Osphena®
(ospemifene) tablets
60 mg

OSPHENA®, THE FIRST AND ONLY TREATMENT FOR MODERATE TO SEVERE VAGINAL DRYNESS AND/OR DYSPAREUNIA:[1,2]

NON-HORMONAL

ADMINISTERED ORALLY

ACTS LOCALLY*,[1,2]

Osphena® (ospemifene) is indicated 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.

*Administered orally, distributed systemically, but active locally as a function of its characteristic tissue selectivity. Osphena® is differentiated by its agonistic activity in vaginal tissue.[2,3]

WARNING: ENDOMETRIAL CANCER and CARDIOVASCULAR DISORDERS

Endometrial Cancer

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.

Cardiovascular Disorders

In clinical trials for OSPHENA (duration of treatment up to 15 months), the incidence rates of thromboembolic and hemorrhagic stroke were 1.13 and 3.39 per thousand women years, respectively, in the OSPHENA 60 mg treatment group and 3.15 and 0 with placebo. The incidence of DVT was 2.26 per thousand women years (2 reported cases) in the OSPHENA 60 mg treatment group and 3.15 per thousand 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 deep vein thrombosis (DVT) in postmenopausal women (50 to 79 years of age) who received daily oral conjugated estrogens (CE) [0.625 mg]-alone therapy over 7.1 years as part of the Women's Health Initiative (WHI).

Please see detailed **Important Safety Information**, including the **Boxed Warning**, throughout, and accompanying Full Prescribing Information.

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Prescribe Osphena®:

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MECHANISM OF ACTION OF ESTROGENS vs. SERMs

ESTROGENS

All estrogens have an **agonist-only** action through the binding of estrogen receptors that are present in estrogen-responsive tissues.[5]

vs.

SERMs

Unlike estrogens, SERMs are synthetic estrogen-receptor (ER) **agonists and antagonists** with tissue-selective effects. Their biological action is mediated through the activation of estrogenic pathways in some tissues (agonism) and blockade of estrogenic pathways in others (antagonism).[1]

The resulting biologic action varies according to the specific type of ER, cofactors, responses and ligands (including the different SERMs), leading to tissue-specific agonist or antagonist activity.[4]

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OFFER YOUR PATIENTS THE CONVENIENCE OF ONCE-DAILY ORAL DOSAGE[1]

60 mg ORAL TABLET

Pill not actual size.

Please see detailed **Important Safety Information**, including the **Boxed Warning** regarding Endometrial Cancer and Cardiovascular Disorders, on front and back covers, and accompanying Full Prescribing Information.

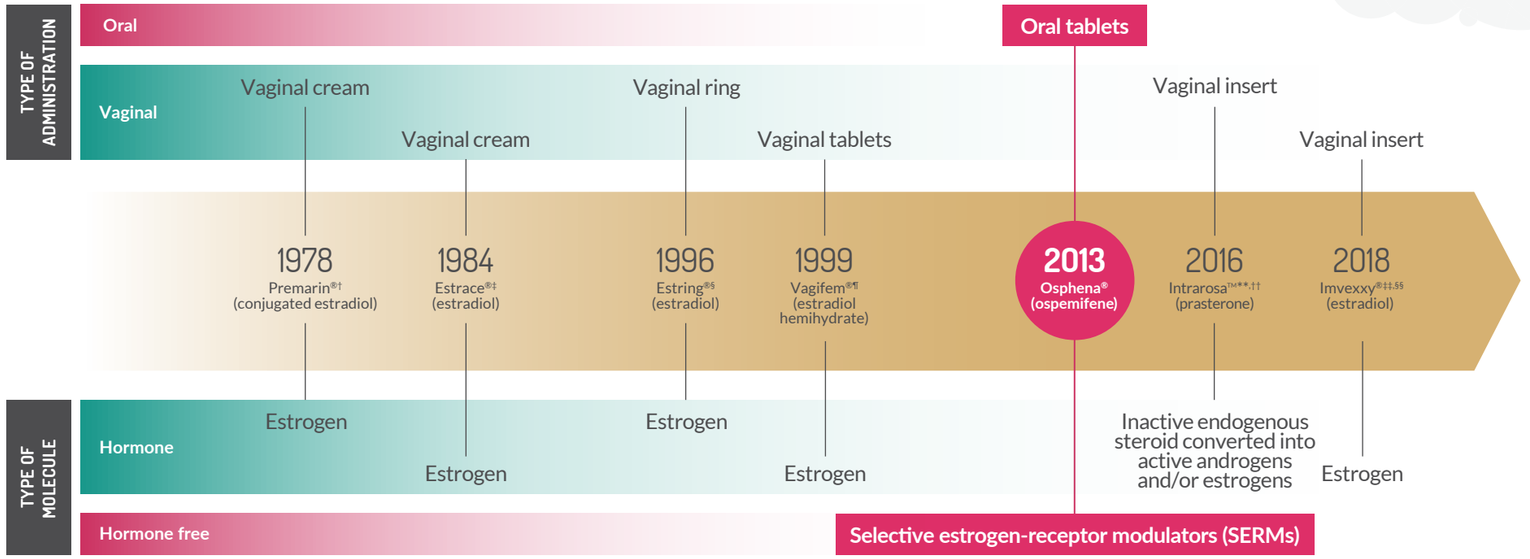
ALTERNATIVE APPROACH TO THE TREATMENT OF MODERATE TO SEVERE VAGINAL DRYNESS AND/OR DYSPAREUNIA DUE TO MENOPAUSE[4]

Osphena® is the first and only SERM indicated for treatment of moderate to severe vaginal dryness and/or dyspareunia due to menopause. All other SERMs have been prescribed for **over 50 years** to treat additional various women's health conditions.[1,5]

Unlike estrogens (or products that are metabolized into estradiol), **SERMs like Osphena® are hormone free.**

A unique feature of Osphena® is that it demonstrates a strong agonistic **effect on vaginal tissue** while exhibiting antagonistic or mild agonistic effects on other tissues.[1,6]

Moreover, Osphena® is the only treatment for moderate to severe vaginal dryness and/or dyspareunia due to menopause, offered conveniently as an **oral administration**.[1]



IMPORTANT SAFETY INFORMATION:
Common side effects may include hot flashes, vaginal discharge, muscle spasms and increased sweating, night sweats, headaches and vaginal hemorrhage. Osphena® should be prescribed for the shortest duration consistent with treatment goals and risks for the individual woman.[1]

Please see detailed **Important Safety Information**, including the **Boxed Warning**, regarding Endometrial Cancer and Cardiovascular Disorders, on front and back covers, and accompanying Full Prescribing Information.

†Premarin® is a registered trademark of Pfizer.
‡Estrace® is a registered trademark of Allergan Pharmaceuticals International Limited.
§Estring® is a registered trademark of Pfizer.
¶Vagifem® is a registered trademark of Novo Nordisk Health Care AG.
**Intrarosa™ is a registered trademark owned by Endoceutics Inc.
††Imvexxy® is a registered trademark of TherapeuticsMD, Inc.
§§Intrarosa™ and Imvexxy® are indicated for the treatment of moderate to severe dyspareunia, a symptom of vulvar and vaginal atrophy, due to menopause.

Indication and Important Safety Information including Boxed Warning

INDICATION:

OSPHENA (ospemifene) is indicated 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

Important Safety Information for OSPHENA®

WARNING: ENDOMETRIAL CANCER and CARDIOVASCULAR DISORDERS

Endometrial Cancer

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Cardiovascular Disorders

In clinical trials for OSPHENA (duration of treatment up to 15 months), the incidence rates of thromboembolic and hemorrhagic stroke were 1.13 and 3.39 per thousand women years, respectively, in the OSPHENA 60 mg treatment group and 3.15 and 0 with placebo. The incidence of DVT was 2.26 per thousand women years (2 reported cases) in the OSPHENA 60 mg treatment group and 3.15 per thousand 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 deep vein thrombosis (DVT) in postmenopausal women (50 to 79 years of age) who received daily oral conjugated estrogens (CE) [0.625 mg]-alone therapy over 7.1 years as part of the Women's Health Initiative (WHI).

CONTRAINDICATIONS

- Undiagnosed abnormal genital bleeding
- Known or suspected estrogen-dependent neoplasia
- Active deep vein thrombosis (DVT), pulmonary embolism (PE), or a history of these conditions
- Active arterial thromboembolic disease (e.g., stroke and myocardial infarction) or a history of these conditions
- Hypersensitivity (for example, angioedema, urticaria, rash, pruritus) to OSPHENA or any of its ingredients
- OSPHENA is contraindicated in women who are or may become pregnant. OSPHENA may cause fetal harm when administered to a pregnant woman. Ospemifene was embryo-fetal lethal with labor difficulties and increased pup deaths in rats at doses below clinical exposures, and embryo-fetal lethal in rabbits at 10 times the clinical exposure based on mg/m^2. If this drug is used during pregnancy, or if a woman becomes pregnant while taking this drug, she should be apprised of the potential hazard to a fetus.

WARNINGS AND PRECAUTIONS

Cardiovascular Disorders

In the clinical trials for OSPHENA (duration of treatment up to 15 months), the incidence rates of thromboembolic and hemorrhagic stroke were 1.13 and 3.39 per thousand women years, respectively in OSPHENA 60 mg treatment group and 3.15 and 0 per thousand women years in placebo. Should thromboembolic or hemorrhagic stroke occur or be suspected, OSPHENA should be discontinued immediately.

In the OSPHENA clinical trials, two cases of myocardial infarctions (MI) occurred in women receiving 60 mg of ospemifene.

In the OSPHENA clinical trials, two cases of DVT occurred in women receiving OSPHENA 60 mg. Should a VTE occur or be suspected, OSPHENA should be discontinued immediately.

If feasible, OSPHENA 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.

Malignant Neoplasms

OSPHENA is an estrogen agonist/antagonist with tissue selective effects. In the endometrium, OSPHENA has agonistic effects. In the OSPHENA clinical trials (60 mg treatment group), no cases of endometrial cancer were seen with exposure up to 52 weeks. There was a single case of simple hyperplasia without atypia. Endometrial thickening equal to 5 mm or greater was seen in the OSPHENA up to 52 weeks treatment groups at a rate of 101.4 per thousand women vs. 20.9 per thousand women for placebo. The incidence of any type of proliferative (weakly plus active plus disordered) endometrium was 26.3 per thousand women in the OSPHENA up to 52 weeks treatment groups vs. 0 per thousand women for placebo. Uterine polyps occurred at an incidence of 19.6 per thousand women in the OSPHENA up to 52 weeks treatment groups vs. 8.3 per thousand women for placebo.

An increased risk of endometrial cancer has been reported with the use of unopposed estrogen therapy in a woman with a uterus. The greatest risk appears to be associated with prolonged use and estrogen dose. Adding a progestin to postmenopausal estrogen therapy has been shown to reduce the risk of endometrial hyperplasia, which may be a precursor to endometrial cancer. There are, however, possible risks that may be associated with the use of progestins with estrogens compared to estrogen-alone regimens. These include an increased risk of breast cancer. The use of progestins with OSPHENA therapy was not evaluated in the clinical trials.

OSPHENA 60 mg has not been adequately studied in women with breast cancer; therefore, it should not be used in women with known or suspected breast cancer.

Severe Hepatic Impairment

OSPHENA should not be used in women with severe hepatic impairment.

In clinical trials the more commonly reported adverse reactions in ≥1 percent of patients treated with OSPHENA 60 mg compared to placebo were:

1. In 12-week, double blind, placebo-controlled clinical trials: hot flush (6.5% vs. 2.6%), vaginal discharge (3.8% vs. 0.4%), muscle spasms (1.8% vs. 0.6%) and hyperhidrosis (1.1% vs. 0.2%)
2. In all clinical trials up to 52 weeks (safety population): headaches (2.8% vs. 2.4%), hot flush (12.2% vs. 4.2%), muscle spasms (4.5% vs. 2.4%), hyperhidrosis (2.5% vs. 1.8%), night sweats (1.2% vs. 0.0%), vaginal discharge (6.00% vs. 0.6%) and vaginal hemorrhage (1.3% vs. 0.0%)

The following adverse reactions have been identified during post-approval use of ospemifene:

- Neoplasms Benign, Malignant and Unspecified (including cysts and polyps); endometrial hyperplasia, endometrial cancer
- Immune System Disorders: allergic conditions including hypersensitivity, angioedema
- Nervous System Disorders: headache
- Vascular Disorders: deep vein thrombosis, thrombosis, pulmonary embolism
- Skin and Subcutaneous Tissue Disorders: rash, rash erythematous, rash generalized, pruritus, urticaria

Drug interactions: OSPHENA is primarily metabolized by CYP3A4 and CYP2C9. CYP2C19 and other pathways contribute to the metabolism of ospemifene. Do not use estrogens or estrogen agonists/antagonists, fluconazole, ketoconazole or rifampin concomitantly with OSPHENA. Co-administration of OSPHENA with drugs that inhibit CYP3A4 and CYP2C9 may increase the risk of OSPHENA-related adverse reactions. OSPHENA is highly protein-bound. Use cautiously with highly protein-bound drugs as use with other highly protein-bound drugs may lead to increased exposure of that drug or ospemifene.

Please see **Full Prescribing Information** for OSPHENA (ospemifene) tablets, including **Boxed Warning** regarding Endometrial Cancer and Cardiovascular Disorders, and **Patient Information** at osphena.com/hcp.

References: 1. Osphena Prescribing Information. January 2019. **2.** Simon JA, Davis SR, Althof SE, et al. Sexual well-being after menopause: an International Menopause Society White Paper. *Climacteric*. 2018;21(5):415–427. **3.** Archer DF, Goldstein SR, Simon JA, et al. Efficacy and safety of ospemifene in postmenopausal women with moderate-to-severe vaginal dryness: a phase 3, randomized, double-blind, placebo-controlled, multicenter trial. *Menopause*. 2019 Jan 28. **4.** Pinkerton JV, Thomas S. Use of SERMs for treatment in postmenopausal women. *J Steroid Biochem Mol Biol*. 2014;142:142–154. **5.** FDA drug database. Available at: https://www.accessdata.fda.gov/scripts/cder/daf/. Accessed on September 19, 2018. **6.** Kangas L, Unkila M. Tissue selectivity of ospemifene: Pharmacologic profile and clinical implications. *Steroids*. 2013;78(12–13):1273–1280.

Visit OSPHENA.COM/HCP for more information.

DUCHESNAY USA

WHAT SETS SERMs APART FROM OTHER VAGINAL DRYNESS AND/OR DYSPAREUNIA TREATMENTS IN MENOPAUSAL WOMEN

WHAT ARE SERMs?

SERMs, or selective estrogen-receptor modulators, are synthetic compounds that have either agonist or antagonist activity on the estrogen receptors of various tissues.[4]

HOW DO SERMs TREAT VULVAR AND VAGINAL ATROPHY SYMPTOMS SUCH AS VAGINAL DRYNESS AND/OR DYSPAREUNIA?

SERMs can **selectively result in agonistic responses** at the estrogen receptors of the vaginal epithelium, minimizing vaginal atrophy.[4]

Did you know that there is a convenient treatment option for your patients with moderate to severe vaginal dryness and/or dyspareunia during menopause?

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 (for example, stroke and myocardial infarction [MI]), or a history of these conditions
- Hypersensitivity (for example, angioedema, urticaria, rash, pruritus) to Osphena® or any ingredients
- Known or suspected pregnancy