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Drug Class Update with New Drug Evaluation: Drugs for Endometriosis and Uterine Fibroids

Date of Review: December 2021

Date of Last Review: March 2019 (Endometriosis); Nov 2019 (Elagolix); Jan 2019 (Hormone replacement); May 2015 (GnRH Agonists)
Dates of Literature Search: 01/01/2019 – 09/01/2021
Brand Name (Manufacturer): MYFEMBREE (Myovant Sciences)
Dossier Received: Yes

Generic Name: Relugolix, Estradiol, and Norethindrone acetate

Current Status of PDL Class:
See **Appendix 1**.

Purpose for Class Update:
This drug class update examines recently published comparative evidence for safety and efficacy of oral contraceptives, progestins, gonadotropin-releasing hormone (GnRH) agonists, danazol, and GnRH antagonists for management of moderate to severe pain due to endometriosis. In addition, evidence supporting FDA approval for relugolix, estradiol, and norethindrone combination therapy for management of heavy menstrual bleeding associated with uterine fibroids in premenopausal populations will be evaluated.

Research Questions:
1. What is the comparative evidence assessing safety and efficacy of drug therapies for the treatment of moderate to severe pain associated with endometriosis?
2. What is the efficacy of relugolix, estradiol, and norethindrone combination therapy compared to placebo or currently available therapy for the management of heavy menstrual bleeding associated with uterine fibroids?
3. Is relugolix, estradiol, and norethindrone combination therapy safe for the management of heavy menstrual bleeding associated with uterine fibroids?
4. Are there any subgroups (based on age, race, ethnicity, comorbidities, disease duration or severity) that would particularly benefit or be harmed from treatment with oral contraceptives, progestins, GnRH agonists, danazol, or GnRH antagonists for endometriosis or uterine fibroids?

Conclusions:
- No new evidence focused on safety and efficacy of pharmacologic agents used to manage pain associated with endometriosis has been published since the last Pharmacy and Therapeutics Committee review in 2019.
- A 2017 systematic review conducted by the Agency for Healthcare Research and Quality (AHRQ) evaluated evidence supporting the safety and efficacy of different treatment strategies for management of uterine fibroids.[1] Gonadotropin-releasing hormone agonists (leuprolide and goserelin) and progesterone

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receptor agents (mifepristone and ulipristal) reduced fibroid size and improved fibroid-related symptoms, including bleeding and quality of life (moderate strength of evidence except quality of life for GnRH agonists; low strength of evidence).[1] Mifepristone is only FDA-approved for one-time use as emergency contraception.[2] Ulipristal acetate is approved outside the US, but post-marketing reports of rare but serious liver injury, including need for liver transplantation, have prompted the European Medicines Agency and other regulatory agencies to significantly limit the use of daily ulipristal acetate for uterine fibroid treatment.[3] Few well-designed trials directly compare different treatment options.[1]

- A 2020 Cochrane review evaluated the effectiveness of progestin or progestin-releasing intrauterine systems in treating premenopausal women with uterine fibroids.[4] Because of low-quality evidence, it is not clear if the levonorgestrel-releasing intrauterine device (IUD) reduces abnormal uterine bleeding, reduces the size uterine fibroids or increases hemoglobin levels in premenopausal women with uterine fibroids, compared to oral contraceptives.[4] There is insufficient evidence to determine whether oral progestins reduce abnormal uterine bleeding as effectively as the GnRH agonist, goserelin acetate, but women reported fewer adverse events, such as hot flashes with oral progestins.[4]
- A 2018 Cochrane meta-analysis assessed the safety and effectiveness of antifibrinolytic medications (tranexamic acid) as a treatment for heavy menstrual bleeding.[5] The evidence was low to moderate quality: the main limitations were risk of bias (associated with lack of blinding, and poor reporting of study methods), imprecision and inconsistency.[5] When compared to placebo, antifibrinolytics were associated with reduced mean blood loss in women with heavy menstrual bleeding (mean difference [MD] -53.20 mL per cycle, 95% confidence interval [CI] -62.70 to -43.70; I^2= 8%; 4 RCTs, participants = 565; moderate-quality evidence).[5] Normal menstrual blood loss has been defined as 30 mL to 40 mL per menstrual cycle, while heavy menstrual bleeding has traditionally been defined as greater than 80 mL blood loss per cycle.[6] There was no clear evidence of a difference between antifibrinolytics and placebo in adverse events (RR 1.05, 95% CI 0.93 to 1.18; 1 RCT, participants = 297; low-quality evidence).[5]
- The National Institute for Health and Care Excellence (NICE) issued guidance in 2018 for assessment and management of heavy menstrual bleeding.[7] Off-label use of the levonorgestrel-releasing IUD is recommended as first line therapy for women with fibroids less than 3 cm diameter which are not causing distortion of the uterine cavity.[7] If a woman with heavy menstrual bleeding declines the levonorgestrel-releasing IUD or is not a suitable candidate , the following off-label pharmacologic treatments can be considered: tranexamic acid, combined hormonal contraception, or cyclic oral progestins.[7] If treatment is unsuccessful, the woman declines pharmacological treatment, or symptoms are severe, consider referral to specialist care for endometrial ablation, hysterectomy or myomectomy.[7] Surgical pretreatment with a GnRH agonist should be considered if uterine fibroids are causing an enlarged or distorted uterus.[7]
- An oral fixed-dose combination of the GnRH receptor antagonist relugolix, estradiol, and norethindrone acetate (MYFEMBREE), was approved by the FDA for management of heavy menstrual bleeding associated with uterine fibroids in premenopausal women May 2021.[8] Food and Drug Administration (FDA) approval of the combination relugolix 40 mg, estradiol 1 mg, and norethindrone acetate 0.5 mg once daily formulation was based on the results of 2 identically designed, 24-week, randomized, double-blind, phase 3 trials (LIBERTY-1 and LIBERTY-2).[9]
- In both LIBERTY trials, significantly more women responded to relugolix combination therapy and achieved the primary endpoint of menstrual blood loss of less than 80 mL and a 50% or greater reduction from baseline in menstrual blood loss over the final 35 days of treatment compared to women who received placebo.[9] Moderate quality evidence demonstrated 73% of the participants in the relugolix combination therapy group in LIBERTY-1 were responders versus 19% in the placebo group (difference 55%; 95% CI 44 to 65; p<0.001; number needed to treat [NNT] 2).[9] Similar results were observed in LIBERTY-2 as 71% of relugolix combination-treated participants were responders, versus 15% in the placebo-treated group (difference 56%; 95% CI 46 to 66; p<0.001; NNT 2).[9]
- The most common adverse reactions observed with relugolix administration (incidence ≥3%) were hot flush, hyperhidrosis or night sweats, hypertension, abnormal uterine bleeding, alopecia, and decreased libido.[8] Because the combination relugolix product contains estrogen and progestin, the prescribing information contains a black boxed warning regarding the risk of thromboembolic disorders and vascular events.[8] Relugolix, estradiol, and norethindrone acetate combination therapy is contraindicated in women with current or a history of thrombotic or thromboembolic disorders and in women at increased

risk for these events, including women over 35 years of age who smoke or women with uncontrolled hypertension.[8] In addition, the use of relugolix therapy should be limited to 24 months due to the risk of bone loss which may not be reversible and it is contraindicated in women with known osteoporosis.[8]
- There is insufficient long term comparative efficacy and safety data for relugolix, estradiol and norethindrone therapy. More information is needed regarding the long-term benefits and risks of relugolix therapy. No trials are available that directly compare relugolix the other FDA-approved treatments for fibroid-associated heavy menstrual bleeding (i.e., elagolix, leuprolide).
- There is insufficient evidence to determine if certain subpopulations would benefit from specific therapies approved for management of fibroid-associated bleeding or pain associated with endometriosis.

Recommendations:
- Implement new prior authorization (PA) criteria for GnRH modifiers to evaluate GnRH antagonists, including include relugolix, estradiol, and norethindrone combination therapy, separately from GnRH agonists (e.g., leuprolide).
- Maintain relugolix combination therapy as non-preferred on the PDL.
- After evaluation of comparative costs of therapy in executive session, no PDL changes were recommended.

Summary of Prior Reviews and Current Policy
The GnRH modulators were last reviewed at the March 2019 Pharmacy and Therapeutics (P & T) meeting. Prior authorization criteria for GnRH agonists and antagonists were combined into one document entitled GnRH modifiers (**Appendix 5**). Additional PA revisions were approved by the P & T Committee to ensure safe and appropriate utilization of GRH modifiers:
- Revise step therapy for elagolix to remove requirement for trial of acetaminophen or a nonsteroidal anti-inflammatory agent prior to trial of elagolix
- Limit PA approval to the FDA recommended duration of therapy for elagolix to minimize bone loss
- Add endometriosis diagnosis with step therapy for leuprolide, goserelin, and nafarelin
- Reinforce warnings about bone mineral density loss with use of GnRH modifiers

Between January 2020 and January 2021 there approximately 500 women currently in Oregon Medicaid Fee-for-Service (FFS) with claims indicative of uterine fibroid-related diagnosis and approximately 300 women with a diagnosis of endometriosis. **Appendix 1** lists the GnRH modulators on the Preferred Drug List (PDL). All of the GnRH modifiers are non-preferred and require PA. In the second quarter of 2021, 1 claim was processed in the FFS population for leuprolide.

Background:
Uterine Fibroids
Uterine fibroids (i.e., leiomyomas) are benign smooth muscle tumors of that arise primarily in 3 regions of the uterus (submucosal, intramural, and subserosal) in women of reproductive age.[10] In the United States (US), an estimated 26 million women between the ages of 15 and 50 have uterine fibroids.[11] Uterine fibroids account for nearly 30% of all hysterectomies among American women ages 18–44 years.[11] Factors that are associated with an increased risk of uterine fibroids include premenopausal status, family history, nulliparity, hypertension, and obesity.[12] On average, Black women are younger at onset of fibroids, and have larger and more numerous tumors, and are more likely to be anemic and have surgical interventions for fibroids.[11] These observed differences are likely due to inequities in social determinants of health as well as implicit and explicit bias among the medical community.[13] Experiences of racism can delay women from seeking care for uterine fibroid symptoms until they are severe, and bias in medicine at the systemic and individual levels may affect the quality of diagnosis and treatment they receive.[13] In addition, differences in social determinants of health such as limitations on access to quality education, jobs, stable housing, safe

neighborhoods, nutritious foods, and health insurance are associated with inequitable uterine fibroid treatment among Black women.[14,15] Racial disparities in treatment, such as higher rates of hysterectomy and myomectomy (compared with nonsurgical therapy) and open hysterectomy (compared with minimally invasive approaches) have been reported among Black women compared with White women.[14] The prevalence of uterine fibroids does not appear to be higher among Latina and Asian women as compared with White women, but data are far more limited for these populations.[14]

Although they are often asymptomatic, uterine fibroids can cause excessive menstrual bleeding, pelvic pain, and other symptoms that seriously affect a woman's quality of life.[11] Normal menstrual blood loss has been defined as 30 mL to 40 mL per menstrual cycle, while heavy menstrual bleeding has been defined as greater than 80 mL blood loss per cycle.[6] Other fibroid symptoms include infertility, increased urinary frequency or incontinence, constipation, abdominal bloating, dyspareunia, and fatigue (due to anemia from heavy bleeding).[11] The evaluation of fibroids is based mainly on the patient's presenting symptoms: abnormal menstrual bleeding, bulk symptoms (i.e., abdominal protrusion, constipation or urinary frequency), pelvic pain, or findings suggestive of anemia.[10] Fibroids are sometimes found in asymptomatic women during routine pelvic examination or incidentally during imaging.[10] In the US, ultrasonography is the preferred initial imaging modality for fibroids.[10] Transvaginal ultrasonography is about 90% to 99% sensitive for detecting uterine fibroids, but it may miss subserosal or small fibroids.[10]

The alkaline hematin technique, which involves chemically measuring the blood content of used sanitary products, is considered the gold standard for menstrual blood loss determination and has traditionally been used to diagnose heavy menstrual bleeding.[16] The alkaline hematin method directly measures the volume of menstrual blood loss by comparing hematin from menstrual products against calibration curves created from a simultaneous venous blood sample.[17] The alkaline hematin laboratory testing of blood stained sanitary products has been utilized as a primary endpoint in a number of trials evaluating heavy menstrual bleeding with the levonorgestrel-releasing IUD, oral contraceptives, and leuprolide.[18] The FDA has found this test to be somewhat more objective than a pictorial bleeding assessment which directs the study participant to grade their volume of bleeding by comparing their sanitary products to pictures of sanitary products that have undergone some degree of saturation with known quantities of blood.[18]

Symptomatic fibroids may require medical or surgical intervention.[11] Surgical treatment includes hysterectomy, myomectomy, uterine artery embolization, and magnetic resonance–guided focused ultrasound surgery.[10] The 3 medications that have FDA-approval for managing fibroid-related bleeding are leuprolide acetate[19] and the 2 GnRH antagonists (i.e., elagolix and relugolix).[8,20] Several medications including oral contraceptives, levonorgestrel-releasing IUD, and tranexamic acid are used off-label to manage heavy menstrual bleeding associated with fibroids.

Slow release injectable leuprolide acetate received FDA approval in 1999 for preoperative management of patients with anemia caused by uterine fibroids.[21] Leuprolide for this indication is limited to 3 months of use. The recommended dosing regimens for uterine fibroids are 3.75 mg once a month for 3 months or a single 11.25 mg injection.[21] These regimens were found to increase hematocrit by 6% or more and hemoglobin by 2 g/dL or more in 77% of study participants at three months of therapy.[1] Although not listed as part of the indication, some clinicians found that the reduction in size of fibroids from leuprolide acetate treatment resulted in less surgical blood loss and less need for blood transfusions.[1] Other FDA-approved indications for leuprolide acetate include management of endometriosis-associated pain, palliative treatment of advanced prostatic cancer, and treatment of pediatric patients with central precocious puberty.[21,22]

Gonadotropin releasing hormone antagonists (i.e., elagolix and relugolix) are available as oral products and are formulated with low-dose hormonal add-back therapy to limit hypoestrogenic side effects. Elagolix received FDA-approval in 2018 for management of severe pain associated with endometriosis.[23] Elagolix causes a dose-dependent decrease in bone mineral density.[23] The extent of bone mineral density loss is greater with increasing duration of elagolix use and may not be completely reversible after discontinuing therapy.[23] For this reason, the duration of elagolix therapy is limited to 24 months in women without

comorbidities.[23] For women with moderate hepatic impairment, the duration of elagolix therapy is limited to 6 months.[23] Evidence for the safety and efficacy of elagolix in management of endometriosis-associated pain was presented at November 2019 P & T Committee meeting. Elagolix in combination with estradiol and norethindrone acetate (ORIAHNN), received FDA-approval in May 2020 for the treatment of fibroid-related heavy menstrual bleeding in premenopausal women for up to 24 months.[20] When the elagolix combination therapy is prescribed for fibroid-associated bleeding, it is dosed twice daily as 1 capsule of the fixed combination product in the morning and 1 capsule of elagolix 300 mg monotherapy in the evening.[20] This dosing regimen can be taken for up to 24 months.[20] More details about relugolix, the newest GnRH antagonist approved for management of fibroid-related bleeding, are discussed later in this class update.

According to NICE guidance, women with heavy menstrual bleeding associated with fibroids can start combined hormonal contraceptives containing estradiol and dienogest to reduce menstrual blood loss.[7] This is an off-label use of oral contraceptives. Levonorgestrel-releasing intrauterine devices have been found to decrease heavy menstrual bleeding in patients with and without uterine fibroids.[24] However, rates of IUD expulsion are higher in patients with uterine fibroids compared with patients without fibroids (11% versus 0 to 3%).[24] The risk of expulsion may be particularly increased in patients with uterine fibroids that distort the uterine cavity.[24] There is insufficient evidence to support the use of a levonorgestrel-IUD for the treatment of uterine fibroid symptoms other than bleeding.[4]

Tranexamic acid is an oral nonhormonal antifibrinolytic agent FDA-approved for the treatment of cyclic heavy menstrual bleeding in females of reproductive potential.[25] Women who cannot or do not wish to take hormonal contraceptives may prefer this treatment. Tranexamic acid 1,300 mg three times a day can be taken for up to 5 days during monthly menstruation to reduce bleeding.[25] Due to the risk of thrombosis, tranexamic acid is contraindicated in patients at risk for thromboembolic disease or when used concomitantly with hormonal contraceptives.[25] Efficacy of tranexamic acid in women with fibroid-associated heavy menstrual bleeding has not been established.[24]

An AHRQ systematic review presented moderate strength of evidence that progesterone receptor modulators (i.e., mifepristone and ulipristal) reduce fibroid size and improve fibroid-related symptoms including bleeding and quality of life.[1] However, neither therapy is available in the US for management of fibroid-related symptoms. Mifepristone is only FDA-approved for one-time use as emergency contraception.[2] Ulipristal acetate is approved outside the US, but post-marketing reports of rare but serious liver injury, including need for liver transplantation, have prompted the European Medicines Agency and other regulatory agencies to significantly limit the use of daily ulipristal acetate for uterine fibroid treatment.[24]

<u>Endometriosis</u>

The goal of endometriosis management is to prevent disease progression and improve patient's quality of life.[26] Although available medical and surgical treatments have been shown to decrease the severity and frequency of patient symptoms, none appear to offer a cure or long-term relief.[26] Drugs that suppress ovulation have been found to be beneficial in managing the pain associated with endometriosis. Danazol, an anabolic steroid which inhibits gonadotropin secretion, was the first FDA-approved agent for endometriosis, but its usefulness has been undermined by a significant adverse effect profile.[27] Androgenic adverse effects, such as acne, hirsutism, and male pattern baldness, often limit the tolerability of danazol in women. Current first-line therapies to manage pain associated with endometriosis are oral contraceptives or progestin.[28] Oral contraceptives have been shown to suppress gonadotropin secretion and estrogen biosynthesis.[27,29] Most of the data supporting the use of oral contraceptives in managing endometriosis pain is observational and low-quality.[28]

Second-line therapeutic options for pain associated with endometriosis are GnRH agonists administered with hormone therapy.[28] Goserelin, leuprolide, and nafarelin are FDA-approved for six months of continuous use for treatment of pelvic pain caused by endometriosis.[27] The FDA recommends the use of add-back hormonal therapy when a GnRH agonist is used for greater than 6 months.[28] Elagolix is the only GnRH antagonist approved to manage pain symptoms associated

with endometriosis. Surgical management, including laparoscopy for definitive diagnosis, lysis of adhesions, and removal of visible implants, is an option in women with endometriosis who do not respond to medical therapy, especially for those who are infertile.[27,29] Hysterectomy has also been recommended for women with severe, debilitating, and refractory endometriosis who do not wish to become pregnant and in whom other therapeutic measures have failed.[26]

Methods:
A Medline literature search for new systematic reviews and randomized controlled trials (RCTs) assessing clinically relevant outcomes to active controls, or placebo if needed, was conducted. The Medline search strategy used for this review is available in **Appendix 2**, which includes dates, search terms and limits used. The OHSU Drug Effectiveness Review Project, Agency for Healthcare Research and Quality (AHRQ), National Institute for Health and Clinical Excellence (NICE), Department of Veterans Affairs, and the Canadian Agency for Drugs and Technologies in Health (CADTH) resources were manually searched for high quality and relevant systematic reviews. When necessary, systematic reviews are critically appraised for quality using the AMSTAR tool and clinical practice guidelines using the AGREE tool. The FDA website was searched for new drug approvals, indications, and pertinent safety alerts.

The primary focus of the evidence is on high quality systematic reviews and evidence-based guidelines. Randomized controlled trials will be emphasized if evidence is lacking or insufficient from those preferred sources.

Systematic Reviews:
Agency of Healthcare Research and Quality: Management of Uterine Fibroids
A 2017 AHRQ systematic review analyzed literature published from January 1985 to September 2016 to evaluate effectiveness and safety of interventions for management of uterine fibroids.[1] Significant outcomes included resolution of symptoms (pain and uterine bleeding) and reduction in the size of uterine fibroids. Patient-reported outcomes were frequently assessed and reported in 63% of studies.[1] Of the 43 RCTs reporting on effectiveness of medications, 10 studies had placebo or no treatment comparison groups.[1] Approximately one third of the RCTs were industry sponsored.[1] Women included in the studies were predominately premenopausal (39 studies).[1] Four RCTs were assessed as good quality, 12 as fair quality, and 27 as poor quality for effectiveness outcomes.[1]

Thirteen studies addressed the GnRH agonist, leuprolide, which included 7 studies of add-back hormonal therapy (2 good-quality RCTs, 2 fair-quality RCTs, and 9 poor-quality RCTs).[1] Three poor-quality studies evaluated goserelin.[1] Most RCTs ranged in sample size from 16 to 101 women.[1] This small study size limits power for discerning differences across treatment groups and virtually prohibits meaningful evaluation of factors that may influence outcomes within groups.[1] As in much of the fibroid literature, lack of follow-up over time is a limitation.[1] Most studies completed their follow-up of participants when treatment ended.[1] Only 7 studies followed women from 3 to 9 months after end of treatment, limiting the information about how durable the effects may be.[1] GnRH agonists reduced the size of fibroids, with reductions in volume of fibroids documented between 64 and 175 cm^3.[1] As a point of reference, the volume of a golf ball is 40 cm^3.[1] Six studies reported complete absence of bleeding during treatment with 3 trials noting statistical significance for clinically important reduction from baseline.[1] No study reported an increase in bleeding or worsening in hemoglobin or hematocrit.[1] Studies consistently reported significant improvement in measures of quality of life symptoms (days of bleeding, heavy menstrual bleeding, pelvic pressure, pelvic pain, urinary frequency, and constipation).[1] Harms associated with GnRH antagonists included onset of menopausal symptoms, unfavorable changes in lipid profile, declines in cognitive function and memory, and bone loss, although some of these can be ameliorated with hormonal add-back therapy.[1] In summary, moderate strength of evidence supports that GnRH agonists (with and without add-back hormonal therapy) reduce the size of fibroids and bleeding symptoms.[1] Low strength of evidence suggests that fibroid-related quality of life improves with and without add-back hormonal therapy.[1]

Seven studies provided data about outcomes after treatment with the anti-progestin, mifepristone.[1] All studies observed a decrease in the size of fibroids at the completion of the period of active treatment.[1] The magnitude of change in size of the largest fibroid ranged from a decrease of 37 cm^3 to 95 cm^3, with an average decrease of 71 cm^3 among the 575 women receiving mifepristone.[1] All studies of mifepristone that assessed bleeding reported reduced bleeding.[1] Harms associated with mifepristone included spotting, elevations in liver function enzymes, and endometrial hyperplasia.[1] In summary, there is moderate strength of evidence that both mifepristone effectively reduced the size of fibroids and bleeding symptoms.[1] Of note, mifepristone is not FDA-approved for management of uterine fibroids.

The levonorgestrel-releasing IUD improved bleeding (the only outcome of interest reported); however, the single available trial was of poor quality including lack of participant masking.[1] Evidence was insufficient to assess the effectiveness of the levonorgestrel-releasing IUD on any outcomes.[1]

Six studies included agents that act at the estrogen receptor.[1] Three studies, 2 of fair quality and 1 of poor quality, investigated raloxifene (which acts as an anti-estrogen in breast and endometrial tissue) in comparison with placebo.[1] Fibroid size decreased by 4.4 cm^3 to 34.2 cm^3 in 2 studies of raloxifene and did not change size in another.[1] In raloxifene studies with premenopausal women, neither bleeding pattern (in 3 studies) nor hemoglobin levels (in 1 study) were improved compared with placebo.[1] A single poor quality study evaluated tamoxifen, which acts as an anti-estrogen within breast tissue and as an estrogen ligand in the endometrium.[1] Tamoxifen use in premenopausal women did not influence length or severity of bleeding compared with placebo.[1] Change in fibroid characteristics was not reported.[1] Two poor quality RCTs had a total of 42 women receiving hormone replacement therapy (transdermal estrogen replacement plus cyclic oral medroxyprogesterone acetate) after menopause.[1] They compared hormone therapy to tibolone (not available in United States) for menopausal symptom management with attention to whether treatment increased size of fibroids.[1] Growth was approximately 10 cm^3, which is a quarter the size of a golf ball.[1] In summary, studies provide low strength of evidence that, if prescribed to women with fibroids for other conditions such as breast cancer prophylaxis, raloxifene will not cause significant growth of existing fibroids or exacerbate bleeding.[1] Evidence is insufficient to assess if tamoxifen or hormone replacement therapy does or does not promote fibroid growth.[1]

Uterine artery embolization (high strength of evidence) as well as high intensity focused ultrasound (low strength of evidence) are effective for decreasing fibroid size/volume.[1] High intensity focused ultrasound reduces fibroid size (low strength of evidence), but impact on quality of life was not measured.[1] Myomectomy and hysterectomy also improve quality of life (low strength of evidence).[30] Few well-designed trials directly compared different treatment options.[1] Evidence to guide choice of intervention is best when applied in the context of individual patient needs and preferences.[1]

Cochrane: Progestin Effectiveness in Uterine Fibroids

A 2020 Cochrane review evaluated the effectiveness of progestin or progestin-releasing intrauterine systems in treating premenopausal women with uterine fibroids. Literature was searched through July 2020 for the most recent update.[4] Four studies including 221 women with uterine fibroids met inclusion criteria.[4] The available evidence was low quality, downgraded for serious risk of bias, due to poor reporting of study methods, and serious imprecision.[4] At 12 months, low-quality evidence from 1 RCT in 44 women showed the levonorgestrel-releasing IUD reduced the percentage of abnormal uterine bleeding, measured with the alkaline hematin test (MD 77.50%, 95% CI 70.44 to 84.56); increased hemoglobin levels (MD 1.50 g/dL, 95% CI 0.85 to 2.15), or reduced fibroid size more than oral contraceptives (MD 1.90%, 95% CI -12.24 to 16.04).[4] The study did not measure adverse events.[4] Vasomotor symptoms (e.g. hot flashes) were only associated with goserelin acetate (55%), not with dienogest (1 RCT, 14 women; low-quality evidence) or with desogestrel (1 RCT, 16 women; low-quality evidence).[4] Because of low-quality evidence, it is not clear if the levonorgestrel-releasing IUD reduces abnormal uterine bleeding, reduces the size uterine fibroids or increases hemoglobin levels in premenopausal women with uterine fibroids, compared to oral contraceptives.[31] There is insufficient evidence to

determine whether oral progestins reduce abnormal uterine bleeding as effectively as the GnRH agonist, goserelin acetate, but women reported fewer adverse events, such as hot flashes with progestins.[4]

Cochrane: Antifibrinolytics in Heavy Menstrual Bleeding

A 2018 Cochrane meta-analysis assessed the safety and effectiveness of antifibrinolytic medications (tranexamic acid) as a treatment for heavy menstrual bleeding.[5] The literature search was conducted through November 2017. The evidence was low to moderate quality: the main limitations were risk of bias (associated with lack of blinding, and poor reporting of study methods), imprecision and inconsistency.[5] When compared to placebo, antifibrinolytics were associated with reduced mean blood loss in women with heavy menstrual bleeding (MD -53.20 mL per cycle, 95% CI -62.70 to -43.70; I^2= 8%; 4 RCTs, participants = 565; moderate-quality evidence).[5] There was no clear evidence of a difference between antifibrinolytics and placebo in adverse events (RR 1.05, 95% CI 0.93 to 1.18; 1 RCT, participants = 297; low-quality evidence).[5] Only one thromboembolic event occurred in the two studies that reported this outcome.[5]

After review, 5 systematic reviews were excluded due to poor quality (e.g., indirect network-meta analyses), wrong study design of included trials (e.g., observational), comparator (e.g., no control or placebo-controlled), or outcome studied (e.g., non-clinical).[32-36]

New Guidelines

High Quality Guidelines:

National Institute for Health and Care Excellence

The National Institute for Health and Care Excellence issued guidance in 2018 for assessment and management of heavy menstrual bleeding due to various causes including fibroids.[7] Management of endometriosis is discussed under separate NICE guidance published in 2017.[37] At the time of publication, neither elagolix or relugolix had received approval for management of fibroid-associated bleeding. NICE guidance for use of these agents is expected in 2022. Heavy menstrual bleeding associated with fibroids should be managed as follows:

Off-label use of the levonorgestrel-releasing IUD is recommended as first line therapy for women with:[7]

- Fibroids less than 3 cm diameter which are not causing distortion of the uterine cavity
- No identified pathology

If a woman with heavy menstrual bleeding declines the levonorgestrel-releasing IUD or is not a suitable candidate the following off-label pharmacologic treatments can be considered:[7]

- Tranexamic acid
- Combined hormonal contraception
- Cyclic oral progestins

If treatment is unsuccessful, the woman declines pharmacological treatment, or symptoms are severe, consider referral to specialist care for:[7]

- Endometrial ablation
- Hysterectomy or myomectomy
- Pretreatment with a GnRH agonist should be considered if uterine fibroids are causing an enlarged or distorted uterus

Additional Guidelines for Clinical Context:

American College of Obstetricians and Gynecologists

The American College of Obstetricians and Gynecologists issued a practice bulletin focused on management of uterine fibroids in 2021.[24] Studies were reviewed and evaluated for quality using methods outlined by the US Preventative Services Task Force.[24] Literature published between January 2000 and July 2020 was reviewed for the recent update. However, the recommendations are not based on a systematic review. Stakeholder involvement, method of consensus, search terms, detailed search strategy and inclusion/exclusion criteria are not reported. When reliable research was not available, expert opinions from obstetrician–gynecologists were used.[24] ACOG recommends medical treatments that reduce bleeding symptoms (levonorgestrel-releasing IUD, contraceptive steroids, tranexamic acid, and GnRH antagonists) or medications that reduce both bleeding and uterine fibroid size (GnRH agonists and selective progesterone receptor modulators) for management of fibroid-associated symptoms.[24] There is insufficient comparative evidence to guide recommendations on first-line medical therapy.[24] Treatment decisions should be guided by an individual patient's symptoms and treatment goals.[24] Medical management should be tailored to the size and location of fibroids, the patient's age, symptoms, desire to maintain fertility, and access to treatment.[24]

New Formulations or Indications:

- 5/1/2020: An extended release formulation of leuprolide acetate (FENSOLVI) received FDA-approval for treatment of pediatric patients 2 years of age and older with central precocious puberty.[19] The dose of this leuprolide formulation is 45 mg subcutaneously once every 6 months administered by a health care provider.[19] In contrast, the 7.5 mg, 11.25 mg, and 15 mg doses of leuprolide depot suspension (LUPRON DEPOT-PED) are administered intramuscularly every month, based on the child's weight, by a health care provider.[22] Two additional 11.25 mg and 30 mg LUPRON DEPOT-PED suspensions are designed to be administered every 3 months.[22]

  The efficacy of FENSOLVI was evaluated in an uncontrolled, open-label, single arm clinical trial in which 64 pediatric patients (62 females and 2 males, naive to previous GnRH agonist treatment) with central precocious puberty received at least one dose of FENSOLVI at a dosing interval of every 3 months and were observed for 12 months.[19] The mean age was 7.5 years (range 4 to 9 years) at the start of treatment. In pediatric patients with central precocious puberty, FENSOLVI reduced stimulated and basal gonadotropins to prepubertal levels.[19] Suppression of peak stimulated luteinizing hormone (LH) concentrations to 4 IU/L or less was achieved in 87% of pediatric patients by month 6 and in 86% of patients by month 12.[19] Suppression of estradiol or testosterone concentration to prepubertal levels at the 6-month assessment was achieved in 97% and 100% of patients, respectively.[19]

- 5/28/2020: A combination product of elagolix 300 mg, estradiol 1 mg, and norethindrone acetate 0.5mg (ORIAHNN) received FDA-approval for management of heavy menstrual bleeding associated with uterine fibroids in premenopausal women.[20] A capsule containing elagolix 300 mg, estradiol 1 mg, and norethindrone acetate 0.5mg is taken in the morning and a capsule containing only elagolix 300 mg is taken in the evening.[20] The product is packaged in weekly blister packs to assist in adherence to the dosing regimen.

  The efficacy of ORIAHNN in the management of heavy menstrual bleeding associated with uterine fibroids was demonstrated in two randomized, double-blind, placebo-controlled studies (Study UF-1 and Study UF-2) in which 790 premenopausal women with heavy menstrual bleeding received elagolix 300 mg, estradiol 1 mg, and norethindrone acetate 0.5 mg in the morning and elagolix 300 mg in the evening or placebo for 6 months.[38] Heavy menstrual bleeding at baseline was defined as having at least two menstrual cycles with greater than 80 mL of menstrual blood loss (MBL) as assessed by alkaline hematin method.[20] The primary endpoint in both studies was the proportion of responders, defined as women who achieved both 1) MBL volume less than 80 mL at the final month and 2) 50% or greater reduction in MBL volume from baseline to the final month.[20] Final month was defined as the last 28 days before and including the last treatment visit date or the last dose date. A higher proportion of elagolix-treated women were responders (68.5%) compared to placebo-

treated women (8.7%) in study UF-1 (difference: 59.8%; 95% CI 51.1 to 68.5; p<0.001).[20] Similar results were observed in Study UF-2 (76.5% [elagolix] vs. 10.5% [placebo], difference: 66%; 95% CI 57.1 to 75.0; p<0.001).[20]

The use of elagolix/estradiol/norethindrone should be limited to 24 months due to the risk of continued bone loss, which may not be reversible.[20] ORIAHNN carries a black boxed warning, similar to other combination estrogen/progestin products, regarding the increased risk of thromboembolic disorders especially in women at increased risk for these events including women over 35 years of age who smoke or women with uncontrolled hypertension.[20]

New FDA Safety Alerts:

Table 1. Description of New FDA Safety Alerts[39]

Generic Name	Brand Name	Month / Year of Change	Location of Change (Boxed Warning, Warnings, CI)	Addition or Change and Mitigation Principles (if applicable)
Leuprolide	ELIGARD, LUPRON	02/2019	Adverse Reactions: Postmarketing Experience Use In Specific Populations: Pregnancy	Adverse Reactions: Pituitary apoplexy-During post-marketing surveillance, rare cases of pituitary apoplexy (a clinical syndrome secondary to infarction of the pituitary gland) have been reported after the administration of gonadotropin-releasing hormone agonists. Nervous System-Convulsions Respiratory System-Interstitial lung disease Pregnancy: Based on findings in animal studies and mechanism of action, leuprolide may cause fetal harm when administered to a pregnant woman. There are no available data in pregnant women to inform the drug-associated risk. Expected hormonal changes that occur with leuprolide treatment increase the risk for pregnancy loss. In animal developmental and reproductive studies, major fetal abnormalities were observed after administration of leuprolide acetate throughout gestation in rats. Advise pregnant patients and females of reproductive potential of the potential risk to the fetus.
Leuprolide	ELIGARD, LUPRON	05/2017	Warnings and Precautions	Postmarketing reports of convulsions have been observed in patients receiving GnRH agonists, including leuprolide acetate. These have included patients with a history of seizures, epilepsy, cerebrovascular disorders, central nervous system anomalies or tumors, and patients on concomitant medications that have been associated with convulsions such as bupropion and SSRIs. Convulsions have also been reported in patients in the absence of any of the conditions mentioned above.

				Psychiatric events have been reported in patients taking GnRH agonists, including leuprolide acetate. Postmarketing reports with this class of drugs include symptoms of emotional lability, such as crying, irritability, impatience, anger, and aggression. Monitor for development or worsening of psychiatric symptoms during treatment with LUPRON
Nafarelin	SYNAREL	05/2017	Warnings and Precautions	Post-marketing reports of convulsions have been observed in patients receiving GnRH agonists. These have included patients with a history of seizures, epilepsy, cerebrovascular disorders, central nervous system anomalies or tumors, and patients on concomitant medications that have been associated with convulsions such as bupropion and SSRIs. Convulsions have also been reported in patients in the absence of any of the conditions mentioned above.
Histrelin	VANTAS	02/2019	Warnings and Precautions	Androgen deprivation therapy may prolong the QT/QTc interval. Providers should consider whether the benefits of androgen deprivation therapy outweigh the potential risks in patients with congenital long QT syndrome, congestive heart failure, frequent electrolyte abnormalities, and in patients taking drugs known to prolong the QT interval. Electrolyte abnormalities should be corrected. Consider periodic monitoring of electrocardiograms and electrolytes.
Histrelin	VANTAS	12/2020	Warnings and Precautions	The safety and efficacy of histrelin have not been established in females. Based on findings from animal studies and its mechanism of action, histrelin can cause fetal harm when administered to a pregnant woman. Advise pregnant patients and females of reproductive potential of the potential risk to the fetus.

Randomized Controlled Trials:
A total of 24 citations were manually reviewed from the initial literature search. After further review, 24 citations were excluded because of wrong study design (e.g., observational), comparator (e.g., no control or placebo-controlled), or outcome studied (e.g., non-clinical).

NEW DRUG EVALUATION: Relugolix/Estradiol/Norethindrone (MYFEMBREE)
See **Appendix 4** for **Highlights of Prescribing Information** from the manufacturer, including Boxed Warnings and Risk Evaluation Mitigation Strategies (if applicable), indications, dosage and administration, formulations, contraindications, warnings and precautions, adverse reactions, drug interactions and use in specific populations.

An oral fixed-dose combination of the GnRH receptor antagonist relugolix, estradiol, and norethindrone acetate (MYFEMBREE), was approved by the FDA for management of heavy menstrual bleeding associated with uterine fibroids in May 2021.[8] The recommended dose is 1 tablet containing relugolix 40mg, estradiol 1mg, and norethindrone acetate 0.5 mg once a day.[8] It is the second oral product to be FDA-approved for this indication. A combination product containing

elagolix, estradiol and norethindrone acetate received FDA approval May 2020.[20] Relugolix was initially FDA-approved for treatment of adult patients with advanced prostate cancer in 2020 under the brand name ORGOVYX.[40] Relugolix, like elagolix, inhibits endogenous GnRH signaling by binding to GnRH receptors in the pituitary gland, suppressing release of LH and follicle stimulating hormone (FSH).[8] Suppression of LH and FSH results in decreased serum concentrations of estradiol and progesterone which curtail endometrial proliferation which in turn reduces menstrual bleeding.[8] Estradiol and norethindrone acetate are included in the fixed-dose combination tablet as hormonal add-back therapy. Estradiol reduces relugolix hypoestrogenic adverse effects, such as vasomotor symptoms and reductions in bone mineral density.[8] Norethindrone helps to prevent endometrial hyperplasia and malignancies associated with unopposed estrogen use.[8] Relugolix combination therapy is currently being investigated for management of endometriosis-associated pain and as an oral contraceptive.

Clinical Efficacy:
FDA approval of the combination relugolix 40 mg, estradiol 1 mg, and norethindrone acetate 0.5 mg formulation was based on the results of 2 identically designed, 24-week, randomized, double-blind, phase 3 trials (LIBERTY-1 and LIBERTY-2).[9] The trials were conducted in a total of 770 premenopausal patients with fibroid-associated heavy menstrual bleeding.[9] Heavy menstrual bleeding was defined as a volume of menstrual blood loss of 80 mL or more per cycle for 2 cycles or a volume of 160 mL or more during 1 cycle.[9] Participants were randomly assigned in a 1:1:1 ratio to receive once-daily placebo, relugolix combination therapy (40 mg of relugolix, 1 mg of estradiol, and 0.5 mg of norethindrone acetate) for 24 weeks, or delayed relugolix combination therapy (40 mg of relugolix monotherapy, followed by relugolix combination therapy, each for 12 weeks).[9] The delayed relugolix combination therapy regimen was added to the protocol to assess the benefit and safety of the addition of estradiol and norethindrone acetate on bone mineral density and vasomotor symptoms.[9] The primary efficacy end point in each trial was the percentage of participants with a response, defined as the volume of menstrual blood loss less than 80 mL and at least 50% reduction in volume from baseline, in the relugolix combination therapy group compared with the placebo group over 24 weeks.[9] Determination of blood loss was assessed using the alkaline hematin test. Key secondary end points were amenorrhea, volume of menstrual blood loss and anemia.

In both trials, significantly more women achieved menstrual blood loss of less than 80 mL and a 50% or greater reduction from baseline in menstrual blood loss over the final 35 days of treatment with relugolix combination therapy than with placebo.[9] A total of 73% of the participants in the relugolix combination therapy group in LIBERTY-1 were responders versus 19% in the placebo group (difference 55%; 95% CI 44 to 65; p<0.001; NNT 2).[9] Similar results were observed in LIBERTY-2 as 71% of relugolix combination-treated participants were responders, versus 15% in the placebo-treated group (difference 56%; 95% CI 46 to 66; p<0.001; NNT 2).[9] More participants in the delayed relugolix combination group also responded to therapy compared to placebo (80% in LIBERTY-1 and 73% in LIBERTY-2), but a statistical analysis was not completed.[9]

Compared with the placebo groups the relugolix combination therapy groups had significant improvements in key secondary end points, including amenorrhea, changes in volume of menstrual blood loss, and anemia assessment.[9] Amenorrhea over the last 35 days of the treatment period occurred in 52% and 50% of the participants receiving relugolix combination therapy in LIBERTY-1 and LIBERTY-2, respectively, as compared with 6% of those receiving placebo (difference 46%; 95% CI 37 to 56; P<0.001) and 3% of placebo-treated patients (difference 47%; 95% CI: 38 to 57; P<0.001), respectively.[9] The mean reduction in menstrual blood loss from baseline to week 24 in the relugolix combination therapy groups was 84% in both LIBERTY-1 and LIBERTY-2, as compared with 23% and 15%, respectively, in the placebo groups (P<0.001 for both comparisons).[9] Fifty percent or more of the participants who had anemia at baseline had an increase of more than 2 g/dL in hemoglobin levels with relugolix combination therapy, as compared with placebo.[9] Additional details about the LIBERTY-1 and LIBERTY-2 trials are described and evaluated below in **Table 5**.

Many patients with self-reported heavy menstrual bleeding and uterine fibroids did not pass screening owing to strict assessment criteria for LIBERTY-1 and LIBERTY-2, which could limit generalizability to the wider population of patients who might benefit from relugolix therapy. In addition, the duration of the trial

was only 6 months. More information is needed regarding the long-term benefits and risks of relugolix therapy. No trials are available that directly compare relugolix the other FDA-approved treatments for fibroid-associated heavy menstrual bleeding (i.e., elagolix, leuprolide).

Clinical Safety:
The most common adverse reactions observed with relugolix combination therapy were hot flush, hyperhidrosis or night sweats, hypertension, abnormal uterine bleeding, alopecia, and decreased libido.[8] The frequency of these adverse events compared with placebo are presented in **Table 3.**

Table 3. Adverse Reactions Occurring in 3% or More of Women Treated with Relugolix/Estradiol/Norethindrone Acetate[8]

Adverse Reaction	Relugolix/Estradiol/Norethindrone N=254	Placebo N=256
Hot flush, hyperhidrosis, or night sweats	10.6%	6.6%
Hypertension	7.0%	0.8%
Abnormal uterine bleeding (includes menorrhagia, vaginal hemorrhage, polymenorrhea)	6.3%	1.2%
Alopecia	3.5%	0.8%
Decreased or loss of libido	3.1%	0.4%

Because the combination relugolix product contains estrogen and progestin, the prescribing information contains a black boxed warning regarding the risk of thromboembolic disorders and vascular events.[8] Estrogen and progestin combination products increase the risk of thrombotic or thromboembolic disorders including pulmonary embolism, deep vein thrombosis, stroke and myocardial infarction, especially in persons at increased risk for these events.[8] Relugolix, estradiol, and norethindrone acetate combination therapy is contraindicated in persons with current or a history of thrombotic or thromboembolic disorders and in women at increased risk for these events, including females over 35 years of age who smoke or have uncontrolled hypertension.[8]

The use of relugolix therapy should be limited to 24 months due to the risk of bone loss which may not be reversible and it is contraindicated in persons with known osteoporosis.[8] In LIBERTY-1 and LIBERTY-2 bone mineral density measured by dual-energy x-ray absorptiometry (DEXA) of the lumbar spine, total hip, and femoral neck was assessed at baseline, week 12 and week 24. In both trials, mean changes from baseline to week 24 in bone mineral density at the lumbar spine were not statistically significantly different between the relugolix combination group and the placebo group.[9] In LIBERTY 1 and LIBERTY 2, the mean percent difference from baseline at 12 weeks in bone mineral density at lumbar spine for relugolix combination therapy versus placebo was the -0.7 (95% CI −1.4 to 0.1) and -1.3 (95% CI -2.0 to -0.6), respectively.[9] In both trials the mean percent difference from baseline at 24 weeks in bone mineral density at lumbar spine for relugolix combination therapy versus placebo was the same (difference −0.4%; 95% CI −1.2 to 0.3).[9] Similar results in LIBERTY 1 and LIBERTY 2 were observed in total hip bone mineral density assessments at 12 weeks between relugolix combination therapy and placebo (MD -0.4, ,95% CI -1.0 to 0.2 and MD -0.9, 95% CI -0.3 to 0.7, respectively).[9] The inclusion of the delayed relugolix combination therapy group in the LIBERTY trials allowed for the comparison of the effects of combination therapy with monotherapy.[9] In the delayed relugolix combination therapy group, the bone mineral density at the lumbar spine decreased from baseline at week 12 with relugolix monotherapy compared with placebo in LIBERTY-1 and LIBERTY-2 (difference -2.2; 95% CI -2.9 to -1.5 and difference -2.4; 95% CI -3.1 To -1.7, respectively).[9] Similar changes in lumbar spine bone density were observed at week 24 in LIBERTY-1 and LIBERTY-2 (difference -1.9, 95% CI -2.6 to -1.1 and difference -2.4, 95% CI -3.2 to -1.7, respectively).[9] Twelve weeks of monotherapy resulted in a loss of bone mineral density and a higher incidence of

vasomotor adverse events, as compared with relugolix combination therapy, and although the transition to relugolix combination therapy prevented further loss of bone mineral density, it did not reverse the changes in bone mass.[9]

Other warnings and precautions associated with relugolix treatment include the risk of: depression, mood disorders, and suicidal ideation; hepatic impairment; elevated blood pressure; changes in menstrual bleeding pattern and reduced ability to recognize pregnancy; early pregnancy loss; and uterine prolapse or expuslsion.[8] Contraindications to relugolix, estradiol and norethindrone combination therapy include: current or history of breast cancer or other hormone-sensitive malignancies; known hepatic impairment or disease; and undiagnosed abnormal uterine bleeding.[8]

Relugolix is metabolized primarily by CYP3A and to a lesser extent by CYP2C8 hepatic enzymes.[8] Concomitant use of an oral P-glycoprotein (P-gp) inhibitor increases serum concentrations of relugolix and is not recommended; if use of an oral P-gp inhibitor is necessary, relugolix should be taken at least 6 hours before the P-gp inhibitor.[8] Concurrent use of a combined P-gp and strong CYP3A inducer can reduce the efficacy of relugolix and should be avoided.[8]

Look-alike / Sound-alike Error Risk Potential: No results identified.

Comparative Endpoints:

Clinically Meaningful Endpoints:
1) Reduced volume of menstrual blood loss (< 80 mL/month)
2) Improvement in anemia
3) Improved pain control
4) Quality of life
5) Serious adverse events
6) Study withdrawal due to an adverse event

Primary Study Endpoint:
1) Reduction in volume of blood loss

Table 4. Pharmacology and Pharmacokinetic Properties[8]

Parameter	
Mechanism of Action	Relugolix is a gonadotropin-releasing hormone antagonist that decreases LH, FSH, estradiol and progesterone to reduce bleeding associated with fibroids.
Oral Bioavailability	62%
Distribution and Protein Binding	Protein binding, albumin 68% to 71%
Elimination	Renal excretion: 4.1%, fecal excretion: 81%
Half-Life	61.5 hours
Metabolism	Extensive hepatic metabolism: substrate of CYP3A, CYP2C8, and P-gp

Abbreviations: FSH = follicle stimulating hormone; LH = luteinizing hormone; P-gp = P-glycoprotein

Table 5. Comparative Evidence Table.

Ref./ Study Design	Drug Regimens/ Duration	Patient Population	N	Efficacy Endpoints	ARR/ NNT	Safety Outcomes	ARR/ NNH	Risk of Bias/ Applicability
1.Al-Hendy A, et al[9] LIBERTY-1 DB, MC, PC, phase 3 RCT	1. Placebo once day x 24 weeks 2. Relugolix combination therapy (relugolix 40 mg, estradiol 1 mg, norethindrone 0.5 mg) x 24 weeks 3. Delayed relugolix combination therapy: relugolix 40mg monotherapy x 12 weeks followed by relugolix combination therapy x 12 weeks	Demographics: 1. Mean age: 42 y 2. Percent ≥ 40 y: 70% 3. Ethnicity: White: 45% Black: 49% Other: 6% 4. Median BMI: 30 kg/m^2 5.Median MBL: 190 mL Key Inclusion Criteria: 1. Premenopausal women 18 to 50 years of age 2. Diagnosis of fibroids confirmed by ultrasound 3. Heavy menstrual bleeding with a volume ≥ 160 mL in 1 cycle or ≥ 80 mL in 2 cycles 4. Regular menses with <14 days duration cycling between 21 to 38 days for at least 3 months prior to screening Key Exclusion Criteria: 1. Bone mineral density z score less than -2.0 (osteoporosis) 2. HMB due to ovarian polyps, cysts, or other gynecological disorders 4. Any surgical procedure for fibroids 6 months prior to screening 5. History metabolic disease (i.e., hyperparathyroidism, hyperthyroidism, anorexia) 6. History of bisphosphonate, teriparatide, denosumab, or calcitonin therapy used to treat bone mineral density loss	ITT: 1. 127 2. 128 3. 132 PP: 1. 105 2. 100 3. 103 Attrition: 1. 22 (17%) 2. 28 (22%) 3. 29 (22%)	Primary Endpoint: Percent of responders defined as: 1) Volume of menstrual blood loss<80 mL and 2) Reduction of ≥ 50% from baseline in volume of MBL over last 35 days of treatment 1. 19% (n=24) 2. 73% (n=93) Difference: 54% 95% CI: 44 to 65 P<0.001 Secondary Endpoints: Achieved amenorrhea over last 35 days of treatment: 1. 6% (n=7) 2. 52% (n=67) Difference: 46% 95% CI: 37 to 56 P<0.001 Percent change from baseline to Week 24 in MBL volume 1. -23% 2. -84% Difference: -61% 95% CI: -74 to -49 Proportion of women with hemoglobin level ≤ 10.5 g/dL at baseline who achieved an increase > 2 g/dL at week 24 1. 22% (n=5/23) 2. 50% (n=15/30) Difference: 28% 95% CI: 4 to 43	54/2 46/3 NA NA	Adverse Events: 1. 66% 2. 62% 3. 73% Serious Adverse Events: 1. 2% 2. 5% 3. 2% Adverse Event Leading to Discontinuation: 1. 4% 2. 5% 3. 12% Hot Flashes 1. 8% 2. 11% 3. 36% Hypertension 1. 0% 2. 5% 3. 2% 95% CI and p-values NR for all outcomes	NA for all	**Risk of Bias (low/high/unclear)**: Selection Bias: Low. Subjects randomized 1:1:1 via interactive website. Baseline demographics well balanced between treatment arms. Subjects stratified by mean volume of MBL (< 225 mL vs ≥ 225 mL) and geographic region (North America v. the rest of the world). Performance Bias: Undear. Placebo tablets and capsules packaged in blister cards similar to active comparators. Method of investigator blinding to treatment not described. Detection Bias: Unclear. Method of outcome assessor blinding not described. Subjects kept electronic diaries to report bleeding and product use, which is subject to recall bias. Attrition Bias: High. Over 20% of subjects in both active comparator arms withdrew due to adverse effects, lack of efficacy, loss to follow up or protocol deviation. Reporting Bias: Low. Protocol available on line. All pre-specified outcomes reported. Other Bias: Unclear. Manufacturer designed trial and analyzed data. **Applicability**: Patient: Stringent exclusion criteria may have limited participation for women who would benefit from therapy. Well diversified based on race. Intervention: Relugolix 40 mg once daily was effective in reducing MBL in Phase 2 trial. Comparator: Placebo is an appropriate comparator, but comparison with a similar agent such as elagolix would have provided meaningful head-to-head data. Outcomes: Proportion of responders using volume of MBL has been used in previous clinical trials evaluating efficacy of other medications used to reduce HMB associated with fibroids. Setting: 80 sites in Africa, Europe, North America and South America. Number of sites by country: United States n=63 Brazil n=3

		7. Breast cancer 8. Thromboembolic disease						Italy n=5 Poland n=5 South Africa n=3 United Kingdom n=1
2. Al-Hendy A, et al[9] LIBERTY-2 DB, MC, PC, phase 3 RCT	1. Placebo once day x 24 weeks 2. Relugolix combination therapy (relugolix 40 mg, estradiol 1 mg, norethindrone 0.5 mg) x 24 weeks 3. Delayed relugolix combination therapy: relugolix 40mg monotherapy x 12 weeks followed by relugolix combination therapy x 12 weeks	Demographics: 1.Mean age: 42 yo 2. Percent ≥ 40 yo: 70% 3. White: 41% Black: 53% Other: 6% 4.Median BMI: 31 kg/m^2 5.Median MBL: 185 ml Key Inclusion Criteria: see LIBERTY-1 Key Exclusion Criteria: see LIBERTY- 1	ITT: 1. 129 2. 125 3. 127 PP: 1. 102 2. 102 3. 98 Attrition: 1. 27 (21%) 2. 23 (18%) 3. 29 (23%)	Co-Primary Endpoints: Percent of responders defined as: 1)Volume of menstrual blood loss <80 mL and 2)Reduction of at least 50% from baseline in volume of MBL over last 35 days of treatment 1. 15% (n=19) 2. 71% (n=89) Difference: 56% 95% CI: 46 to 66 P<0.001 Secondary Endpoints: Achieved amenorrhea over the last 35 days of treatment 1. 3% (n=4) 2. 50% (n=63) Difference: 47% 95% CI: 38 to 57 P<0.001 Percent change from baseline to Week 24 in mean MBL volume 1. -15% 2.- 84% Difference: -69% 95% CI: -84 to -54 Proportion of women with hemoglobin level ≤ 10.5 g/dL at baseline who achieved an increase > 2 g/dL at week 24 1. 5% (n=2/37) 2. 61% (n=19/31) Difference: 56% 95% CI: 37 to 75	56/2 47/3 NA NA	Adverse Events: 1. 59% 2. 60% 3. 71% Serious Adverse Events: 1. 3% 2. 1% 3. 2% Adverse Event Leading to Discontinuation: 1. 5% 2. 2% 3. 11% Hot Flashes 1. 4% 2. 6% 3. 35% Hypertension 1. 3% 2. 4% 3. 6% 95% CI and p-values NR for all outcomes		**Risk of Bias (low/high/unclear)**: Selection Bias: see LIBERTY-1 Performance Bias: see LIBERTY-1 Detection Bias: see LIBERTY-1 Attrition Bias: High. Over 20% of subjects in placebo and 1 active comparator arm withdrew due to adverse effects, lack of efficacy, loss to follow up or protocol deviation. Reporting Bias: Low. Protocol available on line. All pre-specified outcomes reported. Other Bias: see LIBERTY-1 **Applicability**: Patient: see LIBERTY-1 Intervention: see LIBERTY-1 Comparator: see LIBERTY-1 Outcomes: see LIBERTY-1 Setting: 99 sites in Africa, Europe, North America and South America. Number of sites by country: United States n=67 Belgium n=4 Brazil n=4 Chile n=4 Czech Republic n=4 Hungary n=7 Poland n=5 South Africa n=4

Abbreviations: ARR = absolute risk reduction; BMI = body mass index; DB = double blind; CI = confidence interval; dL = deciliter; HMB = heavy menstrual bleeding; ITT = intention to treat; kg = kilogram; m = meter; MBL = menstrual blood loss; MC = multi-center; mg = milligram; ml = milliliters; mITT = modified intention to treat; N = number of subjects; NA = not applicable; NNH = number needed to harm; NNT = number needed to treat; PC = placebo control; PP = per protocol; RCT = randomized clinical trial; yo = years old

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Appendix 1: Current Preferred Drug List

Generic	Brand	Route	Form	PDL
elagolix sodium	ORILISSA	ORAL	TABLET	N
elagolix/estradiol/norethindrone	ORIAHNN	ORAL	CAP SEQ	N
goserelin acetate	ZOLADEX	SUB-Q	IMPLANT	N
histrelin acetate	SUPPRELIN LA	IMPLANT	KIT	N
histrelin acetate	VANTAS	IMPLANT	KIT	N
histrelin acetate	SUPPRELIN	SUB-Q	KIT	N
leuprolide acetate	LUPRON DEPOT-PED	INTRAMUSC	KIT	N
leuprolide acetate	LUPRON DEPOT	INTRAMUSC	SYRINGEKIT	N
leuprolide acetate	LUPRON DEPOT (LUPANETA)	INTRAMUSC	SYRINGEKIT	N
leuprolide acetate	LUPRON DEPOT-PED	INTRAMUSC	SYRINGEKIT	N
leuprolide acetate	LEUPROLIDE ACETATE	SUB-Q	KIT	N
leuprolide acetate	ELIGARD	SUB-Q	SYRINGE	N
leuprolide acetate	FENSOLVI	SUB-Q	SYRINGE	N
leuprolide acetate	LEUPROLIDE ACETATE	SUB-Q	VIAL	N
leuprolide/norethindrone acetate	LUPANETA PACK	MISCELL	KT SYR TAB	N
nafarelin acetate	SYNAREL	NASAL	SPRAY	N
triptorelin pamoate	TRELSTAR	INTRAMUSC	VIAL	N
triptorelin pamoate	TRIPTODUR	INTRAMUSC	VIAL	N
relugolix/estradiol/norethindrone	MYFEMBREE	ORAL	TABLET	N

Appendix 2: Medline Search Strategy

Ovid MEDLINE(R) without Revisions 1996 to August Week 3 2021, Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations 1946 to August 30, 2021

1. Exp ENDOMETRIOSIS/	15420
2. Exp GOSERELIN/	1081
3. Exp LEUPROLIDE/	2161
4. NAFARELIN/	129
5. Elagolix.mp.	80
6. Exp MEDROXYPROGESTERONE ACETATE/	3184
7. NORETHINDRONE/	1119
8. DANAZOL/	878
9. relugolix.mp.	35
10. exp Leiomyoma	12741
11. 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9	8090
12. 1 or 10	27701
13. 11 and 12	886

14. limit 13 to (english language and humans and (clinical trial, all or clinical trial, phase i or clinical trial, phase ii or clinical trial, phase iii or clinical trial, phase iv or clinical trial or comparative study or consensus development conference or controlled clinical trial or equivalence trial or guideline or meta-analysis or multicenter study or practice guideline or pragmatic clinical trial or randomized controlled trial or systematic reviews)) 24

Appendix 3: Prescribing Information Highlights

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use MYFEMBREE safely and effectively. See full prescribing information for MYFEMBREE.

MYFEMBREE® (relugolix, estradiol, and norethindrone acetate) tablets, for oral use
Initial U.S. Approval: 2021

WARNING: THROMBOEMBOLIC DISORDERS AND VASCULAR EVENTS

See full prescribing information for complete boxed warning

- **Estrogen and progestin combinations, including MYFEMBREE, increase the risk of thrombotic or thromboembolic disorders, especially in women at increased risk for these events. (5.1)**
- **MYFEMBREE is contraindicated in women with current or a history of thrombotic or thromboembolic disorders and in women at increased risk for these events, including women over 35 years of age who smoke or women with uncontrolled hypertension. (4)**

——————INDICATIONS AND USAGE——————

MYFEMBREE is a combination of relugolix, a gonadotropin-releasing hormone (GnRH) receptor antagonist, estradiol, an estrogen, and norethindrone acetate, a progestin, indicated for the management of heavy menstrual bleeding associated with uterine leiomyomas (fibroids) in premenopausal women. (1)

Limitations of Use
Use of MYFEMBREE should be limited to 24 months due to the risk of continued bone loss which may not be reversible. (1, 5.2, 6)

——————DOSAGE AND ADMINISTRATION——————

- Exclude pregnancy and discontinue hormonal contraceptives prior to MYFEMBREE initiation. (2.1)
- Take one tablet orally once daily. (2.2)
- Take the missed dose of MYFEMBREE as soon as possible the same day and then resume regular dosing the next day at the usual time. (2.3)
- If concomitant use of oral P-gp inhibitors is unavoidable, take MYFEMBREE at least 6 hours before taking the P-gp inhibitor. (2.4)

——————DOSAGE FORMS AND STRENGTHS——————

Tablets: fixed-dose combination containing relugolix 40 mg, estradiol 1 mg and norethindrone acetate 0.5 mg (3)

——————CONTRAINDICATIONS——————

- High risk of arterial, venous thrombotic, or thromboembolic disorder. (4)
- Pregnancy. (4)
- Known osteoporosis. (4)
- Current or history of breast cancer or other hormone-sensitive malignancies. (4)
- Known hepatic impairment or disease. (4)
- Undiagnosed abnormal uterine bleeding. (4)
- Known hypersensitivity to components of MYFEMBREE. (4)

——————WARNINGS AND PRECAUTIONS——————

- Thromboembolic Disorders and Vascular Events: Discontinue MYFEMBREE if an arterial or venous thrombotic, cardiovascular, or cerebrovascular event occurs. Discontinue MYFEMBREE if there is sudden unexplained partial or complete loss of vision, proptosis, diplopia, papilledema, or retinal vascular lesions and evaluate for retinal vein thrombosis immediately. (5.1)
- Bone Loss: Decreases in bone mineral density (BMD) that may not be completely reversible. Baseline and periodic BMD assessments are recommended. Assess risk-benefit for women with additional risk factors for bone loss. (5.2)
- Depression, Mood Disorders, and Suicidal Ideation: Advise patients to seek medical attention for new onset or worsening depression, anxiety, or other mood changes. (5.4)
- Hepatic Impairment and Transaminase Elevations: Counsel patients on signs and symptoms of liver injury. (5.5)
- Elevated Blood Pressure: Do not use in women with uncontrolled hypertension. For women with well-controlled hypertension, continue to monitor blood pressure and stop MYFEMBREE if blood pressure rises significantly. (5.7)
- Change in Menstrual Bleeding Pattern and Reduced Ability to Recognize Pregnancy: Advise women to use non-hormonal contraception during treatment and for one week after discontinuing MYFEMBREE. MYFEMBREE may delay the ability to recognize pregnancy because it alters menstrual bleeding. Perform testing if pregnancy is suspected and discontinue MYFEMBREE if pregnancy is confirmed. (5.8)
- Risk of Early Pregnancy Loss: Can cause early pregnancy loss. Advise women to use effective non-hormonal contraception. (5.9)
- Uterine Fibroid Prolapse or Expulsion: Advise patients to seek medical attention for severe uterine bleeding. (5.10)
- Hypersensitivity Reactions: Immediately discontinue MYFEMBREE if a hypersensitivity reaction occurs. (5.14)

——————ADVERSE REACTIONS——————

Most common adverse reactions (incidence ≥ 3%) are hot flush, hyperhidrosis or night sweats, uterine bleeding, alopecia, and decreased libido. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Myovant Sciences, Inc. at 1-833-MYOVANT (1-833-696-8268) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

——————DRUG INTERACTIONS——————

- Avoid use of MYFEMBREE with oral P-gp inhibitors. (7.1)
- Avoid use with combined P-gp and strong CYP3A inducers, as the exposure of the components of MYFEMBREE may be decreased. (7.1)

——————USE IN SPECIFIC POPULATIONS——————

- Lactation: Advise women not to breastfeed while taking MYFEMBREE. (8.2)

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.

Revised: 05/2021

Appendix 4: Key Inclusion Criteria

Population	Premenopausal women with uterine fibroids
Intervention	Relugolix/estradiol/norethindrone
Comparator	Placebo
Outcomes	Reduced volume of menstrual blood loss
Timing	6 months
Setting	Outpatient

Appendix 5: Prior Authorization Criteria

Gonadotropin-Releasing Hormone Agonists

Goal(s):

- Restrict pediatric use of gonadotropin-releasing hormone (GnRH) agonists to medically appropriate conditions funded under the Oregon Health Plan (e.g., central precocious puberty or gender dysphoria)
- Promote use that is consistent with medical evidence and product labeling

Length of Authorization:

- Up to 6 months

Requires PA:

- GnRH agonists prescribed for pediatric patients less than 18 years of age
- Non-preferred products

Covered Alternatives:

- Current PMPDP preferred drug list per OAR 410-121-0030 at www.orpdl.org
- Searchable site for Oregon FFS Drug Class listed at www.orpdl.org/drugs/

Approval Criteria		
1. What diagnosis is being treated?	Record ICD10 code.	
2. Is the diagnosis funded by OHP?	**Yes:** Go to #3	**No:** Pass to RPh. Deny; not funded by the OHP.
3. Is the prescriber a pediatric endocrinologist?	**Yes:** Go to #4	**No:** Go to #8
4. What diagnosis is being treated and what is the age and gender of the patient assigned at birth?	Record ICD10 code. Record age and gender assigned at birth	

Approval Criteria		
5. Is the diagnosis central precocious puberty (ICD10 E30.1, E30.8) or other endocrine disorder (E34.9)?	**Yes:** Approve for up to 6 months	**No:** Go to #6
6. Is the diagnosis gender dysphoria (ICD10 F64.2, F64.1)?	**Yes:** Go to #7	**No:** Go to #12
7. Does the request meet **all** of the following criteria? • Diagnosis of gender dysphoria made by a mental health professional with experience in gender dysphoria. • Onset of puberty confirmed by physical changes and hormone levels, but no earlier than Tanner Stages 2. • The prescriber agrees criteria in the Guideline Notes on the OHP List of Prioritized Services have been met.* *From Guideline Note 127: To qualify for cross-sex hormone therapy, the patient must: A) have persistent, well-documented gender dysphoria B) have the capacity to make a fully informed decision and to give consent for treatment C) have any significant medical or mental health concerns reasonably well controlled D) have a comprehensive mental health evaluation provided in accordance with Version 7 of the World Professional Association for Transgender Health (WPATH) Standards of Care (www.wpath.org).	**Yes:** Approve for up to 6 months.	**No:** Pass to RPh; deny for medical appropriateness
8. Is this request for treatment of breast cancer or prostate cancer?	**Yes:** Approve up to 1 year	**No:** Go to #9
9. Is this request for leuprolide for the management of preoperative anemia due to uterine fibroids (leiomyoma)?	**Yes:** Approve for up to 3 months	**No:** Go to # 10
10. Is this request for management of moderate to severe pain associated with endometriosis in a woman ≥18 years of age?	**Yes**: Go to #11	**No:** Pass to RPh. Deny; medical appropriateness

Approval Criteria		
11. Has the patient tried and failed an adequate trial of preferred first line endometriosis therapy options including administration of combined hormonal contraceptives or progestins (oral, depot injection, or intrauterine) alone? -or- Does the patient have a documented intolerance, FDA-labeled contraindication, or hypersensitivity the first-line therapy options?	**Yes:** Approve for 6 months. *Note maximum recommended duration of therapy for nafarelin, leuprolide, and goserelin is 6 months. If requesting continuation of therapy beyond 6 months, pass to RPh. Deny; medical appropriateness.	**No:** Pass to RPh. Deny; medical appropriateness *First-line therapy options such as hormonal contraceptives or progestins do not require PA
12. RPh only: All other indications need to be evaluated as to whether it is funded under the OHP. Refer unique situations to Medical Director of DMAP.		

P&T / DUR Review: *12/21 (DM); 3/19 (DM); 5/15*
Implementation: *1/1/22; 5/1/19*

Gonadotropin-Releasing Hormone Antagonists

Goal(s):

- Promote safe use of elagolix in women with endometriosis-associated pain
- Promote safe use of elagolix/estradiol/norethindrone and relugolix/estradiol/norethindrone for heavy menstrual bleeding associated with uterine fibroids (leiomyoma).
- Promote use that is consistent with medical evidence and product labeling.

Length of Authorization:

- Initial: Up to 6 months
- Elagolix renewal: Up to 6 months for 150 mg daily dose with total cumulative treatment period not to exceed 24 months
- Elagolix/estradiol/norethindrone renewal: Up to 6 months for elagolix 300 mg dosed twice daily with a total cumulative treatment period not to exceed 24 months
- Relugolix/estradiol/norethindrone renewal: Up to 6 months for relugolix component 40 mg dosed once daily with a total cumulative treatment period not to exceed 24 months

Requires PA:

- Elagolix
- Elagolix/estradiol/norethindrone
- Relugolix/estradiol/norethindrone

Covered Alternatives:

- Current PMPDP preferred drug list per OAR 410-121-0030 at www.orpdl.org
- Searchable site for Oregon FFS Drug Class listed at www.orpdl.org/drugs/

Approval Criteria		
1. What diagnosis is being treated?	Record ICD10 code.	
2. Is the diagnosis funded by OHP?	**Yes:** Go to #3	**No:** Pass to RPh. Deny; not funded by the OHP.
3. Is this a request for continuation of therapy previously approved by the FFS program?	**Yes:** Go to **Renewal Criteria**	**No:** Go to #4
4. Is the patient pregnant or actively trying to conceive?	**Yes:** Pass to RPh. Deny; medical appropriateness	**No:** Go to #5
5. Is this request for management of moderate to severe pain associated with endometriosis in a patient ≥18 years of age?	**Yes**: Go to #6	**No:** Go to #11

Approval Criteria		
6. Has the patient tried and failed an adequate trial of preferred first line endometriosis therapy options including administration of combined hormonal contraceptives or progestins (oral, depot injection, or intrauterine) alone? -or- Does the patient have a documented intolerance, FDA-labeled contraindication, or hypersensitivity the first-line therapy options?	**Yes:** Go to #7	**No:** Pass to RPh. Deny; medical appropriateness • First-line therapy options such as combined hormonal contraceptives or progestins do not require PA
7. Is the patient taking any concomitant medications that are strong organic anion transporting polypeptide (OATP) 1B1 inhibitors (e.g. cyclosporine, gemfibrozil, etc.)?	**Yes:** Deny; medical appropriateness	**No:** Go to #8
8. Does the patient have severe hepatic impairment as documented by Child-Pugh class C?	**Yes:** Pass to RPh. Deny; medical appropriateness	**No:** Go to #9
9. Does the patient have moderate hepatic impairment as documented by Child-Pugh class B?	**Yes:** Go to #10	**No:** Approve for 6 months ***** FDA approved dosing for patients with normal liver function or mild liver impairment: 150 mg once daily for up to 24 months or 200 mg twice daily for up to 6 months
10. Is the dose for elagolix 150 mg once daily?	**Yes:** Approve for 6 months ***** FDA approved dosing for moderate hepatic impairment: 150 mg once daily for up to 6 months	**No:** Pass to RPh. Deny; medical appropriateness

Approval Criteria		
11. Is the request for elagolix/estradiol/norethindrone or relugolix/estradiol/norethindrone for management of heavy menstrual bleeding associated with uterine fibroids (leiomyomas)?	**Yes:** Go to #12	**No:** Pass to RPh. Deny; medical appropriateness
12. Has the patient tried and failed a trial of first line therapy options including 1 of the following: a) levonorgestrel-releasing IUD OR b) continuous administration of combined hormonal contraceptives OR c) cyclic progestins OR d) tranexamic acid ? OR Does the patient have a documented intolerance, FDA-labeled contraindication, or hypersensitivity to the first-line therapy options?	**Yes**: Go to #13	**No:** Pass to RPh. Deny; medical appropriateness First-line therapy options such as hormonal contraceptives, progestins, or tranexamic acid do not require PA
13. Does the patient have a diagnosis of osteoporosis or related bone-loss condition? Note: In patients with major risk factors for decreased bone mineral density (BMD) such as chronic alcohol (> 3 units per day) or tobacco use, strong family history of osteoporosis, or chronic use of drugs that can decrease BMD, such as anticonvulsants or corticosteroids, use of GnRH antagonists may pose an additional risk, and the risks and benefits should be weighed carefully.	**Yes:** Pass to RPh. Deny; medical appropriateness	**No:** Approve for 6 months

Renewal Criteria		
1. Has the patient been receiving elagolix/estradiol/norethindrone or relugolix/estradiol/norethindrone for management of uterine fibroids?	**Yes:** Go to #4	**No:** Go to #2
2. Has the patient been receiving therapy with elagolix 150 mg once daily for management of endometriosis?	**Yes:** Go to #3	**No:** Pass to RPh; Deny; medical appropriateness. (Elagolix 200 mg twice daily is limited to 6-month maximum treatment duration per FDA labeling)
3. Does the patient have moderate hepatic impairment as documented by Child-Pugh Class B?	**Yes:** Pass to RPh; Deny; medical appropriateness. (Elagolix 150 mg once daily is limited to 6-month maximum treatment duration in patients with moderate hepatic impairment per FDA labeling)	**No:** Go to #4
4. Has the patient's condition* improved as assessed and documented by the prescriber? *For endometriosis: has pain associated with endometriosis improved? For uterine fibroids: has patient experienced at least a 50% reduction in menstrual blood loss from baseline?	**Yes:** Approve for up to 18 months Document physician attestation received. Total cumulative treatment period not to exceed 24 months.	**No:** Pass to RPh; Deny; medical appropriateness.