PDL DRUG REVIEW

Proprietary Name: Osphena®
Common Name: ospemifene
PDL Category: Hormone Receptor Modulators

Comparable Products	Preferred Drug List Status
Estrace Cream	Non-Preferred
Femring	Non-Preferred
Premarin Cream	Preferred

Summary

Pharmacology/Usage: Ospemifene, the active ingredient of Osphena®, is an estrogen receptor agonist/antagonist with tissue selective effects. Its biological actions are mediated through binding to estrogen receptors, and this binding results in activation of estrogenic pathways in some tissues (agonism) and blockade of estrogenic pathways in others (antagonism). Osphena® is not a hormone.

Indication: For:

- The treatment of moderate to severe dyspareunia, a symptom of vulvar and vaginal atrophy, due to menopause
- The treatment of moderate to severe vaginal dryness, a symptom of vulvar and vaginal atrophy, due to menopause

There is no pregnancy category for this medication; however, the risk summary indicates treatment is contraindicated in women who are or may become pregnant. If this drug is used during pregnancy, or if a woman becomes pregnant while taking this drug, the woman should be apprised of the potential hazard to the fetus. Per animal data, Osphena® is likely to increase the risk of adverse outcomes during pregnancy and labor. The safety and efficacy of use in the pediatric population have not been established.

Dosage Form: Film-Coated Tablets: 60mg

Recommended Dosage: Use for the shortest duration consistent with treatment goals and risks for the individual woman. Postmenopausal women should be re-assessed periodically as clinically appropriate to determine if treatment is still necessary.

Take one tablet with food once daily. Dose adjustments are not required in women with renal impairment or in women with mild or moderate hepatic impairment. Do not use in women with severe hepatic impairment.

Drug Interactions: Osphena® is mainly metabolized by CYP3A4 and CYP2C9. Fluconazole, a moderate CYP3A/strong CYP2C9/moderate CYP2C19 inhibitor, should not be used with Osphena®, as fluconazole increases the systemic exposure of ospemifene by 2.7-fold. Rifampin, a strong CYP3A4/moderate CYP2C9/moderate CYP2C19 inducers, decreases the systemic exposure of ospemifene by 58%. Thus, coadministration of Osphena®

with drugs such as rifampin would be expected to decrease the systemic exposure of ospemifene, which may decrease the clinical effect. Ketoconazole, a strong CYP3A4 inhibitor, increases the systemic exposure of ospemifene by 1.4-fold. Use of ketoconazole chronically with ospemifene may increase the risk of Osphena®-related adverse reactions. Coadministration of Osphena® with a drug known to inhibit CYP3A4 and CYP2C9 may increase the risk of Osphena®-related adverse reactions.

Do not use Osphena® concomitantly with estrogens and estrogen agonists/antagonists. Use of Osphena® with other drug products that are highly protein-bound may lead to increased exposure of either that drug or ospemifene. The effect of ospemifene on clotting time such as INR or PT was not studied, but repeated administration of ospemifene had no effect on the pharmacokinetics of a single 10mg dose of warfarin.

Common Adverse Drug Reactions: *Listed % incidence for adverse drug reactions= reported % incidence for drug (Osphena® 60mg) minus reported % incidence for placebo. Please note that an incidence of 0% means the incidence was the same as or that the active drug was less than placebo.* The most frequently reported adverse events included hot flush (3.9%), vaginal discharge (3.4%), muscle spasms (1.2%), hyperhidrosis (0.9%), headaches (0.4%), night sweats (1.2%), and vaginal hemorrhage (1.3%).

Osphena® has a box warning regarding endometrial cancer and cardiovascular disorders. Osphena® is an estrogen agonist/antagonist with tissue selective effects. In the endometrium, Osphena® has estrogen agonistic effects. There is a potential increased risk of endometrial cancer in a woman with a uterus who uses unopposed estrogens. Adequate diagnostic measures, including directed and random endometrial sampling when indicated, should be undertaken to rule out malignancy in postmenopausal women with undiagnosed persistent or recurring abnormal genital bleeding.

As Osphena® has not been adequately studied in women with breast cancer, it should not be used in women with known or suspected breast cancer.

The box warning also adds that in clinical trials with Osphena®, the incidence rates of thromboembolic and hemorrhagic stroke were 1.13 and 3.39 per 1000 women years, respectively in the Osphena® 60mg treatment group and 3.15 and 0 with placebo. The incidence of DVT was 2.26 per 1000 women years (2 reported cases) in the Osphena® group and 3.15 per 1000 women years (1 reported case) with placebo. Osphena® should be prescribed for the shortest duration consistent with treatment goals and risks for the individual woman. There is a reported increased risk of stroke and DVT in postmenopausal women (50 to 79 years of age) who received daily oral conjugated estrogens (0.625mg)-alone therapy over 7.1 years as part of the Women's Health Initiative.

Risk factors for cardiovascular disorders, arterial vascular disease (for example hypertension, diabetes mellitus, tobacco use, hypercholesterolemia, and obesity) and/or venous thromboembolism should be managed appropriately.

Contraindications: In women with any of the following conditions:

- 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 and MI), or a history of these conditions
- Hypersensitivity to ospemifene or any ingredients of the product
- In women who are or may become pregnant, as Osphena® may cause fetal harm when administered to a pregnant woman

Manufacturer: Shionogi, Inc

Analysis: The safety and efficacy of Osphena® for the treatment of moderate to severe symptoms of vulvar and vaginal atrophy (VVA) in postmenopausal women were assessed in 4 randomized, double-blind, placebo-controlled trials (N=2516 total).

Study 1 was a 12-week parallel-group trial that enrolled generally healthy postmenopausal women (N=826) ages 41 to 81 years (mean age 59 years) who at baseline had ≤5% superficial cells on a vaginal smear, a vaginal pH >5.0, and who identified at least 1 moderate to severe vaginal symptom that was considered the most bothersome to her (vaginal dryness, pain during intercourse [dyspareunia], or vaginal irritation/itching). Treatment groups were 30mg ospemifene (N=282), 60mg ospemifene (N=276), and placebo (N=268). All women were assessed for improvement in the mean change from baseline to week 12 for the co-primary endpoints of most bothersome symptom (MBS) of vulvar and vaginal atrophy (defined as the individual moderate to severe symptom that was identified by the woman as the most bothersome at baseline), % of vaginal superficial and vaginal parabasal cells on a vaginal smear, and vaginal pH.

Study 2 was a 12-week parallel-group trial that included generally healthy postmenopausal women (N=919) between 41 to 79 years of age (mean 59 years of age) who at baseline had ≤5% superficial cells on a vaginal smear, a vaginal pH >5.0, and who identified either moderate to severe vaginal dryness (dryness cohort) or moderate to severe dyspareunia (dyspareunia cohort) as most bothersome to her at baseline. Treatment groups included ospemifene 60mg and placebo, and the primary endpoints were similar to those in study 1.

Study 3 was a 12-week parallel-group trial that included generally healthy postmenopausal women (N=631) between 40 and 80 years of age (mean age 60 years) who at baseline had ≤5% superficial cells on a vaginal smear, a vaginal pH >5.0, and had moderate to severe vaginal dryness as the self-reported most bothersome symptoms of VVA. Treatment groups included ospemifene 60mg and placebo, while the primary endpoints were similar to those in study 1. In addition, 52 women in the ospemifene group and 53 women in the placebo group received treatment for up to 52 weeks.

Study 4 was a 52-week long-term safety study that included generally healthy postmenopausal women between 49 to 79 years of age (mean 62 years of age) with an intact uterus (N=426). Treatment groups included ospemifene 60mg and placebo. There was no further information in the prescribing information regarding this study.

In study 1 and 2, the women treated with ospemifene when compared to placebo demonstrated a statistically significant improvement in the moderate to severe most bothersome symptom of dyspareunia (study 1 p=0.0012; study 2 p<0.0001). A statistically significant increase in the proportion of superficial cells and a corresponding statistically significant decrease in the proportion of parabasal cells on a vaginal smear were also demonstrated (p<0.0001 for both trials). The mean reduction in vaginal pH between baseline and week 12 was also statistically significant (p<0.0001 for both trials). Results can be seen in the tables below, which were adapted from the prescribing information.

Most bothersome moderate to severe symptom at baseline	Study 1		Study 2	
	Osphena® 60mg (N=110)	Placebo (N=113)	Osphena® 60mg (N=301)	Placebo (N=297)
Dyspareunia				
Baseline mean	2.7	2.7	2.7	2.7
Least square mean change from baseline	-1.4	-0.9	-1.5	-1.2
p-value	0.0012		<0.0001	

All 3 trials assessed the most bothersome symptom of vaginal dryness. Study 2 did not demonstrate a statistically significant improvement in the moderate to severe most bothersome symptom of vaginal dryness. In studies 1 and 3, women treated with ospemifene when compared to placebo demonstrated a statistically significant improvement in the moderate to severe most bothersome symptom of vaginal dryness (study 1 p=0.0136; study 3 p<0.0001). A statistically significant increase in the proportion of superficial cells and a corresponding statistically

significant decrease in the proportion of parabasal cells on a vaginal smear were also demonstrated (p<0.0001 for both studies). The mean reduction in vaginal pH between baseline and week 12 was also statistically significant (p<0.0001 for both trials). Results can be seen in the table below, which was adapted from the prescribing information.

Most bothersome moderate to severe symptom at baseline	Study 1		Study 3	
	Osphena® 60mg (N=113)	Placebo (N=104)	Osphena® 60mg (N=269)	Placebo (N=263)
Vaginal Dryness				
Baseline mean	2.5	2.4	2.6	2.6
Change from baseline[1]	-1.3	-0.9	-1.3	-0.9
p-value vs placebo	0.0136		<0.0001	

[1] Least square mean change in study 1; change from baseline (standard deviation) in study 3

Place in Therapy: Osphena® is an estrogen receptor agonist/antagonist indicated for the treatment of moderate to severe dyspareunia, a symptom of vulvar and vaginal atrophy, due to menopause. It is also indicated for the treatment of moderate to severe vaginal dryness, a symptom of vulvar and vaginal atrophy, due to menopause. In clinical studies compared with placebo, ospemifene demonstrated a statistically significant improvement in the moderate to severe most bothersome symptom of dyspareunia and in the moderate to severe most bothersome symptom of vaginal dryness. One study, however, did not demonstrate a statistically significant improvement in moderate to severe vaginal dryness.

There is no evidence to support that Osphena® is safer or more effective than other preferred, more cost-effective medications. It is therefore recommended that Osphena® remain non-preferred and require prior authorization and be available to those who are unable to tolerate or who have failed on preferred medications for the treatment of moderate to severe vaginal dryness, a symptom of vulvar and vaginal atrophy, due to menopause. The treatment of moderate to severe dyspareunia, a symptom of vulvar and vaginal atrophy, due to menopause remains a non-covered diagnosis of use.

PDL Placement:

- ☐ **Preferred**
- ☒ **Non-Preferred**
- ☒ **Refer to DUR for PA Criteria**

References

[1]Osphena [package insert]. Florham Park, NJ: Shionogi Inc; 2019.

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