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Drug Class Update: Drugs for Endometriosis

Date of Review: March 2019

Date of Last Review: May 2015 (GnRH Agonists); Jan 2017 (Hormone Replacement); November 2018 (Elagolix)
Dates of Literature Search: 01/01/1996-12/14/18

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

Purpose for Class Update:
A comprehensive review of drugs used to manage moderate to severe pain associated with endometriosis has never been completed for Pharmacy and Therapeutics (P and T) Committee assessment. This drug class update examines 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.

Research Questions:
1. What is the comparative evidence assessing efficacy of oral contraceptives, progestins, GnRH agonists, danazol, and GnRH antagonists for the treatment of moderate to severe pain associated with endometriosis?
2. What is the comparative evidence assessing long term safety and harms of oral contraceptives, progestins, GnRH agonists, danazol, and GnRH antagonists when used to treatment of moderate to severe pain associated with endometriosis?
3. Are there any subgroups (based on age, 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 pain associated with endometriosis?

Conclusions:
- There is insufficient evidence to support the effectiveness of nonsteroidal anti-inflammatory drugs (NSAIDs) in managing pain caused by endometriosis.[1] A high quality systematic review concluded there is insufficient evidence to support the effectiveness of oral contraceptives compared to placebo or goserelin in managing pain caused by endometriosis.[2]
- A high quality systematic review evaluated available evidence on the safety and efficacy of danazol in managing pelvic pain associated with endometriosis.[3] The authors concluded there is low quality evidence that treatment with danazol significantly reduces total pain scores (based on a 4-point scale) at six months in women with endometriosis pain compared to placebo-treated subjects (weighted mean difference (WMD) -5.7, 95% confidence interval (CI) -7.5 to -3.8).[4] The same trial evaluated adverse effects associated with danazol and found a significant increase in the following symptoms at six months compared to placebo: acne (Odds Ratio [OR] 10.8; 95% CI 2.7 to 42.8), muscle cramps (OR 9.7; 95% CI 1.7 to 55.3) and edema (OR 7.11; 95% CI 1.5 to 31.6).[4] Absolute values were not reported.

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- A high quality systematic review concluded there is limited evidence to support the use of progestins for pain associated with endometriosis.[5] Low quality evidence demonstrates that when compared to placebo, medroxyprogesterone is more effective in reducing pelvic pain at 6 months (Mean Difference [MD] -1.3, 95% CI -1.63 to -0.97, p<0.00001) and reducing of all symptoms associated with endometriosis at 6 months (MD -5.20, 95% CI -6.8 to -3.6, p<0.00001).[5] There is no evidence to suggest a benefit in symptoms for depot or oral progestins compared with oral contraceptives or leuprolide.[5] In clinical studies, patients receiving progestins experienced significantly more cases of adverse effects compared with other medical treatments.[5]
- There is limited evidence from 3 small trials (n=135) that use of postoperative levonorgestrel-releasing intrauterine device (LNG-IUD) reduces the recurrence of painful periods in women with endometriosis.[6] Moderate quality evidence from 2 small trials demonstrates postoperative LNG-IUD was more effective than no treatment in reducing symptoms associated with endometriosis.[6] In addition, one trial provides moderate quality evidence postoperative LNG-IUD and goserelin have similar effects in reducing the intensity of pain associated with endometriosis.[6]
- One high quality systematic review reported low quality evidence of an overall benefit in symptom relief for women with endometriosis for GnRH agonists compared with placebo or no treatment.[7] There was no evidence of a difference in pain relief between GnRH agonists and danazol or leveonorgestrel.[7] However, significantly more women experienced vaginal dryness and hot flushes when treated with GnRH agonists whereas significantly more women experienced weight gain and acne when treated with danazol.[7]
- There is a lack of long-term data on safety and efficacy for elagolix compared to other treatments. Evidence on elagolix compared to GnRH agonists, hormonal contraceptives, and aromatase inhibitors was insufficient to judge the net health benefit.

Recommendations:

- Combine PA criteria for GnRH analogs and antagonists into one document entitled GnRH modifiers (**Appendix 3**). Retire previous criteria for these products (**Appendix 4**).
    - Revise step therapy for elagolix to remove requirement for trial of acetaminophen or a nonsteroidal anti-inflammatory agent prior to trial of elagolix
    - Add endometriosis diagnosis with step therapy for leuprolide, goserelin, and nafarelin
    - Reinforce warnings about bone mineral density (BMD) loss with use of GnRH modifiers
    - Limit PA approval to the FDA recommended duration of therapy for GnRH analogues
- After evaluation of comparative costs of GNRH analogs and antagonists in executive session, no PDL changes were recommended.

Summary of Prior Reviews and Current Policy

Previous P and T Committee recommendations for drugs used to manage endometriosis were included in 2 separate reviews:

- January 2017 - Class Update: Hormone Replacement Therapy (Non-Contraceptive Uses)
    - Recommendation: Combine progestin agents into one PDL class and designate at least one preferred product for FDA-approved indications funded by the OHP (i.e., endometriosis, endometrial cancer, endometrial hyperplasia, abnormal bleeding disorders, and prevention of preterm birth). Based on utilization and comparative drug costs in the executive session add medroxyprogesterone acetate tablets, micronized progesterone capsules, norethindrone acetate tablets, and Depo-Provera injection to the PDL and make all other progestins non-preferred.
- November 2018 - New Drug Evaluation: Elagolix (Orilissa™): Moderate quality evidence from two phase 3 studies showed that a higher proportion of adult women with endometriosis-related pain experienced a statistically significant difference in dysmenorrhea, non-menstrual pelvic pain, and dyspareunia symptoms. However, the clinical significance of these differences is unclear. There is insufficient evidence to compare the safety and efficacy of elagolix to any other analgesics, oral contraceptives, GnRH analogs, danazol, or progestins for treatment of endometriosis-related pain in specific subpopulations.
    - Recommendation: Create a new preferred drug list (PDL) class for gonadotropin-releasing hormone (GnRH) receptor agonists.

- Recommendation: Implement prior authorization criteria for elagolix for use in patients with moderate to severe pain associated with endometriosis.
- Prior authorization is currently required for utilization of GnRH agonists in pediatric patients under 18 years of age for medically appropriate conditions funded under the Oregon Health Plan (e.g., central precocious puberty or gender dysphoria).

There are more than 1500 women currently in Oregon Medicaid Fee-for-Service (FFS) with claims indicative of an endometriosis-related diagnosis between July 2016 and June 2017. The preferred progestin agents medroxyprogesterone acetate, micronized progesterone, and norethindrone are the most requested progestins in the Oregon Medicaid FFS population. Utilization of GnRH agonists is low, with only 2 pharmacy claims for leuprolide during the third and fourth quarters of 2018.

Background:

Endometriosis is a gynecological disorder identified by the presence of ectopic endometrial tissue outside the uterine cavity.[8] There are generally three distinct clinical presentations: endometrial implantation superficially on the peritoneum; endometrial lined ovarian cysts (chocolate cysts) or endometriomas; and endometriotic nodules (a complex, solid mass of endometrial, adipose, and fibromuscular tissue found between the rectum and vagina).[9] Three types of endometriotic lesions have been identified: white, red, and black lesions. The red lesions represent activity with a high level of vascularization, the whitish lesions are later phases of red lesions that have undergone a process of inflammation and fibrosis, and the black lesions are attributable to cyclic tissue decomposition and healing with the subsequent formation of scar tissue.[8] The most common sites of pelvic endometriosis are the ovaries, uterine ligaments, pouch of Douglas, and fallopian tubes.[8] Clinical manifestations of endometriosis include dyspareunia, cyclic menstrual pain, chronic pelvic pain, and dyschezia.[8] In 2017, the prevalence of endometriosis in the United States was estimated to be roughly 5 million women.[10] It is estimated that 1 in 10 women between the ages of 15-49 may experience endometriosis with the highest incidence among those between 25 and 29 years of age.[10] Quality of life and work productivity are negatively impacted by endometriosis pain.[11] Epidemiologic studies have concluded that women with early menarche (<10 years old), with more frequent menstrual cycles (<28 days), and longer menstrual flows (>5-6 days) are at higher risk for endometriosis.[10]

As the most common cause of unexplained pelvic pain, endometriosis may be suspected through ultrasound and confirmed by histologic confirmation of lesions through laparoscopy.[12] During menstruation, the endometriotic tissue responds to hormonal stimulation similarly to the endometrium itself with associated bleeding and inflammation.[13] Over time, the inflammation leads to fibrosis and adhesions which may result in pelvic anatomical changes that range from symptoms of slight discomfort to severe disabling pelvic pain and dyspareunia.[13] The type, duration, and magnitude of pain may vary greatly among individuals and often manifests independently of the menstrual cycle.[14] Up to 50% of women with endometriosis become infertile.[10] It is not uncommon for endometriosis patients to experience depression and other mental health issues because of this condition.[14]

The goal of endometriosis management is to prevent disease progression and improve patient's quality of life.[8] 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.[8] Medical therapy for endometriosis is based on the observation that ectopic tissue is hormonally responsive.[15] 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.[16] 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 continuous combined oral contraceptives (COCs) or progestin.[17] Oral contraceptives have been shown to suppress gonadotropin secretion and estrogen biosynthesis.[16,18] Most of the data supporting the use of COCs in managing endometriosis pain is observational.[17]

Second-line therapeutic options for pain associated with endometriosis are GnRH agonists administered with hormone therapy or in combination with a levonorgestrel-releasing intrauterine device (LNG-IUD).[17] Gonadotropin-releasing hormones (i.e. goserelin, leuprolide, and nafarelin) initially stimulate the release of luteinizing hormone (LH) and follicle stimulating hormone (FSH), resulting in a temporary increase of ovarian steroidogenesis.[15] However, continuous administration of GnRH agonists in women results in suppression of gonadotropin secretion and decreased steroidogenesis of estrogen.[16,18] Goserelin, leuprolide, and nafarelin are FDA-approved for six months of continuous use for treatment of pelvic pain caused by endometriosis.[16] The six-month treatment limitation is due to concern about the significant bone loss that occurs with GnRH agonist therapy. Add-back therapy or the simultaneous use of estrogen and progestin, progestin alone, or progestin plus a bisphosphonate may alleviate some of the GnRH agonist side effects including bone loss.[17] The FDA recommends the use of add-back therapy (estrogen, progestin, bisphosphonates) when a GnRH agonist is used for greater than 6 months.[17]

Elagolix is a GnRH antagonist recently approved to manage pain symptoms associated with endometriosis. Elagolix rapidly suppresses the pituitary-ovarian hormones and produces a dose-dependent suppression of ovarian estrogen production.[19] Randomized controlled studies (RCTs) have compared elagolix to placebo, but there are no comparative trials that evaluate elagolix to other FDA-approved therapies for endometriosis. Another group of estrogen biosynthesis blockers under investigation are the aromatase inhibitors, which are currently used off-label for endometriosis treatment.[16] 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.[16,18] 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.[8] **Table 1** outlines the pharmacotherapies that are approved by the FDA for management of moderate to severe pain associated with endometriosis.

Table 1. FDA-Approved Medications for Management of Pain Associated with Endometriosis[20]

Drug Name (Brand Name)	Formulation	FDA-Approved Endometriosis Dose and Frequency	Safety Precautions (* Indicates a Boxed Warning)
Anabolic Steroid			
Danazol (Danocrine)	Oral Capsule: 50mg, 100 mg, 200 mg	Initial, mild disease: 200 to 400 mg PO given in 2 divided doses; adjust depending on clinical response Moderate to severe disease: 800 mg PO in 2 divided doses; titrate downward depending on clinical response Duration: 3-6 months, may be extended to 9 months if necessary	-Thrombotic events including strokes* -Peliosis hepatis and benign hepatic adenoma* -Intracranial hypertension* -Use in pregnancy is contraindicated* -Lipoprotein changes -Androgen effects
Gonadotropin Releasing Hormone Agonists			
Goserelin acetate (Zoladex)	Subcutaneous Implant: 3.6 mg	3.6 mg SC every 28 days Duration: 6 months maximum	-Hyperglycemia -Loss of BMD -Hypoestrogenism -Serum lipid changes -Use in pregnancy is contraindicated
Leuprolide acetate (Lupron)	Intramuscular depot Injection: 1-month: 3.75 mg 3-month: 11.25 mg	3.75 mg IM monthly for 6 months OR 11.25 mg IM every 3 months for 1 or 2 doses Duration: 6 months maximum	-Loss of BMD -Worsening depression and memory disorders -Convulsions -Use in pregnancy is contraindicated

Drug Name (Brand Name)	Formulation	FDA-Approved Endometriosis Dose and Frequency	Safety Precautions (* Indicates a Boxed Warning)
Nafarelin acetate (Synarel)	Nasal Spray: 200 mcg/actuation	400 mcg/day intranasally by 1 spray (200 mcg) into 1 nostril in the morning and 1 spray (200 mcg) into the other nostril in the evening starting between days and 4 of the menstrual cycle (maximum daily dose = 800 mcg) Duration: 6 months	-Loss of BMD -Worsening depression -Hypoestrogenism -Serum lipid changes -Use in pregnancy is contraindicated
Progestins			
Medroxyprogesterone acetate (Depo-SubQ Provera)	Subcutaneous Depot Injection: 104 mg	104 mg SC every 3 months during the first 5 days of menstrual period Duration: Do not use for longer than 2 years (boxed warning)	-Loss of BMD* -Ocular disorders -Ectopic pregnancy -Bleeding irregularities -Use in pregnancy is contraindicated
Norethindrone Acetate (Aygestin)	Oral Tablets: 5mg	5 mg PO once daily for 2 weeks; increase dose by 2.5 mg per day every 2 weeks until 15 mg once daily is achieved Duration: 6 to 9 months or until breakthrough bleeding demands temporary termination	-Ocular disorders -Worsening depression -Increased risk for thrombosis -Bleeding irregularities -Ectopic pregnancy -Adverse effects on lipid metabolism -Use in pregnancy is contraindicated
Gonadotropin-Releasing Hormone Antagonist			
Elagolix (Orilissa)	Oral Tablet: 150 mg, 200 mg	Initial: 150 mg PO once daily OR Concomitant dyspareunia: 200 mg PO twice daily Duration: 150 mg dose: 24 months 200 mg dose: 6 months	-Loss of BMD -Suicidal ideation -Hepatic transaminase elevations -Use in pregnancy is contraindicated

Abbreviations: BMD = bone mineral density; FDA = Food and Drug Administration; IM = intramuscular; mcg = microgram; mg = milligram; PO = oral; SC = subcutaneous

There are several non-specific assessment scales that have been used to measure patient response to medical treatment intervention. For pain assessment, the visual agonist or verbal rating scale is a numeric rating scale which ranges from a score of 0 (no pain symptoms) to 10 (worst pain imaginable).[21] The ease of administration and scoring allows this tool to be used in a variety of settings, however, it may not be appropriate for low literacy patients.[21] Pain and/or symptom scales that have been developed specifically for endometriosis often have substantial limitations, inconsistencies, or lack validation.[22] A specific tool known as the Biberoglu and Behrman (B & B) Scale is patient-reported symptom assessment tool for dysmenorrhea, chronic pelvic pain, dyspareunia, as well as

pelvic tenderness and induration.[22] The B & B scale is graded on a scale from 0 to 3 (or 4 for dyspareunia) with higher scores representative of more symptoms.[22] However, several organizations including the National Institutes of Health have indicated that the B&B has never been validated nor administered consistently.[22]

In some trials, objective evaluation of improvement of endometriotic implants was assessed by the American Fertility Society (AFS) classification of endometriosis.[23] The AFS was renamed the American Society for Reproductive Medicine (ASRM) in 1995. The ASRM classification stratifies endometriosis into stages based on minimal (Stage I), mild (Stage II), moderate (Stage III), and severe (Stage IV) symptoms. The weighted point score ranges from 1-5 (Stage I); 6-15 (Stage II); 16-40 (Stage III); to greater than 40 points (Stage IV).[23] Assessment of the extent of endometriosis (in centimeters) and presence of adhesions in the peritoneum, ovaries, and tubes is included in the scoring.[23] One study evaluated 244 patients for the correlation between pain symptoms measured by using visual analog scale (VAS) and ARSM stage.[23] No correlation was found between stages I-II and III-IV and acyclic pelvic pain (VAS 5 vs. VAS 4; $p > 0.05$), deep dyspareunia (VAS 5 vs. VAS 1; $p > 0.05$), and dysmenorrhea (VAS 8 vs. VAS 8; $p > 0.05$).[23] Laparoscopic staging of endometriosis does not necessarily correlate with the severity of symptoms.[23] Validation of the AFS classifications as predictors of infertility has been limited to 3 trials.[23]

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:
After review, 3 systematic reviews were excluded due to poor quality (e.g., 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).[24-26]

<u>Nonsteroidal anti-inflammatory drugs</u>
Nonsteroidal anti-inflammatory drugs are effective for treating primary dysmenorrhea, so they are often used as first line treatment for suspected endometriosis.[27] However, a 2017 Cochrane review found insufficient evidence that NSAIDs improve pain associated with endometriosis.[1] One low quality, small RCT (n=24) of short duration (2 menstrual cycles) compared naproxen versus placebo in women with pain due to endometriosis and found no difference in pain relief (odds ratio (OR) 3.27, 95% CI 0.61 to 17.69).[28] The overall risk of bias was unclear owing to lack of methodological detail with a high risk of bias due to imprecision (wide confidence interval and small sample size).[1] There is insufficient evidence to support the effectiveness of NSAIDs in managing pain caused by endometriosis.[1]

<u>Danazol</u>
A 2007 Cochrane review evaluated the effectiveness of danazol compared to placebo in the treatment of symptoms and signs of endometriosis in women of reproductive age.[3] All of the early literature recommending danazol for treatment of endometriosis referenced data from non-controlled, non-randomized clinical trials.[3] For the Cochrane review, literature was searched through April 2007. Two trials comparing danazol to placebo met the inclusion criteria. One study recorded improvement in symptoms as an outcome, while the other trial evaluated changes in fertility using the AFS score as the primary outcome.[3] Patients recorded

occurrence and severe of pain on a four-point scale (0 = symptoms absent, 1 = slight symptoms, 2 = moderate symptoms, 3 = severe symptoms). A significant decrease in the levels of pelvic pain, lower back pain, and defecation pain with danazol therapy compared to placebo was observed.[4] Total pain scores were reduced at six months in those patients who received danazol compared to placebo (WMD -5.7; 95% CI -7.5 to -3.8).[4] Improvement in pain scores was still present six months after discontinuing danazol therapy.[3] However, no significant difference was found between the two groups in dysuria and dyspareunia.[3] The same study evaluated adverse effects and found a significant increase in the following symptoms associated with danazol therapy vs. placebo at six months: acne (OR 10.8; 95% CI 2.7 to 42.8), muscle cramps (OR 9.7; 95% CI 1.7 to 55.3) and edema (OR 7.11; 95% CI 1.5 to 31.6).[3] Absolute values were not reported. The method of randomization was not specified, therefore the results may not be valid as the method of randomization may not have been adequate.[3] The other trial examined changes in AFS scores at laparoscopy six months after stopping danazol and found no significant difference in total AFS score (WMD -0.4; 95% CI -1.5 to 0.7).[3] Neither of the trials was truly double blinded as women who received placebo tablets continued menstruating while women who received danazol became amenorrheic, making identification of therapy possible.[3] Furthermore, the measurement of pain was inadequate as none of the trials used visual analogue scales or other recognized methods for measuring pain.[3] For these reasons, the studies were graded as having a high risk of bias with low quality of evidence.[3]

Combination estrogen/progestin oral contraceptives

A 2018 Cochrane update included literature published through October 2017 to determine the effectiveness and safety of oral contraceptives in the treatment of painful symptoms associated with the diagnosis of laparoscopically proven endometriosis.[2] The other formulations of hormonal contraception such as the transdermal patch, vaginal ring or depot injections were not included in this review.[2] The primary outcome was self-reported pain (dysmenorrhea) at the end of treatment. Eights RCTs conducted in Japan, Italy, Egypt and the United States (U.S) met inclusion criteria. Five trials evaluated COCs versus placebo for durations ranging from 3 to 11 months. Three trials used a monophasic COC containing ethinyl estradiol 0.035 mg and norethindrone 1 mg, 1 trial used ethinyl estradiol 0.02 mg combined with desogestrel 0.15 mg, and the fifth trial used ethinyl estradiol 0.02 mg and drospirenone 3 mg. Three trials compared COCs to a GnRH agonist (leuprolide or goserelin). Four trials used the B & B verbal rating score or a modified version of it to assess pain at the end of treatment, as well as other visual or numerical pain ratings methods.[2]

Treatment with COCs was associated with a lower score on the B & B verbal rating scale (scale 0 to 3) compared with placebo (MD -1.30 points, 95% CI -1.84 to -0.76, 1 RCT, 96 women; very low quality evidence), a lower score on the dysmenorrhea visual analog rating score (no details of scale) compared with placebo (MD -23.68 points, 95% CI -28.75 to -18.62, 2 RCTs, 327 women; very low quality evidence) at the end of treatment and a greater reduction in menstrual pain from baseline to the end of treatment (MD 2.10 points, 95% CI 1.38 to 2.82, 1 RCT, 169 women; very low quality evidence).[2] The trials were assessed as having a high risk of bias due to unclear randomization methods, unclear concealment of allocation, unclear blinding, incomplete outcome data, and selective reporting.[2] Most of the trials were designed and executed by the pharmaceutical company funding the trial.[2] Three trials were at high risk of attrition bias and none of the trials had published protocols.[2]

One small trial (n=50) compared efficacy of COCs with subcutaneous goserelin over 6 months.[29] The study was at high risk of bias as the trial was unblinded and there was insufficient detail to judge allocation concealment and randomization.[2] At the end of treatment, the women in the goserelin group were amenorrheic, and therefore, no comparisons could be made between the groups for the primary outcome.[2] At six months' follow-up, there was no clear evidence of a difference between women treated with the COCs and women treated with goserelin for measures of dysmenorrhea on a visual analogue scale (scale 1 to 10) [MD -0.10, 95% CI -1.28 to 1.08; very low quality evidence] or a verbal rating scale (scale 0 to 3) [MD -0.10, 95% CI -0.99 to 0.79; very low quality evidence].[2] At six months follow-up, there was no clear evidence of a difference between the COCs and goserelin groups in complete absence of pain as measured by the visual agonist scale (risk ratio (RR) 0.36, 95% CI 0.02 to 8.43; very low quality evidence) or the verbal rating scale (RR 1.00, 95% CI 0.93 to 1.08; low quality evidence).[2] In this trial, the power calculation became invalid as a result of a higher than expected recurrence rate of pain in the goserelin group (77% recurrence rather than the 35% that

was used in the power calculation), rendering the study underpowered.[2] It is possible the study may have failed to detect a difference in efficacy between COC and goserelin.[2] This study, which was conducted in Italy, is also unlikely to be generalizable to other settings.[2] The 2 trials that compared COCs with leuprolide did not provide sufficient data that could be included in a meta-analysis.[2]

Based on the limited evidence from 5 trials at high risk of bias with limited data for the prespecified outcomes, there is insufficient evidence to make a judgement on the effectiveness of the COCs compared with placebo and the findings cannot be generalized.[2] In addition, based on the limited evidence from one small trial with high risk of bias, there is insufficient evidence to make a judgement on the effectiveness of the COCs compared with goserelin.[2] Despite limited evidence of effectiveness, hormonal contraceptives are widely used as treatment for pain in women with endometriosis, which could be due to some practical advantages, including contraceptive protection, long-term safety, and control of menstrual cycle.[30]

Progestins

A 2012 Cochrane review focused on identifying evidence for the effectiveness of progestins in the treatment of painful symptoms associated with endometriosis.[5] Twenty studies were identified in which progestins were compared with placebo, danazol, oral contraceptives, or a GnRH agonist. Depo medroxyprogesterone acetate (DMPA), dydrogesterone, cyproterone acetate, medroxyprogesterone acetate (MPA), gestagen and dienogest were the different progestins evaluated in clinical trials for treatment of endometriosis.[5] The 2 progestins available on the U.S. market are DMPA and MPA therefore, only the evidence focused on these products will be presented. The primary outcome was relief of any or all symptoms of endometriosis using qualitative measures such as visual agonist scales.[5] Resolution of endometriotic implants assessed by either the revised AFS score was evaluated in some trials as an objective outcome. Although this is neither a direct or indirect measure of pain, it is an independent assessment of disease resolution.[5]

One small (n=51), low-quality trial compared continuous oral MPA 100 mg or placebo.[4] This trial had an unclear risk of bias due to incomplete information about randomization, concealment of allocation, and blinding, a small sample size, and a high attrition rate (31% of patients withdrew from the trial). When compared to placebo, MPA was more effective in reduction of pelvic pain at 6 months (MD -1.3, 95% CI -1.63 to -0.97, p<0.00001) and reduction of all symptoms at 6 months (MD -5.20, 95% CI -6.8 to -3.6, p<0.00001).[5] Reduction in pelvic pain and all symptoms was sustained after 12 months of follow-up (MD -0.85, 95% CI -1.19 to -0.51, p<0.00001 and MD -7.0, 95% CI -8.61 to -5.39, p<0.00001; respectively).[5] No improvement in AFS scores at 12 months of follow-up (MD -0.58, 95% CI -1.41 to 0.25; p=0.17) was observed.[5] There were more cases of acne (6 vs. 1; OR 9.6; 95% CI 1.00 to 91.96) and edema (11 vs. 1; OR 35.20; 95% CI 3.60 to 344.19) reported in the medroxyprogesterone group than the placebo group.[31]

Two trials reported on the use of depot progestins compared with other treatments. One study compared intramuscular DMPA 150 mg every 3 months with a low dose oral contraceptive pill and 50 mg danazol.[32] A significant reduction was observed in all symptom scores for both the visual analogue score and verbal rating scale in both study groups.[5] The only difference was that dysmenorrhoea was improved in the progesterone only arm at 12 months follow-up.[5] Seventy-two percent of patients in the DMPA group were satisfied after 1 year of therapy compared with 57.5% in the oral contraceptive plus danazol group (p=0.24, OR 1.95, 95% CI 0.76 to 4.97).[32] The other trial compared the efficacy of subcutaneous DMPA 104 mg every 3 months versus intramuscular leuprolide acetate 11.25 mg every 3 months over a 6 month study period.[33] Symptoms of dysmenorrhea were significantly reduced in the DMPA group at six months compared with the leuprolide acetate group (OR 0.19, 95% CI 0.05 to 0.69; p=0.01), but this effect was not sustained at the 12 month follow-up (OR 0.63, 95% CI 0.37 to 1.08).[33] Absolute values were not reported. There was no evidence of a difference between groups for dyspareunia at six months.[33] At 12 months, significantly fewer women in the leuprolide group appeared to report dyspareunia (OR 4.83, 95% CI 2.14 to 10.93; p=0.0002).[33] In the Cochrane meta-analysis, patients receiving depot DMPA experienced more bloating (OR 4.39, 95% CI 1.71 to 11.30; p=0.002), intermenstrual bleeding (OR 20.56, 95% CI 6.44 to 65.56; p<0.00001), weight

gain (OR 2.58, 95% CI 1.03 to 6.46; p=0.04), amenorrhea (OR 21.18, 95% CI 1.18 to 380.9; p=0.04), and nausea (OR 3.86, 95% CI 1.12, 13.26; p=0.03) compared with other treatments.[33] Absolute values were not reported.

Three trials compared oral progestins with other treatments. One study compared oral medroxyprogesterone with danazol[34] and another compared dienogest with leuprolide.[35] The Cochrane meta-analysis shows that in comparison to other treatments, there was no significant difference in self-reported pain (MD 0.10, 95% CI -0.26 to 0.46, NS) at six months, but at 12 months of follow-up, medroxyprogesterone was more effective than danazol in subjective reduction of the sum of all symptoms (MD -3.4, 95% CI -4.83 to -1.97, p<0.00001).[5] Another trial compared the efficacy of oral MPA 15 mg twice daily versus intranasal nafarelin 200 mcg twice daily.[36] Although there was a significant reduction in bleeding, dysmenorrhea, dyspareunia and pelvic pain in the total study group, there was no difference demonstrated between groups at 6 months of treatment or at 12 months of follow-up.[5] Twelve patients given MPA and 6 subjects in the nafarelin group did not complete treatment. Data could not be included in the meta-analysis as it was presented as mean ranks and not raw scores.[5]

In summary, in one trial comparing oral MPA with placebo, low quality evidence identified a benefit for reduction of symptoms in favor of medroxyprogesterone.[5] There was no evidence to suggest a benefit in symptoms for depot or oral administration of progestins compared with other medical treatments and the progestin groups experienced significantly more cases of adverse effects compared with other medical treatments.[5]

Levonorgestrel-releasing intrauterine device

A 2013 Cochrane review focused on the evidence for postoperative LNG-IUD insertion in women with endometriosis to improve pain and reduce recurrence of symptoms.[6] Three small, randomised controlled trials met inclusion criteria. The total number of subjects enrolled in all 3 trials was 135 women with a 12 month duration of follow-up.[6] In two trials, there was a statistically significant reduction in the recurrence of painful periods in the LNG-IUD group compared with the control group that received no treatment (OR 0.14, 95% CI 0.04 to 0.47, 95 women, moderate strength of evidence).[6] Absolute values were not reported. The proportion of women who were satisfied with their treatment was also higher in the LNG-IUD group compared to the control group, but did not reach statistical significance (OR 3.00, 95% CI 0.79 to 11.44, 95 women, 2 trials).[6] The number of women reporting a change in menstruation was significantly higher in the LNG-IUD group versus control group (RR 37.80, 95% CI 5.40 to 264.6).[6] One trial (n=40), showed comparable effectiveness in reducing pain associated with endometriosis between women receiving postoperative LNG-IUD versus women receiving goserelin via injection every 4 weeks for 24 weeks (MD -0.16, 95% CI -2.02 to 1.70).[6] Patients in the LNG-IUD group experienced more irregular bleeding and abdominal pain while patients administered the GnRH agonist experienced more vasomotor symptoms and amenorrhea.[37]

In summary, there is limited evidence of benefit for LNG-IUD in reducing pain associated with endometriosis after surgery for endometriosis.[6] Moderate quality evidence from 2 small trials demonstrates postoperative LNG-IUD was more effective than no treatment in reducing symptoms associated with endometriosis.[6] In addition, one trial provides moderate quality evidence postoperative LNG-IUD and goserelin have similar effects in reducing the intensity of pain associated with endometriosis.[6]

Gonadotrophin Releasing Hormone Agonists

A 2010 Cochrane review and meta-analysis evaluated the safety and efficacy of GnRH agonists in the treatment of painful symptoms associated with endometriosis.[7] Forty-one randomized controlled trials (RCTs) met inclusion criteria encompassing a total of 4,935 pre-menopausal women.[7] The primary outcome was pain relief defined by using both quantitative measures such as the visual analogue scale or categorical outcomes at the end of treatment.[7] Six trials compared GnRH agonists with no treatment or placebo. The evidence suggests that GnRH agonists were more effective at pain relief of dysmenorrhea associated with endometriosis than no treatment/placebo (RR 3.93, 95% CI 1.37 to 11.28).[7] Absolute values were not reported.Twenty-seven trials compared a GnRH with danazol, and no statistically significant difference was observed between GnRH agonists and danazol for relief of dysmenorrhea (RR 0.98, 95%CI 0.92

to 1.04, p=0.53).[7] There was a benefit in overall pain resolution for GnRH agonists (RR 1.10, 95% CI 1.01 to 1.21, p=0.03) compared with danazol.[7] Five of the most commonly reported side effects were vaginal dryness, hot flushes, headaches, weight gain, and acne.[7] Vaginal dryness was compared in 16 studies, and occurrence was more frequent with GnRH agonists versus danazol (RR 1.96, 95% CI 1.68 to 2.30, p<0.00001).[7] Nineteen studies looked at hot flushes and found significantly more patients experienced hot flushes with GnRH agonists versus danazol (RR 1.55, 95% CI 1.47 to 1.65, p<0.00001).[7] Headaches were compared in 16 studies, and a statistically significant benefit was found in favor of danazol compared to GnRH agonists (RR 1.40, 95% CI 1.22 to 1.61, P<0.00001).[7] Weight gain was reported in 12 studies that found evidence to suggest a statistically significant increase in danazol-treated patients compared to GnRH agonists (RR 0.20, 95% CI 0.16 to 0.26, p<0.00001).[7] Acne was reported by 13 studies and evidence suggested a statistically significant increase in danazol-treated patients compared to GnRH agonists (RR 0.55, 95% CI 0.47 to 0.65).[7] Three trials compared GnRH agonists with levonorgestrel. There was no statistically significant difference in overall pain between GnRH agonists and levonorgestrel (Standardized Mean Difference [SMD] -0.25; 95%CI -0.60 to 0.10; p=0.46).[7] Evidence was limited on optimal dosage or duration of treatment for GnRH agonists.[7] No route of administration appeared superior to another.[7]

In summary, low quality evidence shows an overall benefit for GnRH agonists in relieving pain associated with endometriosis compared with placebo or no treatment.[7] There was no evidence of a difference in pain relief between GnRH agonists and danazol.[7] However, the side-effect profile of these two drugs were different, with significantly more women experiencing vaginal dryness and hot flushes when treated with GNRH agonists whereas significantly more women experienced weight gain and acne when treated with danazol.[7] There was no evidence of a difference in pain relief between GnRH agonists and levonorgestrel.[7] There is limited evidence to draw conclusions regarding the benefit of varying doses or length of treatment.[7] The route of administration does not appear to be an important factor in attaining benefit.[7]

Guidelines:

High Quality Guidelines:

National Institute for Health and Care Excellence

In 2017, the National Institute for Health and Care Excellence (NICE) updated guidance documents for management of endometriosis with various treatments including diagnostic recommendations, pharmacotherapy options for pain, and surgery.[38] It is recommended that endometriosis be diagnosed through abdominal and pelvic examination, magnetic resonance imaging (MRI) or ultrasound, and diagnostic laparoscopy with biopsy when needed.[38] NICE recommends that pain from endometriosis be treated with a short trial (i.e. 3 months) of NSAIDs and/or acetaminophen as first-line management.[38] The committee recognized there is insufficient evidence to support using NSAIDs in pain associated with endometriosis. However, according to the World Health Organization pain guidelines, NSAIDs are recommended first line to manage acute or chronic non-malignant pain.[38] For these reasons, the NICE committee concluded a short trial of analgesics for first-line management of endometriosis-related pain is appropriate.[38] For women with suspected, confirmed, or recurrent endometriosis, hormonal treatment with an oral contraceptive or progestin can be initiated.[38] This recommendation was supported by a network meta-analysis completed by the NICE authors.[38] Surgical management is recommended for women with suspected or confirmed endometriosis with bowel, bladder, or ureter involvement.[38] GnRH agonists may be considered as adjunct treatment 3 months prior to surgery for deep endometriosis.[38] NICE recommends a hysterectomy with or without oophorectomy for women with endometriotic complications unresponsive to other treatments.[38]

European Society of Human Reproduction and Embryology

The European Society of Human Reproduction and Embryology (ESHRE) updated recommendations for the management of women with endometriosis in 2013.[30] The guideline was developed and funded by ESHRE, covering expenses associated with the guideline meetings, with the literature searches and with the implementation of the guideline. The guideline group members did not receive payment. All guideline group members disclosed any relevant conflicts of interest.[30] Literature was searched through January 2012. The Grades of Recommendation, Assessment, Development, and Evaluation (GRADE) method was

used to assess published evidence.[39] Grade A recommendations were based on high quality meta-analyses or multiple RCTs.[30] Grade B recommendations were based on moderate quality evidence from meta-analyses or multiple RCTs.[30] Most of the cited evidence is from the Cochrane reviews on different medical treatments for pain associated with endometriosis.[30] The grade A and B recommendations regarding pharmacotherapy are as follows:

- Clinicians can consider prescribing a combined hormonal contraceptive, as it reduces endometriosis-associated dyspareunia, dysmenorrhea and non-menstrual pain (Grade of Recommendation B).[30]
- Clinicians are recommended to use medroxyprogesterone acetate (oral or depot), norethindrone or danazol as one of the options, to reduce endometriosis-associated pain (Grade of Recommendation A).[30]
- Clinicians can consider prescribing a levonorgestrel-releasing intrauterine system (LNG-IUS) as one of the options to reduce endometriosis-associated pain (Grade of Recommendation B).[30]
- Clinicians are recommended to use GnRH agonists (nafarelin, leuprolide, or goserelin), as one of the options for reducing endometriosis-associated pain, although evidence is limited regarding dosage or duration of treatment (Grade of Recommendation A).[30]
- Clinicians are recommended to prescribe hormonal add-back therapy to coincide with the start of GnRH agonist therapy, to prevent bone loss and hypoestrogenic symptoms during treatment. This is not known to reduce the effect of treatment on pain relief (Grade of Recommendation A).[30]

Additional Guidelines for Clinical Context:

After review, 2 guidelines were excluded due to poor quality. The American Society for Reproductive Medicine (ASRM) published recommendations for the treatment of pelvic pain associated with endometriosis in 2014.[40] However, the guideline recommendations did not meet the quality standards outlined in the Appraisal of Guidelines for Research and Evaluation (AGREE) guidance.[41] The publication did not state how the systematic review of the evidence was developed by the ASRM Practice Committee. American College of Obstetricians and Gynecologists (ACOG) published a practice bulletin on the management of endometriosis in 2010.[42] However, the recommendations were not based on a systematic review or grading of the evidence. Stakeholder involvement, method of consensus, and search terms were not reported. Finally, detailed search strategy and inclusion/exclusion criteria not were reported.

Randomized Controlled Trials:

A total of 178 citations were manually reviewed from the initial literature search. After further review, all other citations were excluded because of wrong study design (eg, observational), comparator (eg, no control or placebo-controlled), or outcome studied (eg, non-clinical).

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Appendix 1: Current Preferred Drug List

GNRH agonists and antagonists

Generic	Brand	Formulation	Route	PDL
goserelin acetate	ZOLADEX	IMPLANT	SQ	
leuprolide acetate	ELIGARD	SYRINGE	SQ	
leuprolide acetate	LEUPROLIDE ACETATE	KIT	SQ	
leuprolide acetate	LEUPROLIDE ACETATE	VIAL	SQ	
leuprolide/norethindrone acet	LUPANETA PACK	KT SYR TAB	MC	
leuprolide acetate	LUPRON DEPOT	SYRINGEKIT	IM	
leuprolide acetate	LUPRON DEPOT (LUPANETA)	SYRINGEKIT	IM	
leuprolide acetate	LUPRON DEPOT-PED	KIT	IM	
leuprolide acetate	LUPRON DEPOT-PED	SYRINGEKIT	IM	
nafarelin acetate	SYNAREL	SPRAY	NS	
elagolix sodium	ORILISSA	TABLET	PO	

Progestational Agents

Generic	Brand	Formulation	Route	PDL
medroxyprogesterone acetate	DEPO-PROVERA	VIAL	IM	Y
medroxyprogesterone acetate	MEDROXYPROGESTERONE ACETATE	TABLET	PO	Y
medroxyprogesterone acetate	PROVERA	TABLET	PO	Y
norethindrone acetate	AYGESTIN	TABLET	PO	Y
norethindrone acetate	NORETHINDRONE AC (LUPANETA)	TABLET	PO	Y
norethindrone acetate	NORETHINDRONE ACETATE	TABLET	PO	Y

Other Hormone Therapies

Generic	Brand	Formulation	Route	PDL
danazol	DANAZOL	CAPSULE	PO	

Appendix 2: Medline Search Strategy

Ovid MEDLINE(R) without Revisions 1996 to December Week 1 2018; Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations December 12, 2018

1. Exp ENDOMETRIOSIS/	11944
2. Exp GOSERELIN/	982
3. Exp LEUPROLIDE/	1912
4. NAFARELIN/	124
5. Elagolix.mp.	32
6. Exp MEDROXYPROGESTERONE ACETATE/	2819
7. NORETHINDRONE/	1025
8. DANAZOL/	791
9. 2 or 3 or 4 or 5 or 6 or 7 or 8	7160
10. 1 and 9	570
11. limit 10 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))	178

Gonadotropin-Releasing Hormone Modifiers

Goal(s):

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

Length of Authorization:

- 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.

Requires PA:

- GnRH agonists (i.e., goserelin, histrelin, leuprolide, nafarelin, triptorelin) prescribed for pediatric patients less than 18 years of age.
- Non-preferred GnRH agonist (i.e., goserelin, leuprolide, nafarelin) or antagonist (i.e. elagolix).

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 elagolix therapy previously approved by the FFS program?	**Yes:** Go to **Renewal Criteria**	**No:** Go to #4
4. Is the prescriber a pediatric endocrinologist?	**Yes:** Go to #5	**No:** Go to #9

Approval Criteria		
5. 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	
6. Is the diagnosis central precocious puberty (ICD10 E301, E308) or other endocrine disorder (E34.9)?	**Yes:** Approve for up to 6 months	**No:** Go to #7
7. Is the diagnosis gender dysphoria (ICD10 F642, F641)?	**Yes:** Go to #8	**No:** Go to #9
8. 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
9. Is this request for treatment of breast cancer or prostate cancer?	**Yes:** Approve up to 1 year	**No:** Go to #10
10. Is this request for leuprolide for the management of preoperative anemia due to uterine leiomyoma?	**Yes:** Approve for up to 3 months	**No:** Go to #11

Approval Criteria		
11. Is this request for management of moderate to severe pain associated with endometriosis in a woman ≥18 years of age?	**Yes**: Go to #12	**No:** Pass to RPh. Deny; medical appropriateness
12. Is the request for goserelin, leuprolide, nafarelin or elagolix?	**Yes:** Go to # 13	**No:** Pass to RPh. Deny; medical appropriateness
13. Is the patient pregnant or actively trying to conceive?	**Yes:** Pass to RPh. Deny; medical appropriateness	**No:** Go to #14
14. Has the patient tried and failed an adequate trial of preferred first line therapy options including continuous administration of combined hormonal contraceptives or progestins alone? -or- Does the patient have a documented intolerance, FDA-labeled contraindication, or hypersensitivity the first-line therapy options?	**Yes:** Go to #15	**No:** Pass to RPh. Deny; medical appropriateness • First-line therapy options such as hormonal contraceptives or progestins do not require PA
15. Does the patient have a diagnosis of osteoporosis or related bone-loss condition? *Note: In women 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 modifiers may pose an additional risk, and the risks and benefits should be weighed carefully	**Yes:** Pass to RPh. Deny; medical appropriateness	**No:** Go to #16
16. Is the request for elagolix?	**Yes:** Go to #17	**No:** Approve for up to 6 months

Approval Criteria		
17. 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 #18
18. Does the patient have severe hepatic impairment as documented by Child-Pugh class C?	**Yes:** Pass to RPh. Deny; medical appropriateness	**No:** Go to #19
19. Does the patient have moderate hepatic impairment as documented by Child-Pugh class B?	**Yes:** Go to #20	**No:** 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.
20. Is the dose for elagolix 150 mg once daily?	**Yes:** Approve for 6 months	**No:** Pass to RPh. Deny; medical appropriateness
21. 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.		

Renewal Criteria		
1. Has the patient been receiving therapy with elagolix 150 mg once daily?	**Yes:** Go to #2	**No:** Pass to RPh; Deny; medical appropriateness. (Elagolix 200 mg twice daily is limited to 6-month maximum treatment duration per FDA labeling)
2. 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 #3
3. Has the patient's condition improved as assessed and documented by the prescriber?	**Yes:** Approve for up to 6 months. Total cumulative treatment period not to exceed 24 months. Document baseline assessment and physician attestation received.	**No:** Pass to RPh; Deny; medical appropriateness.

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