Osphena®
(ospemifene) tablets
60 mg

THE FIRST AND ONLY SERM APPROVED FOR MODERATE TO SEVERE VAGINAL DRYNESS

The most common bothersome symptom of vulvar and vaginal atrophy (VVA) due to menaupause[1-4]

Non-hormonal | Administered orally | Acts locally*[1,5]

Osphena® is an estrogen agonist/antagonist 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.

SERM: selective estrogen receptor modulator
*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.[5,6]

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 **Boxed Warning**, throughout, and accompanying Full Prescribing Information.

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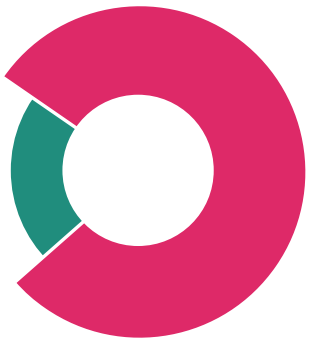
VAGINAL DRYNESS IS THE MOST COMMON BOTHERSOME SYMPTOM AMONG MENOPAUSAL WOMEN[1,2]



79% of women with VVA report symptoms of vaginal dryness.[3]

Left untreated, VVA symptoms such as vaginal dryness and dyspareunia may worsen.[7]

NO NEED FOR VAGINAL ADMINISTRATION

Prescribe Osphena® to offer your patients the convenience of a once-daily oral tablet.
Take with food, ideally at the same time every day.

Commercially insured patients pay as little as

$35 per prescription

- At retail pharmacies with the Osphena® CoPay Savings Card
- By mail order pharmacy through the Osphena At Home® FREE home delivery program

See OSPHENA.COM/HCP for details

IMPORTANT SAFETY INFORMATION

Common side effects include hot flashes, vaginal discharge, muscle spasms, hyperhidrosis, night sweats, headaches and vaginal hemorrhage.

Osphena® should be prescribed for the shortest duration consistent with treatment goals and risks for the individual woman.

IMPORTANT SAFETY INFORMATION

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

Important Safety Information continued on next page.
Please see detailed **Important Safety Information**, including **Boxed Warning**, throughout, and accompanying Full Prescribing Information.

OSPHENA®'S SAFETY AND EFFICACY HAVE BEEN CONFIRMED BY MULTIPLE CLINICAL TRIALS[1]

OVERALL SAFETY[1,8]

2,209

Largest studied population of postmenopausal women with dyspareunia and vaginal dryness

The safety of Osphena® has been assessed in 10 Phase 2/3 trials (n=2,209), with daily dosage ranging from 5 to 90 mg

Long-term safety data up to 52 weeks (n=426) with no cases of endometrial cancer[1]

Osphena has a Boxed Warning regarding Endometrial Cancer and Cardiovascular Disorders.

EFFICACY IN MODERATE TO SEVERE VAGINAL DRYNESS TRIALS[1,6]

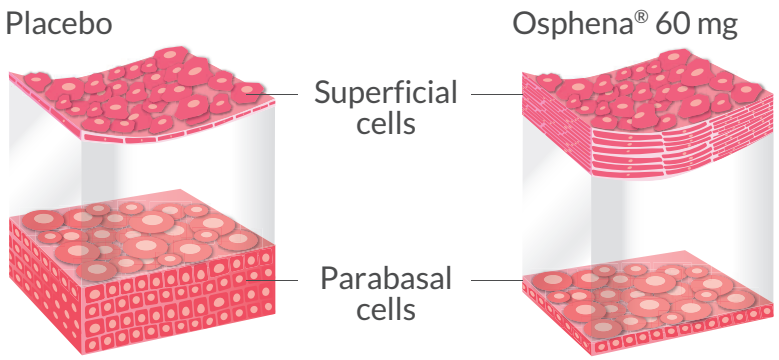
4 Secondary endpoints: significant improvement seen as early as 4 weeks (the most bothersome symptom, vaginal dryness; pH; superficial cells; and parabasal cells)[6]

12 Significant improvement in all coprimary endpoints at 12 weeks in two studies (the mos bothersome symptom, vaginal dryness; pH; superficial cells; and parabasal cells)[1,6]

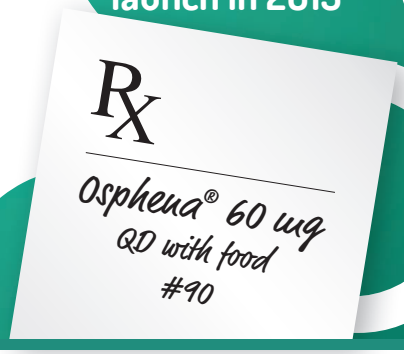
No unanticipated treatment-related adverse events were reported over 12 weeks.[6]

AFTER 12 WEEKS OF TREATMENT[1,6]

Studies showed a statistically significant increase in the proportion of superficial cells and a decrease in the proportion of parabasal cells on a vaginal smear.



Over 1 million prescriptions written since launch in 2013[8]



IMPORTANT SAFETY INFORMATION

Contraindications (continued)

- Active arterial thromboembolic disease (e.g., stroke and myocardial infarction [MI]) or a history of these conditions
- Hypersensitivity (e.g., angioedema, urticaria, rash, pruritus) to OSPHENA® or any of its ingredients
- Known or suspected pregnancy

Important Safety Information continued on next page.
Please see detailed **Important Safety Information**, including **Boxed Warning**, throughout, and accompanying Full Prescribing Information.

IMPORTANT SAFETY INFORMATION

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. Kingsberg SA, Wysocki S, Magnus L, et al. Vulvar and vaginal atrophy in postmenopausal women: findings from the REVIVE (REal Women's VIews of Treatment Options for Menopausal Vaginal ChangEs) survey. *J Sex Med*. 2013;10:1790–1799.
3. Kingsberg SA, Krychman M, Graham S, et al. The women's EMPOWER survey: identifying women's perceptions on vulvar and vaginal atrophy and its treatment. *J Sex Med*. 2017;14:413–424.
4. Simon JA, Altomare C, Cort S, et al. Overall safety of ospemifene in postmenopausal women from placebo-controlled phase 2 and 3 trials. *J Women's Health*. 2018;27(1):14–23.
5. 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.
6. 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.
7. North American Menopause Society. Management of symptomatic vulvovaginal atrophy: 2013 position statement of The North American Menopause Society. *Menopause*. 2013;20(19):888–902.
8. Data on file.

Visit OSPHENA.COM/HCP for more information.

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