PRODUCT MONOGRAPH

INCLUDING PATIENT MEDICATION INFORMATION

Pr OSPHENA®

ospemifene tablets

Tablets, 60mg, Oral

Selective Estrogen Receptor Modulator (SERM)

Duchesnay Inc.

950, boul. Michèle-Bohec

Blainville, Québec

Canada, J7C 5E2

Date of Initial Authorization:
JUL 15, 2021

Submission Control Number: 222001

TABLE OF CONTENTS

Sections or subsections that are not applicable at the time of authorization are not listed.

PART I: HEALTH PROFESSIONAL INFORMATION

1 INDICATIONS

Osphena (ospemifene tablets) is indicated in postmenopausal women for the treatment of moderate to severe dyspareunia and/or vaginal dryness, symptoms of vulvar and vaginal atrophy (VVA), a component of genitourinary syndrome of menopause (GSM).

1.1 Pediatrics

Pediatrics (≤18 years of age): No data are available to Health Canada; therefore, Health Canada has not authorized an indication for pediatric use. Osphena is not indicated in children.

1.2 Geriatrics

Geriatrics (≥65 years of age): Of the 2209 Osphena-treated women enrolled in the ten (10) Phase II/III trials of Osphena, >19 percent were 65 years of age or older. No clinically meaningful differences in safety or effectiveness were observed between these women and younger women less than 65 years of age.

2 CONTRAINDICATIONS

Osphena is contraindicated in patients who are hypersensitive to this drug or to any ingredient in the formulation, including any non-medicinal ingredient, or component of the container. For a complete listing, see Dosage Forms, Strengths, Composition and Packaging.

Osphena is contraindicated in women with any of the following conditions:

- 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 [for example, stroke and myocardial infarction (MI)], or a history of these conditions
- Severe hepatic impairment (see Warnings and Precautions section)
- Women who are or may become pregnant. Ospemifene 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 (see Warnings and Precautions, Special Populations section).
- Hypersensitivity (for example, angioedema, urticaria, rash, pruritus)

3 SERIOUS WARNINGS AND PRECAUTIONS BOX

Serious Warnings and Precautions

Endometrial Cancer:

- **OSPHENA is an estrogen agonist/antagonist with tissue selective effects. In the endometrium, OSPHENA has estrogen 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 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 *[see 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 the OSPHENA 60 mg treatment group and 3.15 and 0 with placebo *[see Warnings and Precautions].***
- **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 *[see Warnings and Precautions].* 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) *[see Warnings and Precautions].***

4 DOSAGE AND ADMINISTRATION

4.1 Dosing Considerations

The following situations may affect dosing of Osphena:

- Concomitant use of ospemifene with estrogens, estrogen agonist/antagonist, fluconazole, rifampin, ketoconazole, highly protein-bound drugs and drugs known to inhibit CYP3A4 and CYP2C9 (see Drug Interactions, Drug-Drug Interactions section).
- Use of Osphena should be for the shortest duration consistent with treatment goals and risks for the individual woman. Postmenopausal women should be re-evaluated periodically as clinically appropriate to determine if treatment is still necessary.
- Osphena patients have significantly greater adherence and persistence compared with non-ring local estrogen therapies (LETs).

4.2 Recommended Dose and Dosage Adjustment

One Osphena (ospemifene) 60 mg tablet with food once daily.

No dose adjustment is required in women with any severity of renal impairment.

No dose adjustment is required with mild (Child-Pugh Class A) or moderate (Child-Pugh Class B) hepatic impairment (see Warnings and Precautions section). Osphena should not be used in women with severe hepatic impairment (see Warnings and Precautions section).

Osphena is indicated for use in postmenopausal women. Osphena is not intended for use in children. Health Canada has not authorized an indication for pediatric use.

4.4 Administration

Osphena (ospemifene) should be consistently taken orally with food, as the presence or absence of food may alter bioavailability.

4.5 Missed Dose

In the event that a dose is missed, the next dose should be taken as soon as possible. If it is almost time for the next dose, the missed dose should be skipped and the next dose should be taken as planned. Doses should not be doubled to make up for a missed dose. The prescribed dosing schedule should be continued.

5 OVERDOSAGE

Osphena (ospemifene) has been administered to subjects in single doses for up to 800mg/day and repeat doses up to 240 mg/day for 7 days and up to 200 mg/day for 12 weeks. There is no specific antidote for Osphena (ospemifene tablets). In the event of overdose, general supportive measures should be initiated based on the patient's signs and symptoms.

For management of a suspected drug overdose, contact your regional poison control centre.

6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING

Table 1– Dosage Forms, Strengths, Composition and Packaging

Route of Administration	Dosage Form / Strength/Composition	Non-medicinal Ingredients
Oral	Tablet 60 mg ospemifene	Colloidal silicon dioxide, hypromellose, lactose monohydrate, magnesium stearate, mannitol, microcrystalline cellulose, polyethylene glycol, povidone, pregelatinized starch, sodium starch glycolate, titanium dioxide, triacetin.

Description

Osphena tablets are white to off-white, oval, biconvex, film-coated tablets engraved with "60" on one side.

Osphena is supplied in HDPE bottles of 90 tablets with a polypropylene cap or in PVC/PVdC aluminum

foil blisters of 30 tablets (2 strips of 15 tablets).

7 WARNINGS AND PRECAUTIONS

Please see 3 SERIOUS WARNINGS AND PRECAUTIONS BOX.

General

Carcinogenesis and Mutagenesis

Endometrial Cancer:

Osphena (ospemifene tablets) is an estrogen receptor agonist/antagonist with tissue selective effects. In the endometrium, Osphena has weak 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 > 52 weeks treatment groups at a rate of 72.5 per thousand women vs. 11.8 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 > 52 weeks treatment groups vs. 0 per thousand women for placebo. Uterine polyps occurred at an incidence of 11.6 per thousand women in the Osphena > 52 weeks treatment groups vs 8.9 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 reported endometrial cancer risk among unopposed estrogen users is about 2 to 12 times greater than in non-users and appears dependent on duration of treatment and on estrogen dose. Most studies show no significant increased risk associated with the use of estrogens for less than 1 year. The greatest risk appears to be associated with prolonged use, with increased risks of 15- to 24-fold for 5 to 10 years or more. This risk has been shown to persist for at least 8 to 15 years after estrogen therapy is discontinued. 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.

Clinical surveillance of all women using Osphena is important. If break-through bleeding or spotting appears after some time on therapy, or continues after treatment has been discontinued, the reason should be investigated. Adequate diagnostic measures, including directed or random endometrial sampling when indicated, should be undertaken to rule out malignancy in postmenopausal women with undiagnosed persistent or recurring abnormal genital bleeding.

Breast Cancer:

Osphena (ospemifene tablets) 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.

Cardiovascular

Risk factors for cardiovascular disorders, arterial vascular disease (for example, hypertension, diabetes mellitus, tobacco use, hypercholesterolemia, and obesity) and/or venous thromboembolism (VTE) (for example, personal history or family history of VTE, obesity, and systemic lupus erythematosus), should be managed appropriately.

Stroke:

In the clinical trials for Osphena (ospemifene tablets) (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 WHI estrogen-alone substudy, a statistically significant increased risk of stroke was reported in women 50 to 79 years of age receiving daily CE (0.625 mg)-alone compared to women in the same age group receiving placebo (45 versus 33 per ten thousand women years). The increase in risk was demonstrated in year 1 and persisted.

Coronary Heart Disease:

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

In the WHI estrogen-alone substudy, no overall effect on coronary heart disease (CHD) events (defined as nonfatal MI, silent MI, or CHD death) was reported in women receiving estrogen-alone compared to placebo.

Venous Thromboembolism:

In the Osphena clinical trials, the incidence of DVT was 2.26 per thousand women years in the 60 mg treatment group and 3.15 per thousand women years in placebo. The incidence of pulmonary embolism (PE) was 0 per thousand women years in the Osphena 60 mg and placebo treatment groups. Should a VTE (including DVT and PE) 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.

In the WHI estrogen-alone substudy, the risk of VTE (DVT and PE) was increased for women receiving daily CE (0.625 mg)-alone compared to placebo (30 versus 22 per ten thousand women years), although only the increased risk of DVT reached statistical significance (23 versus 15 per ten thousand women years). The increase in VTE risk was demonstrated during the first 2 years.

Genitourinary

Vaginal Bleeding

Abnormal vaginal bleeding, due to its prolongation, irregularity or heaviness, occurring during therapy should prompt appropriate diagnostic measures to rule out the possibility of uterine malignancy and the treatment should be re-evaluated.

Hepatic/Biliary/Pancreatic

Osphena 60 mg should not be used in women with severe hepatic impairment (see Pharmacokinetics, Hepatic Insufficiency section).

Reproductive Health: Female and Male Potential

- **Fertility**

Osphena is indicated in postmenopausal women with no childbearing potential. Osphena is contraindicated in women who are or may become pregnant (see Contraindications and Warnings and Precautions, Special Populations sections).

7.1 Special Populations

7.1.1 Pregnant Women

Osphena clinical trials included only postmenopausal women. There were no pregnant women exposed to Osphena (ospemifene tablets) in the clinical trials.

Based on animal data, Osphena is likely to increase the risk of adverse outcomes during pregnancy and labor. Adverse findings at maternally toxic doses included embryo-fetal lethality in rats and rabbits, and neonatal mortality and difficult labor in rats. The reproductive effects observed are consistent with and are considered to be related to estrogen receptor activity of Osphena (see Action and Clinical Pharmacology, Pharmacokinetics and Non-clinical Toxicology sections).

7.1.2 Breast-feeding

It is unknown if the drug is excreted in human milk. There are no data on the effects of Osphena on the breastfed child of the effects on milk production. Patient should not breastfeed while taking Osphena (see Non-clinical Toxicology section).

7.1.3 Pediatrics

Pediatrics (≤18 years of age): No data are available to Health Canada; therefore, Health Canada has not authorized an indication for pediatric use.

7.1.4 Geriatrics

Geriatrics (≥65 years of age): Of the 2209 Osphena-treated women enrolled in the ten (10) Phase II/III trials of Osphena, >19 percent were 65 years of age or older. No clinically meaningful differences in safety or effectiveness were observed between these women and younger women less than 65 years of age.

8 ADVERSE REACTIONS

8.1 Adverse Reaction Overview

The following serious adverse reactions are discussed elsewhere in the Product Monograph:

- Cardiovascular Disorders (see Warnings and Precautions, Cardiovascular section);
- Malignant Neoplasms (see Warnings and Precautions, Carcinogenesis and Mutagenesis section);

The most frequent adverse reactions that occurred in patients treated with Osphena 60 mg once daily in the 12-week double-blind, placebo-controlled clinical trials were hot flush, hyperhidrosis, muscle spasms and vaginal discharge (see Table 2). Pooled analysis of hot flush treatment-emergent adverse events (TEAEs) found that the frequency of hot flushes declined after 4 weeks of ospemifene treatment.

8.2 Clinical Trial Adverse Reactions

Clinical trials are conducted under very specific conditions. The adverse reaction rates observed in the clinical trials; therefore, may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse reaction information from clinical trials may be useful in identifying and approximating drug-related adverse events and for approximating rates.

The safety of Osphena has been assessed in ten (10) Phase II/III trials (n=2209) with doses ranging from 5 to 90 mg per day. The duration of treatment in these studies ranged from 6 weeks to 15 months. Most women (n=1683) had a treatment period of at least 12 weeks, 432 had at least 52 weeks (1 year) of exposure. The long-term safety in patients that had at least 52 weeks of exposure is similar to those listed in Table 2.

The incidence rates of thromboembolic and hemorrhagic stroke were 1.13 per thousand women years (1 reported case of thromboembolic stroke) and 3.39 per thousand women years (3 reported cases of hemorrhagic stroke), respectively in Osphena 60 mg treatment group and 3.15 (1 case of thromboembolic stroke) and 0 per thousand women years, respectively in placebo. The incidence of deep vein thrombosis (DVT) was 2.26 per thousand women years in Osphena 60 mg treatment group (2 reported cases of DVT) and 3.15 (1 case of DVT) in placebo. The incidence of pulmonary embolism was 0 per thousand women years in the Osphena 60 mg and placebo treatment groups.

Table 2 below lists adverse reactions occurring more frequently in the Osphena 60 mg treatment group than in placebo and at a frequency ≥1%.

Table 2 - Adverse Reactions Reported at Frequency ≥ 1.0% in the Osphena Treatment Group (60 mg Once Daily) in the 12-Week Double-Blind, Controlled Clinical Trials with Osphena vs. Placebo

	Ospemifene 60 mg n = 1459 (%)	Placebo n = 1136 (%)
Musculoskeletal and Connective Tissue Disorders Muscle Spasms	1.8	0.6
Reproductive System and Breast Disorders Vaginal Discharge	3.8	0.1
Skin and Subcutaneous Tissue Disorders Hyperhidrosis	1.1	0.2
Vascular Disorders Hot Flush	6.5	2.6

8.3 Less Common Clinical Trial Adverse Reactions

The following lists the treatment-related adverse events occurring in > 0.1% and < 1% but exceeding the placebo rate that occurred in women treated with Osphena in the 12-week double-blind, controlled

Phase III clinical trials.

Gastrointestinal Disorders: Abdominal pain, abdominal pain lower, diarrhea, dyspepsia, nausea
General Disorders and Administration Site Conditions: Edema peripheral
Immune System Disorder: Drug hypersensitivity
Infections and Infestations: Fungal infection, urinary tract infection, vulvovaginal candidiasis, vulvovaginal mycotic infection
Investigations: Blood creatine phosphokinase increased; weight increased
Musculoskeletal and Connective Tissue Disorders: Arthralgia, myalgia
Neoplasms Benign, Malignant and Unspecified: Uterine leiomyoma
Nervous System Disorders: Restless legs syndrome
Psychiatric Disorders: Depression, insomnia
Renal and Urinary Disorders: Pollakiuria
Reproductive System and Breast Disorders: Breast mass, breast pain, breast tenderness, endometrial hypertrophy
Respiratory, Thoracic and Mediastinal Disorders: Dyspnea
Skin and Subcutaneous Tissue Disorders: Acne, hirsutism, pruritus, rash

8.5 Post-Market Adverse Reactions

The following adverse reactions have been identified during post-approval use of Osphena. Because these reactions are reported voluntarily from a population of uncertain size, it is not possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Immune System Disorders: Allergic conditions including hypersensitivity, angioedema

Nervous System Disorders: Headache

Skin and Subcutaneous Tissue Disorders: Rash, rash erythematous, rash generalized, pruritus, urticaria

Vascular Disorders: deep vein thrombosis, thrombosis, pulmonary embolism

9 DRUG INTERACTIONS

9.2 Drug Interactions Overview

Osphena is primarily metabolized by CYP3A4 and CYP2C9. CYP2C19 and other pathways contribute to the metabolism of ospemifene. In order of decreasing potency, ospemifene was suggested to be a weak inhibitor for CYP2B6, CYP2C9, CYP2C19, CYP2C8, CYP2D6 and CYP3A4 in *in vitro* studies. Ospemifene is not a significant P-glycoprotein substrate *in vitro*; no *in vitro* transporter study was conducted.

9.4 Drug-Drug Interactions

The drugs listed in this table are based on either drug interaction case reports or studies, or potential interactions due to the expected magnitude and seriousness of the interaction (i.e., those identified as contraindicated).

Table 3 - Established or Potential Drug-Drug Interactions

[Proper/Common name]	Source of Evidence	Effect	Clinical comment
Fluconazole	CT	Increase the systemic exposure of ospemifene by 2.7-fold	Fluconazole, a moderate CYP3A / strong CYP2C9 / moderate CYP2C19 inhibitor, should not be used with Osphena. Administration of fluconazole with ospemifene may increase the risk of Osphena-related adverse reactions.
Rifampin	CT	Decrease the systemic exposure of ospemifene by 58%	Co-administration of Osphena with drugs such as rifampin which induce CYP3A4, CYP2C9 and/or CYP2C19 inducer activity would be expected to decrease the systemic exposure of ospemifene, which may decrease the clinical effect.
Ketoconazole	CT	Increase the systemic exposure of ospemifene by 1.4-fold	Administration of ketoconazole, a strong CYP3A4 inhibitor, chronically with ospemifene may increase the risk of Osphena-related adverse reactions.
Warfarin	CT	None	Repeated administration of ospemifene had no effect on the pharmacokinetics of a single 10 mg dose of warfarin. No study was conducted with multiple doses of warfarin. The effect of ospemifene on clotting time such as the International Normalized Ratio (INR) or prothrombin time (PT) was not studied.
Omeprazole	CT	Increase the systemic exposure of ospemifene by 1.17-fold	Multiple doses of omeprazole in fourteen postmenopausal women increased C_{max} and $AUC_{0\text{-}inf}$ by 1.20- and 1.17-fold, respectively. It is unclear if ospemifene will affect the pharmacokinetics of drugs metabolized by CYP2C19 due to the significant time gap between ospemifene and omeprazole administration.

Bupropion	CT	None	There was no evidence of CYP2B6 inhibition by ospemifene.
Midazolam	CT	None	Repeated doses of ospemifene did not affect CYP3A4 activity, for which midazolam is a substrate.
Highly Protein-Bound Drugs	T	Increase exposure of ospemifene or another highly protein-bound drug	Ospemifene is more than 99% bound to serum proteins and might affect the protein binding of other drugs. Use of Osphena with other drug products that are highly protein bound may lead to increased exposure of either that drug or ospemifene.
Multiple Enzyme Inhibition	T	Increase of Osphena-related adverse reactions	Co-administration of Osphena with a drug known to inhibit CYP3A4 and CYP2C9 isoenzymes may increase the risk of Osphena-related adverse reactions.
Estrogens and estrogen receptor agonist/antagonist	T	Unknown	Osphena should not be use concomitantly with estrogens and estrogen receptor agonists/antagonists. The safety of concomitant use of Osphena with estrogens and estrogen receptor agonists/antagonists has not been studied.

Legend: C = Case Study; CT = Clinical Trial; T = Theoretical

9.5 Drug-Food Interactions

Osphena should be administered with food as the presence of food may increase its bioavailability (see Dosage and Administration and Pharmacokinetics sections).

9.6 Drug-Herb Interactions

Interactions with herbal products have not been established.

9.7 Drug-Laboratory Test Interactions

Interactions with laboratory tests have not been established.

10 CLINICAL PHARMACOLOGY

10.1 Mechanism of Action

Osphena is an estrogen receptor agonist/antagonist (ERAA) with tissue selective effects, commonly referred to as 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).

10.2 Pharmacodynamics

Ospemifene has an effect on the receptors of estrogens in the vagina increasing the cellular maturation and mucification of the vaginal epithelium.

Ospemifene has an effect on the receptor of estrogens on the vaginal epithelium in normal and ovariectomized (OVX) rats. In OVX rats, 3 mg/kg/day or higher dose of ospemifene increases the height of the vaginal epithelium to the extent seen with full agonist, 17α-ethinylestradiol. The EC_{50} dose of orally administered ospemifene for this parameter is 0.39 mg/kg/day. Upon histological analysis, multilayered epithelium with keratinized top layer as seen with estrogen was not evident in ospemifene treated rats. The ospemifene response is often limited to 1 to 3 layers, with prominent mucification and vacuolization. The vacuolization appears to be dose dependent to some extent, being more prominent at doses > 1 mg/kg/day.

In dogs and monkeys *in vivo*, ospemifene did not cause any effects on ECG parameters, including QT and QTc intervals. A Phase I thorough QTc study with moxifloxacin as a positive control and ospemifene used at the expected therapeutic dose of 60 mg and a supra-therapeutic dose of 240 mg ospemifene was done in healthy men and women. Ospemifene showed no signal of any effect on heart rate, AV conduction or cardiac depolarization as measured by the PR and QRS interval durations.

10.3 Pharmacokinetics

Table 4 - Summary of Ospemifene Pharmacokinetic Parameters in Postmenopausal Women with a High Fat/Calorie Meal

	C_{max}	T_{max}	$t_{½}$ (h)	$AUC_{0\text{-last}}$	$AUC_{0\text{-inf}}$
Single dose mean	1198 ng/mL	2.5 h	24.2	7188 ng·hr/mL	7521 ng·hr/mL

Table 5 - Summary of Ospemifene Pharmacokinetic Parameters in Postmenopausal Women in the Fasted State

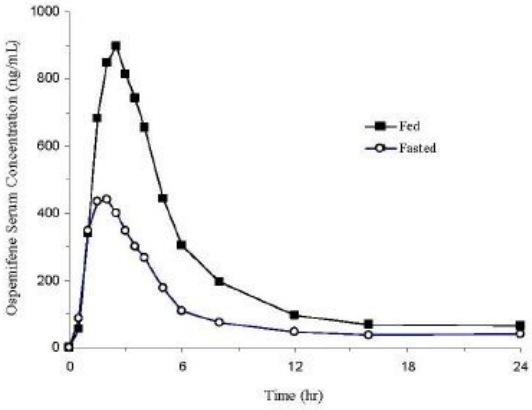
	C_{max}	T_{max}	$t_{½}$ (h)	$AUC_{0\text{-last}}$	$AUC_{0\text{-inf}}$
Single dose mean	533 ng/mL	2.0 h	26.4	3781 ng·hr/mL	4165 ng·hr/mL

Absorption

Following a single oral administration of ospemifene 60 mg tablet in postmenopausal women under fasted condition, peak median serum concentrations was reached at approximately 2 hours (range: 1 to 8 hours) post-dose (see Figure 1). Mean ospemifene C_{max} and $AUC_{0\text{-inf}}$ were 533 ng/mL and 4165 ng·hr/mL, respectively. After a single oral administration of ospemifene 60 mg tablet in postmenopausal women with a high fat/high calorie (860 kcal) meal, C_{max} was reached at approximately 2.5 hours (range: 1 to 6 hours) post-dose. Mean ospemifene C_{max} and $AUC_{0\text{-inf}}$ were 1198 ng/mL and 7521 ng·hr/mL, respectively. The absolute bioavailability of ospemifene was not evaluated.

Ospemifene exhibits less than dose-proportional pharmacokinetics from 25 to 200 mg with ospemifene capsule formulation. Accumulation of ospemifene with respect to $AUC_{0\text{-}inf}$ was approximately 2 after twelve weeks of daily administration. Steady-state was reached after nine days of ospemifene administration.

Figure 1 - Mean Serum Concentration Profile of Ospemifene Following a Single Oral Administration of Ospemifene 60 mg Tablet in Postmenopausal Women Under Fed (n=28) and Fasted (n=91) Conditions



In general, food increased bioavailability of ospemifene by approximately 2-3 fold. In a cross-study comparison, single dose of ospemifene 60 mg tablet administered with a high fat/high calorie meal (860 kcal) in postmenopausal women increased C_{max} and $AUC_{0\text{-}inf}$ by 2.3- and 1.7-fold, respectively, compared to fasted condition. Elimination half-life and time to maximum concentration (T_{max}) were unchanged in the presence of food. In two food effect studies in healthy males using different ospemifene tablet formulations, C_{max} and $AUC_{0\text{-}inf}$ increased by 2.3- and 1.8-fold, respectively, with a low fat/low calorie meal (300 kcal) and increased by 3.6- and 2.7-fold, respectively, with a high fat/high calorie meal (860 kcal), compared to fasted condition. Ospemifene should be taken with food (see Dosage and Administration section).

Distribution:

Ospemifene is highly (> 99 percent) bound to serum proteins. The apparent volume of distribution is 448 L.

Metabolism:

In vitro experiments with human liver microsomes indicated that ospemifene primarily undergoes metabolism via CYP3A4, CYP2C9 and CYP2C19. The major metabolite was 4-hydroxyospemifene. The apparent total body clearance is 9.16 L/hr using a population approach.

Elimination

The apparent terminal half-life of ospemifene in postmenopausal women is approximately 25 hours. Following an oral administration of ospemifene in postmenopausal women, approximately 75% and 7% of the dose was excreted in feces and urine, respectively. Less than 0.2% of the ospemifene dose was excreted unchanged in urine.

Special Populations and Conditions

- **Pediatrics:** The pharmacokinetics of ospemifene in pediatric patients has not been evaluated.

- **Geriatrics:** No differences in ospemifene pharmacokinetics were detected with regard to age (range 40 to 80 years).
- **Sex:** No significant pharmacokinetics differences have been observed between males and females.
- **Pregnancy and Breast-feeding:** The effects of ospemifene on embryo-fetal development were studied in rats (0.1, 1, or 4 mg/kg/day) and rabbits (3, 10, or 30 mg/kg/day) when treated from implantation through organogenesis. In rabbits, there was an increase in the incidence of total resorptions at 30 mg/kg/day (10 times the human exposure based on the surface area mg/m^2). Drug-induced malformations were not observed in either rats or rabbits.

  The effects of ospemifene on pre- and post-natal development were studies in pregnant rats (0.01, 0.05, and 0.25 mg/kg/day) treated from implantation through lactation. Pregnant rats given 0.05 or 0.25 mg/kg/day Ospemifene (0.8% to 4% the human exposure based on surface area mg/m^2) had significantly prolonged and difficult gestation, increased post-implantation loss, increased number of dead pups at birth, and an increased incidence of post-natal loss. Ospemifene did not induce adverse effects in the surviving offspring of pregnant rats at drug exposures up to 4% the human exposure.

  In a non-clinical study, ospemifene was excreted in rat milk and detected at concentrations higher than that in maternal plasma (see Warnings and Precautions, Special Populations section).
- **Ethnic Origin:** Ethnic origin did not have clinically relevant effect on ospemifene pharmacokinetics.
- **Hepatic Insufficiency:** Ospemifene is primarily metabolized by the liver. In postmenopausal women with mild hepatic impairment (Child-Pugh Class A), the C_{max} and $AUC_{0\text{-}inf}$ for ospemifene following a single 60 mg dose administered with a high fat/high calorie meal were lower by 21% and 9.1%, respectively, compared to women with normal hepatic function. In women with moderate hepatic impairment (Child-Pugh Class B), the C_{max} and $AUC_{0\text{-}inf}$ for ospemifene following a single 60 mg dose administered with a high fat/high calorie meal were higher by 1% and 29%, respectively, compared to women with normal hepatic function. The effect of severe hepatic impairment on the pharmacokinetics of ospemifene has not been evaluated. Osphena should not be used in women with severe hepatic impairment (see Dosage and Administration and Warnings and Precautions sections).
- **Renal Insufficiency:** In postmenopausal women with severe renal impairment (CrCL < 30 mL/min), the C_{max} and $AUC_{0\text{-}inf}$ for ospemifene following a single 60 mg dose administered with a high fat/high calorie meal were lower by 21% and higher by 20% respectively. Ospemifene is unlikely to be affected by renal impairment because renal clearance of unchanged drug is a minor pathway of elimination (less than 0.2% of the ospemifene dose is excreted unchanged). Although large pharmacokinetic variability was observed, results indicated that there were no clinically important pharmacokinetic differences between subjects with severe renal impairment and control subjects with normal renal function (see Dosage and Administration section).

11 STORAGE, STABILITY AND DISPOSAL

Store at room temperature (15° to 30°C).

Keep out of reach and sight of children.

12 SPECIAL HANDLING INSTRUCTIONS

This information is not available for this drug product.

PART II: SCIENTIFIC INFORMATION

13 PHARMACEUTICAL INFORMATION

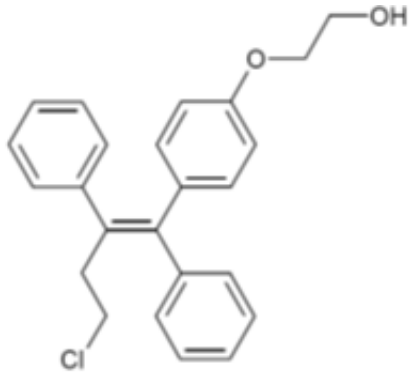
Drug Substance

Proper/Common Name: Ospemifene

Chemical name: Ospemifene

Molecular formula and molecular mass: $C_{24}H_{23}ClO_2$, 378.9 g/mol

Structural formula:



Physicochemical properties:

Ospemifene is a white or almost white, crystalline powder. At room temperature, ospemifene is insoluble in water, freely soluble in acetone, methylehylketone, methylisobutylketone, ethylacetate and tetrahydrofurane, soluble in ethanol, propanol, butanol, butylacetate, toluene and acetonitrile and very slightly soluble in isopropanol. In boiling solvents, ospemifene is insoluble in water and freely soluble in ethanol, isopropanol, n-propanol, butanol, butylacetate, toluene and acetonitrile. The molecule can have two geometrical isomeric forms. Ospemifene is the Z-isomer, which means that the parasubstituted phenyl ring and the chloroalkyl side chain are on the opposite sides of the double bond. No polymorphism was revealed in X-ray powder diffraction studies.

14 CLINICAL TRIALS

14.1 Trial Design and Study Demographics

Table 6 - Summary of patient demographics for phase III clinical trials in postmenopausal women with severe to moderate dyspareunia and/or dryness

Study #	Study design	Dosage, route of administration and duration	Study subjects (n)	Mean age (Range)	Sex
15-50310	Multi-center, randomized, double-blind, parallel group, placebo-controlled	Ospemifene 30 mg or 60 mg tablet orally once per day or matching placebo orally once per day	30 mg: 282 60 mg: 276 Placebo: 268	59 (41-80)	Postmenopausal women
15-50821	Multi-center, randomized, double-blind, parallel group, placebo-controlled	Ospemifene 60 mg tablet orally once per day or matching placebo orally once per day	Ospemifene: 463 Placebo: 456	59 (40-79)	Postmenopausal women
1517I0231	Randomized, double-blind, parallel-group, placebo-controlled	Ospemifene 60 mg orally once per day or matching placebo orally once per day	Ospemifene: 313 Placebo: 314	60 (41-80)	Postmenopausal women
15-50718	Multi-center, randomized, double-blind, parallel group, placebo-controlled	Ospemifene 60 mg tablet orally once per day or matching placebo orally once per day	Ospemifene: 363 Placebo: 63	62 (49-79)	Postmenopausal women with an intact uterus

Study #15-50310 was a 12-week, randomized, double-blind, placebo-controlled, parallel-group study that enrolled 826 generally healthy postmenopausal women between 41 and 80 years of age (mean 59 years of age) who at baseline had ≤5 percent superficial cells on a vaginal smear, a vaginal pH >5.0, and who identified at least one 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 included 30 mg Osphena (n=282), 60 mg Osphena (n=276), and placebo (n=268). All women were assessed for improvement in the mean change from Baseline to Week 12 for co-primary efficacy variables 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 most bothersome at baseline), percentage of vaginal superficial and vaginal parabasal cells on a vaginal smear, and vaginal pH. Following completion of 12-weeks, women with an intact uterus were allowed to enroll in a 40-week double-blind extension study, and women without an intact uterus were allowed to enroll in a 52-week open-label extension study.

Study #15-50821 was a 12-week, randomized, double-blind, placebo-controlled, parallel-group study that enrolled 919 generally healthy postmenopausal women between 40 and 79 years of age (mean 59 years of age) who, at baseline, had ≤5 percent 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 60 mg Osphena (n=463) and placebo (n=456). Primary endpoints and study conduct were similar to those in Study #15-50310.

Study #1517I0231 was a 12-week, randomized, double-blind, placebo-controlled study that enrolled 631 generally healthy postmenopausal women between 41 and 80 years of age (mean 60 years of age) who, at baseline, had ≤5 percent superficial cells on a vaginal smear, a vaginal pH > 5.0 and had moderate to severe vaginal dryness as the self-reported MBS of VVA. Treatment groups included 60 mg Osphena (n=313) and placebo (n=314). All women were assessed for the following primary endpoints of: percentages of parabasal and superficial cells in the maturation index, vaginal pH and severity of MBS of vaginal dryness.

Study #15-50718 was a 52-week, randomized, double-blind, placebo-controlled, long-term safety study that enrolled 426 generally healthy postmenopausal women between 49 and 79 years of age (mean 62 years of age) with an intact uterus. Treatment groups included 60 mg Osphena (n=363) and placebo (n=63).

14.2 Study Results

Study #15-50310:

Study 15-50310 included postmenopausal women who had the following criteria for VVA: 5% or fewer superficial cells confirmed by maturation index in the vaginal smear, at least one moderate or severe symptom of VVA and vaginal pH greater than 5.0.

For the ITT population, ospemifene was found to be effective in the treatment of VVA with an MBS of vaginal dryness and dyspareunia. For all four co-primary endpoints, ospemifene 60 mg/day demonstrated statistically significant superiority over placebo. For all four co-primary endpoints, ospemifene 60 mg/day was more effective than 30 mg/day.

For the modified intent-to-treat population (mITT), results demonstrated a statistically significant improvement in the moderate to severe MBS of dyspareunia (p=0.0012) versus placebo from baseline to Week 12. 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 was also demonstrated (p<0.0001) for dyspareunia. The mean reduction in vaginal pH between baseline and Week 12 was also statistically significant (p<0.0001).

The improvement between treatment groups (ospemifene versus placebo) for percentage of parabasal cells, percentage of superficial cells and vaginal pH were also statistically significant and observed at Week 4 and continued at Week 12.

Table 7 - Results of study #15-50310 primary endpoints in the treatment of VVA with MBS of vaginal dryness and dyspareunia in postmenopausal women: mean change from baseline to week 12 (Intent-to-Treat (ITT) population)/Last Observation Carried Forward (LOCF)

Primary Endpoints	Associated value and statistical significance for ospemifene 60 mg	Associated value for Placebo
1. Percentage of parabasal cells in the maturation index of the vaginal smear (p-value vs placebo)[a]	-30.1% (p<0.001)	3.98%
2. Percentage of superficial cells in the maturation index of the vaginal smear (p-value vs placebo)[b]	10.8% (p<0.001)	2.18%
3. Vaginal pH (p-value vs placebo)[c]	-1.01% (p<0.001)	-0.10%
4. Severity of the MBS (p-value vs placebo): • MBS vaginal dryness • MBS dyspareunia	-1.26 (p<0.05) -1.19 (p<0.05)	-0.84 -0.89

[a] The objective criteria was to decrease parabasal cells.
[b] The objective criteria was to increase superficial cells.
[c] The objective criteria was to decrease vaginal pH.

Study #15-50821:

Study 15-50821 included postmenopausal women who had the following criteria: 5% or fewer superficial cells in the maturation index of the vaginal smear, vaginal pH greater than 5.0 and moderate to severe vaginal dryness or dyspareunia as the self-reported MBS.

For the Dyspareunia Stratum (MBS of vaginal pain associated with sexual activity) (Table 9), ospemifene 60 mg daily demonstrated statistically significant superiority over placebo in the ITT population for all 4 co-primary efficacy endpoints with a p-value of ≤ 0.0001.

For the modified intent-to-treat population (mITT), results demonstrated a statistically significant improvement in the moderate to severe MBS of dyspareunia (p<0.0001) versus placebo from baseline to Week 12. 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 was also demonstrated (p<0.0001) for dyspareunia. The mean reduction in vaginal pH between baseline and Week 12 was also statistically significant (p<0.0001).

The improvement between the ospemifene 60 mg and placebo treatment groups for percentage of parabasal cells, percentage of superficial cells and vaginal pH were also statistically significant and observed at Week 4 and continued at Week 12.

With LOCF analysis, for the Dryness Stratum (MBS of vaginal dryness) (Table 8), ospemifene 60 mg daily demonstrated statistically significant superiority over placebo in the ITT population for all co-primary efficacy endpoints except for severity of the MBS of vaginal dryness, for which ospemifene approaches statistical significance (p=0.0803) in the intent-to-treat (ITT) population and was statistically significantly superior to placebo in the per-protocol (PP) population (p=0.0143). When the analysis was redone using GEE analysis instead of LOCF, the odds ratio for change from baseline in severity of the MBS of vaginal dryness at Week 12 was 1.84 (p=0.0081). Therefore, subjects in the ospemifene group had a statistically significant greater likelihood (1.84 times) of a decrease in severity of the MBS of vaginal dryness compared with the placebo group at Week 12.

Table 8 - Results of study #15-50821 primary endpoints in the treatment of VVA in postmenopausal women (Dryness Stratum): mean change from baseline to week 12 (ITT population)/LOCF

Primary Endpoints	Associated value and statistical significance for ospemifene 60 mg	Associated value for Placebo
1. Percentage of parabasal cells in the maturation index of the vaginal smear (LS mean ± SE)[a] p-value vs placebo	-31.7 ± 2.11 (p<0.0001)	-3.9 ± 2.18
2. Percentage of superficial cells in the maturation index of the vaginal smear (median [min, max])[b] p-value vs placebo	7.0 (-4, 65) (p<0.0001)	0.0 (-11, 57)
3. Vaginal pH (LS mean ± SE)[c] p-value vs placebo	-0.95 ± 0.067 (p<0.0001)	-0.25 ± 0.068
4. Severity of the most bothersome symptom (MBS) of VVA of vaginal dryness (n (%)):	p=0.0803[d]	
• -3 (severe to none)	23 (14.4%)	14 (9.1%)
• -2 (severe to mild or moderate to none)	51 (31.9%)	39 (25.3%)
• -1 (severe to moderate, moderate to mild or mild to none)	39 (24.4%)	52 (33.8%)
• 0 (no change)	44 (27.5%)	44 (28.6%)
• 1 (none to mild, mild to moderate or moderate to severe)	3 (1.9%)	5 (3.2%)

[a] The objective criteria was to decrease parabasal cells.
[b] The objective criteria was to increase superficial cells.
[c] The objective criteria was to decrease vaginal pH.

[d] Calculated using the LOCF analysis. When the analysis was redone using GEE analysis instead of LOCF, the odds ratio for change from baseline in severity of the MBS of vaginal dryness at Week 12 was 1.84 (p=0.0081).

Table 9 - Results of study #15-50821 primary endpoints in the treatment of VVA in postmenopausal women (Dyspareunia Stratum): mean change from baseline to week 12 (ITT population)/LOCF

Primary Endpoints	Associated value and statistical significance for ospemifene 60 mg	Associated value for Placebo
1. Percentage of parabasal cells in the maturation index of the vaginal smear (LS mean ± SE)[a] p-value vs placebo	-40.3 ± 1.56 (p<0.0001)	-0.4 ± 1.57
2. Percentage of superficial cells in the maturation index of the vaginal smear (median [min, max])[b] p-value vs placebo	7.0 (-6, 79) (p<0.0001)	0.0 (-5, 85)
3. Vaginal pH (LS mean ± SE)[c] p-value vs placebo	-0.94 ± 0.050 (p<0.0001)	-0.07 ± 0.050
4. Severity of the most bothersome symptom (MBS) of VVA of dyspareunia (n (%)): • -3 (severe to none) • -2 (severe to mild or moderate to none) • -1 (severe to moderate, moderate to mild or mild to none) • 0 (no change) • 1 (none to mild, mild to moderate or moderate to severe)	p=0.0001 67 (22.1%) 93 (30.7%) 82 (27.1%) 55 (18.2%) 6 (2.0%)	 47 (15.6%) 70 (23.2%) 76 (25.2%) 102 (33.8%) 7 (2.3%)

[a] The objective criteria was to decrease parabasal cells.
[b] The objective criteria was to increase superficial cells.
[c] The objective criteria was to decrease vaginal pH.

Study #1517I0231:

Study 1517I0231 included postmenopausal women with the following criteria: 5% or fewer superficial cells in the maturation index of the vaginal smear, vaginal pH > 5.0 and moderate to severe vaginal dryness as the self-reported MBS of VVA.

Ospemifene was found to be effective in the treatment of VVA in subjects with the most bothersome

VVA symptom of vaginal dryness. Ospemifene 60 mg daily demonstrated statistically significant superiority over placebo in the ITT population for all co-primary efficacy endpoints. The MBS of vaginal dryness was statistically significant improved at Week 4 and continued to Weeks 8 and 12. Ospemifene was also reconfirmed to be effective in the treatment of VVA with symptoms of severe or moderate vaginal pain associated with sexual activity.

Table 10 - Results of study #1517I0231 primary endpoints in the treatment of VVA in postmenopausal women with vaginal dryness as MBS: mean change from baseline to week 12 (ITT population)/Generalized Estimating Equations (GEE)

Primary Endpoints	Associated value and statistical significance for ospemifene 60 mg[a]	Associated value for Placebo
1. Percentage of parabasal cells in the maturation index of the vaginal smear (LS mean ± SE)[b] p-value vs placebo	-23.7 ± 1.4 (p<0.0001)	-1.9 ± 1.4
2. Percentage of superficial cells in the maturation index of the vaginal smear (LS mean ± SE)[c] p-value vs placebo	7.8 ± 0.7 (p<0.0001)	0.6 ± 0.7
3. Vaginal pH (LS mean ± SE)[d] p-value vs placebo	-1.01 ± 0.04 (p<0.0001)	-0.29 ± 0.04
4. Severity of the most bothersome symptom (MBS) of VVA of vaginal dryness (n (%)): • -3 (severe to none) • -2 (severe to mild or moderate to none) • -1 (severe to moderate, moderate to mild or mild to none) • 0 (no change) • 1 (none to mild, mild to moderate or moderate to severe)	(p<0.0001) 39 (14.1%) 73 (26.4%) 94 (33.9%) 70 (25.3%) 1 (0.4%)	 15 (5.3%) 63 (22.4%) 94 (33.5%) 99 (35.2%) 10 (3.6%)

[a] MMRM model for changes in percentages of parabasal and superficial cells in the maturation index and in vaginal pH; GEE model for changes in percentages of MBS of vaginal dryness.
[b] The objective criteria was to decrease parabasal cells.
[c] The objective criteria was to increase superficial cells.
[d] The objective criteria was to decrease vaginal pH.

Study #15-50718:

The results of the study demonstrated that ospemifene 60 mg once daily was effective, safe and well-

tolerated in relieving the signs of VVA in postmenopausal women with an intact uterus. The beneficial effects were sustained over a treatment period of 1 year.

Table 11 - Results of study #15-50718 primary endpoints in the treatment of vulvar and vaginal atrophy (VVA) in postmenopausal women: mean changes from baseline to week 12 (ITT population)/LOCF

Primary Endpoints	Associated value and statistical significance for ospemifene 60 mg	Associated value for Placebo
Percentage of parabasal cells in the MI (median (range))[a] p-value vs placebo	-40 (-100 to 75) (p<0.0001)	0 (-90 to 98)
Percentage of superficial cells in the maturation index (MI) (median (range))[b] p-value vs placebo	5 (-5 to 60) (p<0.0001)	0 (-5 to 28)
Vaginal pH (mean (SD))[c] p-value vs placebo	-1.21 (0.912) (p<0.0001)	-0.16 (0.945)

[a] The objective criteria was to decrease parabasal cells.
[b] The objective criteria was to increase superficial cells.
[c] The objective criteria was to decrease vaginal pH.

15 MICROBIOLOGY

No microbiological information is required for this drug product.

16 NON-CLINICAL TOXICOLOGY

General Toxicology:

Single-dose Toxicity:

Three (3) preclinical single dose toxicity studies of ospemifene were conducted in the rat, hamster and minipig.

In the rat and hamster, ospemifene was well-tolerated. No drug-induced mortality/morbidity or abnormal clinical signs were detected. The acute oral toxicity of ospemifene was low. In the rat and hamster, the no observed effect level (NOEL) was more than 2 000 mg/kg and 1 000 mg/kg, respectively.

In the minipig, ospemifene was well-tolerated at single doses up to 500 mg/kg/day in the female minipig; no drug-induced mortality/morbidity or clinical signs were detected. Based on AUC values, the animal exposure increased dose-proportionally from 15 to 50 mg/kg but less than dose-proportionally when the dose was increased further. The NOEL was more than 500 mg/kg.

Repeated-dose Toxicity:

Two (2) preclinical repeated-dose toxicity studies of ospemifene were conducted in the rat and monkey and support the market authorization.

In a 26-week toxicity study in the female Sprague Dawley rats, daily doses of 3, 30 or 300 mg/kg/day were administered by gavage. There were no unscheduled deaths or clinical signs of toxicity. A reduction in mean body weight gain was found in all groups receiving ospemifene, with reductions of 9-11% compared to control; this was accompanied by reduced food consumption throughout the study. A marginal increase in relative liver weights (6-10%) was detected at intermediate and high doses. The main treatment-related effects were observed in the reproductive tract: relative uterus weights were decreased in all treated groups, with a thin uterus observed macroscopically due to atrophy of the endometrial stroma in all animals at all dose levels. Endometrial epithelial hypertrophy/hyperplasia was noted in all treated animals. Relative ovary weights were decreased at the lowest dose, and increased at the highest dose, with a dose-related trend of increased number of cysts considered to be due to cyclic arrest of the ovaries in the follicular stage. In 4/20 high-dose animals, there was cystopapillary hyperplasia of the granulosa cells within the cystic follicles resembling the early phase of neoplasia. In the vagina, the incidence of mucification increased dose-dependently (from 5% to 95%). In the mammary gland, ductal hypertrophy was observed in 4/20 and 12/19 intermediate and high dose animals, respectively. In the pituitary, vacuolation increased dose-dependently in treated animals. Hypertrophy of hepatic cells was found in the high dose animals, and is considered to be a physiological adaptive change to the increased metabolic activity. The changes in the reproductive organs are in line with the SERM-like activity of ospemifene and can be considered to be exaggerated pharmacological actions. The NOEL was < 3 mg/kg/day and NOAEL was ≥ 300 mg/kg/day of ospemifene (with respect to human postmenopausal safety).

In a 39-week toxicity study in female cynomolgus monkeys, ospemifene was administered by gavage at doses of 15, 50 or 150 mg/kg/day. There were no unscheduled deaths or clinical signs. Body weight gain and food consumption were considered to be not affected by treatment. Oral administration of ospemifene at any dose did not produce any major toxicity. Principal drug-related findings included organ weight changes of ovaries, macroscopic necropsy findings of ovarian cysts, and histopathological changes in the ovary, uterus, vagina and mammary gland of dosed females. These findings are considered to be exaggerated pharmacological effects of repeated doses of ospemifene. Elevated serum estradiol levels and ovarian findings suggest that hormonal imbalance was induced in the fertile monkey. Drug-related changes in ALT levels and elevated hepatic glycogen storage across all treated groups may be also related to the SERM-like hepatic activity of ospemifene. Singly elevated γ-GT levels are of unclear origin as no liver toxicity was seen in histopathological studies. Animal exposure to ospemifene increased with increasing dose but less than dose-proportionally. The exposure to the active metabolite was at the same level as the parent drug at the two lowest dose levels but increased at the highest dose level, maybe due to increased metabolism. The NOEL was < 15 mg/kg/day and the NOAEL ≥ 150 mg/kg/day.

Carcinogenicity:

In a 2-year carcinogenicity study in female mice, ospemifene was orally administered at 100, 400, or 1500 mg/kg/day. No evaluation for carcinogenicity was conducted in male mice. There was significant increase in adrenal subcapsular cell adenomas at 4 and 5 times the human exposure based on AUC, and adrenal cortical tumors at 5 times the human exposure. In the ovary, an increase in sex cord/stromal tumors, tubulostromal tumors, granulosa cell tumors, and luteomas were also seen. These findings occurred at doses 2 to 5 times the human exposure based on AUC, and are probably related to estrogenic/antiestrogenic effect of ospemifene in mice.

In a 2-year carcinogenicity study in rats, ospemifene was administered at 10, 50, or 300 mg/kg/day. A significant increase in thymomas was recorded for males and thymomas for females at all ospemifene dose levels, or 0.3 to 1.2 times the human exposure based on AUC. In the liver, an increase in hepatocellular tumors were recorded for females at all ospemifene dose levels.

Genotoxicity:

Ospemifene was not genotoxic *in vitro* in the Ames test in strains of *Salmonella typhimurium* or at the thymidine kinase (tk) locus of mouse lymphoma L5178Y cells in the absence and in the presence of a metabolic activator system. In *in vivo* testing, ospemifene was not genotoxic in a standard mouse bone marrow micronucleus test or in a determination of DNA adducts in the liver of rats.

Reproductive and Developmental Toxicology:

The effect of ospemifene on fertility was not directly evaluated. In female rats and monkeys, decreases in ovarian and uterine weights, decreased corpora lutea number, increased ovarian cysts, uterine atrophy, and disrupted cycles were observed when given repeated daily oral doses. In male rats, atrophy of the prostate and seminal vesicles was noted. The effects on reproductive organs observed in animals are consistent with the estrogen receptor activity of ospemifene and potential for impairment of fertility.

The embryo-fetal studies with ospemifene did not reveal any teratogenic effects. In the two-generation reproductive study in Han Wistar rats, ospemifene did not induce adverse effects in the F1 generation even at the highest dose tested (0.25 mg/kg/day). However, dose range-finding studies revealed that ospemifene doses of 1 mg/kg/day or higher caused severe impairment in maternal body weight gain, dam deaths at delivery, increased post-implantation losses and pup deaths. This reproductive toxicity may be partly explained by the observed severe reduction in body weight gain, but probably the hormonal properties of ospemifene were involved in causing the disability to normal delivery.

In the milk, ospemifene was detected in 2 of 3 animals in the 0.05 mg/kg/day group (6.2 or 7.7 ng/mL, 7.0 in average), and in 3 or 3 animals in the 0.25 mg/kg/day group (15.1-37.2 ng/mL, 24.0 in average). Compared to human average ospemifene plasma level, 654 ng/mL, at clinical doses in steady state, the dam exposure was low.

PATIENT MEDICATION INFORMATION

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

Pr OSPHENA®

Ospemifene Tablets

Read this carefully before you start taking **Osphena** and each time you get a refill. This leaflet is a summary and will not tell you everything about this drug. Talk to your healthcare professional about your medical condition and treatment and ask if there is any new information about **Osphena**.

Serious Warnings and Precautions

- **Endometrial Cancer (cancer of the lining of the uterus):** Osphena is a drug that activates or blocks the estrogen receptors. Osphena activates the estrogen receptors in the lining of the uterus (womb). The risk of getting endometrial cancer is increased in a woman with a uterus who uses estrogen therapy alone without progesterone. Your healthcare professional will conduct an examination to rule out cancer if you are experiencing persistent or recurring unexplained vaginal bleeding.
- **Circulatory system problems:** Taking Osphena can increase your risk of developing:
  - a thromboembolic stoke (artery is blocked by blood clot)
  - a hemorrhagic stroke (bleeding in your brain from a torn blood vessel)
  - deep vein thrombosis (blood clot in the deep veins of the leg or arm)

What is Osphena used for?

Osphena is used in postmenopausal (after menopause) women to treat some symptoms of Genitourinary Syndrome of Menopause (GSM). GSM is a condition caused by lowering levels of the female hormone oestrogen in your body. Osphena is used to treat moderate to severe symptoms such as:

- pain during sex due to changes in and around the vagina;
- dryness due to changes in and around the vagina.

How does Osphena work?

Low levels of the female hormone estrogen can cause the vaginal walls to become thinner. Osphena is not estrogen but is believed to work in a similar way as estrogen in the vagina. It does this by increasing the thickness of the vaginal walls. It also restores the vaginal pH.

What are the ingredients in Osphena?

Medicinal ingredients: ospemifene.
Non-medicinal ingredients: colloidal silicon dioxide, hypromellose, lactose monohydrate, magnesium stearate, mannitol, microcrystalline cellulose, polyethylene glycol, povidone, pregelatinized starch, sodium starch glycolate, titanium dioxide, triacetin.

Osphena comes in the following dosage forms:

60 mg tablets

Do not use Osphena if:

- You have unexplained vaginal bleeding
- You currently have or have had certain cancers which are sensitive to estrogens. If you have or have had cancer, talk with your healthcare professional about whether you should take Osphena.
- You currently have or have had a blood clots in a vein (thrombosis). Examples include blood clots in your legs (deep vein thrombosis) or lungs (pulmonary embolism).
- You currently have or has a blood clot in an artery. Examples include a stroke or heart attack
- Have severe liver problems
- You are allergic or have a history of serious allergic reactions to ospemifene or any other ingredients in Osphena. Symptoms include swelling, hives, rash, red itchy welts. If you are not sure about this, talk to your doctor before taking Osphena.
- You are pregnant or may become pregnant. **Osphena** is not for pregnant women. Osphena may cause harm to your unborn baby. If you think you may be pregnant, you should have a pregnancy test and know the results. Do not take Osphena if the test is positive and talk to your healthcare professional.

To help avoid side effects and ensure proper use, talk to your healthcare professional before you take Osphena. Talk about any health conditions or problems you may have, including if you:

- Have or have had a cancer of the lining of the uterus (womb)
- Have or have had breast cancer
- Are at risk of developing a blood circulation problem (i.e. high blood pressure, diabetes, smoker, high cholesterol, obese)
- Have or have had blood clots
- Had a heart attack or other heart conditions. Taking Osphena can increase your risk of experiencing a heart attack.
- Have severe liver problems
- Are going to have surgery or will be on bed rest
- Have any unusual vaginal bleeding
- Think you are or may become pregnant. Osphena may cause harm to your unborn baby.
- Are breast feeding. It is not known if Osphena can pass into your breast milk. You should not breastfeed while taking Osphena.

Other warnings you should know about:

Treatment with Osphena could increase your risk of certain side effects, including:

- Endometrial Cancer. Osphena is a medicine that works like estrogen in the lining of the uterus (womb), and may increase your chance of getting cancer of the lining of the uterus (endometrial cancer). Endometrial cancer has been reported in women on longterm treatment with estrogen. This risk can continue for at least 8 to 15 years after estrogen therapy is stopped. Your doctor will monitor your condition during your treatment. Speak to your doctor if you experience unusual vaginal bleeding.
- Strokes. Your doctor may stop your treatment with Osphena immediately if you experience a stroke.

Tell your healthcare professional about all the medicines you take, including any drugs, vitamins, minerals, natural supplements or alternative medicines.

The following may interact with Osphena:

- antifungals (drugs used to treat fungal infections, such as fluconazole and ketoconazole);
- antibiotics such as rifampin;
- proton-pump inhibitors (drugs used for heartburn or stomach ulcers such as omeprazole);
- estrogens;
- hormone replacement therapy (ERT / HRT) or estrogens agonist / antagonist (estrogen-like medications such as tamoxifen and bazedoxifene);
- medications used to reduce the formation of clots (warfarin);
- medications used to treat osteoporosis (raloxifene).

How to take Osphena:

- Take exactly how your healthcare professional tells you to take it
- Talk to your healthcare professional often (every 3 to 6 months) about your dose. Your healthcare professional will decide if you still need treatment with Osphena.

Usual dose:

Take one 60 mg tablet once a day with food. Take the Osphena tablet by mouth.

Overdose:

If you think you, or a person you are caring for, have taken too much Osphena, contact a healthcare professional, hospital emergency department, or regional poison control centre immediately, even if there are no symptoms.

Missed Dose:

If you missed a dose of this medication, take it as soon as you remember. But if it is almost time for your next dose, skip the missed dose and continue with your next scheduled dose. Go back to the regular dosing schedule. Do not take two doses at the same time.

What are possible side effects from using Osphena?

These are not all the possible side effects you may have when taking Osphena. If you experience any side effects not listed here, tell your healthcare professional.

The side effects of Osphena are:

- Acne, red itchy skin;
- Diarrhea;
- Excess hair on the face, chest, abdomen or legs;
- Feeling hot (hot flushes or flashes);
- Headache;
- Increased / excessive sweating;

- Joint or muscle pain;
- Muscle spasms, such as leg cramps;
- Nausea;
- Swelling of legs and hands;
- Stomach pain;
- Urge to move legs;
- Vaginal discharge~~;~~

Serious side effects and what to do about them			
Symptom / effect	**Talk to your healthcare professional**		**Stop taking drug and get immediate medical help**
	Only if severe	**In all cases**	
UNCOMMON			
Breast mass (breast lump) pain, tenderness in breast		✓	
Hypersensitivity reaction: rash, itchiness along with difficulty breathing with or without swelling of the face, lips, tongue and throat.			✓
Depression: persistent sad mood.		✓	
Urinary tract infection (infection in urinary system including kidneys, ureters, bladder and urethra): Pain or burning sensation while urinating, frequent urination, blood in urine, pain in the pelvis, strong smelling urine, cloudy urine		✓	
Shortness of breath			✓
Vaginal infection (fungal, yeast or bacterial infection of the vulva or vagina): vaginal discharge, vaginal redness, vaginal swelling, vaginal burning sensation and vaginal discomfort		✓	
Ovarian cyst: pelvic pain, abdominal bloating / swelling, frequent need to urinate, painful bowel movements, vaginal bleeding.		✓	
Vulvovaginal hemorrhage (vaginal bleeding): unexplained vaginal bleeding.		✓	
RARE			
Deep vein thrombosis: swelling of your foot, ankle, or leg, usually on			✓

Serious side effects and what to do about them			
Symptom / effect	Talk to your healthcare professional		Stop taking drug and get immediate medical help
	Only if severe	In all cases	
one side; cramping pain in your affected leg that usually begins in your calf; severe, unexplained pain in your foot and ankle; an area of skin that feels warmer than the skin on the surrounding areas; skin over the affected area turning pale or a reddish or bluish color.			
VERY RARE			
Myocardial infarction also known as heart attack: pressure, tightness, pain or a squeezing sensation in chest or arms that may spread to neck, jaw or back, nausea, heartburn or abdominal pain, shortness of breath, lightheadedness or sudden dizziness.			✓
Pulmonary embolism (blood clot in lungs): sudden shortness of breath or sudden chest pain that may be worse with breathing or coughing, coughing blood.			✓
Transient ischemic attack (TIA) / Cerebrovascular accident also known as stroke: severe and sudden headache, sudden numbness / weakness / paralysis, sudden trouble walking, talking or understanding, sudden trouble seeing / blurred vision in one or both eyes, loss of balance / lack of coordination.			✓
Visual impairment: sudden partial or complete loss of vision.			✓

If you have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, tell your healthcare professional.

Reporting Side Effects

You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting (https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada.html) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

Storage:

Store Osphena at room temperature between 15°C to 30°C.

Keep out of reach and sight of children.

If you want more information about Osphena:

- Talk to your healthcare professional
- Find the full product monograph that is prepared for healthcare professionals and includes this Patient Medication Information by visiting the Health Canada website: (https://health-products.canada.ca/dpd-bdpp/index-eng.jsp); the manufacturer's website (https://www.duchesnay.com/en/), or by calling 1-888-666-0611.

This leaflet was prepared by Duchesnay Inc.

Last Revised JUL 15, 2021