Ospemifene (OSPHENA)

National Drug Monograph

October 2015

VA Pharmacy Benefits Management Services, Medical Advisory Panel, and VISN Pharmacist Executives

The purpose of VA PBM Services drug monographs is to provide a comprehensive drug review for making formulary decisions. Updates will be made when new clinical data warrant additional formulary discussion. Documents will be placed in the Archive section when the information is deemed to be no longer current.

FDA Approval Information	
Description/Mechanism of Action	Ospemifene is a selective estrogen receptor modulator (SERM) with agonist actions on vaginal tissue, the endometrium and bone. Antagonist actions suggest antitumor effects in experimental breast cancer models. Ospemifene is not interchangeable with other SERMs such as raloxifene or tamoxifen, nor they with it.
Indication(s) Under Review in this document (may include off label)	Ospemifene is an estrogen agonist/antagonist indicated for the treatment of moderate to severe dyspareunia, a symptom of vulvar and vaginal atrophy, due to menopause.
Dosage Form(s) Under Review	Tablet (oral), 60 mg
REMS	☐ REMS X No REMS ☐ Postmarketing Requirements *See Other Considerations for additional REMS information*
Pregnancy Rating	X

Executive Summary	
Efficacy	• After 12 weeks ospemifene reduced the symptom score of dyspareunia significantly more than placebo. Thirty-eight percent of postmenopausal women taking ospemifene reported no pain upon intercourse compared to 28% taking placebo. • Ospemifene significantly improved the Maturation Index (composed of percent of vaginal parabasal and superficial cells, and vaginal pH) after 12 and 52 weeks of treatment. • Vaginal dryness symptom scores improved significantly more with ospemifene than placebo. Use of vaginal lubricant decreased more in women taking ospemifene than placebo.
Safety	• Ospemifene shares the box warning on endometrial cancer and cardiovascular disorders with the estrogens. As stated in ospemifene's label, the incident rates of stroke and venous thromboembolism for 0.625 mg conjugated estrogen-alone from the Women's Health Initiative are greater than those with ospemifene 60 mg. • The incident rates of thromboembolic and hemorrhagic stroke and DVT were greater with ospemifene 60 mg than placebo. • No cases of endometrial cancer were reported in the ospemifene trials. The incidence of endometrial thickening ≥0.5mm (in the absence of a progestin), any type of proliferative endometrium and uterine polyps was greater with ospemifene than placebo. • Common adverse effects include hot flushes, urinary tract infection, urinary

	candidiasis, vulvar and vaginal mycotic infections, and headache.
Potential Impact	• Ospemifene is an alternative to vaginal or systemic estrogen therapy in women who do not have adequate relief of dyspareunia from vaginal lubricant or moisturizer, and who cannot or will not take an estrogen. • Taking oral ospemifene daily may be more acceptable than using a vaginal estrogen cream or tablet daily or twice a week. • Oral ospemifene avoids the need to instill vaginal estrogen at least 12 hours before sexual intercourse in order avoid transmission to a partner may be an advantage for patients and partner.

Background

Purpose for review

Issues to be determined:

- To review the evidence supporting ospemifene's efficacy for the treatment of dyspareunia associated with vulvar and vaginal atrophy (VVA).
- To identify ospemifene's place in therapy relative to formulary and non-formulary alternatives.
- To review the safety of ospemifene as a treatment of dyspareunia associated with VVA and offer a perspective on how it differs from alternative treatments.

Other therapeutic options[1,2]

Estrogen is the gold standard treatment as it promotes vaginal cell growth and maturation, increases elasticity, vaginal blood flow and pH. Vaginal estrogens afford the lowest dose and are preferred when symptoms of VVA are the only complaint.

Formulary Alternatives	Other Considerations	CFU, Restrictions or Other Guidance
Vaginal lubricant, water based (K-Y Jelly equivalent)	Provides symptomatic relief during intercourse for most women; does not treat the underlying cause. Complaints of viscosity and difficult to administer. An alternative to estrogen-based treatment.	
Vaginal moisturizer, silicone based (Replens equivalent)	Has been shown to improve vaginal moisture, fluid volume, lower pH and elasticity, and reduces symptoms; does not improve vaginal maturation index. An alternative to estrogen-based treatment.	
Conjugate estrogen 0.625 mg/gm vaginal cream	0.5 - 2 gm administered cyclically for 21 days per month or twice weekly. Should be administered 12 hours before intercourse to avoid transmission to partner. Considered to be messy and measuring a dose can be difficult. Contraindicated in women taking an aromatase inhibitor. Avoid in women with a history of breast cancer.	
Systemic estrogen:	Use lowest dose based on patient's response. All may require concurrent cycling with a progestin. Contraindicated in women taking an aromatase inhibitor. Avoid in women with a history of breast cancer. Estrogens have been associated with an increased risk of stroke, gallbladder disease, venous thromboembolism, endometrial cancer and dementia.	
Conjugated, tab	Oral: 0.3 – 1.2 mg per day taken cyclically for 21 days per month or daily. Use lowest dose based on patient's response.	
Estradiol, tab, transdermal & IM	Oral: 1-2 mg/day cyclically (3-weeks on/1 week off); Transdermal: weekly or bi-weekly; IM: 10-20 mg every 4 weeks.	

Esterified estrogen, tab	Oral: 0.3 to ≥1.25 mg per day taken cyclically for 21 days per month or daily. Use lowest dose based on patient's response.	

Non-formulary Alternative	Other Considerations	CFU, Restrictions or Other Guidance
Vaginal lubricants and moisturizers	Some water-based gels can be hyperosmolar which damage and toxic to epithelial cells. The safety of propylene glycol and parabens is unknown. Oil-based lubricants can damage condoms.	
Estradiol 0.1mg/gm vaginal cream (Estrace)	Administer 2-4 gm per day for 1-2 weeks, then 1 gm per day. No RCTs with estradiol vaginal cream. Should be administered 12 hours before intercourse to avoid transmission to partner. Considered to be messy and measuring a dose can be difficult. Contraindicated in women taking an aromatase inhibitor. Avoid in women with a history of breast cancer.	
17β-estradiol 2 mg vaginal ring (Estring)	Insert one ring every 3 months; releases 7.5 µg estradiol per day. Can become dislodged. May be difficult to remove or insert. Avoid in women with a history of breast cancer.	
Estradiol heihydrate 10 µg & 25 µg vaginal tab (Vagifem)	Insert 1 tablet once daily for 2 weeks, then 1 tablet twice a week. Dissolves slowly over several hours. No guidance on how before intercourse a tablet should be inserted to avoid transmission to partner. Contraindicated in women taking an aromatase inhibitor. Avoid in women with a history of breast cancer.	
Systemic estrogen:		
Estradiol acetate 0.05 or 0.1 mg/day vaginal ring (Femring)	Insert 1 ring every 3 months. Can become dislodged. May be difficult to remove or insert. Avoid in women with a history of breast cancer.	
Estradiol 0.06% topical gel (EstroGel)	Topical: 1.25 gm applied daily. Avoid in women with a history of breast cancer.	

Efficacy (FDA Approved Indications)

Literature Search Summary

A literature search was performed on PubMed/OVID Medline (2000 to April 2015), ClinicalTrials.gov using the search terms ospemifene, dyspareunia, vulvar vaginal atrophy. Searches were conducted on authors of clinical trials. The search was limited to studies performed in humans and published in the English language. Reference lists of review articles and the clinical trials were searched for relevant clinical trials. Ospemifene's FDA drug approval package was reviewed for additional unpublished clinical trials. All randomized controlled trials published in peer-reviewed journals were included.

Review of Efficacy
The FDA approval of ospemifene was based on two pivotal 12-week Phase 3 multicenter, randomized, placebo-controlled, parallel group design trials, one trial having a 40-week open-label extension phase, and one Phase 3 52-week safety trial. All 3 trials, the extension and sub-analyses were sponsored by QuatRx, which has divested its portfolio to Forendo Pharma, based in Turku, Finland. Additional funding was provided by Shionogi Inc.

Quality of the Evidence – High (See Appendix A)
The women studied may or may not be representative of the female Veteran population of similar age as nearly 90% of women studied were white and the mean BMI was ~26 kg/m^2.

12-week Phase 3 Clinical Trials[4-6]

- Subjects were randomized to 30mg or 60 mg ospemifene or matching placebo daily. Results for the 30 mg dose are not presented as this dose is not marketed. All participants were given vaginal lubricant to use as needed. The use of progestin was prohibited.
- Primary efficacy outcome measures were the Maturation Index (as percentage changes in vaginal superficial, parabasal cells), vaginal pH, endometrial thickness, and dyspareunia and vaginal dryness compared to baseline.
- Dyspareunia and vaginal dryness were self-assessed using a 4-point Likert scale (0=none, 1=mild, 2= moderate, and 3=severe).
- Inclusion and exclusion criteria were uniform in the trials. All subjects were post-menopause (natural or surgical), with a Maturation Index of ≤5% superficial cells, a vaginal pH>5.0 and moderate-severe dyspareunia symptoms.
- In both trials the mean age of subjects was 58.6 years, nearly 90% were white, with mean BMIs ~26 kg/m^2, and ~50% had had a hysterectomy. Totals of 426 and 605 subjects were randomized in each trial with >80 completion rates in both ospemifene and placebo groups.
- Symptom scores for dyspareunia were significantly decreased with ospemifene 60 mg, -1.19 and -1.5, compared to placebo, -0.89 and -1.2, respectively. No pain upon intercourse was reported by 38% assigned to ospemifene mg and 28% assigned to placebo.
- Ospemifene 60 mg favorably improved the Maturation Index compared to placebo. Vaginal dryness symptom scores were significantly decreased with ospemifene compared to placebo (-1.22 vs. -0.84).
- After 12-weeks of ospemifene 60 mg, the proportion of women with no clinical signs of vaginal dryness, petechiae, pallor, friability or vaginal redness on visual vaginal exam had increased significantly compared to placebo.
- A moderate decrease in the use of vaginal lubricant was found between Week 1 and Week12: Ospemifene 60 mg 33.2% to 22.3% and 41.7% to 35.1%, and placebo 34% to 29.4% and 43.1% to 39.3%, respectively. Thus, ospemifene is unlikely to negate the need for a vaginal lubricant in many women.

Long-term Trials[7]

- A 52-week trial of 426 women with an intact uterus found results significantly favoring ospemifene compared to placebo with respect to changes in the percentage of parabasal and superficial cells, and vaginal pH.

Systematic Review and Meta-analysis[8]

- Included 5 RCTs, three 12-week and two 52-week trials.
- Quality of studies "A" based on the Cochrane Handbook for Systematic Reviews of Interventions.
- The difference in changes in parabasal cells, vaginal pH and dyspareunia were significant and favored ospemifene. The differences in endometrial thickness at weeks 12 and 52 were significant reflecting greater thickening associated with ospemifene.

Measure	N=Ospemifene 60 mg	Placebo	SMD	95% CI
Parabasal cells, %	619	609	-37.5	-41.83, -33.17
Superficial cells, %	619	609	9.24	7.70, 10.79
Vaginal pH	579	570	-0.89	-0.98, -0.80
Dyspareunia	579	570	-0.37	-0.43, -0.30
Endometrial thickness, 12 wks,mm	619	609	0.51	0.32, 0.70
Endometrial thickness, 52 wks, mm	432	112	0.90	0.58, 1.23

SMD – standard mean difference

Potential Off-Label Use

- Vaginal dryness – although evidence from the clinical trials failed to support an FDA label indication.
- Osteoporosis – in two 3-month Phase II trials ospemifene demonstrated significant effects on biomarkers of bone resorption and bone formation; similar to raloxifene in one trial.

Safety [3-5. 8-12]

(for more detailed information refer to the product package insert)

	Comments
Boxed Warning	WARNING: ENDOMETRIAL CANCER AND CARDIOVASCULAR DISORDERS *See full prescribing information for complete boxed warning.* Ospemifene is an estrogen agonist/antagonist with tissue selective effects. In the endometrium, ospemifene 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. Estrogen-alone therapy has an increased risk of stroke and deep vein Thrombosis (DVT). Ospemifene 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 ospemifene 60 mg is 1.45 per thousand women vs. 1.04 per thousand women in placebo.
Contraindications	• Undiagnosed abnormal genital bleeding • Known or suspected estrogen-dependent neoplasia • Active DVT, pulmonary embolism (PE), or a history of these conditions • Active arterial thromboembolic disease (e.g., stroke, myocardial infarction) or history of these conditions. • Women who are or may become pregnant
Warnings/Precautions	The Women's Health Initiative estrogen-alone substudy reported statistically significant increased risk of stroke in women 50 to 79 years, an increased risk of DVT and PE, but no overall effect on coronary heart disease events in those taking 0.625 mg of conjugated estrogen daily. • The incidence rates of thromboembolic and hemorrhagic stroke with ospemifene 60 mg daily was 0.72 and 1.45 per 1000, respectively, compared to 1.04 and 0 per 1000 women assigned to placebo. • The incidence of DVT was 1.45 per 1000 in women assigned to ospemifene compared to 1.04 per 1000 in the placebo group. If possible, ospemifene should be discontinued at least 4 to 6 weeks before surgery of the type associated with an increased risk of thromboembolism, or during periods of prolonged immobilization. • One women assigned to ospemifene 60 mg experienced a myocardial infarction in the clinical trials. Effects on the endometrium – ospemifene has agonist effects in the endometrium. The use of progestins with ospemifene was not evaluated in the clinical trials. • No cases of endometrial cancer were noted in women assigned to ospemifene 60 mg with exposure up to 52 weeks. A single case of simple hyperplasia without atypia was reported. • Women with endometrial thickening 0.5 mm or greater was 60.1/1000 with ospemifene vs. 21.2/1000 for placebo. • The incidence of any type of proliferative endometrium was 86.1/1000 with ospemifene vs. 13.3/1000 for placebo. • Uterine polyps had an incidence of 5.9/1000 with ospemifene vs. 1.8/1000 with placebo.

Breast cancer – use not adequately studied in women with breast cancer.

- Ospemifene should not be used in women with known or suspected breast cancer or with a history of breast cancer.

Safety Considerations (see also Warnings/Precautions)

- Ospemifene's long-term safety was assessed in an extension trial in which 180 women with an intact uterus continued an additional 40 weeks (52-weeks total) on the randomized treatment from the 12-week study, i.e., ospemifene 60 mg (n=69) or placebo (n=44). A second extension trial included of 301 hysterectomized women given open-label ospemifene 60 mg per day for an additional 52 weeks (64 weeks total).
  - Among women with an intact uterus, 36% and 17.4% assigned to placebo and ospemifene discontinued the study, with 2% and 5.8% secondary to treatment emergent adverse effects, respectively. The mean change (SD) in endometrial thickness declines slightly with placebo, -0.04 mm (1.15) and increase slightly with ospemifene, 1.14 mm (1.56). No cases of endometrial hyperplasia or carcinoma were observed. Proliferative pattern tissue was found in 1 patient assigned to ospemifene and none assigned to placebo.
  - Nearly 39% of hysterectomized women discontinued the other extension trial; 11.3% because of TEAEs.
  - Sinusitis 24%, UTI 8.6%, and hot flushes 10.3% were the most common TEAEs.
- A study in healthy women 8-9 years past their last menses randomized to ospemifene 60 mg or placebo found mean concentrations of FSH, LH, estradiol, and insulin-like growth factor decreased from baseline after 3 months. Only the changes in FSH and insulin-like growth factor were significant compared to placebo. Neither group had significant changes in climacteric symptoms using the Kupperman Index, the Work Ability Index (quality of life), depression, anxiety or sexual desire.
- Daily ospemifene 60 mg for 12 weeks did not result in changes from baseline in total cholesterol, low-density lipoprotein, high-density lipoprotein, or triglycerides.
- A 3month trial in 160 postmenopausal women (≥12 months since last menses) found ospemifene 60 mg reduced FSH and insulin-like growth factor I and did not change estradiol or LH concentrations. Ospemifene did not stimulate the endothelium or aggravate hot flashes.
- The safety of ospemifene in women with a history of breast cancer or at high risk for breast cancer is controversial. FDA states ospemifene should not be prescribed to such women cited inadequate studies in women with breast cancer. Critics of this decision have argued that women who cannot or should not, or will not take estrogen are candidates for ospemifene. Their argument is supported by other SERMs that have been adequately studied have reduced the risk of breast cancer without suggested harms.
- Another criticism concerns FDA's inclusion of the boxed warning on "the increased risk of endometrial cancer in woman with a uterus who uses unopposed estrogen. Adding a progestin to estrogen therapy reduces the risk of endometrial hyperplasia, which may be a precursor to endometrial cancer." Citing 1-year incidence of proliferation and hyperplasia of 3% and 0% for raloxifene and 1% and 0.3% for ospemifene compared to 39% and 23% with unopposed estrogen, critics feel the box warning is unjustified. Concurrent use of a progestin was an exclusion in the ospemifene clinical trials, yet it label included a statement that one is generally prescribed to women with an intact uterus also prescribed a drug with estrogenic effects on the uterus.

Adverse Reactions

Common adverse reactions

- Hot flushes were reported by 44/619 women (7.1%) exposed to 60 mg ospemifene compared to 22/609 women (3.6%) exposed to placebo in the 12-week trials [OR=2.02 (95% CI 1.2, 3.40)]. These rates were 51/432 (11.8%) and 6/112 (5.4%) in the 52-week trials, respectively, OR=2.06 (0.84, 5.04).
- Urinary tract infection, vaginal candidiasis, vulvar and vaginal mycotic infection
- Headache

Death/Serious adverse reactions: See **Warnings/Precautions**

Discontinuations due to adverse reactions

Event	Ospemifene	Placebo	OR	95% CI
TEAE	350/579	294/570	1.43	1.14, 1.81
DC2°AE	30/619	33/609	0.89	0.54, 1.47

SAE	4/579	8/570	0.52	0.17, 1.64

TEAE = treatment emergent adverse event, DC2°AE = discontinued due to an adverse event, SAE = serious adverse event, OR – odds ratio

Drug-Drug Interactions

- Estrogen agonist/antagonist
- Fluconazole, ketoconazole – increase in ospemifene concentrations
- Rifampin – decrease in ospemifene concentrations
- Cytochrome 3A4 and CYP2C9 inhibitors may increase the risk of ospemifene adverse reactions
- Ospemifene is >99% bound to serum proteins and thus may be displaced by other highly protein bound drug or displace other drugs.

Risk Evaluation

As of September 30, 2015

	Comments
Sentinel event advisories	• None • Sources: ISMP, FDA, TJC

Look-alike/sound-alike error potentials

NME Drug Name	Lexi-Comp	First DataBank	ISMP	Clinical Judgment
Ospemifene 60mg tab	Raloxifene Toremifene	None	None	Oseltamivir Orphenadrine
Osphena	None	None	None	Opana Orencia

Dosing and Administration[3]

- One 60 mg tablet with food once daily.
- Generally, a progestin is prescribed to postmenopausal women with uterus when a product with estrogenic agonist effects on the endometrium is prescribed as a means to reduce the risk of endometrial cancer.
- Ospemifene should be taken for the shortest duration consistent with treatment goals and risks for the individual woman. The need for treatment should be re-evaluated periodically.

Special Populations (Adults)[3, 13]

	Comments
Elderly	• Women ≥65 years accounted for 19% (n=514) of subjects in the Phase 2 and 3 trials. No information on the number of women ≥75 years or their experience is provided; although the upper age limit for at least one trial was 81 years. Per the FDA medical reviewer, TEAEs were higher in women ≥65 exposed to ospemifene than those <65 years, while the percent of TEAEs with placebo was similar in both age groups. The higher TEAE rates were accompanied by higher discontinuation rates in women ≥65, thus older women may not tolerate ospemifene as well as younger women. The package label reports no clinically meaningful differences were observed between subjects 65 years and older compared to younger women.
Pregnancy	• Pregnancy Category X
Lactation	• Unknown if excreted in human breast milk

Renal Impairment	• No dosage adjustment is required with renal impairment
Hepatic Impairment	• No dosage adjustment is required with mild-moderate hepatic impairment • Avoid in severe hepatic impairment – not studied
Pharmacogenetics/genomics	• No data identified

Projected Place in Therapy (this section may be edited prior to final approval of document and web posting) [1, 14-15]

- Vulvovaginal atrophy (VVA) is marked by lack of lubrication and pain with intercourse (dyspareunia) affecting 20% to 45% of middle age and older woman. The condition is unlikely to resolve and more likely to progress without intervention. In surveys such symptoms negatively affect up to 80% of affected women's sexual health and quality of life, while ⅓ to ½ reporting negative consequences in their marriage or relationship. In VA between ~5000 to 5200 veterans were diagnosed with VVA in each of FY 2012, 2013 and 2014 with a cumulative of 13,800 unique women receiving the diagnosis. Over this same time period, between 39,000 to 41,000 veterans were diagnosed with premature menopause, or menopause or postmenopausal conditions. Thus, dyspareunia may be an underreported condition.
- Treatment with vaginal estrogen therapy is more effective than with systemic oral estrogens with 80%-90% reporting a favorable response compared to 75% using oral estrogens.
- Postmenopausal women (spontaneous menopause) using vaginal estrogen may be at a higher risk for vulvovaginal candidiasis.
- Vaginal estrogen should be instilled at least 12 hours before intercourse to avoid transmission to a partner.
- Ospemifene is an alternative to vaginal or systemic estrogen therapy in women who do not have adequate relief of dyspareunia from vaginal lubricant or moisturizer, and who cannot or will not take an estrogen. Whether ospemifene should be prescribed instead of an estrogen to treat dyspareunia in any postmenopausal woman is complicated by the box warning for endometrial cancer and cardiovascular disorder as well as the general recommendation to provide a progestin to women with an intact uterus despite not being done in the clinical trials.

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Appendix A: GRADEing the Evidence

Designations of Quality

Quality of evidence designation	Description
High	Evidence includes consistent results from well-designed, well-conducted studies in representative populations that directly assess effects on health outcomes (2 consistent, higher-quality randomized controlled trials or multiple, consistent observational studies with no significant methodological flaws showing large effects).
Moderate	Evidence is sufficient to determine effects on health outcomes, but the number, quality, size, or consistency of included studies; generalizability to routine practice; or indirect nature of the evidence on health outcomes (1 higher-quality trial with > 100 participants; 2 higher-quality trials with some inconsistency; 2 consistent, lower-quality trials; or multiple, consistent observational studies with no significant methodological flaws showing at least moderate effects) limits the strength of the evidence.
Low	Evidence is insufficient to assess effects on health outcomes because of limited number or power of studies, large and unexplained inconsistency between higher-quality studies, important flaws in study design or conduct, gaps in the chain of evidence, or lack of information on important health outcomes.

Please refer to Qaseem A, et al. The development of clinical practice guidelines and guidance statements of the American College of Physicians: Summary of Methods. Ann Intern Med 2010;153:194-199.