

Class Update with New Drug Evaluation: Hormone Replacement Therapy (non-contraceptive uses)

Date of Review: January 2017

Generic Name: Ospemifene

End Date of Literature Search: September 2016

Brand Name (Manufacturer): Osphena (Shionogi, Inc)

Dossier Received: Yes

Current Status of PDL Class:

See **Appendix 1**.

Purpose for Class Update:

Evidence for the comparative effectiveness of estrogen preparations was last reviewed by the Oregon Pharmacy & Therapeutic Committee (P&T) in November 2014. A comprehensive review of progestin products has never been completed. This review examines new comparative evidence of estrogen replacement therapy published since 2014 and provides a comprehensive evaluation of evidence published since 2010 for the comparative efficacy of progestin preparations. Ospemifene, a new selective estrogen receptor modulator (SERM), for the treatment of vaginal symptoms associated with menopause is also reviewed.

Research Questions:

1. Is there any new comparative evidence assessing efficacy of hormone replacement therapy (HRT; including estrogens, progestins, estrogen/progestin combinations, estrogen-basedoxifene combinations, and estrogen-androgen combinations) in the treatment of symptoms associated with menopause?
2. Is there any new comparative evidence on the long-term benefits and harms of HRT?
3. Are there subpopulations of adults (specifically > 60 years of age, > 10 years since menopause, with or without a uterus) for which HRT for menopause is more effective or associated with more long-term adverse effects?
4. What is the evidence for efficacy and safety of ospemifene for the treatment of vaginal dryness and dyspareunia associated with menopause?
5. What is the comparative evidence assessing efficacy of progestin agents and formulations for treatment of endometrial conditions (including endometriosis, endometrial cancer, and endometrial hyperplasia), abnormal uterine bleeding, and prevention of preterm labor?

Conclusions:

Efficacy of HRT and ospemifene for menopause symptoms

- Estrogens are the most effective agents at relieving common symptoms associated with menopause.¹ They can be utilized as monotherapy or in combination with other hormone products.
 - No meaningful differences were observed between estrogen dose (moderate strength of evidence) or route of administration (high strength of evidence) for the treatment of vasomotor symptoms.¹
 - There is moderate strength evidence demonstrating no difference in pain during intercourse or quality of life between estrogen formulations.¹

- There is moderate strength evidence demonstrating no difference in sleep between low or standard dose estrogens.¹
- There is insufficient evidence comparing efficacy of different estrogen doses or formulations in treatment of psychological or urogenital symptoms.¹
- There is insufficient evidence to evaluate differences in efficacy of ospemifene versus other hormone therapies for improvement of menopause symptoms. There is low strength evidence that ospemifene improves urogenital symptoms of dyspareunia with (mean difference [MD] of 0.51 to 0.36 points compared to placebo).^{2,3} Symptoms were measured on a 4-point severity scale (0 = none, 1 = mild, 2 = moderate, 3 = severe). The minimum clinically important difference with this scale has not been established.
- There is insufficient evidence evaluating the efficacy of progestin only products for the treatment of menopause symptoms, and there is no new comparative evidence evaluating safety or efficacy of combination estrogen/bazedoxifene for the treatment of menopause symptoms.
- There is insufficient evidence to evaluate differences in efficacy of estrogen products in specific populations based on age, symptom severity, time since menopause and uterine status.

Long-term safety of HRT

- Both estrogen only and estrogen/progestin combinations increase risk of gallbladder disease, venous thromboembolism (VTE), and stroke (high strength of evidence) and decrease risk for osteoporotic fractures (moderate strength of evidence).¹
- Breast cancer risk is increased with estrogen/progestin combinations (high strength of evidence), but may decrease with estrogen alone (low strength of evidence with inconsistent results).¹
- There is low strength of evidence that estrogen/progestin combinations decrease risk of colorectal cancer but moderate strength of evidence that estrogen alone has no effect.¹
- Risk for coronary heart disease is increased with estrogen/progestin combinations but is not affected by estrogen alone (moderate strength of evidence).¹
- There is moderate strength evidence that HRT is not associated with increased risk of diabetes.^{4,5}
- There is low strength evidence from direct and indirect comparisons of observational studies that oral HRT (with or without progestins) is associated with greater risk of VTE compared to transdermal formulations.^{1,4}
- There is insufficient evidence to evaluate differences in other long-term adverse effects between individual products, formulations, or doses of estrogen only or estrogen/progestin combinations. There is also insufficient evidence to evaluate the long-term safety of ospemifene.
- Low quality evidence from systematic reviews with inconsistent results which demonstrates that risk of myocardial infarction (MI), cardiovascular disease, or cardiovascular mortality may not increase in women less than 65 years of age treated with estrogen or combined estrogen/progestin formulations.⁴
- There is low quality evidence, from systematic reviews limited by population size and quality of trials, that use of HRT does not increase the risk of endometrial cancer in patients with a prior history of surgery for endometrial or ovarian cancer.^{6,7}

Efficacy and safety of progestins for other indications

- There is low quality evidence that use of progestins does not improve symptoms of pain or fertility outcomes associated with endometriosis.⁸ However, despite limited evidence, guidelines recommend the use of progestins for the treatment of pain associated with endometriosis.^{9,10} There is insufficient evidence to determine differences between formulations.
- There is low quality evidence from multiple systematic reviews with inconsistent results that use of a levonorgestrel intrauterine device (IUD) in women with heavy uterine bleeding may be associated with greater reduction in bleeding compared to oral therapy.¹¹⁻¹³ There is insufficient evidence to assess efficacy of other progestin products or formulations.

- There is moderate quality evidence from systematic reviews of observational studies that use of progestins results in initial cancer regression in approximately 70% of women with endometrial carcinoma or atypical complex endometrial hyperplasia.^{14,15} There is high quality evidence that use of progestins as fertility-sparing treatment in women in this population results in significant relapse rates (range 20.1 to 40.6%) upon long-term follow-up.^{14,15} There is insufficient evidence comparing safety or efficacy of different progestin formulations in the treatment of endometrial carcinoma or atypical complex endometrial hyperplasia.
- There is moderate quality evidence that use of progestins in high risk women with a short cervix (<25 mm) and history of preterm birth is associated with decreased perinatal mortality and preterm birth at 34 or 37 weeks.¹⁶⁻¹⁹ No improvement in clinical neonatal outcomes was observed in women without a history of preterm birth. There is low quality evidence based on direct and indirect comparisons demonstrating benefit with both vaginal and systemic formulations.^{16,20}

Recommendations:

- Combine progestin agents into one PDL class and designate at least one preferred product for FDA-approved indications funded by the Oregon Health Plan (endometriosis, endometrial cancer, endometrial hyperplasia, abnormal bleeding disorders, and prevention of preterm birth) based utilization and comparative drug costs in the executive session.
- Evaluate comparative costs of oral, vaginal and topical estrogen and estrogen/progestin combination products in the executive session.
- Restrict coverage of ospemifene subject to prior authorization. Dyspareunia is a non-funded condition and there is insufficient evidence that other symptoms of vaginal atrophy improve with treatment.
- No changes to current clinical prior authorization (**Appendix 4**) recommended.

Previous Conclusions:

- There is high quality evidence that estrogens are the most effective agents at relieving common symptoms associated with menopause, including vasomotor symptoms and quality of life, with no significant differences between doses or mode of administration. There is high strength of evidence that vaginal estrogen reduces pain during intercourse and insufficient evidence for oral estrogen.
- There is no new significant comparative evidence on the efficacy or safety of hormone replacement therapy medications.
- Conjugated estrogens/bazedoxifene (CE/BZA; DUAVEE) has not been compared with current therapies for postmenopausal vasomotor symptoms. Only one phase 3 poor quality trial (SMART 2) and one supportive poor quality sub-study (SMART 1) comparing CE/BZA with placebo provide low quality evidence.
- CE/BZA significantly reduced the number and severity of hot flashes (mean difference in the daily number of moderate and severe hot flashes between CE/BZA and placebo was -2.71 in SMART 2 and -6.29 in sub-study SMART 1).
- Evidence that CE/BZA improves health-related quality of life (HRQOL) is insufficient. One combined analysis provides low quality evidence that CE/BZA versus placebo results in a meaningful change in vasomotor functioning scores.
- The poor quality SMART 5 trial provides low quality evidence CE/BZA significantly increases lumbar spine and total hip bone mineral density (BMD) compared with placebo (placebo subtracted difference 1.51% for the lumbar spine and 1.21% for the total hip). However, the researchers observed no statistically significant difference between the CE/MPA subgroup and CE/BZA and did not evaluate fracture risk.
- Clinical trials provide low quality evidence for the CE/BZA indications for treatment of vasomotor symptoms and prevention of osteoporosis. The incidences of all-cause mortality, serious adverse events, venous thromboembolism (VTE), and endometrial hyperplasia or endometrial malignancy in patients taking CE/BZA were similar to placebo. However, the adverse effects associated with use in a general, menopausal population remain unexplored. The potential

implications of discontinuing CE/BZA, such as the rapid bone loss associated with CE-alone use, are unclear. CE/BZA comes with the CE-related risk of VTE and ischemic stroke, and the benefits of oral hormone therapy are more likely to outweigh the risks before age 60 or within 10 years of menopause.

Previous Recommendations:

- There is no further review or research needed for estrogen replacement therapy at this time.
- Make CE/BZA non-preferred and subject to clinical prior authorization criteria due to insufficient evidence comparing it with currently available therapies and low quality evidence of efficacy compared with placebo.

Background:

Hormone replacement therapy (HRT) refers to the use of estrogen alone or in combination with progestin products. The most common indication for estrogen therapy is for the treatment of menopausal symptoms, though estrogens also have FDA indications for palliative treatment of metastatic breast cancer, metastatic prostate cancer, and postmenopausal osteoporosis.²¹ They can also be used off-label as cross-sex hormone replacement in gender dysphoria (see Class Review, Nov 2015).²²

Symptoms of menopause result from a decrease in estrogen and progesterone levels leading to more sensitive body temperature regulation as well as decreased vaginal blood flow and secretions.²³ Up to 75% of postmenopausal women experience vasomotor symptoms (hot flashes, night sweats or sleep disturbances) and up to 50% may experience urogenital symptoms (including sexual dysfunction, vaginal dryness, discharge, itching, and dyspareunia or pain with sexual intercourse).⁴ Vasomotor symptoms typically start within 1 year after the last menstrual period and resolve spontaneously in the majority of women after 5 years though they can last for longer than 10 years.²³

For mild menopause symptoms, lifestyle modifications including diet, exercise, environmental temperature regulation, and vaginal lubricants may be sufficient to manage symptoms. For more severe menopause symptoms, first-line medication management includes HRT with an estrogen product. Preparations of estrogen include vaginal, transdermal, and oral formulations. A list of available estrogen products and their PDL status is available in Appendix 1. Potential long-term risks of estrogen include increased risk of cardiovascular complications and breast cancer. Caution is advised for patients with predisposing risk factors for these conditions.^{4,24} Estrogens may also increase risk for endometrial cancer in women with a uterus.²⁵ Guidelines recommend concurrent use of a progestin in these women to decrease risk of endometrial cancer; all estrogens carry an FDA warning for endometrial cancer associated with estrogen only therapy.^{4,24} For women who have contraindications to or are not willing to use hormone products, additional second-line treatment options for symptoms of menopause include selective serotonin reuptake inhibitors (SSRIs), serotonin norepinephrine reuptake inhibitors (SNRIs), gabapentin, pregabalin, ospemifene or clonidine. Long-term benefits of HRT include decreased risk of osteoporotic fractures and colorectal cancer, but HRT is not recommended for prevention of long-term conditions such as osteoporosis as the potential risks may outweigh any benefits.⁴

Ospemifene is a new selective estrogen receptor modulator (SERM) approved in 2013 for the treatment of moderate to severe dyspareunia in women with vulvar and vaginal atrophy as a result of menopause. Vaginal atrophy falls within the covered conditions on the prioritized list, but dyspareunia is not a covered condition. Ospemifene acts as an antagonist in the endometrium and as an agonist in the uterus, bone, and breast tissue. Ospemifene was approved on the basis of 2 phase 3 clinical trials supporting efficacy in the treatment of moderate to severe dyspareunia. Supporting data were provided from other phase 2 and 3 trials. The phase 3 studies included 1,745 patients aged 40-80 years with menopause and vulvovaginal symptoms that were randomized to ospemifene (either 30 mg or 60 mg) or placebo with follow-up at 12 weeks.²⁶⁻²⁸ Extension studies to determine safety up to 1 year were also conducted. In efficacy trials, all participants were allowed to utilize vaginal lubricants as needed. Outcomes for these trials included vaginal pH, maturation index, and improvement in

symptoms of dyspareunia and vaginal dryness. Vaginal pH has been used to determine stage of menopause with a pH less than 4.5 associated with low estrogen levels indicative of perimenopause or menopause.^{29,30} Use of vaginal maturation index, measured by a decrease in superficial cells and an increase in parabasal cells upon vaginal smear, has also been used for determining stage of menopause. This method involves obtaining cells from the vaginal wall to determine the percentages of parabasal, intermediate and superficial cells. A higher percentage of parabasal cells has been documented in postmenopausal women compared to premenopausal women.²³ However, vaginal pH and maturation index are surrogate endpoints which have not been correlated with symptom improvement in postmenopausal women, and a minimum clinically important difference has not been established in the literature. Assessment of the most bothersome moderate to severe symptom (either vaginal dryness or dyspareunia) was measured on a 4-point Likert scale (0 = none, 1 = mild, 2 = moderate, 3 = severe). There is currently no consistently used scale for assessment of menopause symptoms, and the minimal clinical important difference with the use of a 4-point severity scale has not been established. Important clinical outcomes would include improvement in symptoms and rates of long-term adverse events. Additional studies to establish efficacy in patients with other genitourinary symptoms associated menopause are ongoing.³¹

Progestin products are recommended in combination with estrogen treatment to decrease risk of endometrial cancer in women with a uterus utilizing HRT for menopause symptoms. Progestins are also FDA approved for use in contraception, prevention of preterm labor and a wide variety of endometrial conditions including endometrial carcinoma, endometrial hyperplasia, endometriosis, and abnormal uterine bleeding. Indications are specific to the agent and formulation (see Table 1). Currently, medroxyprogesterone intramuscular (IM) or subcutaneous (SC) injections are the only progestin products that have indications for both contraception and endometrial disorders. Hydroxyprogesterone caproate injection is the only product FDA approved for prevention of preterm labor, though other progestins may be used off-label for this indication. Efficacy of hydroxyprogesterone caproate for use in preterm labor was previously reviewed by the P&T Committee in 2013.³²

Because progestins induce development of the secretory endometrium and block follicular maturation and ovulation, they are commonly used for endometriosis and regulation of abnormal uterine bleeding.²¹ Endometriosis is a condition where endometrial tissue located outside the uterus causes pelvic pain and infertility.²¹ When used for the treatment of endometriosis, progestins are thought to improve pain by decreasing proliferation of endometrial tissue outside of the uterus.³³ Guidelines recommend progestins as an option for the treatment of pain associated with endometriosis but note that they do not improve fertility in patients with endometriosis.^{9,10} Agents approved by the FDA for treatment of endometriosis include medroxyprogesterone acetate subcutaneous injection and norethindrone acetate. Abnormal uterine bleeding is defined as changes in the volume, regularity, frequency or duration of menstrual periods.³⁴ Typical duration of menstrual periods is 3 to 8 days with consistent cycles every 24 to 38 days.³⁴ Diagnosis of abnormal uterine bleeding is typically patient specific and evaluates impact of the woman's quality of life.³⁴ Studies examining efficacy of medications utilize several methods to evaluate the impact on menstrual bleeding. Methods to measure the volume of blood lost per cycle include the use of the pictorial bleeding assessment chart (PBAC) scores or the alkaline haematin method. The alkaline haematin method utilizes spectroscopy to estimate the amount of alkaline haematin in blood samples which can be correlated accurately to the volume of blood in the sample.³⁵ PBAC score utilizes the subjective patient assessment of bleeding intensity and number of sanitary items to evaluate volume of blood loss.³⁶ Validity of PBAC scores has been evaluated in several studies which suggest that, due to the subjective nature of the test, inter-patient variability may be high.^{36,37} However, PBAC scores may have some utilization in determination of change in blood loss over time as their documented intra-patient variability is low.³⁶ Clinically important outcomes for abnormal uterine bleeding include symptom improvement, improved quality of life, and signs of blood loss. Correlation between improved quality of life and blood loss is difficult due to interpatient variability in the assessment of and blood loss and quality of life.

In endometrial carcinoma, total hysterectomy with bilateral oophorectomy is the recommended standard of care. Surgery is also recommended in women with endometrial hyperplasia with atypia, persistent hyperplasia or hyperplasia refractory to medical treatment.^{38,39} However, progestins may be considered as a

fertility-sparing option in women hoping to conceive or those who wish to preserve their fertility.³⁸ Progestins are also utilized as adjuvant therapy in recurrent or metastatic disease, in endothelial hyperplasia without atypia, and in women who are poor surgical candidates.³⁸ For use of progestins as fertility-sparing therapy, women must have well-differentiated endometrial cancer, absence of suspicious or metastatic disease, disease limited to the endometrium, no contraindications to medical therapy or pregnancy.³⁸ Guidelines also recommend counseling that fertility-sparing therapy is not the standard of care.³⁸

This review evaluates the comparative efficacy of estrogens, progestins, and ospemifene for the treatment of menopause symptoms. Comparative evidence of progestin products for other FDA-approved indications except for contraception is also reviewed.

Table 1. FDA Indications and Dosing of Progestin Products.^{21,40}

Drug Name	Indication(s)	Strength/Route	Dose and Frequency
Medroxyprogesterone acetate	<ul style="list-style-type: none"> Abnormal uterine bleeding unrelated to menstrual cycle (tablets) Contraception (SC/IM injection) Recurrent/metastatic endometrial carcinoma (IM injection) Prophylaxis of estrogen-induced endometrial hyperplasia (tablets) Pain associated with endometriosis (SC injection) Secondary physiologic amenorrhea (tablets) 	<ul style="list-style-type: none"> 2.5, 5, 10 mg oral tablet 150, 400 mg/mL IM suspension 104/0.65 mg/mL SC suspension 	<ul style="list-style-type: none"> 5-10 mg PO once daily 150 mg IM or 104 mg SC every 3 months for contraception 400-1000 mg IM per week for cancer 104 mg SC every 3 months for endometriosis
Hydroxyprogesterone caproate	<ul style="list-style-type: none"> Prevention of preterm birth (brand name Makena® only) Stage III or IV adenocarcinoma of uterus (generic) Amenorrhea (generic) Endometrial disorder (generic) 	<ul style="list-style-type: none"> 250 mg/mL IM solution 	<ul style="list-style-type: none"> 250 mg once weekly beginning as early as 16-20 weeks and continuing until 37 weeks or delivery for preterm birth 1-7 grams weekly for adenocarcinoma 375 mg once or 250 mg every 4 weeks as cyclic therapy for amenorrhea or endometrial disorders
Norethindrone acetate	<ul style="list-style-type: none"> Secondary amenorrhea Dysfunctional uterine bleeding Endometriosis 	<ul style="list-style-type: none"> 5 mg oral tablet 	<ul style="list-style-type: none"> 2.5-10 mg once daily for amenorrhea or uterine bleeding 5-15 mg daily for endometriosis
Progesterone	<ul style="list-style-type: none"> Abnormal uterine bleeding unrelated to menstrual cycle (injection) Adjunct therapy to assisted reproductive technology for female infertility (gel, inserts) Endometrial hyperplasia prophylaxis (capsule) Secondary physiologic amenorrhea (capsule, injection, gel) 	<ul style="list-style-type: none"> 50 mg/mL IM oil 4%, 8% vaginal gel 100 mg vaginal tablet 100 mg, 200 mg oral capsule 	<ul style="list-style-type: none"> 5-10 mg IM once daily x6-8 days for uterine bleeding or amenorrhea 100 mg vaginal insert BID or TID; 90 mg (8%) daily to BID for infertility 200 mg PO at bedtime for hyperplasia 45-90 mg (4-8% gel) every other day; 400 mg PO at bedtime for amenorrhea

Abbreviations: BID = twice daily; IM = intramuscular; IUD = intrauterine device; PO = orally; SC = subcutaneous; TID = three times daily

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 3**, which includes dates, search terms and limits used. The OHSU Drug Effectiveness Review Project, Agency for Healthcare Research and Quality (AHRQ), Cochrane Collection, National Institute for Health and Clinical Excellence (NICE), Department of Veterans Affairs, BMJ Clinical Evidence, and the Canadian Agency for Drugs and Technologies in Health (CADTH) resources were manually searched for high quality and relevant systematic reviews. Search for high quality and relevant systematic reviews was limited to the time frame of 2010 to the present. 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. Finally, the AHRQ National Guideline Clearinghouse (NGC) was searched for updated and recent evidence-based guidelines.

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:***Menopause***

A systematic review and meta-analysis published by the Agency for Healthcare Research and Quality (AHRQ) in 2015 examined the comparative effectiveness, long-term benefits, and long-term adverse effects of medical treatment for menopause symptoms.¹ Symptom relief with commercially prepared estrogen formulations was examined from 283 trials. There was insufficient evidence to evaluate safety or efficacy of compounded hormone therapies. Trials reporting symptoms were included if they were at least 12 weeks in duration. Data were not reported in every trial, but age ranged from 43.8 to 63.5 years with an average 4.1 years since menopause.¹ Approximately 75% of women had a uterus.¹ Results were reported separately for vasomotor symptoms, psychological symptoms, sexual function, urogenital atrophy, sleep disturbances, and quality of life. Because trial outcomes were recorded with different scales and metrics, results were reported using standard mean difference (SMD) with lower numbers indicating a lower frequency of events and higher numbers associated with more events.

There is high strength of evidence that estrogen therapy (at any dose) is more effective than placebo or other medications in treatment of vasomotor symptoms (estrogen vs. placebo SMD ranged from -0.64 to -0.50 corresponding to a decrease of 2 to 3 hot flushes per day).¹ No meaningful difference was observed between estrogen dose (moderate strength of evidence) or route of administration (high strength of evidence).¹ There is high strength of evidence that both SSRI/SNRIs (SMD range -0.43 to -0.31) and estrogen products (SMD range -0.36 to -0.26) improve psychological symptoms (including depression, anxiety, and global psychological well-being).¹ There was insufficient evidence to compare different estrogen strengths, products or formulations. The authors note that presence of these symptoms was typically required for inclusion in trials, but women were often excluded if they were taking psychoactive medications, had a very high score on the assessment tool or had suicidal thoughts.¹ As a result, data may only be applicable to women who have more mild symptoms and who are not on concomitant psychotherapeutic medications. There is high strength of evidence that treatment with vaginal estrogens improve pain with sexual intercourse (SMD -0.54, 95% CI -0.73 to -0.34) and that all estrogens improve overall symptoms of sexual function (SMD 0.27, 95% CI 0.19 to 0.35).¹ There is moderate strength of evidence that oral estrogens improve pain during intercourse (SMD -0.22, 95% CI -0.35 to -0.09), and that all estrogens improve sexual interest (SMD 0.18, 95% CI 0.10 to 0.26).¹ Compared to oral estrogens, vaginal estrogens had a larger treatment effect, but results were not statistically significant (moderate strength of evidence).¹ Because trials reported a variety of outcomes with significant heterogeneity between trials, analysis of differences in dose was not completed. There is high strength of evidence that urogenital symptoms improve with ospemifene (SMD -0.75, 95% CI -1.05 to -0.45), vaginal

estrogens (SMD -0.44, 95% CI -0.65 to -0.23) and oral or transdermal estrogens (SMD -0.35, 95% CI -0.44 to -0.26) compared to placebo with a greater magnitude of effect seen with vaginal versus oral estrogens.¹ Strength of evidence for differences in formulations were not evaluated due to heterogeneity between routes of administration. Evaluation of estrogens on sleep demonstrates a modest improvement compared to placebo (SMD 0.32, 95% CI 0.24 to 0.46; high strength of evidence) with similar treatment effects with other agents (including SSRIs or gabapentin).¹ No difference was observed between standard or low/ultralow doses of estrogen with a SMD of -0.08 (95% CI -0.16 to 0.01) (moderate strength of evidence).¹ Though estrogens have not been directly compared with other sleep therapies, one study did examine the effect of eszopiclone in a similar patient population with a resulting effect size approximately 3-times that of estrogen (SMD 1.08, 95% CI 0.53 to 1.62).¹ Quality of life also improves with estrogen therapy compared to placebo (SMD>0.35) with high strength of evidence.¹ No significant differences were observed between dose or route of administration (moderate strength of evidence).¹ Other agents demonstrate less of an effect on quality of life or have lower quality of evidence.¹ Due to significant heterogeneity between trials, a pooled analysis stratifying patients by age, symptom severity, time since menopause, or uterine status could not be completed.

For evaluation of long-term safety and adverse effects, inclusion criteria required a minimum follow-up of 5 years for trials reporting cancers and a minimum follow-up of at least 1 year for trials reporting other long-term adverse effects.¹ Much of the data from this review were obtained from the Woman's Health Initiative which enrolled a large population of patients who were older and had less severe menopausal symptoms. In order to provide a realistic estimate of the adverse effects in a younger population with more severe symptoms, large observational studies with the target population were included in the meta-analysis. Absolute rates of each adverse effect were not calculated; however, gallbladder disease occurred most frequently with thromboembolic events, stroke and breast cancer occurring less frequently.¹ Combination estrogen/progestin treatment demonstrated an association with increased risk for gallbladder disease (moderate strength of evidence), venous thromboembolism (moderate strength of evidence), stroke (moderate strength of evidence), breast cancer (high strength of evidence), coronary heart disease (moderate strength of evidence), and ovarian cancer (low strength of evidence).¹ Estrogen/progestin combinations decrease colorectal cancer (low strength of evidence) and osteoporotic fractures (moderate strength of evidence) but have no effect on endometrial cancer (moderate strength of evidence).¹ Estrogen alone increases risk for gallbladder disease (moderate strength of evidence), venous thromboembolism (high strength of evidence), and stroke (moderate strength of evidence).¹ Estrogen alone may also decrease risk for breast cancer (low strength of evidence) and osteoporotic fractures (moderate strength of evidence) and have no effect on colorectal cancer (moderate strength of evidence) or coronary heart disease (moderate strength of evidence).¹ Overall, similar trends in long-term adverse effects were demonstrated when patients were stratified based on age or time since menopause.¹ One notable exception was an increased risk of breast cancer in women taking estrogen alone within 5 years of menopause.¹ These results should be interpreted with caution as they were exploratory endpoints based on only a few studies. Other systematic reviews have noted similar increased risk of stroke in women currently on therapy (HR 1.32, 95% CI 1.12 to 1.56; p=0.001) which decreased after treatment discontinuation (HR 1.00, 95% CI 0.85 to 1.16; p=0.958).⁴¹

Another analysis of HRT was published by the National Institute for Health and Care Excellence (NICE) in a 2015 systematic review and guideline update.⁴ The review included both RCTs and observational studies and examined the short and long-term risks and benefits of HRT. Because direct comparison between different interventions was not available, a network meta-analysis was used to estimate relative treatment effects. Separate analyses were conducted for individual patient populations (i.e. women with a uterus or women with a history of breast cancer).⁴ The analyses were limited by availability of data; a number of studies were excluded due to lack of reported data on outcomes or individual patient populations.⁴ Because many studies were excluded, there was considerable uncertainty in the estimates of treatment effects; and guideline recommendations regarding effective treatment were strongly influenced by current practice standards and clinical expertise.⁴ In women with a uterus (n=4,165), estrogen/progestin combination patches were the most effective compared to placebo for the treatment of vasomotor symptoms (mean ratio [MR] 0.23, 95% CI 0.09 to 0.57).⁴ Indirect comparisons between agents suggested that non-oral estrogens were more effective than raloxifene (MR 7.12, 95% CI 1.86 to 27.63) or SSRI/SNRIs (MR 3.63, 95% CI 1.33, 9.93).⁴ Other comparisons failed to

demonstrate statistical differences for the treatment of vasomotor symptoms.⁴ In addition, non-oral estrogen/progestin and estrogen/bazedoxifene combinations were overall better tolerated than SSRI/SNRIs with fewer patients discontinuing therapy.⁴ Data in women without a uterus were not used to influence guideline recommendations due to lack of relevant included data on hormonal interventions.⁴ Guideline recommendations for women without a uterus were based on extrapolated data from the analysis of women with a uterus.⁴ Therapies analyzed for the treatment of vaginal symptoms included local estrogens or ospemifene. Evidence supporting the use of local estrogens was low quality, with moderate quality evidence for ospemifene.⁴ Evidence was insufficient to evaluate differences in efficacy between estrogen dose.⁴

Long-term effects of HRT were also assessed in the 2015 systematic review by NICE using observational and randomized control data. Estimated magnitude of treatment effects were summarized based on study type (RCT or observational), timing and duration of treatment, and type of therapy (estrogen alone, estrogen/progestin combinations, or any HRT).⁴ A summary of results from these analyses is presented here. Overall, oral HRT (with and without progestins) increased risk of VTE compared to placebo.⁴ Risk was not significantly different from placebo when comparing transdermal HRT to placebo.⁴ An analysis of VTE risk associated with different progestin products was not conducted because individual trials demonstrated significantly heterogeneous outcomes.⁴ No correlation was observed between cardiovascular disease or coronary heart disease risk and use of HRT (with and without a progestin) based on low quality evidence.⁴ Evidence from some observational studies does suggest an increased risk of stroke associated with HRT, but absolute risk remains low.⁴ There was insufficient evidence to evaluate the cardiovascular risk associated with differences in specific preparations, formulations, or dosages.⁴ Evidence also demonstrated that risk of MI, cardiovascular disease, or cardiovascular mortality was not increased in women less than 65 years of age treated with estrogen or combined estrogen/progestin formulations.⁴ Risk of stroke was increased in women treated with HRT, but absolute risk remained small.⁴ Limited evidence suggested that transdermal estrogen may have lower risk of stroke compared to oral preparations.⁴ Risk of CHD was not increased with estrogen alone, and there was little to no risk with combination estrogen and progestin treatment.⁴ In addition, risk of bone fractures was decreased in women currently taking HRT, but risk returned to baseline once HRT was discontinued.⁴ Patients with longer duration of therapy may have larger benefit upon discontinuation.⁴ Patients taking combination estrogen/progestin therapy also demonstrated an increased risk of breast cancer, but little to no change was observed in women taking estrogen only therapy.⁴ Risk was correlated with treatment duration and returned to normal after treatment discontinuation.⁴ No correlation was observed between HRT use and development of type 2 diabetes or adverse effects on blood glucose control (low quality of evidence).⁴

A systematic review specifically examined risk of endometrial cancer from HRT in patients with a prior history of surgical treatment for endometrial cancer.⁶ The review included 1 RCT and 5 observational studies (n=1,975).⁶ Overall, use of HRT did not increase risk of cancer recurrence in patients with prior surgical treatment of endometrial cancer. Results demonstrate that risk of endometrial cancer was, in fact, decreased in patients who received HRT (OR 0.53, 95% CI 0.30 to 0.96).⁶ However, there was moderate heterogeneity between studies ($I^2=49\%$).⁶ In addition, estrogen dose and baseline risk factors for recurrence varied between study groups.⁶ Due to limitations in reporting and observational study design, authors recommend interpretation of these results with caution.⁶ Results cannot exclude the potential for increased risk of endometrial cancer in women with prior history, but overall results demonstrate that magnitude of this risk is likely small.⁶ Similarly, in a review of patients with a prior history of surgical treatment for epithelial ovarian cancer, HRT use was not associated with decreased survival (HR 0.69, 95% CI 0.61 to 0.79).⁷ Two RCTs and 4 cohort studies (n=1448 [n=419 with HRT]) were included in this analysis.⁷ Authors note that due to the limitations in population and study design of included trials, further well-designed trials are necessary to verify these results.⁷

A Cochrane systematic review updated in 2015 examined the risks and benefits of oral HRT (with or without a progestin) for use in the primary or secondary prevention of cardiovascular disease in postmenopausal women.⁴² The review included 19 randomized controlled trials which enrolled over 40,000 women at an average age of 64 years.⁴² Interventions included 17 β -estradiol, estradiol valerate, and conjugated equine estrogen alone or in combination with medroxyprogesterone acetate or norethindrone.⁴² Mean follow-up in the majority of patients was more than 5 years, and 7 trials were discontinued early as

benefits of therapy were unlikely to outweigh cardiovascular risks. With use in primary prevention, there was no difference in all-cause mortality (RR 1.00, 95% CI 0.89 to 1.12) or any cardiovascular disease outcomes.⁴² Risk of stroke (RR 1.32, 95% CI 1.12 to 1.56), venous thromboembolism (RR 1.92, 95% CI 1.24 to 2.99), and pulmonary embolism (RR 1.89, 95% CI 1.17 to 3.04) were significantly increased in women taking HRT compared to placebo.⁴² Similarly, when used as secondary prevention, an increased risk of venous thromboembolism was observed (RR 2.02, 95% CI 1.13 to 3.62) but no difference was seen in other cardiovascular or mortality outcomes.⁴² However, patient population utilizing HRT as secondary prevention were significantly smaller compared to primary prevention trials and may not have been sufficient to detect differences in these outcomes. Exploratory analyses were conducted examining how duration and timing of treatment affected outcomes. Caution should be taken when interpreting the results of these analyses as there was significant heterogeneity between hormone therapy regimens and patient populations in different trials.⁴² Differences in outcomes at different times may be due to differences in population studied. Overall, there was no difference in mortality for patients taking hormone therapy for one to 8 years.⁴² However, based on the results from 2 studies, patients treated for 10 years with HRT had a higher survival rate than those given placebo (RR 0.55, 95% CI 0.31 to 0.96).⁴² Subgroup analysis for timing of HRT (less than or greater than 10 years) after menopause were also completed. If information on time since menopause was not available, mean age of participants greater or less than 60 years was used as a surrogate.⁴² Compared to placebo, all-cause death (RR 0.70, 95% CI 0.52 to 0.95; p=0.01) and coronary heart disease (a composite of death from cardiovascular disease and non-fatal myocardial infarction [MI]; RR 0.52, 95% CI 0.29 to 0.96; p=0.02) and venous thromboembolism (RR 1.74, 95% CI 1.11 to 2.73) were significantly higher in women starting HRT within 10 years of menopause (n=9,629).⁴² In women starting HRT more than 10 years after menopause (n=28,705), no difference was seen in mortality (RR 1.06, 95% CI 0.95 to 1.18) or coronary heart disease (RR 1.07, 95% CI 0.96 to 1.20) compared to placebo.⁴² However, these women did have a higher risk of stroke (RR 1.21, 95% CI 1.06 to 1.38) and venous thromboembolism (RR 1.96, 95% CI 1.37 to 2.80).⁴² Overall thromboembolic events were observed more frequently in patients taking combination estrogen and progestin therapy.⁴² Incidence of stroke was mainly driven by ischemic rather than hemorrhagic events.⁴²

Other systematic reviews examining efficacy of low dose transdermal estrogens (defined as less than 0.05 mg of 17 β -estradiol or equivalent)⁴³ and bioidentical hormone products⁴⁴ have demonstrated similar improvements for the treatment of vasomotor symptoms. Bioidentical hormone products are typically compounded preparations and contain hormones with an identical chemical structure to hormones produced by the ovaries. Low dose transdermal estrogens decreased the number of daily hot flashes by an average of 7.07 to 9.36 depending on the estrogen dose compared to an average decrease of 5.07 in the placebo groups.⁴³ Frequency of hot flashes with use of bioidentical hormone products was also reduced in 793 women using a patch, 356 women on oral formulations, and 458 women on intranasal formulations with treatment effects of SMD -0.68 (95% CI -0.83 to -0.53), SMD -0.80 (95% CI -1.03 to -0.57), and SMD -3.04 (95% CI -4.05 to -2.03) respectively.⁴⁴ In comparison to conjugated estrogens, bioidentical hormone patches or oral formulations did not demonstrate any significant difference in frequency of hot flashes, though the authors note that the quality of evidence was too low to reach a definitive conclusion.⁴⁴ Reports of adverse effects compared to conjugated estrogens were inconsistent with one trial reporting more frequent breast pain and vaginal bleeding in the bioidentical hormone group and others reporting no difference in adverse effects.⁴⁴

A systematic review conducted in 2014 specifically examined the efficacy of vaginal estrogens for the treatment of genitourinary symptoms of menopause including vaginal dryness, burning, dyspareunia, dysuria, urgency or frequency.⁴⁵ The review included 44 studies in postmenopausal women with genitourinary symptoms of menopause.⁴⁵ Trials compared vaginal estrogen to placebo, other types of vaginal estrogen, formulations designed to deliver a systemic dose of estrogen (i.e. vaginal ring, transdermal patch, or oral administration), and non-hormonal moisturizers or lubricants.⁴⁵ A meta-analysis was not completed, but evidence was graded based on scientific merit, likelihood of bias and completeness of reporting. Overall, estrogen formulations improved complaints of dryness, itching, burning and dyspareunia (moderate quality evidence), urinary complaints including dysuria and urinary urgency (low to very low quality evidence), stress urinary incontinence (low quality evidence), and urgency urinary incontinence (moderate quality evidence).⁴⁵ No difference was observed in symptom improvement between vaginal estrogen and systemic formulations (low to very-low quality evidence).⁴⁵

A systematic review performed in 2014 by CADTH examined risks and benefits of oral progesterone for the treatment of menopausal symptoms.⁴⁶ The review included 6 studies from the Women's Health Initiative (WHI), data from the Million Women prospective cohort study, and 2 RCTs from Canada and Finland. The mean age of women in the WHI (63.2 years) was significantly older than women in other included studies (mean range 52.5 to 56.7 years).⁴⁶ The review found that compared to placebo, combined conjugated equine estrogen and medroxyprogesterone increase risk of breast cancer (2.6 vs. 1.3 per 10,000 women per year), death due to breast cancer (5.3 vs. 3.4 per 10,000 women per year), and deaths due to lung cancer (HR 1.71, 95% CI 1.16 to 2.52, p=0.01) largely based on data from the WHI.⁴⁶ However, as lung cancer was not a pre-specified outcome in the WHI, these results should be interpreted with caution. Increased risk of atrial fibrillation was not associated with medroxyprogesterone use. In the Million Women Study, women taking estrogen with medroxyprogesterone also had increased risk of VTE (RR 2.67, 95% CI 2.25 to 3.17) compared to women who had never used HRT.⁴⁶ Rates of VTE were also significantly higher with medroxyprogesterone use than norethindrone or norgestrel.⁴⁶ Only one small study examined the efficacy of oral progestins in the treatment of vasomotor symptoms. The study, conducted in early postmenopausal women, found decreased vasomotor symptoms with oral progestins which were not statistically significant compared to placebo.⁴⁶ The study was limited by small sample size, short treatment duration, and unblinding of treatments during the study. There were no other studies directly examining comparative efficacy or safety of different oral progestins.

Another systematic review examined association of low dose HRT (with or without progestins) with metabolic control in postmenopausal women with diabetes mellitus.⁵ Previous epidemiologic studies and trials have noted the relationship between HRT and improved diabetes risk, but this is the first systematic review which summarizes this data.⁵ The review included 8 studies (n=16,807) which evaluated the risk of diabetes in women on HRT and 8 studies (n=1,164) evaluating the effect of HRT on glycemic control in current diabetics via fasting blood glucose, glycated hemoglobin (HbA1c), and lipid profiles.⁵ Results indicate that patients who had used HRT had a significantly lower rate of diabetes compared to patients who had never used HRT (OR 0.61, 95% CI 0.55 to 0.68).⁵ In patients who were currently diabetic, diabetic indices including HbA1c (mean difference [MD] -0.73%, 95% CI -1.28 to -0.18%) and LDL (MD -0.43 mM/L, 95% CI -0.71 to -0.14 mM/L) demonstrated statistically significant improvement compared to placebo, though results may not be clinically significant.⁵

Uterine Bleeding

A Cochrane systematic review conducted in 2015 examined the safety and efficacy of progestin products (including oral and IUD) for reduction of heavy menstrual bleeding.¹¹ They included 21 studies, 7 of which examined efficacy of oral medications compared to an IUD.¹¹ Effectiveness was measured using either PBAC scores or the alkaline haematin method.¹¹ There was no statistically significant difference in efficacy between a levonorgestrel IUD and 15-25-day oral progestins or 10-day medroxyprogesterone acetate, but combined oral contraceptives had significantly less reduction of heavy menstrual bleeding compared to an IUD (alkaline haematin: MD 66.91 mL, 95% CI 42.1 to 91.20 mL; PBAC: MD 55.05 mL, 95% CI 27.83 to 82.28 mL).¹¹ Studies had significant heterogeneity, but the direction of treatment effect consistently favored use of an IUD compared to oral progestins.¹¹ Adverse effects and serious adverse events were mostly similar between groups with an increase in pelvic pain (RR 2.68, 95% CI 1.00 to 7.18), breast tenderness (RR 2.85, 95% CI 1.29 to 6.29) and ovarian cysts (RR 3.28, 95% CI 1.31 to 8.21) in women with a levonorgestrel IUD.¹¹ Other systematic reviews demonstrated similar trends^{12,13} with greatest reduction in menstrual blood loss with levonorgestrel IUD (71% to 95%) compared to combined oral contraceptives (35 to 69%) or oral progestins (20 to 67%).¹²

Endometrial carcinoma and hyperplasia

A systematic review of 34 observational studies (n=559) published in 2012 examined regression, relapse and live birth rates in women using progestins for treatment of atypical complex endometrial hyperplasia and endometrial carcinoma.¹⁴ Women included in these studies generally had well-differentiated endometrial carcinoma.¹⁴ Half-of the studies included in this review were prospective cohort studies, none were blinded to treatment assignment, and only six had an adequate follow-up of 5 years.¹⁴ Case reports or case series were excluded if they reported fewer than 5 cases.¹⁴ Follow-up ranged from 11 to 72

months.¹⁴ In women diagnosed with endometrial carcinoma, rates of cancer regression and live births were 76.2% (95% CI 68 to 85.3%) and 28.0% (95% CI 21.6 to 36.3%), respectively.¹⁴ Similar rates were observed in women with endometrial hyperplasia.¹⁴ However, relapse rates after initial regression were also high in women with endometrial carcinoma (40.6%, 95% CI 33.1 to 49.8%) and endometrial hyperplasia (26%, 95% CI 18.5 to 37.4%).¹⁴ In addition, 20 women (3.6%) developed ovarian malignancies during follow-up.¹⁴ The authors concluded that fertility-sparing treatment with progestins may be an option for women with endometrial cancer who would like to conceive.¹⁴ However, because of high relapse rates, the authors continue to recommend typical treatment of surgery as soon as possible after conception.¹⁴ Similar results were noted in another systematic review examining the efficacy of oral progestins for treatment of endometrial carcinoma or hyperplasia over a mean follow-up time of 45.8 months.¹⁵ Rates of complete pathological response to progestins were 74% (95% CI 65 to 81%) in women with endometrial carcinoma and 72% (95% CI 62 to 80%) in women with endometrial hyperplasia.¹⁵ Live births occurred in 34 (34.0%) of patients trying to conceive, and relapse upon long term follow-up occurred in 32 patients (20.1%).¹⁵

Another systematic review examined the efficacy of levonorgestrel IUD compared to oral progestin therapy in women with endometrial hyperplasia without atypia.⁴⁷ Seven RCTs (n=766) conducted in Turkey, Egypt, Kuwait and Iran were included in the analysis.⁴⁷ Patients in these trials were randomized to oral medroxyprogesterone acetate or norethindrone acetate versus levonorgestrel IUD. Therapeutic response was significantly improved in patients receiving an IUD compared to patients receiving oral therapy at all time points measured from 3 months (OR, 2.30, 95% CI 1.39 to 3.82; P=0.001, 5 trials, n=376) to 24 months (OR, 7.46; 95% CI 2.55 to 21.78; P=0.0002, 1 trial, n=104).⁴⁷ Therapeutic response was defined slightly differently in various trials but typically consisted of proliferative or atrophic pattern endometrium upon biopsy.⁴⁷ Rates of irregular vaginal bleeding were significantly more common in patients with an IUD than oral therapy (OR 1.92, 95% CI 1.14 to 3.23, 3 trials, p=0.01).⁴⁷

Endometriosis

A Cochrane systematic review examined the efficacy of various interventions in the improvement of pain and fertility outcomes in women with endometriosis. This review compiled results from multiple Cochrane systematic reviews to evaluate best treatment options for endometriosis. Oral progestins examined in this review included combination estrogen and progestins or progestins alone versus placebo. Results demonstrated no consistent difference in pain or fertility outcomes compared to placebo though evidence was of low quality.⁸ The authors concluded that evidence for oral progestins has not demonstrated significant benefits in pain relief or improved fertility outcomes.⁸

Another systematic review conducted in 2011 examined efficacy of various treatments including progestins, combined oral contraceptives, and gonadotropin releasing hormone agonists.³³ The analysis included a total of 7 RCTs (n=1096), 5 of which included progestin therapy, and defined an improvement in pain as at least a 1 point improvement in pain score at the end of treatment.³³ Mean duration of treatment was 7 months (range 3 to 12 months).³³ Overall, for the treatment of pain progestins (either IUD, depot-medroxyprogesterone acetate, or combined oral contraceptives) demonstrated no significant difference from gonadotropin releasing hormone agonists (RD 0.036, 95% CI 0.03 to 0.102).³³ Upon comparison of IUD versus depot-medroxyprogesterone acetate, no difference in endometriosis associated pain was observed (RD -0.006, 95% CI -0.124 to 0.162).³³ Data from 1 trial demonstrated that progestins were also less effective than combined oral contraceptives for the treatment of pain with endometriosis (RD 0.321, 95% CI -0.066 to 0.707).³³ These results were limited by the small sample size and quality of included studies.

Prevention of preterm birth

A Cochrane systematic review in 2013 examined 36 randomized control trials (8523 women and 12,515 infants) utilizing progesterone (intramuscular, oral or vaginal) for the prevention of preterm birth.¹⁶ Women included in the study had a history of spontaneous preterm birth, short cervix identified on ultrasound, or a multiple pregnancy. Results demonstrated that women with a history of spontaneous preterm birth had a significant reduction of perinatal mortality (RR 0.50,

95% CI 0.33 to 0.75), preterm birth at 34 weeks (RR 0.31, 95% CI 0.14 to 0.69), and preterm birth at 37 weeks (RR 0.55, 95% CI 0.42 to 0.74) with progesterone use compared to placebo.¹⁶ Secondary outcomes of infant birthweight, assisted ventilation, necrotizing enterocolitis, and admission to neonatal ICU were also statistically lower in women taking progesterone.¹⁶ In women with a short cervix, progesterone use was associated with similar decreased risk of preterm birth at 34 weeks (RR 0.64, 95% CI 0.45 to 0.90), but had no difference in perinatal mortality or other secondary outcomes compared to placebo.¹⁶ No difference in efficacy was observed between doses or routes of administration.¹⁶ In addition, in women with a multiple pregnancy or women with threatened preterm labor, there was no difference in any outcome including perinatal death or preterm birth as 34 weeks.¹⁶ Other systematic reviews have demonstrated similar trends for women with a history of preterm birth in reduction of clinical neonatal outcomes with the use of vaginal¹⁷⁻¹⁹ and systemic progestins.^{19,48}

A review conducted by NICE in 2015 examined 13 studies to determine the efficacy of oral or vaginal progesterone for prevention of preterm birth in high-risk women.⁴⁹ High-risk women were defined as women with a previous history of spontaneous preterm birth or a short cervix.⁴⁹ The intramuscular formulation of hydroxyprogesterone caproate was not evaluated in this study. Significant heterogeneity existed between trials with differences in assessment of cervical length, inclusion criteria, dosing, timing and duration of progesterone use. However, direction of effect was consistent, demonstrating benefit with progesterone use. In women with a history of spontaneous preterm birth, significantly lower risk of preterm birth was demonstrated with vaginal progesterone at 37 weeks (moderate quality evidence) and oral progesterone at 34 weeks (moderate to high quality evidence).⁴⁹ However, results for other outcomes (including preterm birth at other times, perinatal mortality, neonatal death, and neonatal sepsis) failed to reach statistical significance.⁴⁹ In women with ultrasound identified short cervix, vaginal progesterone significantly decreased preterm births at 28, 33 and 35 weeks compared to placebo.⁴⁹ No difference was observed in other outcomes of perinatal mortality, intrauterine fetal death, neonatal death, preterm birth at 37 weeks, bronchopulmonary dysplasia or neonatal sepsis (moderate to low quality evidence).⁴⁹ In addition in one small RCT, no difference was observed between perinatal death, neonatal morbidity or preterm birth upon comparison of prophylactic cerclage and prophylactic progesterone (low quality evidence).⁴⁹

A review from CADTH was published in 2014 specifically examining the efficacy of vaginal micronized progesterone capsules for the prevention of miscarriage and preterm birth. The review was primarily based on 3 studies which included 1027 women.⁵⁰ Because of variability in population between the studies, a meta-analysis was not conducted. Overall, results from the studies suggest that progesterone capsules compared to placebo may decrease risk of preterm birth at less than 37 or 34 weeks.⁵⁰ However, statistical significance in individual studies varied, and the authors recommend careful interpretation of these results.⁵⁰ For example, relative risk for preterm birth at 37 weeks reached statistical significance in only 1 trial (RR 0.32, 95% CI 0.14 to 0.72).⁵⁰ For prevention of preterm birth at 34 weeks, all 3 trials demonstrated similar trends, but only 1 trial achieved statistical significance (RR 0.58, 95% CI 0.35 to 0.87).⁵⁰ Results also varied for the 2 trials reporting improvement with birth weight less than 2,500 g (RR 0.96, 95% CI 0.73 to 1.27) and (RR 0.88, 95% CI 0.79 to 0.98) and admission to the neonatal intensive care unit (RR 0.11, 95% CI 0.01 to 2.01) and (RR 0.89, 95% CI 0.79 to 0.99).⁵⁰ All other maternal or neonatal outcomes failed to reach statistical significance.⁵⁰

Another systematic review in 2015 examined effectiveness of progestins in women with twin pregnancies based on a review of individual patient level data.⁵¹ The review included 13 RCTs (n=3,768 women, 7,536 babies) that compared vaginal progesterone or intramuscular hydroxyprogesterone caproate to placebo or no treatment.⁵¹ Women were on average 32 years of age, Caucasian (78-90%), and had a mean gestational age of 19-20 weeks at randomization.⁵¹ The primary outcome was a composite of adverse perinatal outcomes defined based on the availability of data in the trials.⁵¹ It included perinatal death (fetal death or death before hospital discharge) or significant neonatal morbidity.⁵¹ Significant morbidity was a composite of respiratory distress syndrome, bronchopulmonary dysplasia, intraventricular hemorrhage, necrotizing enterocolitis, and culture-proven sepsis for the hydroxyprogesterone caproate group, but only included respiratory distress syndrome, intraventricular hemorrhage, and necrotizing enterocolitis for the vaginal progesterone group.⁵¹ Overall, there was no difference in adverse perinatal outcomes for women given hydroxyprogesterone caproate versus placebo (RR 1.2, 95% CI 0.87 to 1.5) or vaginal progesterone (RR 0.96, 95%

CI 0.83 to 1.1).⁵¹ Individual components of the composite were also similar between groups.⁵¹ A pre-specified subgroup analysis of adverse perinatal outcomes in women with a cervical length of less than 25 mm was significantly improved in women receiving vaginal progesterone compared to placebo (RR 0.57, 95% CI 0.47 to 0.70; NNT 10).⁵¹ Outcomes were not improved in a similar population (women with a cervical length <25 mm) receiving hydroxyprogesterone caproate or in other populations receiving vaginal progesterone.⁵¹ In a prior systematic review published in 2013, use of vaginal estrogen had demonstrated improved neonatal morbidity and mortality in women with twin gestation, short cervix, and no previous preterm birth (RR 0.52, 95% CI 0.29 to 0.93).¹⁸ This review was limited by the small number of included studies (n=5) and a limited patient population (n=775 women, 827 infants).¹⁸

A recently published systematic review examined evidence comparing intramuscular hydroxyprogesterone caproate and vaginal progesterone for prevention of recurrent preterm birth in women with a singleton pregnancy.²⁰ The review included 3 randomized control trials directly comparing vaginal progesterone formulations to 250 mg intramuscular hydroxyprogesterone (n=680).²⁰ Formulations of vaginal progesterone included 90 mg vaginal gel daily and 100 and 200 mg suppositories daily.²⁰ Women in these trials had a history of prior preterm birth and were on average 16 weeks pregnant at the time of randomization. Overall, women treated with vaginal progesterone had a significantly lower rate of preterm birth at 34 weeks (17.5% vs 25.0%; RR 0.71, 95% CI 0.53 to 0.95) and 32 weeks (8.9% vs 14.5%; RR 0.62, 95% CI 0.40 to 0.94) compared to intramuscular hydroxyprogesterone, but no difference at 37, 28 or 24 weeks.²⁰ In addition, vaginal progesterone was associated with a lower rate of admission to the neonatal intensive care unit (18.7% vs 23.5%; RR 0.63, 95% CI 0.47 to 0.83).²⁰ No difference was observed in other clinically important neonatal outcomes.²⁰ Adverse drug reactions were also reported more frequently in women randomized to intramuscular hydroxyprogesterone compared to vaginal progesterone (7.1% vs 13.2%; RR 0.53, 95% CI 0.31 to 0.91).²⁰ The specific nature of these adverse effects was not reported, but common adverse effects associated with hydroxyprogesterone caproate include injection site reactions. All outcomes were graded as low quality of evidence due to the small population size, large variance associated with the estimated treatment effect, and differences in vaginal formulations.²⁰

Clinical Practice Guidelines:

Menopause Symptoms

The Endocrine Society developed new clinical practice guidelines in 2015 assessing management and treatment of symptoms of menopause.²⁴ HRT can be considered for treatment of vasomotor symptoms in women less than 60 years of age or less than 10 years past menopause who do not have contraindications to therapy including high cardiovascular or breast cancer risk (weak recommendation with low quality evidence).²⁴ Authors note that there is no consensus opinion among professional societies regarding relative and absolute contraindications, but they generally recommend avoiding HRT in women with unexplained vaginal bleeding, active liver disease, and history of breast cancer, endometrial cancer, or cardiovascular disease (stroke, transient ischemic attack, pulmonary embolism, VTE, and MI).²⁴ Caution is advised in patients with diabetes, hypertriglyceridemia greater than 400 mg/dL, active gallbladder disease, increased risk of cardiovascular disease or breast cancer, and migraine with aura.²⁴ Estrogen alone can be utilized in women without a uterus, but estrogen plus progestin therapy is recommended in women with a uterus due to increased risk of endometrial hyperplasia and cancer with estrogen alone (weak recommendation with low quality evidence).²⁴ Combination conjugated equine estrogens with bazedoxifene may also be utilized in postmenopausal women with a uterus to relieve vasomotor symptoms and prevent bone loss (weak recommendation based on moderate quality evidence).²⁴ Non-hormonal agents are recommended as first-line therapy in women with high risk of cardiovascular disease or high (5-year risk >5%) to intermediate (5-year risk >1.67%) risk of breast cancer (weak recommendation with low quality evidence).²⁴ High-risk cardiovascular conditions include prior MI, cerebrovascular disease, peripheral arterial disease, abdominal aortic aneurism, diabetes, chronic kidney disease or a 10-year cardiovascular disease risk greater than 10%. Women with moderate (unspecified) cardiovascular risk may consider transdermal estradiol and progestins without an adverse metabolic profile (weak recommendation with low quality evidence).²⁴ In women a prior history of VTE, preferred therapy includes low-dose, non-oral estrogens (strong recommendation with low quality evidence) and a progestin such as progesterone with fewer adverse coagulation parameters (strong recommendation with moderate quality evidence).²⁴ Preferred treatment for

moderate to severe genitourinary symptoms is low-doses vaginal estrogen after a failed trial of vaginal moisturizers or lubricants (strong recommendation with moderate quality evidence).²⁴ In women with a uterus utilizing low dose vaginal estrogen, concurrent progestin therapy for prevention of endometrial hyperplasia is not required (weak recommendation with very low quality evidence).²⁴ Ospemifene may be considered in women with moderate to severe dyspareunia (weak recommendation with moderate quality evidence), but is not recommended in women with a history of breast cancer (strong recommendation with very low quality evidence).²⁴ In patients with a history of estrogen dependent cancer, prescription vaginal estrogen should be considered only in consultation with an oncologist.²⁴

Guidelines from NICE for the evaluation and treatment of menopause were updated in 2015 based on a recent systematic review.⁴ The review included both RCTs and observational studies and evaluated quality of evidence for both short and long-term risks and benefits of HRT. Strength of recommendations was not assessed. Because many studies were excluded from the analysis, there was considerable uncertainty in the estimates of treatment effects; and guideline recommendations were strongly influenced by current practice standards and clinical expertise.⁴ Guidelines suggest utilization of estrogen plus progesterone (oral or transdermal) in women with a uterus, and estrogen alone in women without a uterus as first-line treatment of vasomotor symptoms.⁴ HRT are also the preferred pharmacological options for mood symptoms as a result of menopause, though cognitive behavioral therapy may also be used as initial treatment.⁴ SSRIs/SNRIs are not recommended as a first-line option due to their significant adverse effect profile and their lack of data in women who have not been diagnosed with depression.⁴ Vaginal HRT was recommended as the preferred first-line treatment for vaginal symptoms, and it may be used in combination with systemic HRT formulations.⁴ Due to limitations in economic data, no recommendations were made regarding ospemifene for the treatment of vaginal symptoms. Treatment should be individualized based on patient specific risk factors for adverse effects including breast cancer, endometrial cancer, and VTE.⁴ Other long-term factors that may influence treatment choice include a patient's individual risk for MI, stroke, fragility fractures, or dementia. Transdermal estrogens are recommended in patients with increased or high risk of VTE as they have demonstrated a lower risk compared to oral therapy.⁴ Referral to a hematological specialist may be beneficial to assess appropriate therapy in patients with high risk of VTE.⁴ There was insufficient evidence to recommend HRT over combined oral contraception in women with primary ovarian insufficiency (POI).⁴ In POI, treatment with either HRT or combined oral contraceptives are recommended until the age of natural menopause (unless contraindicated).⁴ Evidence to support recommendations for the optimum time to assess efficacy and safety of HRT was also lacking.⁴ Current practice includes assessment after 3 months to determine effectiveness and tolerability and at least annually thereafter.⁴ Upon comparison of abrupt discontinuation compared to tapering methods, no strong difference was found in short- or long-term symptom relief.⁴ Guidelines recommend discontinuation methods be individualized based on patient preferences.⁴

Uterine Bleeding

NICE guidelines, published in 2007 and updated in 2016, recommend use of either hormonal or non-hormonal therapy in cases of heavy menstrual bleeding without presence of fibroids or with fibroids less than 3 cm in diameter (based on non-comparative studies or expert opinion).⁵² Options are considered in the following order, but should take individual circumstances into account: 1) levonorgestrel IUD if at least 12 months of use is anticipated (based on high quality evidence from at least 1 systematic review or RCT), 2) non-hormonal options or combined oral contraceptives (based on high quality systematic reviews of observational studies with consistent direction of effect), and 3) norethindrone 15 mg daily from days 5 to 26 or injected long-acting progestins (based on high-quality evidence from at least 1 systematic review or RCT).⁵² Guidelines recommend against the use of oral progestins given for only 12 to 14 days each month due to decreased efficacy (based on high quality evidence from at least 1 systematic review or RCT).⁵²

Guidelines from the Society of Obstetrics and Gynaecology of Canada (SOGC) recommend use of hormonal therapy to reduce heavy menstrual bleeding in women who desire effective contraception after malignancy or significant pelvic pathology has been ruled out.³⁴ Recommended regimens include combined oral contraceptives, depot-medroxyprogesterone acetate or levonorgestrel IUD.³⁴ Use of long phase progestins (from days 5 to 26) may also be considered though

they may be associated with more adverse effects.³⁴ However, use of cyclic oral progestins taken for 12 to 14 days each month is not recommended as a specific treatment for heavy menstrual bleeding because these regimens are less effective at reducing blood loss.³⁴ Recommendations were based on good evidence from at least one RCT.³⁴ Recommendations from the American College of Obstetricians and Gynecologists include similar treatment options of combined oral contraceptives, oral progestins, and the levonorgestrel-releasing IUD (based on limited or inconsistent scientific evidence).⁵³ Choice of medical treatment is individualized based on the goals of treatment (i.e. to stop acute bleeding, avoid future irregular bleeding, provide contraception, or prevent future complications of anemia, surgery and decreased quality of life) (based on limited data and expert opinion).⁵³

Endometrial carcinoma and endometrial hyperplasia

National Comprehensive Cancer Network guidelines for the treatment of uterine neoplasms have strict recommendations for the use of fertility-sparing options for treatment of endometrial carcinoma.³⁸ All recommendations regarding use of progestins as fertility-sparing therapy for endometrial carcinoma are based on low level evidence with uniform consensus from panel members.³⁸ Typical standard of care for endometrial cancer includes either surgery or radiation. Hormone therapy may be considered in patients who are not candidates for surgery or radiation or in women desiring fertility-sparing treatment options.³⁸ Because use of progestins is not the typical standard of care in endometrial cancer, women considering progestin use must have a well-differentiated endometrioid adenocarcinoma limited to the endometrium with absence of suspicious or metastatic disease.³⁸ Recommended progestins include megestrol acetate, medroxyprogesterone or a levonorgestrel IUD.³⁸ Treatment option should be individualized based on patient specific risk factors and contraindications with follow-up every 3 to 6 month to assess disease response. In women with early stage endometrial cancer, data suggest that though the recurrence rate is high (35%) in women taking progestins, therapy has not been associated with an increased risk of cancer-related mortality.³⁸ For women trying to conceive, consultation with a fertility expert prior to therapy is recommended.³⁸ Surgery with total hysterectomy is recommended if patients have a documented progression, continued disease, or have completed childbearing.³⁸ Hormone therapy (including the use of progestational agents, aromatase inhibitors or selective estrogen receptor modulators) also has a role as systemic therapy for recurrent, metastatic or high-risk disease in patients with low grade endometrial histology, small tumor volume, or carcinoma with an indolent growth rate.³⁸

Endometriosis

Guidelines published in 2010 from Society of Obstetrics and Gynaecology of Canada for the treatment of endometriosis recommend continuous combined oral contraceptives or progestin therapy alone (oral, injected, or IUD) as first-line therapy (Grade 1A: good evidence to recommend action from at least 1 RCT).¹⁰ The guideline authors note that though these medications are commonly used in practice, little evidence compares their efficacy with other medications.¹⁰ Indeed, more recently published systematic reviews (discussed in detail above) note that progestins have limited utility for improvement of pain-related outcomes in endometriosis.^{8,33} Agents specifically mentioned in these guidelines include norethindrone acetate 5 to 20 mg daily, intramuscular or subcutaneous medroxyprogesterone acetate, and the levonorgestrel-releasing IUD.¹⁰ Choice of therapy depends on adverse effects. Norethindrone acetate and medroxyprogesterone acetate can have heavy breakthrough bleeding. In addition, injection therapy is not the best option for women trying to conceive as it can result in prolonged delay in resumption of ovulation.¹⁰ The interuterine system is another long-term treatment which is inserted for 5 years and delivers levonorgestrel directly to the site of action. It can be effective at managing pain but is associated with an increased risk of pelvic infections.¹⁰ Regarding infertility associated with endometriosis, no medications have been identified which improve fertility outcomes and medication management should not be offered (Grade 1E: good evidence to recommend against action from at least 1 RCT).¹⁰

Similar treatment options are recommended for endometrial associated pain by the American College of Obstetricians and Gynecologists in a practice bulletin published in 2010 and reaffirmed in 2014.⁹ Medical suppressive therapy may be used to improve pain associated with endometriosis but has no effect on fertility outcomes (recommendation based on good and consistent evidence).⁹ Hormonal treatment options include combined oral contraceptives or progestin therapy

alone. The guidelines make recommendations for oral contraceptives, oral norethindrone or depot-medroxyprogesterone acetate in women with known endometriosis and dysmenorrhea (based on limited or inconsistent evidence).⁹ They also note that long-term use of oral contraceptives (>24 months) has been shown to reduce endometrioma recurrence and symptoms of dysmenorrhea (based on limited or inconsistent evidence).⁹

Prevention of preterm birth

NICE guidelines for prevention of preterm labor suggest offering prophylactic progesterone to women with a cervical length of less than 25 mm (with or without previous history of preterm birth or pregnancy loss).⁴⁹ Progesterone may also be considered in women with a cervical length less than 25 mm who have had pre-term pre-labor rupture of membranes in a previous pregnancy or women with a history of cervical trauma.⁴⁹ Both progesterone and cervical cerclage have demonstrated benefit in women with a history of preterm birth, but there is limited evidence regarding their comparative efficacy and safety.⁴⁹ NICE guidelines recommend against the use of intramuscular or vaginal progesterone to prevent spontaneous preterm birth in twin or triplet pregnancies.⁵⁴ Strength of these recommendations was not rated. The guideline committee concluded that evidence for benefit of therapy was not high enough to recommend for all women at risk of preterm birth, and evidence for risks of therapy was not high enough to recommend against its use in this population.⁴⁹

New Safety Alerts:

Since 2014, contraindications for Estrasorb® (estradiol topical emulsion), Evamist® (estradiol transdermal spray), and Cenestin® (synthetic conjugated estrogens, A) were updated to include anaphylactic reactions and angioedema.⁵⁵ Contraindication labeling was also added to Estrasorb®, Evamist®, and Enjuvia® (synthetic conjugated estrogens, B) for known protein C, protein S, antithrombin deficiency or other thrombophilic disorders.⁵⁵

In March 2015, the contraindications labeling for Cenestin® was also updated to include known or suspected pregnancy. Labeling states, “there is no indication for Cenestin® in pregnancy. There appears to be little or no increased risk of birth defects in children born to women who have used estrogens and progestins from oral contraceptives inadvertently during early pregnancy.”⁵⁵

In 2015, safety labeling for Estrasorb® and Enjuvia® was updated for the boxed warning of endometrial cancer, cardiovascular disorders, breast cancer and probable dementia. Warnings were edited to emphasize that women with a uterus who use unopposed estrogens have an increased risk of endometrial cancer.⁵⁵ Labeling also advises that estrogen alone or in combination with progestins should not be used for the prevention of cardiovascular disease or dementia.⁵⁵ Results from the WHI demonstrate an increased risk of stroke and VTE with estrogen alone and increased risk of VTE, stroke, and MI with combination therapy.⁵⁵ Results from WHI Memory Study demonstrate an increased risk of probable dementia in postmenopausal women greater than 65 years of age.⁵⁵ Warnings also included data from the WHI estrogen plus progestin study which reported an increased risk of invasive breast cancer.⁵⁵

New Formulations or Indications:

No new estrogen or progestin formulations identified.

Randomized Controlled Trials:

No new RCTs were identified. A total of 418 citations were manually reviewed from the literature search. Only trials reporting new comparative evidence were considered for inclusion. After manual review all trials were excluded due to wrong study design, comparator, outcome studied, or lack of reported comparative outcome data.

NEW DRUG EVALUATION:

See **Appendix 2** for **Highlights of Prescribing Information** from the manufacturer, including Black Boxed Warning 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.

Clinical Efficacy:

Ospemifene was approved primarily on the basis of 2 phase 3 clinical trials (Studies 15-50310 and 15-50821) which examined the efficacy of ospemifene for the treatment of moderate to severe dyspareunia and vaginal dryness in women with vulvar and vaginal atrophy as a result of menopause²⁶⁻²⁸. Therapy was given in addition to background therapy of as needed vaginal lubricants. Women who were on concomitant HRT were excluded from these studies or were required to undergo a washout period before screening²⁶⁻²⁸. The number of patients who had previously taken HRT was not reported. A third phase 3 trial was not considered for FDA approval as it did not assess improvement in symptoms.² Further extension studies from these trials provided additional efficacy and safety data for up to 12 months. The following primary outcomes were reported as a change from baseline to 12 weeks: vaginal pH, severity of the most bothersome symptom, percent of superficial cells, and percent of parabasal cells upon vaginal smear.²

Overall, the phase 3 trials used for FDA approval had a low to moderate risk of bias. These studies were randomized, double-blinded, placebo-controlled trials. The methods used to randomize patients were not reported but baseline characteristics were balanced in both studies. Matching placebo was used to blind patients, but blinding methods of providers and outcome assessors for vaginal smears was not stated. Attrition was comparable between groups; the most common reasons for discontinuation were adverse effects and withdrawal from the study.² Missing data were imputed using last observation carried forward which may overestimate treatment effect if symptoms typically return after treatment discontinuation. The studies were funded by QuatRx Pharmaceuticals and Shionogi, Inc. who developed and market the medication.²⁶⁻²⁸

The majority of women included in these trials were postmenopausal Caucasian women with an average age of 58 to 59 years.²⁶⁻²⁸ Women included in the study had a diagnosis of vulvovaginal atrophy defined as superficial cells of less than 5% on a vaginal smear, vaginal pH greater than 5, and at least 1 moderate to severe vaginal symptom.²⁶⁻²⁸ Symptom severity was assessed on a 4-point scale with moderate or severe symptoms corresponding to a score of 2 or 3. Exclusion criteria limit ospemifene use in patients with history of endocrine cancer, abnormal gynecological findings upon exam, or in combination with strong CYP 3A4 inhibitors.

Approval for ospemifene was based on symptomatic improvement from baseline to 12 weeks in a modified intention-to-treat (mITT) population including only patients who met *all* the pre-specified inclusion criteria of vulvovaginal atrophy (i.e. superficial cells <5% on vaginal smear, pH >5, and at least one moderate to severe symptom of dyspareunia or vaginal dryness). Patients who did not meet these criteria (1-7% of the population) were excluded from the FDA analysis.² Improvement in symptoms was measured on a 4-point scale (0 = none, 1 = mild, 2 = moderate, 3 = severe). Other endpoints including change in superficial cells, parabasal cells and vaginal pH were not considered clinically meaningful outcomes.² In both phase 3 trials, ospemifene 60 mg demonstrated a statistically significant mean reduction in dyspareunia symptoms compared to placebo on a 4-point scale. In the modified intention-to-treat population of Study 15-50310, dyspareunia improved an average of 1.39 points (SD 0.11) in the ospemifene group compared to a 0.89 point (SD 0.11) improvement in the placebo group (MD 0.51, 95% CI 0.20 to 0.81, p=0.0012).^{2,3} In Study 15-50821, average improvement in dyspareunia symptoms was 1.55 points (SD 0.06) in the ospemifene groups compared to 1.29 points (SD 0.07) in the placebo group (MD 0.36, 95% CI 0.18 to 0.53, p<0.001).³ Improvement in vaginal dryness achieved statistical significance in only one study (15-50310), with a difference of 1.29 points (SD 0.09) in the ospemifene 60 mg group compared to 0.92 points (SD 0.10) in the

placebo group (MD 0.37, 95% CI 0.11 to 0.63, $p=0.0136$).³ In Study 15-50821, ospemifene failed to achieve statistical significance for the improvement of vaginal dryness (mean change in ospemifene group of 1.33 (SD 0.08) vs. 1.11 (SD 0.08) in placebo; (MD 0.22, 95% CI 0.003 to 0.44, $p=0.0853$).³ Similar effect sizes were observed in the intention-to-treat population conducted by the manufacturers.²⁶⁻²⁸ Having failed to reach statistical significance in both trials, improvement in vaginal dryness was not included in the FDA indication.

However, despite the fact that ospemifene demonstrates a statistically significant change in dyspareunia, questions remain about its efficacy. In these trials a large placebo response was observed with a mean improvement in symptoms of 0.89 and 1.2 points. This large placebo response may be attributed to the use of background lubricants which participants could use as needed. Overall, rates of lubricant use in both placebo and ospemifene groups decreased with time. In patients taking ospemifene, 22-35% of patients in the ospemifene groups and 29-39% of patients in placebo groups were using non-hormonal lubricant at 12 weeks. Statistical significance was not reported. In addition, the 4-point scale utilized in the trials has not been validated as an assessment tool for evaluation of menopause symptoms, and the minimum clinically important difference with this scale has not been established.

Clinical Safety:

Safety analyses were conducted in 2654 participants included in double-blind phase 2 and 3 trials who received at least one dose of ospemifene. Extension studies of phase 3 trials evaluating ospemifene use for up to 1 year were also included in the safety analysis. A total of 1242 received the FDA approved dose of 60 mg.² Secondary analyses conducted with all patients in phase 1, 2, and 3 trials demonstrated similar trends.² Serious adverse effects were reported in 39 patients (2.3%) taking ospemifene 30 or 60 mg doses and in 17 patients (1.8%) taking placebo.² No serious adverse occurred more in more than 2 subjects per group. Respective serious adverse events that occurred more than once in patients taking ospemifene compared to placebo included appendicitis (2 vs. 0), cerebrovascular accident (2 vs. 1), diverticulitis (2 vs. 1) and DVT (2 vs. 0).² Discontinuation due to adverse events was higher in the treatment group (7.1%) compared to placebo (3.7%).² Most common adverse events leading to treatment discontinuation were hot flashes, headaches and nausea. The most common adverse events reported in patients taking ospemifene included hot flashes (7.5%), vaginal discharge (3.7%), and headache (3.1%).² Additional adverse reactions that have been potentially identified through post-marketing experience include hypersensitivity reactions, angioedema, rash and urticaria.⁵⁶

Assessments for long-term safety outcomes of endometrial, cardiovascular and breast cancer risk included patients in 3 long-term studies with mean follow-up times of approximately 36, 44, and 46 weeks.² Assessment of endometrial and uterine safety outcomes demonstrated an increase in endometrial thickness without reports of hyperplasia or carcinoma. Only one case of endometrial hyperplasia without atypia was documented in a patient taking ospemifene 3 months after treatment discontinuation.² In phase 2 and 3 trials, endometrial thickness greater than 4 mm was documented in 16.6% of women taking ospemifene 60 mg compared to 5.1% of women taking placebo.² Uterine polyps were identified in 10 patients (1.1%) taking 60 mg ospemifene versus 2 patients (0.35%) on placebo.² Overall, endometrial adverse effects were consistent with rates in postmenopausal women and demonstrate the agonist effects of ospemifene in the endometrium and uterus.² Thromboembolic events (including cerebrovascular accident, DVT, acute MI, cerebral hemorrhage and hemorrhagic stroke) occurred in 6 (0.34%) patients taking ospemifene versus 1 (0.1%) in placebo.² Estimated risk of VTE was 2.12 VTEs/1000 patient years, similar to rates observed with other SERMs and low-dose estrogen products.² Similar to estrogen products, warnings for increased risk of DVT, stroke and endometrial cancer are included in a box warning for ospemifene. Rates of breast cancer were rare in either group ($n=3$) and no difference in those treated with ospemifene versus placebo was found.² Other serious adverse events included vaginal bleeding or spotting in women with a uterus (17 patients [1.5%] in ospemifene groups vs. 5 patients [0.9%] in placebo groups), urinary symptoms or infection (161 patients [9.5%] on ospemifene vs. 60 [6.3%] on placebo), and pelvic organ prolapse (3 events in ospemifene groups vs. 1 in placebo).² Overall, studies of ospemifene conducted for almost 1 year demonstrated a numerically higher rate of serious adverse events indicating a potential increased risk for VTE, breast or endometrial cancer, and cardiovascular events. However, as these events are rare, long-term studies with a larger population of patients to evaluate risk and safety will need to be conducted.

Pharmacology and Pharmacokinetic Properties:^{21,56}

Parameter	
Mechanism of Action	Mixed estrogen receptor agonist/antagonist with tissue selective effects. In the vagina, ovaries, and bone, ospemifene acts as an agonist. In the endometrium and mammary glands, ospemifene has antagonist effects. ²
Absorption	Bioavailability increases when taken with food (T_{max} = 2-2.5 hours)
Distribution and Protein Binding	Volume of distribution is approximately 448 L 99% protein bound
Metabolism	Primarily metabolized via CYP3A4, CYP2C9 and CYP2C19; weak inhibitor of CYP2B6, CYP2C9, CYP2C19, CYP2C8, CYP2D6, and CYP3A4
Half-Life	26 hours
Elimination	75% in feces, 7% in urine

Abbreviations: T_{max} = time to maximum concentration

Comparative Clinical Efficacy:

Clinically Relevant Endpoints:

- 1) Improvement or resolution of vaginal symptoms (sexual dysfunction, vaginal dryness, discharge, itching, and dyspareunia)
- 2) Health-related quality of life
- 3) Early study withdrawal due to adverse event(s)
- 4) Serious adverse effects

Primary Study Endpoints:

- 1) Change in symptom severity (dyspareunia and vaginal dryness)
- 2) Change in superficial cells on vaginal smear
- 3) Change in parabasal cells on vaginal smear
- 4) Change in vaginal pH

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. Bachmann, et al. ²⁶ FDA Summary Review ² Study #: 15-50310 Phase 3, MC, DB, PC, RCT	1. Ospemifene 30 mg daily 2. Ospemifene 60 mg daily 3. Placebo 1:1:1 12 weeks	<p><u>Demographics:</u></p> <ul style="list-style-type: none"> - Mean age: 58.6 years - White: 99% - Time since last menstrual period: 15 years - Hysterectomy: 54.1% - Proportion w/dyspareunia: 46%; Mean baseline severity: 2.6 - Proportion w/vaginal dryness: 39%; Mean baseline severity: 2.4 <p><u>Key Inclusion Criteria:</u></p> <ul style="list-style-type: none"> - Postmenopausal women* - Age 40-80 years - VVA (superficial cells <5% on vaginal smear, pH >5, and ≥1 moderate to severe symptom) - Moderate to severe dyspareunia or vaginal dryness (score >2) <p><u>Key Exclusion Criteria:</u></p> <ul style="list-style-type: none"> - Endometrial thickness >4 mm - Pathological findings on endometrial exam or other gynecological abnormalities - Suspicion of malignancy or history of malignancy within 10 years - Abnormal labs, ECG, mammogram, breast or physical exam - History or current blood or thromboembolic disorder - BMI >37 kg/m² - BP >180/100 mmHg - Severe renal or hepatic impairment - Alcohol >14 drinks/week 	<p><u>ITT:</u></p> <ol style="list-style-type: none"> 1. 282 2. 276 3. 268 <p><u>mITT (patients meeting all 3 criteria for VVA):²</u></p> <ol style="list-style-type: none"> 1. NR 2. 223 3. 223 <p><u>Attrition:</u></p> <ol style="list-style-type: none"> 1. 20.2% 2. 15.2% 3. 14.2% 	<p><u>Primary Endpoints at 12 weeks (ITT population):</u></p> <p>Change in vaginal dryness (0-3 scale): mean (SD NR)</p> <ol style="list-style-type: none"> 1. 1.22 (p=0.04 vs. PBO) 2. 1.26 (p=0.021 vs. PBO) 3. 0.84 <p>Change in dyspareunia (0-3 scale): mean (SD NR)</p> <ol style="list-style-type: none"> 1. 1.02 (p=NS vs. PBO) 2. 1.19 (p=0.023 vs. PBO) 3. 0.89 <p><u>Secondary Endpoints:</u></p> <p>Proportion of patients using non-hormonal lubricant at 12 weeks:</p> <ol style="list-style-type: none"> 1. 31% 2. 22% 3. 29% <p>p-values NR</p>	NA NA NA NA	<p><u>Serious ADE:</u></p> <ol style="list-style-type: none"> 1. 5 (1.8%) 2. 0 (0.0%) 3. 4 (1.5%) <p>p-values NR</p> <p><u>DC due to ADE:</u></p> <ol style="list-style-type: none"> 1. 15 (5.3%) 2. 13 (4.7%) 3. 13 (4.9%) <p>p-values NR</p> <p><u>Change in endometrial thickness:</u></p> <p>mean (SD)</p> <ol style="list-style-type: none"> 1. 0.42 (1.35) mm 2. 0.72 (1.59) mm 3. -0.02 (1.03) mm <p>p-values NR</p>	NA NA NA	<p>Risk of Bias (low/high/unclear):</p> <p><u>Selection Bias:</u> UNCLEAR. Randomization method and allocation concealment NR. Baseline characteristics were balanced.</p> <p><u>Performance Bias:</u> LOW. Patients blinded via matching placebo. Specific blinding of providers NR.</p> <p><u>Detection Bias:</u> HIGH. Patients were blinded, but subjective assessment of symptomatic outcomes increases risk of bias. Blinding of assessors for vaginal smears NR. Endometrial biopsies assessed by 2 independent blinded pathologists.</p> <p><u>Attrition Bias:</u> HIGH. Overall attrition was high (14-20%) but comparable between groups; reasons for discontinuation were NR. LOCF was used for missing values which may increase magnitude of treatment effect. Analysis of ITT and PP populations, but not mITT suggested by the FDA. Power assumptions were NR.</p> <p><u>Reporting Bias:</u> HIGH. Measures of variance NR leading to uncertain effect size. Funding for studies provided by QuatRx Pharmaceuticals; manuscript funding provided by Shionogi, Inc.</p> <p>Applicability:</p> <p><u>Patient:</u> Majority of patients were Caucasian limiting applicability to other populations. Older population with an average 15 years since menopause onset. Efficacy and safety in a younger population or patients with less severe symptoms is unclear. The number of patients who were on HRT prior to enrollment in the study was not reported.</p> <p><u>Intervention:</u> Background use of lubricant and large placebo response makes assessment of magnitude of effect difficult.</p> <p><u>Comparator:</u> Placebo adequate. Lack of active control makes place in therapy less clear.</p> <p><u>Outcomes:</u> Surrogate outcomes of vaginal pH and change in endometrial cells upon exam with unclear correlation to symptom improvement. Minimum clinically significant difference with use of a 4 point Likert scale for MBS is unclear. Safety evaluated in an extension study for up to 52 weeks, but duration</p>

Results are reported separately for patients with dyspareunia and patients with vaginal dryness as their MBS (see Portman, et al, 2013).			1. 127 2. 137 <u>Attrition:</u> 1. 22 (13.8%) 2. 17 (11.0%)	1. 21.7% 2. 33.0% p-value NR		<u>Thickness:</u> mean (SD) 1. 0.82 (1.68) mm 2. -0.11 (1.20) mm p-values NR		<u>Patient:</u> See Study 15-50310. <u>Intervention:</u> See Study 15-50310. <u>Comparator:</u> See Study 15-50310. <u>Outcomes:</u> Wide standard deviations indicate imprecise estimate of treatment effect. Minimum clinically important difference for MBS is unclear with use of a 4 point scale. <u>Setting:</u> See Portman, et al. 2013.
<p><u>Abbreviations:</u> ADE = adverse drug events; ARR = absolute risk reduction; BMI = body mass index; BP = blood pressure; CI = confidence interval; DC = discontinuation; DB = double-blinded; ECG = electrocardiogram; HRT = hormone replacement therapy; ITT = intention to treat; LOCF = last observation carried forward; MBS = most bothersome symptom; MC = multicenter; mITT = modified intention to treat; N = number of subjects; NA = not applicable; NNH = number needed to harm; NNT = number needed to treat; NR = not reported; NS = not significant; PBO = placebo; PC = placebo controlled; PP = per protocol; RCT = randomized control trial; SD = standard deviation; VVA = vulvovaginal atrophy</p> <p>*Post-menopause was defined as >12 months since last spontaneous menstrual bleeding, >6 weeks since bilateral oophorectomy, or FSH >40 IU/L in women with hysterectomy and intact ovaries.</p>								

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Appendix 1: Current Status on Preferred Drug List

ESTROGEN REPLACEMENT, ORAL

ROUTE	FORMULATION	BRAND	GENERIC	PDL
ORAL	TABLET	ESTRACE	ESTRADIOL	Y
ORAL	TABLET	ESTRADIOL	ESTRADIOL	Y
ORAL	TABLET	ESTROPIPATE	ESTROPIPATE	Y
ORAL	TABLET	ANGELIQ	DROSPIRENONE/ESTRADIOL	N
ORAL	TABLET	COVARYX	ESTROGEN,ESTER/ME-TESTOSTERONE	N
ORAL	TABLET	COVARYX H.S.	ESTROGEN,ESTER/ME-TESTOSTERONE	N
ORAL	TABLET	DUAVEE	ESTROGENS,CONJ/BAZEDOXIFENE	N
ORAL	TABLET	EEMT	ESTROGEN,ESTER/ME-TESTOSTERONE	N
ORAL	TABLET	EEMT H.S.	ESTROGEN,ESTER/ME-TESTOSTERONE	N
ORAL	TABLET	ENJUVA	ESTROGENS,CONJ.,SYNTHETIC B	N
ORAL	TABLET	ESTRADIOL-NORETHINDRONE ACETAT	ESTRADIOL/NORETHINDRONE ACET	N
ORAL	TABLET	ESTROGEN & METHYLTESTOSTERONE	ESTROGEN,ESTER/ME-TESTOSTERONE	N
ORAL	TABLET	ESTROGEN-METHYLTESTOSTERONE	ESTROGEN,ESTER/ME-TESTOSTERONE	N
ORAL	TABLET	FEMHRT	NORETHINDRONE AC-ETH ESTRADIOL	N
ORAL	TABLET	FYAVOLV	NORETHINDRONE AC-ETH ESTRADIOL	N
ORAL	TABLET	JEVANTIQUE LO	NORETHINDRONE AC-ETH ESTRADIOL	N
ORAL	TABLET	JINTELI	NORETHINDRONE AC-ETH ESTRADIOL	N
ORAL	TABLET	LOPREEZA	ESTRADIOL/NORETHINDRONE ACET	N
ORAL	TABLET	MENEST	ESTROGENS,ESTERIFIED	N
ORAL	TABLET	MIMVEY	ESTRADIOL/NORETHINDRONE ACET	N
ORAL	TABLET	MIMVEY LO	ESTRADIOL/NORETHINDRONE ACET	N
ORAL	TABLET	NORETHINDRON-ETHINYL ESTRADIOL	NORETHINDRONE AC-ETH ESTRADIOL	N
ORAL	TABLET	PREFEST	ESTRADIOL/NORGESTIMATE	N
ORAL	TABLET	PREMARIN	ESTROGENS, CONJUGATED	N
ORAL	TABLET	PREMPHASE	ESTROGEN,CON/M-PROGEST ACET	N
ORAL	TABLET	PREMPRO	ESTROGEN,CON/M-PROGEST ACET	N

ESTROGEN REPLACEMENT, TRANSDERMAL

ROUTE	FORMULATION	BRAND	GENERIC	PDL
TRANSDERM	PATCH TDSW	ALORA	ESTRADIOL	Y
TRANSDERM	PATCH TDSW	ESTRADIOL	ESTRADIOL	Y
TRANSDERM	PATCH TDSW	MINIVELLE	ESTRADIOL	Y
TRANSDERM	PATCH TDSW	VIVELLE-DOT	ESTRADIOL	Y
TRANSDERM	PATCH TDWK	CLIMARA	ESTRADIOL	Y
TRANSDERM	PATCH TDWK	ESTRADIOL	ESTRADIOL	Y
TRANSDERM	GEL MD PMP	ELESTRIN	ESTRADIOL	N
TRANSDERM	GEL PACKET	DIVIGEL	ESTRADIOL	N
TRANSDERM	PATCH TDSW	COMBIPATCH	ESTRADIOL/NORETHINDRONE ACET	N
TRANSDERM	PATCH TDWK	CLIMARA PRO	ESTRADIOL/LEVONORGESTREL	N
TRANSDERM	PATCH TDWK	MENOSTAR	ESTRADIOL	N
TRANSDERM	SPRAY	EVAMIST	ESTRADIOL	N

ESTROGEN REPLACEMENT, VAGINAL

ROUTE	FORMULATION	BRAND	GENERIC	PDL
VAGINAL	CREAM/APPL	PREMARIN	ESTROGENS, CONJUGATED	Y
VAGINAL	TABLET	VAGIFEM	ESTRADIOL	Y
VAGINAL	TABLET	VAGIFEM	ESTRADIOL	Y
VAGINAL	CREAM/APPL	ESTRACE	ESTRADIOL	N
VAGINAL	CREAM/APPL	ESTRACE	ESTRADIOL	N
VAGINAL	VAG RING	ESTRING	ESTRADIOL	N
VAGINAL	VAG RING	ESTRING	ESTRADIOL	N
VAGINAL	VAG RING	FEMRING	ESTRADIOL ACETATE	N
VAGINAL	VAG RING	FEMRING	ESTRADIOL ACETATE	N

PROGESTINS

ROUTE	FORMULATION	BRAND	GENERIC	PDL
INTRAMUSC	VIAL	HYDROXYPROGESTERONE CAPROATE	HYDROXYPROGESTERONE CAPROATE	Y
INTRAMUSC	VIAL	MAKENA	HYDROXYPROGESTERONE CAPROATE	Y
ORAL	TABLET	MEDROXYPROGESTERONE ACETATE	MEDROXYPROGESTERONE ACETATE	
ORAL	TABLET	PROVERA	MEDROXYPROGESTERONE ACETATE	
ORAL	TABLET	NORETHINDRONE ACETATE	NORETHINDRONE ACETATE	
ORAL	TABLET	AYGESTIN	NORETHINDRONE ACETATE	
INTRAMUSC	VIAL	PROGESTERONE	PROGESTERONE	
VAGINAL	SUPPOSITORY	FIRST-PROGESTERONE VGS	PROGESTERONE	
VAGINAL	INSERT	ENDOMETRIN	PROGESTERONE	
ORAL	CAPSULE	PROGESTERONE	PROGESTERONE, MICRONIZED	
ORAL	CAPSULE	PROMETRIUM	PROGESTERONE, MICRONIZED	
VAGINAL	GEL	CRINONE	PROGESTERONE, MICRONIZED	

Appendix 2: Highlights of Prescribing Information

OSPHERA- ospemifene tablet, film coated Shionogi Inc.

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use OSPHERA safely and effectively. See full prescribing information for OSPHERA.

OSPHERA[®] (ospemifene) tablets, for oral use
Initial U.S. Approval: 2013

WARNING: ENDOMETRIAL CANCER AND CARDIOVASCULAR DISORDERS

See full prescribing information for complete boxed warning.

OSPHERA is an estrogen agonist/antagonist with tissue selective effects. In the endometrium, OSPHERA has estrogen agonistic effects. There is an increased risk of endometrial cancer in a woman with a uterus who uses unopposed estrogens. Adding a progestin to estrogen therapy reduces the risk of endometrial hyperplasia, which may be a precursor to endometrial cancer [see *Warnings and Precautions* (5.2)]. Estrogen-alone therapy has an increased risk of stroke and deep vein thrombosis (DVT). OSPHERA 60 mg had cerebral thromboembolic and hemorrhagic stroke incidence rates of 0.72 and 1.45 per thousand women, respectively vs. 1.04 and 0 per thousand women, respectively in placebo. For deep vein thrombosis, the incidence rate for OSPHERA 60 mg is 1.45 per thousand women vs. 1.04 per thousand women in placebo [see *Warnings and Precautions* (5.1)].

RECENT MAJOR CHANGES

- CONTRAINDICATIONS (4)

02/2015

INDICATIONS AND USAGE

OSPHERA is an estrogen agonist/antagonist indicated for the treatment of moderate to severe dyspareunia, a symptom of vulvar and vaginal atrophy, due to menopause (1)

DOSAGE AND ADMINISTRATION

- One tablet taken orally once daily with food (2.1)

DOSAGE FORMS AND STRENGTHS

Tablet: 60 mg (3)

CONTRAINDICATIONS

- Undiagnosed abnormal genital bleeding (4)
- Known or suspected estrogen-dependent neoplasia (4, 5.2)
- Active DVT, pulmonary embolism (PE), or a history of these conditions (4, 5.1)
- Active arterial thromboembolic disease (for example, stroke and myocardial infarction [MI]), or a history of these conditions (4, 5.1)
- Hypersensitivity (for example, angioedema, urticaria, rash, pruritus) to OSPHERA or any ingredients (4)
- Known or suspected pregnancy (4, 8.1)

WARNINGS AND PRECAUTIONS

- Venous Thromboembolism: Risk of DVT and pulmonary embolism (5.1)
- Known, suspected, or history of breast cancer (5.2)
- Severe Hepatic Impairment (5.3, 8.7, 12.3)

ADVERSE REACTIONS

Adverse reactions (≥ 1 percent) include: hot flush, vaginal discharge, muscle spasms, genital discharge, hyperhidrosis. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Shionogi Inc. at 1-855-OSPHERA (1-855-677-4362) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

DRUG INTERACTIONS

- Do not use estrogens or estrogen agonist/antagonist concomitantly with OSPHERA (7.1, 12.3)
- Do not use fluconazole concomitantly with OSPHERA. Fluconazole increases serum concentrations of OSPHERA (7.2, 12.3)
- Do not use rifampin concomitantly with OSPHERA. Rifampin decreases serum concentration of OSPHERA (7.2, 12.3)

USE IN SPECIFIC POPULATIONS

- Nursing Mothers: It is not known whether OSPHERA is excreted in human breast milk (8.3)

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

Revised: 8/2015

Appendix 3: Medline Search Strategy

Ovid MEDLINE(R) 1946 to September Week 4, 2016.

1	exp Menopause/	51731
2	exp Vasomotor System/	16967
3	exp Osteoporosis, Postmenopausal/	11972
4	hypoestrogenism.mp.	381
5	vaginal atrophy.mp.	385
6	vulval atrophy.mp.	3
7	1 or 2 or 3 or 4 or 5 or 6	78449
8	estropipate.mp.	48
9	exp Estrogens/	152946
10	exp Estrogen Replacement Therapy/	14636
11	8 or 9 or 10	161478
12	exp Progestins/	64782
13	exp Norpregnanes/	20040
14	exp Progesterone/	66993
15	12 or 13 or 14	90340
16	exp endometriosis/ or exp endometrial hyperplasia/	21969
17	uterine bleeding.mp. or exp Uterine Hemorrhage/	20507
18	exp Endometrial Neoplasms/	18200
19	11 or 15	205383
20	exp obstetric labor, premature/ or exp premature birth/	21466
21	16 or 17 or 18 or 20	78493
22	7 or 21	153438
23	19 and 22	25646
24	limit 23 to (english language and humans and yr="2014 -Current" and (clinical trial, all or clinical trial, phase iii or clinical trial, phase iv or clinical trial or comparative study or controlled clinical trial or meta analysis or multicenter study or pragmatic clinical trial or randomized controlled trial or systematic reviews))	418

Estrogen Derivatives

Goal(s):

- Restrict use to medically appropriate conditions funded under the OHP

Length of Authorization:

- Up to 12 months

Requires PA:

- Non-preferred estrogen derivatives
- All estrogen derivatives for patients <18 years of age

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 estrogen requested for a patient ≥18 years old?	Yes: Go to #3	No: Go to #4
3. Will the prescriber consider a change to a preferred product? Message: <ul style="list-style-type: none"> • Preferred products do not require a co-pay. Preferred products are evidence-based reviewed for comparative effectiveness and safety by the Oregon Pharmacy & Therapeutics (P&T) Committee. 	Yes: Inform prescriber of covered alternatives in class and approve for up to 12 months.	No: Approve for up to 12 months.
4. Is the medication requested for gender dysphoria (ICD10 F642, F641)?	Yes: Go to #5	No: Go to #6

Approval Criteria

<p>5. Have all of the following criteria been met?</p> <ul style="list-style-type: none"> • Patient has the capacity to make fully informed decisions and to give consent for treatment; and • If patient <18 years of age, the prescriber is a pediatric endocrinologist; and • The prescriber agrees criteria in Guideline Notes on the OHP List of Prioritized Services have been met. 	<p>Yes: Approve for up to 6 months</p>	<p>No: Pass to RPh. Deny; medical appropriateness</p>
<p>6. Is the medication requested for hypogonadism?</p>	<p>Yes: Approve for up to 6 months</p>	<p>No: Go to #7</p>
<p>7. RPh only: All other indications need to be evaluated to see if funded under the OHP.</p>	<p>If funded and prescriber provides supporting literature: Approve for up to 12 months.</p>	<p>If non-funded: Deny; not funded by the OHP</p>

P&T / DUR Review: 11/16 (SS); 11/15 (KS)
 Implementation: 1/1/16

Conjugated Estrogens/Bazedoxifene (Duavee®)

Goal(s):

- Approve conjugated estrogens/bazedoxifene only for indications where there is evidence to support its use and safety.
- Support the use of agents with clinical efficacy and safety supported by the medical literature and guidelines.

Initiative:

- Prior Authorization

Length of Authorization:

- 6-12 months

Requires PA:

- Conjugated estrogens/bazedoxifene

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/

Step Therapy Required Prior to Coverage:

Prevention of vasomotor symptoms: conventional hormone therapy (see preferred drug list options at www.orpdl.org)

Prevention of osteoporosis: bisphosphonates (see preferred drug list options at www.orpdl.org).

Approval Criteria		
1. What is the diagnosis?	Record ICD10 code	
2. Is patient a postmenopausal woman within 10 years of menopause?	Yes: Go to #3	No: Pass to RPh. Deny; medical appropriateness.
3. Is the patient <60 years of age with an intact uterus?	Yes: Go to #4	No: Pass to RPh. Deny; medical appropriateness

Approval Criteria

<p>4. Will the prescriber consider a change to a preferred product?</p> <p>Message:</p> <ul style="list-style-type: none"> Preferred products do not require a co-pay. Preferred products are evidence-based reviewed for comparative effectiveness and safety by the Oregon Pharmacy & Therapeutics (P&T) Committee. 	<p>Yes: Inform prescriber of covered alternatives in class.</p>	<p>No: Go to #5</p>
<p>5. Is the patient being prescribed the medication for the prevention of osteoporosis?</p>	<p>Yes: Go to #6</p>	<p>No: Go to #7</p>
<p>6. Has the patient tried and failed, or is there a contraindication to, bisphosphonates?</p>	<p>Yes: Approve for up to 12 months</p>	<p>No: Pass to RPh. Deny; medical appropriateness</p>
<p>7. Is the medication being prescribed for the prevention of vasomotor symptoms?</p>	<p>Yes: Go to #8</p>	<p>No: Pass to RPh. Deny; medical appropriateness</p>
<p>8. Has the patient tried and failed or has a contraindication to conventional hormone therapy?</p>	<p>Yes: Approve for up to 12 months</p>	<p>No: Pass to RPh. Deny; medical appropriateness</p>

P&T Review: 11/14
 Implementation: 1/1/15

Hydroxyprogesterone caproate (Makena®)

Goal(s):

- To ensure appropriate drug use and limit to patient populations in which hydroxyprogesterone caproate injection has been shown to be effective and safe.

Length of Authorization:

Up to 20 weeks

Requires PA:

- Hydroxyprogesterone caproate injection

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 patient between 16 weeks and 36 weeks 6 days gestation with a singleton pregnancy?	Yes: Go to #3	No: Pass to RPh. Deny; medical appropriateness
3. Has the patient had a prior history of preterm delivery before 37 weeks gestation (spontaneous preterm singleton birth)?	Yes: Go to #4	No: Pass to RPh. Deny; medical appropriateness
4. Is treatment being initiated at 16 weeks, 0 days and to 20 weeks, 6 days of gestation?	Yes: Approve through week 37 of gestation or delivery, whichever occurs first (no more than 20 doses).	No: Pass to RPh. Deny; medical appropriateness

P&T Review: 11/16 (SS); 5/13
 Implementation: 1/1/14