have gynecological surgery within 3 months to elevate hemoglobin and enable less-invasive surgical methods, are delaying surgery for fertility, or anticipate menopause within a couple of years.

The clinical expert indicated that patients receiving RGX-E2-NETA would be adults in premenopause because symptoms of UFs tend to diminish after menopause. Additionally, patients most likely to respond to treatment with RGX-E2-NETA include those with HMB associated with UFs and bulk symptomatology secondary to UFs. The expert also noted that patients with anemia secondary to severe abnormal uterine bleeding, severe pain, and ureteric obstruction by UFs are most in need of treatment.

Patients best suited for treatment with RGX-E2-NETA would be identified based on clinical history, physical examination, and investigations (e.g., Papanicolaou test, biopsy, complete blood count, pregnancy testing, and sonohysterography hysteroscopy). As part of confirming a diagnosis, endometrial and cervical pathology must be ruled out based on the patient's age and risk factors.

As per the clinical expert, the main outcomes used to assess treatment response in practice include qualitative clinical assessments for a reduction in primary symptomatology (i.e., reduced HMB), reduction in pain and bulk symptoms, return to normal function (e.g., activities of daily living, work), and fertility success (if this is the patient's goal). Clinicians also focus on the patient's satisfaction with the treatment rather than quantitative measures, such as MBL volume. However, physicians may measure hemoglobin levels with the goal of increasing them to normal values in patients experiencing anemia. The expert explained that although the outcomes used in clinical trials may be informative, they are generally not used in practice (aside from measuring and improving hemoglobin levels).

The clinical expert stated that RGX-E2-NETA should be discontinued upon successful surgery or procedure, plans for pregnancy, menopause, a meaningful decline in BMD, or adverse effects that are intolerable. Although the Health Canada product monograph states that use of RGX-E2-NETA should be limited to 24 months due to the risk of continued and irreversible bone loss, the expert suggested that treatment beyond 2 years may be considered if the patient is maintaining the goals for symptom improvement and has a healthy BMD. However, if RGX-E2-NETA is used to treat HMB and anemia in anticipation of planned surgery or medical procedure, treatment duration tends to be shorter than 2 years. As noted by the expert, the benefit of reducing the size of the uterus and fibroids in preparation for surgery is achieved by 3 months. If wait times are longer than the 3 months, the benefit can be maintained by longer use of the treatment.

RGX-E2-NETA would be used in a community setting, acute care hospital, or specialty clinic. Although diagnosis and initial prescription of the drug would be performed by an obstetrician-gynecologist, the expert noted that follow-up management and monitoring may be done by a primary care physician.

Clinician Group Input

No input was received from clinician groups for this review.

Drug Program Input

Input was obtained from the drug programs that participate in the reimbursement review process. The following were identified as key factors that could potentially impact the implementation of a recommendation for RGX-E2-NETA:

- considerations for relevant comparators
- considerations for initiation of therapy
- considerations for continuation or renewal of therapy
- system and economic issues.

The clinical expert consulted for the review provided advice on the potential implementation issues raised by the drug programs.

Table 2: Responses to Questions From the Drug Programs

Implementation issues	Response
Relevant comparators	
The sponsor selected 2 identical studies (LIBERTY 1 and LIBERTY 2) from a systematic literature review. Both trials studied the combination of RGX-E2-NETA, against placebo. There was an ITC to leuprolide acetate plus add-back therapy which is used off-label to treat this condition when surgery is not an option. Lupron (leuprolide acetate) is a regular benefit in most jurisdictions and has restricted use criteria in the other jurisdictions. It is also a slow-release injectable, whereas RGX-E2-NETA includes RGX as a daily oral formulation.	According to the clinical expert consulted for this review, nafarelin, buserelin, goserelin, and degarelix are not commonly used because they do not have a Health Canada indication for the treatment of UFs, and some have associated adverse effects that patients wish to avoid. The expert stated that goserelin may be used instead of leuprolide acetate for patients who cannot receive intramuscular injections (e.g., patients who are on anticoagulants or those with diseases affecting coagulation, such as von Willebrand disease). In general, none of the treatments would be considered a comparator for RGX-E2-NETA.

Implementation issues	Response
Outside of off-label use of leuprolide acetate plus add-back hormonal therapy, would the following off-label agents also be appropriate comparators (in addition to add-back therapy)? • GnRH analogue — nafarelin • LHRH analogues — buserelin and goserelin • GnRH antagonist — degarelix	
Of note, Myfembree is a fixed-dose, oral tablet containing all 3 drugs (RGX, E2, and NETA). The LIBERTY trials used 2 separate tablets, RGX and E2-NETA (Activelle), in their studies. The sponsor has confirmed that a study was conducted to demonstrate the bioequivalence of the fixed-dose tablet compared to the coadministration of RGX and E2-NETA tablets. Are there any concerns with this approach?	CDEC and the clinical expert had no concerns with the approach used in the trial (RGX available as a tablet separate to the combined E2-NETA) compared to how RGX-E2-NETA is available commercially (as a combined tablet).
Considerations for initiation of therapy	
The LIBERTY studies required that diagnosis of UFs be confirmed by a transvaginal ultrasound, and at least 1 UF must be verified to meet at least 1 of the following criteria: • subserosal, intramural, or < 50% intracavitary submucosal fibroid with a diameter ≥ 2 cm (longest diameter) • multiple small fibroids with a total uterine volume of ≥ 130 cm^3. Considering diagnostic imaging, although the LIBRERTY studies required transvaginal ultrasound, would 1 of the following 3 tests be acceptable for meeting diagnostic criteria: hysteroscopy, ultrasonography, and MRI? Do you agree with the other above-listed requirements having to be met to access the medication?	The clinical expert noted that of the 3 imaging methods listed, ultrasonography (specifically sonohysterography) is the preferred method because of its accuracy. Hysteroscopy may be an option but is less preferred because it does not show fibroids located outside of the uterus. MRI is rarely used because ultrasound methods are better for imaging UFs and are less costly. The expert stated the importance of the location of the UFs for diagnosing severity and deciding on treatment. Therefore, the criteria used in the trial are reasonable.
Patients who are premenopausal and aged 18 to 50 years were included. Would patients who are premenopausal and outside of this age range be eligible for treatment?	CDEC and the clinical expert agreed that patients aged 18 years and older in the premenopausal stage would be eligible for treatment with RGX-E2-NETA.
Because the use of hormonal contraceptive to treat UFs is considered to be off-label in Canada, are there any appropriate prior therapies that should be required?	As per the Society of Obstetricians and Gynaecologists of Canada clinical practice guidelines for abnormal uterine bleeding in women in the premenopausal stage, nonhormonal drugs (e.g., nonsteroidal anti-inflammatory drugs and antifibrinolytics) can be used to treat HMB that is cyclic or has predictable timing. Combined hormonal contraceptives, progestins, depot medroxyprogesterone acetate, and levonorgestrel-releasing intrauterine systems are hormonal drugs that can address HMB. CDEC and the clinical expert stated that these are options that patients may try to treat abnormal uterine bleeding or HMB associated with UFs.

Implementation issues	Response
Considerations for continuation or renewal of therapy	
Response is shown by improvement in bleeding, including experiencing amenorrhea and anemia, where applicable. The primary end point in the LIBERTY studies was defined by the percentage of participants who experienced a MBL of < 80 mL and ≥ 50% reduction from baseline MBL over the last 35 days of the treatment. Measurement of MBL in the real-world setting is not practical. How will MBL reduction be monitored and assessed? Given that persons with HMB associated with UF often have iron-deficiency anemia requiring treatment, a key secondary end point in the studies was the proportion of patients with hemoglobin ≤ 10.5 g/dL at baseline who experienced an increase of ≥ 2 g/dL from baseline at week 24. This increase is in-line with the expected increase in hemoglobin following transfusion of 2 units of red blood cells. Is it possible that a patient would meet a significant increase in hemoglobin independent of meeting the specified MBL reduction? For CDEC consideration: Consider whether renewal criteria might allow for renewal of drug eligibility for patients with HMB who have demonstrated an increase in hemoglobin compared to baseline.	As per the clinical expert, exact quantification of MBL volume (such as using the alkaline hematin method) is not performed in practice; MBL volume reduction is monitored through clinical assessment based on improvement reported by the patient and improvement of hemoglobin levels to normal in practice. Furthermore, the focus of treatment is to have a reduction in MBL volume that the patient is satisfied with and for hemoglobin levels to improve such that the HMB and anemia no longer affect the patient's HRQoL or activities of daily living. Because the goals of treatment differ from the outcomes in a clinical trial, it can be difficult to know if a patient has met the significant increase in hemoglobin independent of meeting the specified MBL volume reduction. CDEC agreed with the clinical expert and noted that for reimbursement of RGX-E2-NETA to be renewed, the treating physician must provide proof of clinical response, defined as reduction in MBL volume, reduction in pain, improvement in hemoglobin (in patients with anemia), or improvement in HRQoL.
System and economic issues	
When estimating the costs of comparative treatments, the sponsor assumed treatment unit costs for leuprolide acetate plus add-back (Activelle) equates only with the cost of the leuprolide since Activelle is not publicly funded. Since Activelle is not publicly funded, are there situations where patients who wish to be treated with leuprolide acetate plus add-back would replace the Activelle with a different hormonal alternative that is covered? This cost may not be captured and would affect the BIA. For CDEC consideration: For jurisdictions who list leuprolide acetate as an open or free benefit, it may not be possible to estimate the proportion of leuprolide acetate usage that is attributable to patients who are premenopausal with HMB and UFs.	The clinical expert confirmed that the add-back therapy does not have to be Activelle but can be another similar treatment that is covered by health insurance or public drug plans. In previous clinical studies, standard add-back has been NETA 5 mg, which the expert noted is less expensive than Activelle. This is a comment from the drug programs to inform CDEC deliberations.

BIA = budget impact analysis; CDEC = Canadian Drug Expert Committee; E2 = estradiol; GnRH = gonadotropin-releasing hormone; HMB = heavy menstrual bleeding; HRQoL = health-related quality of life; ITC = indirect treatment comparison; LHRH = luteinizing hormone-releasing hormone; MBL = menstrual blood loss; NETA = norethindrone acetate; RGX = relugolix; UF = uterine fibroid.

Clinical Evidence

Systematic Review

Description of Studies

Two phase III, double-blind RCTs (the LIBERTY 1 trial: N = 388; the LIBERTY 2 trial: N = 382) including female patients aged 18 to 50 years with a confirmed diagnosis of UFs and HMB that assessed the efficacy and safety of once-daily RGX-E2-NETA (relugolix 40 mg, estradiol 1 mg, and norethindrone acetate 0.5 mg) (n = 128 and 126, respectively) compared to placebo (n = 128 and n = 129, respectively) at 24 weeks. Efficacy was measured by the primary end point of MBL volume response rate and defined as the proportion of patients with a response (MBL volume of less than 80 mL and a 50% or greater reduction in MBL volume from baseline). Other clinically relevant outcomes included improvement of anemia, pain, symptom severity, and HRQoL.

The LIBERTY 1 and LIBERTY 2 trials were mostly identical in design; the main differences were the countries where the studies took place and the order of statistical testing of secondary outcomes. The mean age across the studies was approximately 42 years. For both studies, there were imbalances between the treatment groups in the proportion of patients who were Black (46.1% versus 51.2% in the LIBERTY 1 trial and 49.6% versus 57.4% in the LIBERTY 2 trial) and white (50.0% versus 44.1% in the LIBERTY 1 trial and 46.4% versus 38.0% in the LIBERTY 2 trial). Proportions of other race groups reported in the studies (American Indian or Alaska Native, Asian, other race, multiple races, and not reported) were generally balanced between treatment groups and across the studies. Mean hemoglobin concentration was similar across the treatment groups in both studies; however, anemia (hemoglobin concentration less than 12 g/dL) was slightly more prevalent in the placebo groups compared to the RGX-E2-NETA groups.

Efficacy Results

Response Rate for Change in MBL Volume

Response to treatment was defined as an MBL volume of less than 80 mL and a 50% or greater reduction in MBL volume from baseline over the last 35 days of treatment as measured by the alkaline hematin method.

In the LIBERTY 1 trial, 73.4% (95% CI, 64.9% to 80.9%) of patients who received RGX-E2-NETA compared to 18.9% (95% CI, 12.5% to 26.8%) of patients who received placebo had HMB associated with UFs that responded to treatment. The treatment difference in the response rate for change in MBL volume at week 24 was 54.5% (95% CI, 44.3% to 64.7%; P < 0.0001) in favour of RGX-E2-NETA.

In the LIBERTY 2 trial, 71.2% (95% CI, 62.4% to 79.0%) of patients who received RGX-E2-NETA compared to 14.7% (95% CI, 9.1% to 22.0%) of patients who received placebo had HMB associated with UFs that responded to treatment. The treatment difference in the response rate for change in MBL volume at week 24 was 56.5% (95% CI, 46.6% to 66.5%; P < 0.0001) in favour of RGX-E2-NETA.

Improvement of Anemia

For the subset of patients who had a hemoglobin level of 10.5 g/dL or lower at baseline, response was defined as an increase of 2 g/dL or more at week 24.

In the LIBERTY 1 trial, 15 (50.0%) and 5 (21.7%) patients in the subset of patients with anemia in the RGX-E2-NETA and placebo groups, respectively, experienced an increase of 2 g/dL or more in their hemoglobin levels. The treatment difference in the proportion of patients who experienced an improvement in anemia at week 24 was 28.3% (95% CI, 3.7% to 52.8%; P = 0.0377) in favour of RGX-E2-NETA.

In the LIBERTY 2 trial, 19 (61.3%) and 2 (5.4%) patients in the subset of patients with anemia in the RGX-E2-NETA and placebo groups, respectively, experienced an increase of 2 g/dL or more in their hemoglobin levels. The treatment difference in the proportion of patients who experienced an improvement in anemia at week 24 was 55.9% (95% CI, 37.3% to 74.5%; P < 0.0001) in favour of RGX-E2-NETA.

Improvement of Pain

For the subset of patients who had a maximum NRS score for UF-associated pain of 4 points or greater during the 35 days before randomization, response to treatment was defined as a maximum NRS score of 0 or 1 point over the last 35 days of treatment in this subset.

In the LIBERTY 1 trial, [redacted], respectively, experienced a maximum NRS score of 0 or 1 point for UF-associated pain. The treatment difference in the proportion of patients who experienced an improvement in pain to a maximum NRS score of 0 or 1 point was [redacted].

In the LIBERTY 2 trial, [redacted], respectively, experienced a maximum NRS score of 0 or 1 point for UF-associated pain. The treatment difference in the proportion of patients who experienced an improvement in pain to a maximum NRS score of 0 or 1 point was [redacted].

Change in the UFS-QOL Symptom Severity Score and HRQoL Total Score

The UFS-QOL is a disease-specific questionnaire used to assess symptom severity and HRQoL in patients with UFs during the past month. The symptom severity scale consists of 8 items and the HRQoL scale consists of 29 items. These are scored on a 5-point Likert scale, ranging from “not at all” to “a very great deal” for symptom severity items and “none of the time” to “all of the time” for HRQoL items. Symptom severity and HRQoL scale scores were summed and transformed into a scale ranging from 0 to 100 points. Higher symptom severity scores indicate more severe UF symptoms, while higher HRQoL scores indicate better HRQoL.

In the LIBERTY 1 trial, the least squares mean (LSM) change from baseline to week 24 in UFS-QOL symptom severity score was –30.9 points (95% CI, –36.1 to –25.8 points) and –10.5 points (95% CI, –15.5 to –5.5 points) for patients in the RGX-E2-NETA and placebo groups, respectively. The treatment difference in the LSM change from baseline to week 24 in UFS-QOL symptom severity score was –20.4 points (95% CI, –27.1 to –13.7 points) in favour of RGX-E2-NETA.

In the LIBERTY 2 trial, the LSM change from baseline to week 24 in UFS-QOL symptom severity score was –36.1 points (95% CI, –41.2 to –31.0 points) and –13.7 points (95% CI, –18.8 to –8.5 points) for patients in the RGX-E2-NETA and placebo groups, respectively. The treatment difference in the LSM change from baseline to week 24 in UFS-QOL symptom severity score was –22.4 points (95% CI, –29.4 to –15.4 points) in favour of RGX-E2-NETA.

In the LIBERTY 1 trial, the LSM change from baseline to week 24 in UFS-QOL HRQoL total score was 38.0 points (95% CI, 32.4 to 43.5 points) and 12.8 points (95% CI, 7.5 to 18.2 points) for patients in the RGX-E2-NETA and placebo groups, respectively. The treatment difference in the LSM change from baseline to week 24 in UFS-QOL HRQoL total score was 25.1 points (95% CI, 17.9 to 32.3 points) in favour of RGX-E2-NETA.

In the LIBERTY 2 trial, the LSM change from baseline to week 24 in UFS-QOL HRQoL total score was 37.8 points (95% CI, 32.9 to 42.6 points) and 13.8 points (95% CI, 8.9 to 18.8 points) for patients in the RGX-E2-NETA and placebo groups, respectively. The treatment difference in the LSM change from baseline to week 24 in UFS-QOL HRQoL total score was 23.9 points (95% CI, 17.2 to 30.7 points) in favour of RGX-E2-NETA.

Harms Results

In the LIBERTY 1 trial, 61.7% of patients who received RGX-E2-NETA and 66.1% of patients who received placebo had a treatment-emergent adverse event (TEAE). Headache (10.9% RGX-E2-NETA versus 15.0% placebo) and hot flush (10.9% RGX-E2-NETA versus 7.9% placebo) were the most common TEAEs. In the LIBERTY 2 trial, 60.3% of patients who received RGX-E2-NETA and 58.9% of patients who received placebo had a TEAE. Headache (8.7% RGX-E2-NETA versus 11.6% placebo) was the most common TEAE. In general, types and frequencies of TEAEs were similar between the treatment groups for both studies and across studies.

In the LIBERTY 1 trial, 7 (5.5%) patients who received RGX-E2-NETA reported 10 serious adverse events (SAEs) and 2 (1.6%) patients who received placebo reported 2 SAEs. In the LIBERTY 2 trial, 1 (0.8%) patient who received RGX-E2-NETA reported 1 SAE and 4 (3.1%) patients who received placebo reported 5 SAEs.

In the LIBERTY 1 trial, 7 (5.5%) of patients who received RGX-E2-NETA stopped treatment due to a total of 12 TEAEs and 5 (3.9%) patients who received placebo stopped treatment due to a total of 13 TEAEs. In the LIBERTY 2 trial, 3 (2.4%) patients who received RGX-E2-NETA stopped treatment due to a total of 3 TEAEs and 6 (4.7%) patients who received placebo stopped treatment due to a total of 7 TEAEs.

There were no deaths reported in either study.

The treatment difference in the percent change from baseline to week 24 in BMD of the lumbar spine was –0.41% (95% CI, –1.16% to 0.34%) for the LIBERTY 1 trial and –0.44% (95% CI, –1.23% to 0.34%) for the LIBERTY 2 trial.

Critical Appraisal

For both the LIBERTY 1 and LIBERTY 2 trials, there was a lower proportion of patients who were Black and higher proportion of patients who were white in the RGX-E2-NETA groups compared to the placebo groups

(people who are Black are at higher risk of developing UFs) and the mean MBL volume was higher in the RGX-E2-NETA group compared to the placebo group. Although it is possible that the baseline imbalances could have biased the study results (the direction and magnitude of bias are unknown), the clinical expert consulted for this review did not expect the imbalances to meaningfully impact interpretation of the results. There was a potential risk of bias for the improvement in anemia and pain outcomes, and the treatment effects were notably different between the studies for both outcomes. The reason for the inconsistency was unclear and may have had to do with the fewer number of patients contributing data (outcomes used subpopulations) and/or a loss of prognostic balance. Patients who had anemia at baseline or new anemia during the study started iron therapy or continued existing iron therapy. Although the iron supplementation protocol was consistent across the treatment groups and studies, it is unknown if improvement in anemia was a result of iron therapy or reduced MBL volume, and information on changes in the amount of iron throughout the studies was not available to clarify this. Bias may have also arisen from the missing data (between 5% and 30%) for the anemia, pain, UFS-QOL, and BMD outcomes (and reasons why data were missing were not available), which reduces certainty in the results. Considering the large difference in efficacy between the RGX-E2-NETA and placebo groups for the primary outcome, patients may have been able to infer which treatment they received in the study, which consequently impacts subjective outcomes (pain, UFS-QOL, and harms).

According to the clinical expert, eligibility criteria that do not reflect clinical practice were exclusions based on an upper age limit (patients had to be adults in premenopause) and receiving gynecological surgery or ablation procedures for UFs within the 6 months before treatment. Moreover, the definition for HMB used in the clinical trials, although acceptable for the setting, is not used in practice. Instead, HMB is identified through clinical assessment and is described as abnormal uterine bleeding that interferes with a patient's HRQoL and activities of daily living. Furthermore, although the study end points inform on patient-important outcomes (i.e., pain, bulk symptoms, and HRQoL), they are not used in practice. Rather than quantifying treatment effect by measuring MBL volume, clinicians assess patient satisfaction with how well the treatment relieves symptoms and if the patient can participate in daily activities without interference from HMB and UFs. The 24-week study duration was deemed acceptable for meeting the clinical end points; however, the clinical expert does not expect most patients to use RGX-E2-NETA as a long-term treatment, but rather as a bridging therapy to surgery or menopause. The expert indicated there are rare instances in which treatment beyond 24 months may be warranted, such as in patients whose HMB associated with UFs responds well to treatment without intolerable TEAEs, but it is noted in the Health Canada product monograph that use of the drug should be limited to 24 months due to the risk of irreversible bone loss. Should the drug be used long term, regular BMD scans would be important to ensure that the patient is not experiencing clinically important bone loss. If so, discontinuation of the drug should be considered.

GRADE Summary of Findings and Certainty of the Evidence

For pivotal studies and RCTs identified in the sponsor's systematic review, Grading of Recommendations Assessment, Development and Evaluation (GRADE) was used to assess the certainty of the evidence for outcomes considered most relevant to inform expert committee deliberations, and a final certainty rating was determined as outlined by the GRADE Working Group.

Following the GRADE approach, evidence from RCTs started as high-certainty evidence and could be rated down for concerns related to study limitations (which refers to internal validity or risk of bias), inconsistency across studies, indirectness, imprecision of effects, and publication bias.

When possible, certainty was rated in the context of the presence of an important (nontrivial) treatment effect; if this was not possible, certainty was rated in the context of the presence of any treatment effect (i.e., the clinical importance is unclear). In all cases, the target of the certainty of evidence assessment was based on the point estimate and where it was located relative to the threshold for a clinically important effect (when a threshold was available) or to the null. The target of the certainty of evidence assessment was the presence or absence of an important effect, informed by the clinical expert consulted for this review, for response rate for change in MBL volume, improvement of anemia, improvement of pain, and change in the UFS-QOL symptom severity score and HRQoL total score, and the presence or absence of any (non-null) effect for change in BMD at the lumbar spine.

For the GRADE assessments, findings from the LIBERTY 1 and LIBERTY 2 trials were assessed together per outcome because these studies were similar in population, intervention, design, and outcome measures.

The selection of outcomes for GRADE assessment was based on the sponsor's Summary of Clinical Evidence, consultation with a clinical expert, and input received from patient groups and public drug plans. The following list of outcomes was finalized in consultation with expert committee members:

- response rate for change in MBL volume
- improvement of anemia
- improvement of pain
- change in the UFS-QOL (symptom severity score and HRQoL total score)
- change in BMD.

Table 3: Summary of Findings for RGX-E2-NETA vs. Placebo for Patients With HMB Associated With UFs

Outcome and follow-up	Patients, N (studies)	Effect	Certainty	What happens
MBL volume response				
Proportion of patients who experienced an MBL volume of < 80 mL and ≥ 50% reduction from baseline MBL volume (95% CI) Follow-up: 24 weeks	255 (the LIBERTY 1 trial) 254 (the LIBERTY 2 trial)	**The LIBERTY 1 trial** • **RGX-E2-NETA**: 734 per 1,000 (649 to 809 per 1,000) • **Placebo**: 189 per 1,000 (125 to 268 per 1,000) • **Difference**: 545 more per 1,000 (443 to 647 more per 1,000) **The LIBERTY 2 trial** • **RGX-E2-NETA**: 712 per 1,000 (624 to 790 per 1,000) • **Placebo**: 147 per 1,000 (91 to 220 per 1,000) • **Difference**: 565 more per 1,000 (466 to 665 more per 1,000)	High	RGX-E2-NETA results in a clinically important increase in the proportion of patients who experienced an MBL volume response compared with placebo.
Anemia improvement				
Proportion of patients who experienced an increase in hemoglobin of > 2 g/dL from baseline in the subset of patients with a hemoglobin level ≤ 10.5 g/dL at baseline (95% CI) Follow-up: 24 weeks	53 (the LIBERTY 1 trial) 68 (the LIBERTY 2 trial)	**The LIBERTY 1 trial** • **RGX-E2-NETA**: 500 per 1,000 (313 to 687 per 1,000) • **Placebo**: 217 per 1,000 (75 to 437 per 1,000) • **Difference**: 283 more per 1,000 (37 to 528 more per 1,000) **The LIBERTY 2 trial** • **RGX-E2-NETA**: 613 per 1,000 (422 to 782 per 1,000) • **Placebo**: 54 per 1,000 (7 to 182 per 1,000) • **Difference**: 559 more per 1,000 (373 to 745 more per 1,000)	Low[a]	RGX-E2-NETA may result in a clinically important increase in the proportion of patients who experienced improvement in anemia compared with placebo.
Pain improvement				
Proportion of patients who experienced a maximum NRS score ≤ 1 for UF-associated pain	179 (the LIBERTY 1 trial) 188 (the LIBERTY 2 trial)	[redacted]	Low[b]	RGX-E2-NETA may result in a clinically important increase in the proportion of patients who experience

Outcome and follow-up	Patients, N (studies)	Effect	Certainty	What happens
over the last 35 days of treatment in the subset of patients with a maximum pain score ≥ 4 during the 35 days before randomization (95% CI) Follow-up: 24 weeks		[redacted]		an improvement in pain compared with placebo.
UFS-QOL				
UFS-QOL symptom severity score (0 [best] to 100 [worst]) (points), LSM change from baseline (95% CI) Follow-up: 24 weeks	200 (the LIBERTY 1 trial) 191 (the LIBERTY 2 trial)	**The LIBERTY 1 trial** • **RGX-E2-NETA**: –30.9 (–36.1 to –25.8) • **Placebo**: –10.5 (–15.5 to –5.5) • **Difference**: –20.4 (–27.1 to –13.7) **The LIBERTY 2 trial** • **RGX-E2-NETA**: –36.1 (–41.2 to –31.0) • **Placebo**: –13.7 (–18.8 to –8.5) • **Difference**: –22.4 (–29.4 to –15.4)	Moderate[c]	RGX-E2-NETA likely results in a clinically important reduction in UFS-QOL symptom severity score compared with placebo.
UFS-QOL HRQoL total score (100 [best] to 0 [worst]) (points), LSM change from baseline (95% CI) Follow-up: 24 weeks	200 (the LIBERTY 1 trial) 191 (the LIBERTY 2 trial)	**The LIBERTY 1 trial** • **RGX-E2-NETA**: 38.0 (32.4 to 43.5) • **Placebo**: 12.8 (7.5 to 18.2) • **Difference**: 25.1 (17.9 to 32.3) **The LIBERTY 2 trial** • **RGX-E2-NETA**: 37.8 (32.9 to 42.6) • **Placebo**: 13.8 (8.9 to 18.8) • • **Difference**: 23.9 (17.2 to 30.7)	Moderate[d]	RGX-E2-NETA likely results in a clinically important increase in UFS-QOL HRQoL total score compared with placebo.
Harms				
BMD for lumbar spine (%), percent change from baseline (95% CI) Follow-up: 24 weeks	202 (the LIBERTY 1 trial) 190 (the LIBERTY 2 trial)	**The LIBERTY 1 trial** • **RGX-E2-NETA**: –0.36 (–0.93 to 0.22) • **Placebo**: 0.05 (–0.52 to 0.62) • **Difference**: –0.41 (–1.16 to 0.34) **The LIBERTY 2 trial** • **RGX-E2-NETA**: –0.13 (–0.71 to 0.46)	Low[e]	RGX-E2-NETA may result in a greater proportion of patients who experience a reduction in BMD compared with placebo. The clinical relevance of the decrease is uncertain.

Outcome and follow-up	Patients, N (studies)	Effect	Certainty	What happens
		• **Placebo**: 0.32 (–0.26 to 0.89) • **Difference**: –0.44 (–1.23 to 0.34)		

BMD = bone mineral density; CI = confidence interval; HMB = heavy menstrual bleeding; HRQoL = health-related quality of life; MBL = menstrual blood loss; NRS = numerical rating scale; RGX-E2-NETA = relugolix-estradiol–norethindrone acetate; UF = uterine fibroid; UFS-QOL = Uterine Fibroid Symptom Quality of Life.

Note: Study limitations (which refer to internal validity or risk of bias), inconsistency across studies, indirectness, imprecision of effects, and publication bias were considered when assessing the certainty of the evidence. All serious concerns in these domains that led to the rating down of the level of certainty are documented in the table footnotes.

[a]Rated down 1 level for study limitations because this outcome used a subpopulation and prognostic balance may have been lost. Did not rate down for inconsistency; although the magnitude of the between-group difference differs across the 2 studies, the point estimate of the between-group difference was considered clinically meaningful in each, according to the clinical expert consulted for the review. Rated down 1 level for imprecision because there was no known threshold for a clinically important effect and the presence of an important effect was informed by the clinical expert consulted for this review. The point estimates in both studies suggest the presence of a clinically important effect; however, the lower bound of the 95% CI for the LIBERTY 1 trial is consistent with an effect that would not be considered clinically important for patients.

[b]Rated down 1 level for study limitations because this outcome used a subpopulation and prognostic balance may have been lost. Did not rate down for inconsistency; although the magnitude of the between-group difference differs across the 2 studies, the point estimate of the between-group difference was considered clinically meaningful in each, according to the clinical expert consulted for the review. Rated down 1 level for imprecision because there was no known threshold for a clinically important effect, and the presence of an important effect was informed by the clinical expert consulted for this review. The point estimates in both studies suggest the presence of a clinically important effect; however, the lower bound of the 95% CIs for the LIBERTY 1 and LIBERTY 2 trials are consistent with an effect that would not be considered clinically important for patients.

[c]Rated down 1 level for study limitations because data were missing for 24% and 19% of patients in the RGX-E2-NETA and placebo groups, respectively, in the LIBERTY 1 trial and 23% and 26%, respectively, in the LIBERTY 2 trial. Did not rate down for imprecision because there was no known threshold for a clinically important effect, and the presence of an important effect was informed by the clinical expert consulted for this review. The point estimates in both studies suggest the presence of a clinically important effect; although the lower bound of the 95% CIs for the LIBERTY 1 and LIBERTY 2 trials are consistent with an effect that would not be considered clinically important for patients, the review team did not rate down because the lower bound of the CIs likely do not considerably cross the minimum threshold for a clinically important effect. Analysis of this outcome was not adjusted for multiplicity, and the results are considered as supportive evidence.

[d]Rated down 1 level for study limitations because data were missing for 24% and 19% of patients in the RGX-E2-NETA and placebo groups, respectively, in the LIBERTY 1 trial and 23% and 26%, respectively, in the LIBERTY 2 trial. Did not rate down for imprecision because there was no known threshold for a clinically important effect, and the presence of an important effect was informed by the clinical expert consulted for this review. The point estimates and lower bound of the 95% CIs in both studies suggest the presence of a clinically important effect. Analysis of this outcome was not adjusted for multiplicity, and the results are considered as supportive evidence.

[e]Rated down 1 level for study limitations because data were missing for 22% and 20% of patients in the RGX-E2-NETA and placebo groups, respectively, in the LIBERTY 1 trial and 25% and 26%, respectively, in the LIBERTY 2 trial. Did not rate down for indirectness because the follow-up was limited to 24 weeks, which may be insufficient to detect clinically important BMD loss; however, the clinical expert consulted for this review expects most patients would not be using RGX-E2-NETA for long-term treatment. Rated down 1 level for imprecision because there was no known threshold for a clinically important effect. The point estimate suggested a decrease with RGX-E2-NETA, but the 95% CI included the potential for no difference and an increase. Analysis of this outcome was not adjusted for multiplicity, and the results are considered as supportive evidence.

Source: The LIBERTY 1 and LIBERTY 2 Clinical Study Reports and sponsor's Summary of Clinical Evidence.

Long-Term Extension Studies

Description of Studies

The LIBERTY EXTENSION study was a single-arm, phase III, 28-week OLE study in patients who completed either pivotal trial. In the OLE, the long-term efficacy and safety of RGX-E2-NETA were evaluated for an additional 28 weeks (after the 24 weeks of treatment during either parent study, the LIBERTY 1 and LIBERTY 2 trials).

The LIBERTY RWS study was a double-blind, phase III, placebo-controlled, 52-week study that enrolled those patients who completed the LIBERTY EXTENSION study and whose HMB associated with UFs responded to treatment at the week 48 visit (experienced a MBL volume of less than 80 mL and a 50% or greater reduction in MBL volume from the pivotal study baseline). Patients were rerandomized in a 1:1 ratio to receive either oral RGX-E2-NETA or placebo once daily for up to 52 weeks. For patients whose HMB recurred during the LIBERTY RWS study (MBL volume ≥ 80 mL), blinded treatment was stopped and re-treatment with open-label RGX-E2-NETA was offered.

Efficacy Results

The LIBERTY EXTENSION Study

At week 52 of the LIBERTY EXTENSION study, 87.7% (95% CI, 81.7% to 92.3%) of patients who received RGX-E2-NETA since the parent study baseline (RGX-E2-NETA group) had HMB associated with UFs that responded and 75.6% (95% CI, 68.3% to 82.0%) of patients who received placebo in the parent studies but switched to RGX-E2-NETA during the OLE (placebo to RGX-E2-NETA group) had HMB associated with UFs that responded.

For the anemia outcome (hemoglobin ≤ 10.5 g/dL at baseline with an increase of ≥ 2 g/dL), 23 of 39 (59.0%) patients in the RGX-E2-NETA group and 16 of 38 (42.1%) patients in the placebo to RGX-E2-NETA group experienced an improvement in anemia at week 52.

At week 52, the LSM for the UFS-QOL symptom severity scale score was –37.3 points (standard error [SE] = 2.5 points) in the RGX-E2-NETA group and –35.0 points (SE = 2.5 points) in the placebo to RGX-E2-NETA group. The LSM for the UFS-QOL HRQoL total score was 40.4 points (SE = 2.5 points) in the RGX-E2-NETA group and 39.0 points (SE = 2.6 points) in the placebo to RGX-E2-NETA group.

The LIBERTY RWS Study

At week 76, 78.4% (95% CI, 69.3% to 85.1%) of patients in the rerandomized RGX-E2-NETA group and 15.1% (95% CI, 8.9% to 22.8%) of patients in the rerandomized placebo group had HMB associated with UFs that responded to treatment. The difference in response rates between treatment groups was 63.4% (95% CI, 52.9% to 73.9%), in favour of RGX-E2-NETA.

At week 104, 69.8% (95% CI, 59.7% to 77.8%) of patients in the rerandomized RGX-E2-NETA group and 11.8% (95% CI, 6.3% to 19.0%) of patients in the rerandomized placebo group had HMB associated with UFs that responded to treatment. The difference in response rates between treatment groups was 58.0% (95% CI, 47.0% to 69.1%), in favour of RGX-E2-NETA.

At week 76, for the UFS-QOL symptom severity score, patients had a change from rerandomization baseline (i.e., week 52 of total study treatment) of 2.2 points (standard deviation [SD] = 18.2 points) in the rerandomized RGX-E2-NETA group and 14.1 points (SD = 21.1 points) in the rerandomized placebo group. For the UFS-QOL HRQoL total score, patients had a change from rerandomization baseline of –0.8 points (SD = 16.8 points) in the rerandomized RGX-E2-NETA group and –9.1 points (SD = 22.4 points) in the rerandomized placebo group.

At week 104, for the UFS-QOL symptom severity score, patients had a change from rerandomization baseline (i.e., week 52 of total study treatment) of 0.1 points (SD = 15.9 points) in the rerandomized RGX-E2-NETA group and –4.3 points (SD = 42.2 points) in the rerandomized placebo group. For the UFS-QOL HRQoL total score, patients had a change from rerandomization baseline of 1.1 points (SD = 15.3 points) in the rerandomized RGX-E2-NETA group and 8.2 points (SD = 42.1 points) in the rerandomized placebo group.

Harms Results

The LIBERTY EXTENSION Study

During the OLE study, 54.6% of patients in the RGX-E2-NETA group and 62.8% of patients in the placebo to RGX-E2-NETA group experienced at least 1 TEAE. Nasopharyngitis (6.1%) was the most common TEAE in the RGX-E2-NETA group while hot flush (7.9%), headache (6.7%), and hypertension (6.1%) were the most common TEAEs in the placebo to RGX-E2-NETA group.

Overall, 1 (0.6%) patient in the RGX-E2-NETA group and 11 (6.7%) patients in the placebo to RGX-E2-NETA group experienced at least 1 SAE. No SAE was reported by more than 2 patients.

Two (1.2%) patients in the RGX-E2-NETA group and 9 (5.5%) patients in the placebo to RGX-E2-NETA group stopped treatment due to a TEAE. No TEAE leading to treatment discontinuation was reported by more than 1 patient.

There were no deaths in the OLE study.

At the end of the LIBERTY EXTENSION study (after 52 weeks of study treatment), the LSM percent change in BMD at the lumbar spine was –0.80% (95% CI, –1.36% to –0.25%) for the RGX-E2-NETA group and –0.78% (95% CI, –1.32% to –0.23%) for the placebo to RGX-E2-NETA group.

The LIBERTY RWS Study

In the LIBERTY RWS study, 58.6% of patients in the rerandomized RGX-E2-NETA group and 64.3% of patients in the rerandomized placebo group experienced at least 1 TEAE. Nasopharyngitis (11.2%) was the most common TEAE in the rerandomized RGX-E2-NETA group while nasopharyngitis (10.7%), hot flush (7.1%), dysmenorrhea (7.1%), hypertension (5.4%), and upper respiratory tract infection (5.4%) were the most common TEAEs in the rerandomized placebo group.

Overall, 2 (1.7%) patients in the rerandomized RGX-E2-NETA group and 2 (1.8%) patients in the rerandomized placebo group experienced at least 1 SAE. No SAE was reported by more than 1 patient.

Two (1.7%) patients in the rerandomized RGX-E2-NETA group and 3 (2.7%) patients in the rerandomized placebo group stopped treatment due to a TEAE. No TEAE leading to treatment discontinuation was reported by more than 1 patient.

There were no deaths in the LIBERTY RWS study.

At the end of the LIBERTY RWS study (104 weeks of study treatment), the LSM percent change in BMD at the lumbar spine was 0.81% (95% CI, 0.20% to 1.41%) in the rerandomized RGX-E2-NETA group and 0.10% (95% CI, –0.52% to 0.71%) in the rerandomized placebo group. The LSM percent change between-group difference was 0.71% (95% CI, –0.13% to 1.55%).

Critical Appraisal

There is the possibility of selection bias in the LIBERTY EXTENSION study because eligible patients must have had successfully completed either the LIBERTY 1 or LIBERTY 2 trials; thus, patients were more likely to be those who responded to treatment and did not experience intolerable TEAEs. The single-arm OLE study was noncomparative, preventing conclusions from being made about the benefits or harms attributable to RGX-E2-NETA versus any comparator. The open-label design could also bias the assessment of subjective patient-reported outcomes (i.e., UFS-QOL and harms). The lack of data beyond week 52 in the OLE study makes it challenging to draw conclusions on the long-term sustainability of the treatment effect. Treatment in the LIBERTY RWS study was double-blinded, which is important given the subjective nature of the patient-reported outcomes. However, there is the risk of unblinding of the treatment received due to the large difference in efficacy results between the RGX-E2-NETA and placebo groups. In both extension studies, the reasons for missing data for each outcome were not available; as such, the effect of missing data remains uncertain. In the LIBERTY RWS study, there is a risk of bias due to missing outcome data, particularly at the longer follow-up times for the UFS-QOL symptom severity score, HRQoL total score, and BMD.

Because patients who were enrolled in the extension studies must have successfully completed the parent trials, the extension studies have the same generalizability issues as the parent trials. Of note, the clinical expert consulted for this review confirmed that patients receiving RGX-E2-NETA would not be restricted by an upper age limit, but rather by premenopausal status, and that recent or planned gynecological surgery or procedures for UFs would not preclude patients from using the drug. The efficacy outcomes, although relevant to patients and practice, are not used in a clinical setting (aside from measuring hemoglobin); therefore, the results in a real-world clinical setting may differ from those observed in extension studies.

Indirect Comparisons

The sponsor submitted a systematic review with NMA to estimate the efficacy and safety of RGX-E2-NETA compared with LA with or without add-back for the treatment of HMB associated with UF in people in the premenopausal stage.

An ITC was required because of a lack of studies directly comparing RGX-E2-NETA with LA with and without add-back, which is the only authorized treatment for UFs in the Canadian setting.

To support the NMA, the sponsor did the following:

- conducted a systematic literature review (SLR) to identify RCTs to estimate the relative efficacy and safety of RGX-E2-NETA versus LA (with or without add-back)
- performed an NMA to assess the relative efficacy and safety of RGX-E2-NETA versus LA (without add-back) for the treatment of HMB associated with UF in people in the premenopausal stage; a comparison of RGX-E2-NETA to LA with add-back was considered infeasible by the sponsor.

Outcomes of interest for the NMA included effectiveness, TEAEs, and tolerability. The specific effectiveness outcomes were MBL volume resolution and UFS-QOL HRQoL total score and symptom severity score. TEAEs included hot flushes and headaches. Tolerability outcomes were discontinuations due to TEAEs.

Of 228 reports identified in the literature, 31 trials were retained from the SLR, from which data from 12 trials were included in the NMA.

The NMA included treatments of ulipristal acetate (UPA) 5 mg and UPA 10 mg, and mifepristone (MFP) 10 mg to establish a network connection between RGX-E2-NETA and LA. Although UPA 5 mg, UPA 10 mg, and MFP 10 mg are not considered relevant comparators, they were maintained in the NMA to establish network connections between RGX-E2-NETA and LA without add-back. These comparators were excluded from the main results even though they were retained to establish a network connection between RGX-E2-NETA and LA.

Efficacy Results

MBL Volume Resolution

For the comparison of RGX-E2-NETA versus LA (without add-back), [redacted]. A sensitivity analysis included a study with a different outcome definition of MBL volume and overall came to the same conclusion as the base case.

UFS-QOL

[redacted].

Two sensitivity analyses were performed for the UFS-QOL total score and UFS-QOL symptom score by first excluding 2 studies (with < 10% of patients who were Black), and second by excluding a study with high heterogeneity. [redacted].

Harms Results

Hot Flushes

[redacted]. A sensitivity analysis was conducted that included studies beyond 1 month after end of treatment. This sensitivity analysis was consistent with the base case.

Headaches

For the outcome of headaches, the risk ratio (RR) estimate was imprecise, suggesting the direction of the effects are inconclusive. [redacted]. A sensitivity analysis was conducted for the time point estimate of headaches, which found the estimate was consistent with the base case, with a similarly high level of imprecision.

Discontinuation Due to TEAEs

The point estimate for the RR of the tolerability outcome, discontinuation due to TEAEs, [redacted]. No sensitivity analysis was reported for this outcome.

Critical Appraisal

A systematic review of the published literature and grey literature was conducted to identify studies for the NMA. Although a prespecified protocol for the SLR and NMA could not be obtained, the CDA-AMC review team appraised the submitted SLR using the AMSTAR 2 (A Measurement Tool to Assess Systematic Reviews) criteria. The searches were overall comprehensive, and the methods for data extraction and risk of bias appraisal were overall adequate to reduce the risk of error and bias in these procedures. Although study selection was done by 2 independent reviewers with consensus, there was inconsistent rationale for why certain studies were excluded from the networks. Of the 31 studies identified via the SLR, 12 were retained for the NMAs. Although certain studies of comparators not used in Canada were included in the networks to allow connections between RGX-E2-NETA and LA, other studies with the same comparators were excluded (e.g., a study that compared placebo and MFP 10 mg was included to connect the network, whereas other studies including a MFP 10 mg treatment group were excluded because treatments were not of interest). The

selective inclusion of studies in the network may result in risk of bias due to missing results in the syntheses, the magnitude and direction of which cannot be predicted.

A Bayesian NMA included some but not all outcomes, including effectiveness, safety, and tolerability. Outcomes deemed relevant by patients and clinicians that were not included in the constructed networks were efficacy outcomes, such as anemia and pain, and the harms outcome of BMD. BMD as a safety outcome was not included due to lack of comparative data. As such, this NMA cannot inform on the comparative effects of RGX-E2-NETA and LA (without add-back) for these outcomes.

There are limitations to both fixed-effects and random-effects models, which were both used in this NMA. Models were selected based on better model fit (smaller deviance information criterion). Given that most outcomes were modelled with fixed effects, we expect that the true magnitude of uncertainty was underestimated. Because the effect estimates for these end points were already affected by important imprecision, reliance on the results of the unselected models would not have changed the CDA-AMC review team's conclusions about the estimated effects.

A key limitation of this NMA is the clinically relevant comparator LA did not contain add-back. Although hormonal add-back is a part of RGX-E2-NETA, according to the sponsor, LA with add-back was excluded from the NMA due to feasibility reasons. This means that RGX-E2-NETA compared with LA (without add-back) does not reflect how the actual comparator is prescribed in Canada.

The sponsor found that RGX-E2-NETA had a reduced RR of hot flushes compared with LA. All other efficacy, safety, and tolerability outcomes crossed the null, with wide credible intervals. This suggests that either RGX-E2-NETA or LA (without add-back) could be favoured.

There were other notable limitations of the overall NMA because the assumptions of exchangeability, similarity of outcomes, and consistency (coherence) could not be satisfied.

Overall, due to the absence of comparisons between RGX-E2-NETA and LA (with add-back), the high degree of imprecision represented in the RR or mean difference credible intervals, which could favour either RGX-E2-NETA or LA (without add-back), and the inability to satisfy key NMA assumptions (exchangeability, homogeneity, and consistency), definitive conclusions on the relative treatment effects of RGX-E2-NETA versus LA (with add-back) cannot be drawn based on this NMA.

Studies Addressing Gaps in the Evidence From the Systematic Review

There were no studies addressing gaps in the systematic review evidence submitted by the sponsor.

Economic Evidence

Economic Evaluation and Budget Impact

RGX-E2-NETA is available as oral tablets (relugolix 40 mg, estradiol 1 mg, and norethindrone acetate 0.5 mg). At the submitted price of $9.00 per tablet, the annual cost of RGX-E2-NETA for the management of HMB associated with UF is expected to be $3,285 per patient, based on the Health Canada–recommended dosage.

Based on the results of the sponsor's base case, and despite inconclusive evidence on clinical similarity between comparators, RGX-E2-NETA is expected to be associated with lower costs to the health care system (including drug acquisition costs) compared to LA plus add-back (incremental savings = $1,385). This is driven by reduced costs associated with drug acquisition.

CDA-AMC estimates that the budget impact of reimbursing RGX-E2-NETA for the management of HMB associated with UF in patients in the premenopausal stage will be approximately $7,620,729 over the first 3 years of reimbursement compared to the amount currently spent on comparators, with an estimated expenditure of $49,083,074 on RGX-E2-NETA over this period. The actual budget impact of reimbursing RGX-E2-NETA is uncertain and will depend on the proportion of patients who would otherwise undergo watchful waiting without active treatment.

CDEC Information

Members of the Committee

Dr. Peter Jamieson (Chair), Dr. Sally Bean, Daryl Bell, Dan Dunsky, Dr. Trudy Huyghebaert, Morris Joseph, Dr. Dennis Ko, Dr. Christine Leong, Dr. Kerry Mansell, Dr. Alicia McCallum, Dr. Srinivas Murthy, Dr. Nicholas Myers, Dr. Krishnan Ramanathan, Dr. Marco Solmi, Dr. Edward Xie, and Dr. Peter Zed.

Meeting date: June 25, 2025

Regrets: Two expert committee members did not attend.

Conflicts of interest: None

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Questions or requests for information about this report can be directed to Requests@CDA-AMC.ca.