INDICATIONS AND IMPORTANT SAFETY INFORMATION INCLUDING **BOXED WARNING**

INDICATIONS:

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

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).

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 [MI]) or a history of these conditions
- Hypersensitivity (e.g., 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**, and Patient Information at osphena.com/hcp.

References: 1. Data on file. Duchesnay USA Inc. **2.** Osphena Prescribing Information. January 2019. **3.** Portman DJ, Bachmann GA, Simon JA; Ospemifene Study Group. Ospemifene, a novel selective estrogen receptor modulator for treating dyspareunia associated with postmenopausal vulvar and vaginal atrophy. *Menopause*. 2013;20(6):623–630. **4.** Food and Drug Administration. Office Director Memo. Center for Drug Evaluation and Research. Application number: 203505Orig1s000. February 26, 2013. **5.** The Women's Health Initiative Study Group. Design of the Women's Health Initiative clinical trial and observational study. *Control Clinical Trials*. 1998;19(1):61–109. **6.** ACOG Practice Bulletin Number 141: Management of menopausal symptoms. American College of Obstetricians and Gynecologists. *Obstet Gynecol*. 2014;123(1):202–216. **7.** North American Menopause Society. Management of symptomatic vulvovaginal atrophy 2013 position statement of the North American Menopause Society. *Menopause*. 2013;20(9):888–902. **8.** Constantine GD, Goldstein SR, Archer DF. Endometrial safety of ospemifene: results of the Phase 2/3 clinical development program. *Menopause*. 2015;1(22):36–43. **9.** 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;26(6):1–11.

DUCHESNAY USA

Visit OSPHENA.COM/HCP for more information.

OSP-2018-0041-02 June 2019

Osphena®
(ospemifene) tablets
60 mg

Osphena® has been prescribed more than one million times in the U.S. since its launch in 2013[1]

OFFER YOUR PATIENTS A UNIQUE TREATMENT SUPPORTED BY MULTIPLE CLINICAL STUDIES[1,2]

Osphena® is the only once-daily, oral, non-hormonal treatment indicated for:

- Moderate to severe dyspareunia, a symptom of vulvar and vaginal atrophy, due to menopause.
- Moderate to severe vaginal dryness, a symptom of vulvar and vaginal atrophy, due to menopause.

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

OFFER YOUR PATIENTS A UNIQUE TREATMENT SUPPORTED BY MULTIPLE CLINICAL STUDIES[1,2]

- Largest population of postmenopausal women with dyspareunia (n=2,209)[2,3]
- Ten Phase 2/3 trials[2]
- Long-term safety data up to 52 weeks in duration[1,2]
  > 847 postmenopausal women were studied for up to 52 weeks in safety studies.
- Unlike clinical trials involving estrogen-based products, Osphena® clinical trials were performed without adding a progestin.[2]

UNDERSTANDING THE BOXED WARNING

Osphena® is a selective estrogen receptor modulator (SERM). Its biological actions are mediated through binding to estrogen receptors. This binding results in activation of estrogenic pathways in some tissues (agonism) and blockade of estrogenic pathways in others (antagonism).[2]

The FDA Office Director's Memo states that because Osphena® has estrogen agonist activity in select tissues, some of the safety concerns applicable to estrogens as a class are applicable to Osphena®.[4]

Endometrial cancer and cardiovascular disorders are listed as the Osphena® warnings.[2]

Osphena® has an estrogen agonistic effect in the endometrium, which applies to the safety concern that women with a uterus who use unopposed estrogens have a potential increased risk of endometrial cancer.[2]

The 2002 Women's Health Initiative (WHI) study showed that treatment with estrogen alone can increase the risk of stroke and venous thromboembolism (VTE). No SERMs were part of the 2002 WHI study.[5]

IMPORTANT SAFETY INFORMATION

Common side effects may 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. 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.

CONTRAINDICATIONS

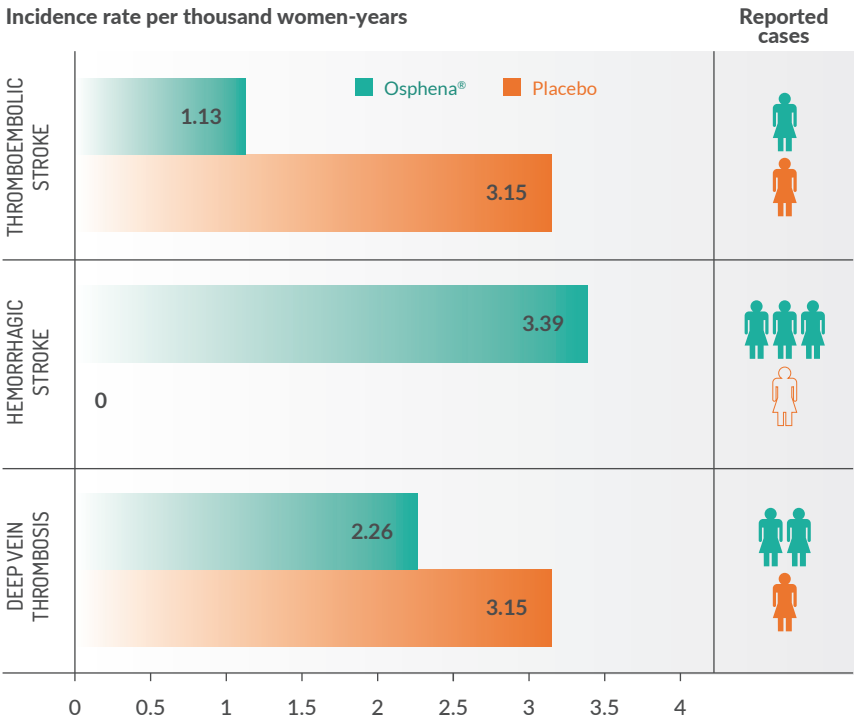
- Undiagnosed abnormal genital bleeding
- Known or suspected estrogen-dependent neoplasia
- Active deep vein thrombosis (DVT), pulmonary embolism (PE), or a history of these conditions
- Active arterial thromboembolic disease (e.g., stroke and myocardial infarction [MI]), or a history of these conditions
- Hypersensitivity (e.g., angioedema, urticaria, rash, pruritus) to Osphena® or any of its ingredients
- Known or suspected pregnancy

Received Level A treatment designation by ACOG and NAMS based on scientific evidence for moderate to severe dyspareunia[6,7]

OSPHENA® CLINICAL TRIAL SAFETY DATA

CARDIOVASCULAR DATA

Phase 2/3 clinical studies of Osphena® 60 mg, which included postmenopausal women (aged 40–80 years) with vulvar and vaginal atrophy (VVA), demonstrated the following:[2,8,9]



ENDOMETRIAL DATA

Osphena® 60 mg Phase 2/3 trials (postmenopausal women aged 40–80 years) demonstrated the following:[8,9]

- **1,654 women** with intact uterus were randomized to receive either Osphena® 60 mg (n=979) or placebo (n=675); no exogenous progestin use
- **0 cases** of endometrial cancer observed with exposure up to 52 weeks
- **1 simple** hyperplasia without atypia
- **No** endometrial carcinomas, complex hyperplasia or simple hyperplasia with atypia up to one year after study completion

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