CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

203505Orig1s000

<u>LABELING</u>

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use OSPHENA safely and effectively. See full prescribing information for OSPHENA.

OSPHENA™ (ospemifene) tablets, for oral use
Initial U.S. Approval: 2013

WARNING: ENDOMETRIAL CANCER AND CARDIOVASCULAR DISORDERS
See full prescribing information for complete boxed warning.

OSPHENA is an estrogen agonist/antagonist with tissue selective effects. In the endometrium, OSPHENA has estrogen agonistic effects. There is an increased risk of endometrial cancer in a woman with a uterus who uses unopposed estrogens. Adding a progestin to estrogen therapy reduces the risk of endometrial hyperplasia, which may be a precursor to endometrial cancer *[see Warnings and Precautions (5.2)]*.

Estrogen-alone therapy has an increased risk of stroke and deep vein thrombosis (DVT). OSPHENA 60 mg had cerebral thromboembolic and hemorrhagic stroke incidence rates of 0.72 and 1.45 per thousand women, respectively vs. 1.04 and 0 per thousand women, respectively in placebo. For deep vein thrombosis, the incidence rate for OSPHENA 60 mg is 1.45 per thousand women vs. 1.04 per thousand women in placebo *[see Warnings and Precautions (5.1)]*.

----------INDICATIONS AND USAGE----------

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 (1)

----------DOSAGE AND ADMINISTRATION----------

- One tablet taken orally once daily with food (2.1)

----------DOSAGE FORMS AND STRENGTHS----------

Tablet: 60 mg (3)

----------CONTRAINDICATIONS----------

- Undiagnosed abnormal genital bleeding (4)
- Known or suspected estrogen-dependent neoplasia (4, 5.2)
- Active DVT, pulmonary embolism (PE), or a history of these conditions (4, 5.1)
- Active arterial thromboembolic disease (for example, stroke and myocardial infarction [MI]), or a history of these conditions (4, 5.1)
- Known or suspected pregnancy (4, 8.1)

----------WARNINGS AND PRECAUTIONS----------

- Venous Thromboembolism: Risk of DVT and pulmonary embolism (5.1)
- Known, suspected, or history of breast cancer (5.2)
- Severe Hepatic Impairment (5.3, 8.7, 12.3)

----------ADVERSE REACTIONS----------

Adverse reactions (≥1 percent) include: hot flush, vaginal discharge, muscle spasms, genital discharge, hyperhidrosis. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Shionogi Inc. at 1-855-OSPHENA (1-855-677-4362) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

----------DRUG INTERACTIONS----------

- Do not use estrogens or estrogen agonist/antagonist concomitantly with OSPHENA (7.1,12.3)
- Do not use fluconazole concomitantly with OSPHENA. Fluconazole increases serum concentrations of OSPHENA (7.2, 12.3)
- Do not use rifampin concomitantly with OSPHENA. Rifampin decreases serum concentration of OSPHENA (7.2, 12.3)

----------USE IN SPECIFIC POPULATIONS----------

- Nursing Mothers: It is not known whether OSPHENA is excreted in human breast milk (8.3)

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling

Revised: 02/2013

FULL PRESCRIBING INFORMATION: CONTENTS*

WARNING: ENDOMETRIAL CANCER AND CARDIOVASCULAR DISORDERS
1. INDICATIONS AND USAGE
2. DOSAGE AND ADMINISTRATION
2.1 Treatment of Moderate to Severe Dyspareunia, a Symptom of Vulvar and Vaginal Atrophy, due to Menopause
3. DOSAGE FORMS AND STRENGTHS
4. CONTRAINDICATIONS
5. WARNINGS AND PRECAUTIONS
5.1 Cardiovascular Disorders
5.2 Malignant Neoplasms
5.3 Severe Hepatic Impairment
6. ADVERSE REACTIONS
6.1 Clinical Trials Experience
7. DRUG INTERACTIONS
7.1 Estrogens and estrogen agonist/antagonist
7.2 Fluconazole
7.3 Rifampin
7.4 Ketoconazole
7.5 Warfarin
7.6 Highly Protein-Bound Drugs
7.7 Multiple Enzyme Inhibition
8. USE IN SPECIFIC POPULATIONS
8.1 Pregnancy
8.3 Nursing Mothers
8.4 Pediatric Use
8.5 Geriatric Use
8.6 Renal Impairment
8.7 Hepatic Impairment
10. OVERDOSAGE
11. DESCRIPTION
12. CLINICAL PHARMACOLOGY
12.1 Mechanism of Action
12.3 Pharmacokinetics
13. NONCLINICAL TOXICOLOGY
13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
14. CLINICAL STUDIES
16. HOW SUPPLIED/STORAGE AND HANDLING
16.1 How Supplied
16.2 Storage and Handling
17. PATIENT COUNSELING INFORMATION
17.1 Hot Flashes or Flushes
17.2 Vaginal Bleeding

* Sections or subsections omitted from the Full Prescribing Information are not listed.

Reference ID: 3267292

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 an increased risk of endometrial cancer in a woman with a uterus who uses unopposed estrogens. Adding a progestin to estrogen therapy reduces the risk of endometrial hyperplasia, which may be a precursor to endometrial cancer. 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 (5.2)]*.

Cardiovascular Disorders

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 (5.1)]*.

In the clinical trials for OSPHENA (duration of treatment up to 15 months), the incidence rates of thromboembolic and hemorrhagic stroke were 0.72 and 1.45 per thousand women, respectively in OSPHENA 60 mg treatment group and 1.04 and 0 in placebo *[see Warnings and Precautions (5.1)]*. The incidence of DVT was 1.45 per thousand women in OSPHENA 60 mg treatment group and 1.04 per thousand women in placebo *[see Warnings and Precautions (5.1)]*. OSPHENA should be prescribed for the shortest duration consistent with treatment goals and risks for the individual woman.

1. INDICATIONS AND USAGE

OSPHENA is indicated for the treatment of moderate to severe dyspareunia, a symptom of vulvar and vaginal atrophy, due to menopause.

2. DOSAGE AND ADMINISTRATION

OSPHENA is an estrogen agonist/antagonist which has agonistic effects on the endometrium. Generally, when a product with estrogen agonistic effects on the endometrium is prescribed for a postmenopausal woman with a uterus, a progestin should be considered to reduce the risk of endometrial cancer. A woman without a uterus does not need a progestin *[see Warnings and Precautions (5.2)]*.

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.

2.1 Treatment of Moderate to Severe Dyspareunia, a Symptom of Vulvar and Vaginal Atrophy, due to Menopause

Take one 60 mg tablet with food once daily.

3. DOSAGE FORMS AND STRENGTHS

OSPHENA tablets are white to off-white, oval, biconvex, film coated tablets containing 60 mg of ospemifene and engraved with "60" on one side.

4. CONTRAINDICATIONS

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

- Undiagnosed abnormal genital bleeding

Reference ID: 3267292

- Known or suspected estrogen-dependent neoplasia
- Active DVT, pulmonary embolism (PE), or a history of these conditions
- Active arterial thromboembolic disease [for example, stroke and myocardial infarctions (MI)], or a history of these conditions
- 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.

5. WARNINGS AND PRECAUTIONS

5.1 Cardiovascular Disorders

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 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.

In the clinical trials for OSPHENA (duration of treatment up to 15 months), the incidence rates of thromboembolic and hemorrhagic stroke were 0.72 and 1.45 per thousand women, respectively in OSPHENA 60 mg treatment group and 1.04 and 0 per thousand women in placebo.

Should thromboembolic or hemorrhagic stroke occur or be suspected, OSPHENA should be discontinued immediately.

Coronary Heart Disease

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. In the OSPHENA clinical trials, a single MI occurred in a woman receiving 60 mg of ospemifene.

Venous Thromboembolism

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.

In the OSPHENA clinical trials, the incidence of DVT was 1.45 per thousand women in OSPHENA 60 mg treatment group and 1.04 per thousand women in placebo. 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.

Reference ID: 3267292

5.2 Malignant Neoplasms

Endometrial Cancer

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 treatment groups at a rate of 60.1 per thousand women vs. 21.2 per thousand women for placebo. The incidence of any type of proliferative (weakly plus active plus disordered) endometrium was 86.1 per thousand women in OSPHENA vs. 13.3 per thousand women for placebo. Uterine polyps occurred at an incidence of 5.9 per thousand women vs. 1.8 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. 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 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 or with a history of breast cancer.

5.3 Severe Hepatic Impairment

OSPHENA should not be used in women with severe hepatic impairment *[see Use in Specific Populations (8.7), and Clinical Pharmacology (12.3)]*.

6. ADVERSE REACTIONS

The following serious adverse reactions are discussed elsewhere in the labeling:

- Cardiovascular Disorders *[see Boxed Warning, Warnings and Precautions (5.1)]*
- Malignant Neoplasms *[see Boxed Warning, Warnings and Precautions (5.2)]*

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

The safety of OSPHENA has been assessed in nine phase 2/3 trials (N=1892) 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=1370) had a treatment period of at least 12 weeks, 409 had at least 52 weeks (1 year) of exposure.

Reference ID: 3267292

The incidence rates of thromboembolic and hemorrhagic stroke were 0.72 per thousand women (1 reported case of thromboembolic stroke) and 1.45 per thousand women (2 reported cases of hemorrhagic stroke), respectively in OSPHENA 60 mg treatment group and 1.04 and 0 per thousand women, respectively in placebo. The incidence of deep vein thrombosis (DVT) was 1.45 per thousand women in OSPHENA 60 mg treatment group (2 reported cases of DVT) and 1.04 (1 case of DVT) in placebo.

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

Table 1: Adverse Reactions Reported More Common in the OSPHENA Treatment Group (60 mg Once Daily) and at Frequency ≥1.0% in the Double-Blind, Controlled Clinical Trials with OSPHENA vs. Placebo

	Ospemifene 60 mg (N=1242) %	**Placebo (N=958) %**
Vascular Disorders		
Hot flush	7.5	2.6
Reproductive System and Breast Disorders		
Vaginal discharge	3.8	0.3
Genital discharge	1.3	0.1
Musculoskeletal and Connective Tissue Disorders		
Muscle spasms	3.2	0.9
Skin and Subcutaneous Tissue Disorders		
Hyperhidrosis	1.6	0.6

7. DRUG INTERACTIONS

OSPHENA is primarily metabolized by CYP3A4 and CYP2C9. CYP2C19 and other pathways contribute to the metabolism of ospemifene.

7.1 Estrogens and estrogen agonist/antagonist

OSPHENA should not be used concomitantly with estrogens and estrogen agonists/antagonists. The safety of concomitant use of OSPHENA with estrogens and estrogen agonists/antagonists has not been studied.

7.2 Fluconazole

Fluconazole, a moderate CYP3A / strong CYP2C9 / moderate CYP2C19 inhibitor, should not be used with OSPHENA. Fluconazole increases the systemic exposure of ospemifene by 2.7-fold. Administration of fluconazole with ospemifene may increase the risk of OSPHENA-related adverse reactions *[see Clinical Pharmacology (12.3)]*.

7.3 Rifampin

Rifampin, a strong CYP3A4 / moderate CYP2C9 / moderate CYP2C19 inducer, decreases the systemic exposure of ospemifene by 58%. Therefore, co-administration of OSPHENA with drugs such as rifampin which

Reference ID: 3267292

induce CYP3A4, CYP2C9 and/or CYP2C19 activity would be expected to decrease the systemic exposure of ospemifene, which may decrease the clinical effect *[see Clinical Pharmacology (12.3)]*.

7.4 Ketoconazole

Ketoconazole, a strong CYP3A4 inhibitor increases the systemic exposure of ospemifene by 1.4-fold. Administration of ketoconazole chronically with ospemifene may increase the risk of OSPHENA-related adverse reactions *[see Clinical Pharmacology (12.3)]*.

7.5 Warfarin

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 *[see Clinical Pharmacology (12.3)]*.

7.6 Highly Protein-Bound Drugs

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 *[see Clinical Pharmacology (12.3)]*.

7.7 Multiple Enzyme Inhibition

Co-administration of OSPHENA with a drug known to inhibit CYP3A4 and CYP2C9 isoenzymes may increase the risk of OSPHENA-related adverse reactions.

8. USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Teratogenic effects:

Pregnancy Category X *[see Contraindications (4)]*.

Risk Summary

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 embryofetal 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.

Animal Data

The effects of OSPHENA 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 surface area mg/m^2). Drug-induced malformations were not observed in either rats or rabbits.

The effects of OSPHENA on pre-and postnatal development were studied 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 OSPHENA (0.8% to 4% the human exposure based on surface area mg/m^2), had a significantly prolonged and difficult gestation, increased post-implantation loss, increased number of dead pups at birth, and an increased incidence of postnatal loss. OSPHENA did not induce adverse effects in the surviving offspring of pregnant rats at drug exposures up to 4% the human exposure.

8.3 Nursing Mothers

It is not known whether OSPHENA is excreted in human breast milk.

Reference ID: 3267292

In a nonclinical study, ospemifene was excreted in rat milk and detected at concentrations higher than that in maternal plasma.

8.4 Pediatric Use

OSPHENA is not indicated in children. Clinical studies have not been conducted in the pediatric population.

8.5 Geriatric Use

Of the 1892 OSPHENA-treated women enrolled in the nine phase 2/3 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.

8.6 Renal Impairment

The pharmacokinetics of ospemifene in women with severe renal impairment (CrCL <30 mL/min) was similar to those in women with normal renal function *[see Clinical Pharmacology (12.3)]*.

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

8.7 Hepatic Impairment

The pharmacokinetics of ospemifene has not been studied in women with severe hepatic impairment (Child-Pugh Class C); therefore, OSPHENA should not be used in women with severe hepatic impairment *[see Warnings and Precautions (5.3), and Clinical Pharmacology (12.3)]*.

No clinically important pharmacokinetic differences with OSPHENA were observed between women with mild to moderate hepatic impairment and healthy women *[see Clinical Pharmacology (12.3)]*.

No dose adjustment of OSPHENA is required in women with mild (Child-Pugh Class A) or moderate (Child-Pugh Class B) hepatic impairment.

10. OVERDOSAGE

There is no specific antidote for OSPHENA.

11. DESCRIPTION

OSPHENA is an estrogen agonist/antagonist. The chemical structure of ospemifene is shown in Figure 1.

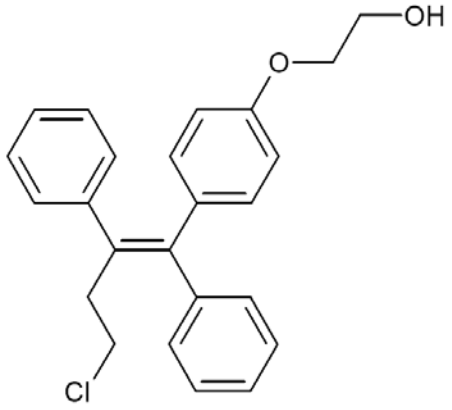


Figure 1: Chemical structure

The chemical designation is Z-2-[4-(4-chloro-1,2-diphenylbut-1-enyl)phenoxy]ethanol, and has the empirical formula $C_{24}H_{23}ClO_2$, which corresponds to a molecular weight of 378.9. Ospemifene is a white to off-white crystalline powder that is insoluble in water and soluble in ethanol.

Reference ID: 3267292

Each OSPHENA tablet contains 60 mg of ospemifene. Inactive ingredients include colloidal silicon dioxide, hypromellose, lactose monohydrate, magnesium stearate, mannitol, microcrystalline cellulose, polyethylene glycol, povidone, pregelatinized starch, sodium starch glycolate, titanium dioxide, and triacetin.

12. CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

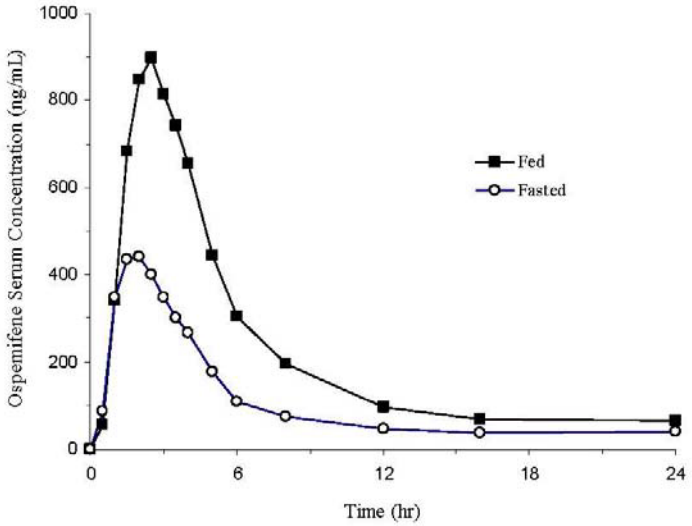
OSPHENA is an estrogen agonist/antagonist with tissue selective effects. Its biological actions are mediated through binding to estrogen receptors. This binding results in activation of estrogenic pathways in some tissues (agonism) and blockade of estrogenic pathways in others (antagonism).

12.3 Pharmacokinetics

Absorption

Following a single oral administration of OSPHENA 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 2). 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 OSPHENA 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 2: Mean serum concentration profile of ospemifene following a single oral administration of OSPHENA 60 mg tablet in postmenopausal women under fed (N=28) and fasted (N=91) conditions



Food Effect

In general, food increased the bioavailability of ospemifene by approximately 2-3 fold. In a cross-study comparison, single dose OSPHENA 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 $AUC_{0\text{-}}$

Reference ID: 3267292

$_{inf}$ 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. OSPHENA should be taken with food *[see Dosage and Administration (2.1)]*.

Distribution

OSPHENA 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.

Excretion

The apparent terminal half-life of ospemifene in postmenopausal women is approximately 26 hours. Following an oral administration of ospemifene, 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.

Use in Specific Populations

Pediatric
The pharmacokinetics of ospemifene in pediatric patients has not been evaluated *[see Use in Specific Populations (8.4)]*.

Geriatric
No differences in ospemifene pharmacokinetics were detected with regard to age (range 40 to 80 years) *[see Use in Specific Populations (8.5)]*.

Race
Race did not have clinically relevant effect on ospemifene pharmacokinetics.

Renal Impairment
In 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 *[see Use in Specific Populations (8.6)]*.

Hepatic Impairment
In 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 *[see Warnings and Precautions (5.3), and Use in Specific Populations (8.7)]*.

Drug Interactions

Ospemifene is metabolized primarily 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 vivo* transporter study was conducted.

Effect of Co-Administered Drugs on the Pharmacokinetics of Ospemifene

Fluconazole (CYP3A4/CYP2C9/CYP2C19 Inhibitor)

Reference ID: 3267292

Fluconazole (a moderate CYP3A / strong CYP2C9 / moderate CYP2C19 inhibitor) 400 mg was given on Day 1 followed by 200 mg on Days 2 to 5 under fasted condition. On Day 5 approximately one hour after fluconazole administration, ospemifene 60 mg was administered after breakfast (two slices of bread with ham, cheese, a few slices of cucumber and/or tomatoes, and juice). Fluconazole 200 mg was taken for three additional days under fasted condition. Multiple doses of fluconazole in fourteen postmenopausal women increased the C_{max} and $AUC_{0\text{-}inf}$ of ospemifene by 1.7- and 2.7-fold, respectively *[see Drug Interactions (7.2)]*.

Rifampin (CYP3A4/CYP2C9/CYP2C19 Inducer)
Rifampin 600 mg was given once daily for 5 consecutive days (given at least one hour before or two hours after a meal) in the late afternoon. On Day 6 after an overnight fast, ospemifene 60 mg was administered in the morning after under fed condition (two slices of bread with ham, cheese, a few slices of cucumber and/or tomatoes, and juice). Multiple doses of rifampin 600 mg in twelve postmenopausal women reduced C_{max} and $AUC_{0\text{-}inf}$ of ospemifene by 51% and 58%, respectively. Rifampin and other inducers of CYP3A4 are expected to decrease the systemic exposure of ospemifene *[see Drug Interactions (7.3)]*.

Ketoconazole (CYP3A4 Inhibitor)
Ketoconazole 400 mg was given once daily for 4 consecutive days after breakfast. On Day 5 after an overnight fast, ketoconazole 400 mg and ospemifene 60 mg were co-administered under fed condition (two slices of bread with ham, cheese, a few slices of cucumber and/or tomatoes, and juice). Ketoconazole administration once daily continued for an additional 3 days (Days 6 to 8). Co-administration of a single 60 mg dose of ospemifene and multiple doses of ketoconazole in twelve postmenopausal women increased C_{max} and $AUC_{0\text{-}inf}$ by 1.5- and 1.4-fold, respectively *[see Drug Interactions (7.4)]*.

Omeprazole (CYP2C19 Inhibitor)
Omeprazole (a moderate CYP2C19 inhibitor) 40 mg was given for 5 days. On Day 5, approximately one hour after omeprazole administration, ospemifene 60 mg was administered after breakfast (two slices of bread with ham, cheese, a few slices of cucumber and/or tomatoes, and juice). Multiple doses of omeprazole in fourteen postmenopausal women increased C_{max} and $AUC_{0\text{-}inf}$ by 1.20- and 1.17-fold, respectively.

Effect of Ospemifene on the Pharmacokinetics of the Co-Administered Drug

Warfarin
Ospemifene 60 mg was given after a light breakfast (two slices of bread with ham and cheese and juice) once daily for 12 days in sixteen postmenopausal women who were determined to be rapid metabolizers of CYP2C9 (CYP2C9*1/*1 or CYP2C9*1/*2). On Day 8, a single dose of warfarin 10 mg and vitamin K 10 mg were administered one hour after a light breakfast. The geometric mean ratio (90% CI) for S-warfarin with and without ospemifene for C_{max} and $AUC_{0\text{-}inf}$ were 0.97 (0.92-1.02) and 0.96 (0.91-1.02), respectively. Multiple doses of ospemifene did not significantly affect the pharmacokinetics of a single dose of warfarin. No study was conducted with multiple doses of warfarin.

Omeprazole
Ospemifene 60 mg was administered once daily for 7 days after a light meal in the late afternoon in fourteen postmenopausal women. On Day 8 after an overnight fast, a single 20 mg dose of omeprazole was administered in the morning of at least 10 hrs; ospemifene was not given on Day 8. The geometric mean ratios for the metabolic index (omeprazole/5-hydroxyomeprazole) at the concentration at the 3 hr time point and for $AUC_{0\text{-}8hr}$ was 0.97 with and without ospemifene. 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
Ospemifene 60 mg was administered once daily for seven consecutive days after the evening meal in sixteen postmenopausal women (not homozygous for CYP2B6*6). On the Day 8 after overnight fast, a single 150 mg dose of sustained release bupropion was administered in morning under fasted condition. The geometric mean

Reference ID: 3267292

ratio (90% CI) for bupropion with and without ospemifene for C_{max} and $AUC_{0\text{-}inf}$ were 0.82 (0.75-0.91) and 0.81 (0.77-0.86), respectively. The geometric mean ratio (90% CI) for hydroxybupropion, an active metabolite formed via CYP2B6, with and without ospemifene for C_{max} and $AUC_{0\text{-}inf}$ were 1.16 (1.09-1.24) and 0.98 (0.92-1.04), respectively.

13. NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis

In a 2-year carcinogenicity study in female mice, ospemifene administration of 100, 400 or 1500 mg/kg/day was well tolerated. 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 administration of 10, 50, or 300 mg/kg/day was well tolerated. 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 at for females at all ospemifene dose levels.

Mutagenesis

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.

Impairment of Fertility

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.

14. CLINICAL STUDIES

The effectiveness and safety of OSPHENA on moderate to severe symptoms of vulvar and vaginal atrophy in postmenopausal women were examined in three placebo-controlled clinical trials (two 12-week efficacy trials and one 52-week long-term safety trial). In the three placebo-controlled trials, a total of 787 women received placebo and 1102 women received 60 mg OSPHENA.

The first clinical trial was a 12-week, randomized, double-blind, placebo-controlled, parallel-group study that enrolled 826 generally healthy postmenopausal women between 41 to 81 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 the 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

Reference ID: 3267292

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.

The second clinical trial was a 12-week, randomized, double-blind, placebo-controlled, parallel-group study that enrolled 919 generally healthy postmenopausal women between 41 to 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 Trial 1.

The third clinical trial was a 52-week, randomized, double-blind, placebo-controlled, long-term safety study that enrolled 426 generally healthy postmenopausal women between 49 to 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).

Effects on Dyspareunia

In the 1st and 2nd clinical trial, the modified intent-to-treat population of women treated with OSPHENA when compared to placebo, demonstrated a statistically significant improvement (least square mean change from Baseline to Week 12) in the moderate to severe most bothersome symptom (MBS) of dyspareunia (1st trial p=0.0012, 2nd trial p<0.0001). See Table 2. 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 both). The mean reduction in vaginal pH between baseline and Week 12 was also statistically significant (p<0.0001).

Table 2: Week 12 Effects on Dyspareunia (the Woman's Self-Identified Most Bothersome Moderate to Severe Symptom of Vulvar and Vaginal Atrophy at Baseline). Mean Change in Severity at Week 12 with Last Observation Carried Forward (LOCF), Modified Intent-to-Treat Population[a]

1st Clinical Trial Results		
Most Bothersome Moderate to Severe Symptom at Baseline	OSPHENA 60 mg (N=110)	Placebo (N=113)
Dyspareunia		
Baseline Mean (SD)	2.7 (0.44)	2.7 (0.45)
LS Mean Change from Baseline (SE)	-1.39 (0.11)	-0.89 (0.11)
p-value vs. placebo	0.0012	---
2nd Clinical Trial Results		
Most Bothersome Moderate to Severe Symptom at Baseline	OSPHENA 60 mg (N=301)	Placebo (N=297)
Dyspareunia		
Baseline Mean (SD)	2.7 (0.47)	2.7 (0.47)
LS Mean Change from Baseline (SE)	-1.55 (0.06)	-1.29 (0.07)
p-value vs. placebo	<0.0001	---

Reference ID: 3267292

a. The modified intent-to-treat population (mITT) included only women in the ITT population who at baseline met the inclusion criteria of ≤5 percent superficial cells on a vaginal smear, a vaginal pH > 5.0, and who identified moderate or severe dyspareunia as her most bothersome vaginal symptom.

Definitions: LOCF = last observation carried forward; SD = standard deviation; SE = standard error; LS = least square

16. HOW SUPPLIED/STORAGE AND HANDLING

16.1 How Supplied

OSPHENA tablets are white to off-white, oval, biconvex, film coated tablets containing 60 mg of ospemifene and engraved with "60" on one side. They are available as follows:

NDC 59630-580-10	Bottle of 100 tablets
NDC 59630-580-30	Blister pack of 30 tablets containing 2 blister cards of 15 tablets each

16.2 Storage and Handling

Store at 20º to 25ºC (68º to 77ºF); excursions permitted to 15º to 30ºC (59º to 86ºF) [see USP Controlled Room Temperature].

17. PATIENT COUNSELING INFORMATION

See FDA-approved patient labeling (Patient Information)

17.1 Hot Flashes or Flushes

OSPHENA may initiate or increase the occurrence of hot flashes in some women.

17.2 Vaginal Bleeding

Inform postmenopausal women of the importance of reporting unusual vaginal bleeding to their healthcare providers as soon as possible *[see Warnings and Precautions (5.2)]*.

Reference ID: 3267292

Patient Information

OSPHENA™ (os fee' nah)
(ospemifene)
tablets

Read this Patient Information before you start taking OSPHENA and each time you get a refill. There may be new information. This information does not take the place of talking to your healthcare provider about your medical condition or your treatment.

What is the most important information I should know about OSPHENA ?

- **OSPHENA is a medicine that works like estrogen in the lining of the uterus (womb), but can work differently in other parts of the body.**
- **Taking estrogen-alone or OSPHENA may increase your chance of getting cancer of the lining of the uterus (womb). Vaginal bleeding after menopause may be a warning sign of cancer of the lining of the uterus (womb). Your healthcare provider should check any unusual vaginal bleeding to find out the cause. Tell your healthcare provider right away if you have any unusual vaginal bleeding while you are taking OSPHENA.**
- **OSPHENA may increase your chance of getting strokes and blood clots.**
- **You and your healthcare provider should talk regularly about whether you still need treatment with OSPHENA.**

What is OSPHENA?

OSPHENA is an oral prescription medicine used to treat painful intercourse, a symptom of changes in and around your vagina, due to menopause.

Who should not take OSPHENA?

Do not start taking OSPHENA if you:

- **have unusual vaginal bleeding**

Vaginal bleeding after menopause may be a warning sign of cancer of the lining of the uterus (womb). Your healthcare provider should check any unusual vaginal bleeding to find out the cause.

- **currently have or have had certain cancers**

  Estrogen may increase the chances of getting certain types of cancers, such as cancer of the lining of the uterus. If you have or have had cancer, talk with your healthcare provider about whether you should take OSPHENA.

- **currently have or have had blood clots**

Reference ID: 3267292

- **had a stroke or heart attack**
- **think you may be pregnant**

  OSPHENA is not for pregnant women. 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 provider.

What should I tell my healthcare provider before taking OSPHENA?

Before you take OSPHENA, tell your healthcare provider if you:

- **have any unusual vaginal bleeding**

  Vaginal bleeding after menopause may be a warning sign of cancer of the lining of the uterus (womb). Your healthcare provider should check any unusual vaginal bleeding to find out the cause.
- **have any other medical conditions**

  Such as severe liver problems.
- **are going to have surgery or will be on bed rest**

  Your healthcare provider will let you know if you need to stop taking OSPHENA.
- **are breast feeding**

  It is not known if OSPHENA can pass into your breast milk.

Tell your healthcare provider about all medicines you take, including prescription and non-prescription medicines, vitamins, and herbal supplements. Some medicines may affect how OSPHENA works. OSPHENA may also affect how other medicines work. Keep a list of your medicines and show it to your healthcare provider and pharmacist each time you get a new medicine.

How should I take OSPHENA?

- Take OSPHENA exactly how your healthcare provider tells you to take it.
- Take OSPHENA by mouth 1 time each day with food.
- You and your healthcare provider should talk regularly (every 3 to 6 months) about the dose you are taking and whether or not you still need treatment with OSPHENA.

What are the possible side effects of OSPHENA?

See "**What is the most important information I should know about OSPHENA**?"

Serious, but less common side effects include:

- stroke
- blood clots
- cancer of the lining of the uterus (womb)

Reference ID: 3267292

Call your healthcare provider right away if you get any of the following warning signs or any other unusual symptoms that concern you:

- unusual vaginal bleeding
- changes in vision or speech
- sudden new severe headaches
- severe pains in your chest or legs with or without shortness of breath, weakness and fatigue

Less serious, but common side effects include:

- hot flushes or flashes
- vaginal discharge
- muscle spasms
- increased sweating

These are not all the possible side effects of OSPHENA. For more information, ask your healthcare provider or pharmacist. Tell your healthcare provider about any side effects that bother you or does not go away.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

What can I do to lower my chances of a serious side effect with OSPHENA?

- Talk with your healthcare provider regularly about whether you should continue taking OSPHENA.
- If you have a uterus, talk with your healthcare provider about whether the addition of a progestin is right for you.
- See your healthcare provider right away if you develop vaginal bleeding while taking OSPHENA.
- Have a pelvic exam, breast exam and mammogram (breast x-ray) every year unless your healthcare provider tells you something else.
- If members of your family have had breast cancer or if you have ever had breast lumps or an abnormal mammogram (breast x-ray), you may need to have breast exams more often.
- If you have high blood pressure, high cholesterol (fat in the blood), diabetes, are overweight, or use tobacco, you may have a higher chance of getting heart disease.

Ask your healthcare provider for ways to lower your chances of getting heart disease.

How should I store OSPHENA?

- Store OSPHENA at room temperature between 68°F to 77°F (20°C to 25°C).

Keep OSPHENA and all medicines out of the reach of children.

Reference ID: 3267292

General information about the safe and effective use of OSPHENA.

Medicines are sometimes prescribed for conditions that are not mentioned in patient information leaflets. Do not take OSPHENA for conditions for which it was not prescribed. Do not give OSPHENA to other people, even if they have the same symptoms you have. It may harm them.

This leaflet summarizes the most important information about OSPHENA. If you would like more information, talk with your healthcare provider or pharmacist. You can ask your healthcare provider or pharmacist for more information about OSPHENA that is written for health professionals.

For more information, go to www.osphena.com or call Shionogi Inc. at 1-855-OSPHENA (1-855-677-4362).

What are the ingredients in OSPHENA?

Active Ingredient: ospemifene

Inactive ingredients: colloidal silicon dioxide, hypromellose, lactose monohydrate, magnesium stearate, mannitol, microcrystalline cellulose, polyethylene glycol, povidone, pregelatinized starch, sodium starch glycolate, titanium dioxide, and triacetin.

This Patient Information has been approved by the U.S. Food and Drug Administration.

Manufactured for:

Shionogi Inc.

Florham Park, NJ 07932

Manufactured by:

Penn Pharmaceutical Services Ltd.

23-24 Tafarnauback Industrial Estate

Tredegar, Gwent, South Wales

NP22 3AA, United Kingdom

Made in UK

Approved: February 2013

Reference ID: 3267292

15 COUNT

USUAL ADULT DOSAGE: See package insert.

Keep this and all drugs out of the reach of children.

Store at 20° to 25°C (68° to 77°F);
excursions permitted to 15° to 30°C (59° to 86°F)
[see USP Controlled Room Temperature].

Manufactured for:
Shionogi Inc.
Florham Park, NJ 07932

Manufactured by:
Penn Pharmaceutical Services Ltd.
23-24 Tafarnaubach Industrial Estate
Tredegar, Gwent, South Wales NP22 3AA, UK

Made in UK

OSP-SBL-01

www.osphena.com

Lot No.: XXXXXXXXXX
Exp. Date: MM/YYYY

3 59630 58015 5

15 tablets

Osphena™ (ospemifene) tablets 60 mg

www.osphena.com

NDC 59630-580-15
Rx only

15 tablets

Osphena™

(ospemifene) tablets
60 mg

For oral use only

Each tablet contains 60 mg ospemifene.

Professional Sample—Not to be Sold

SHIONOGI INC.

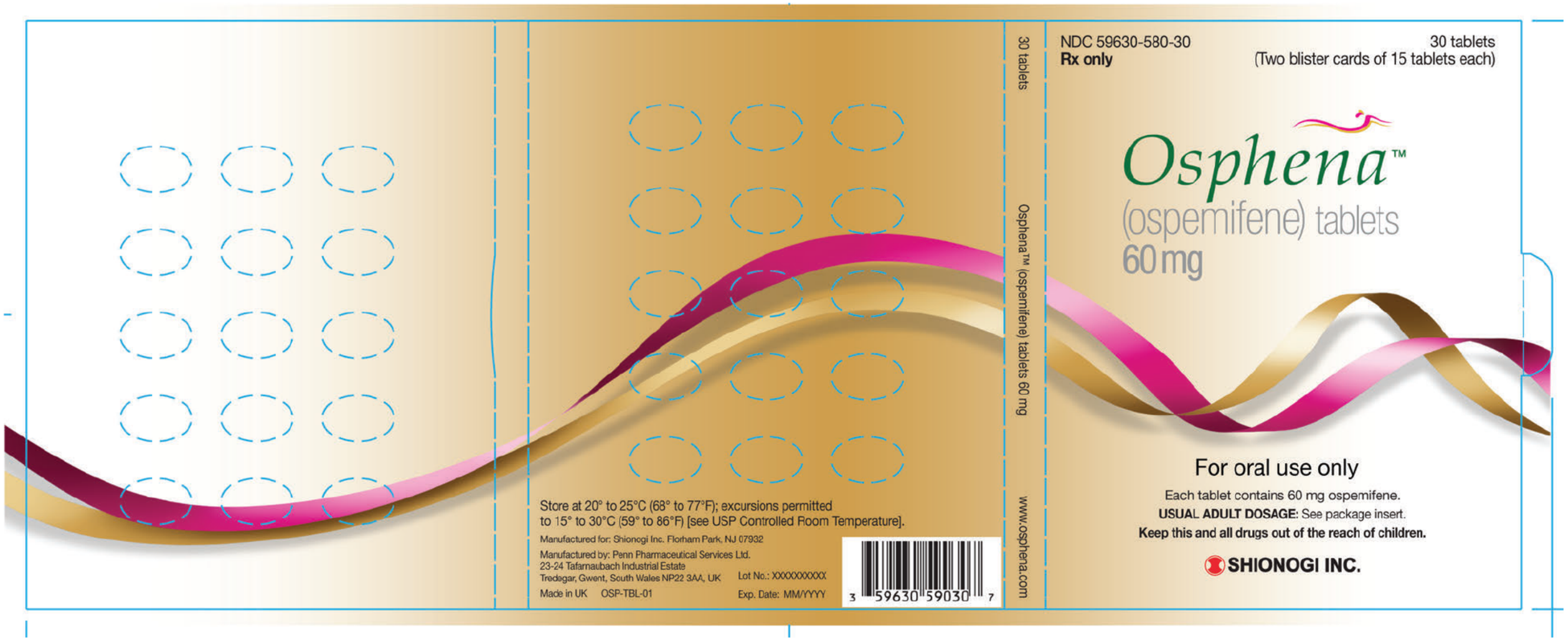
Osphena™
(ospemifene) tablets
60 mg

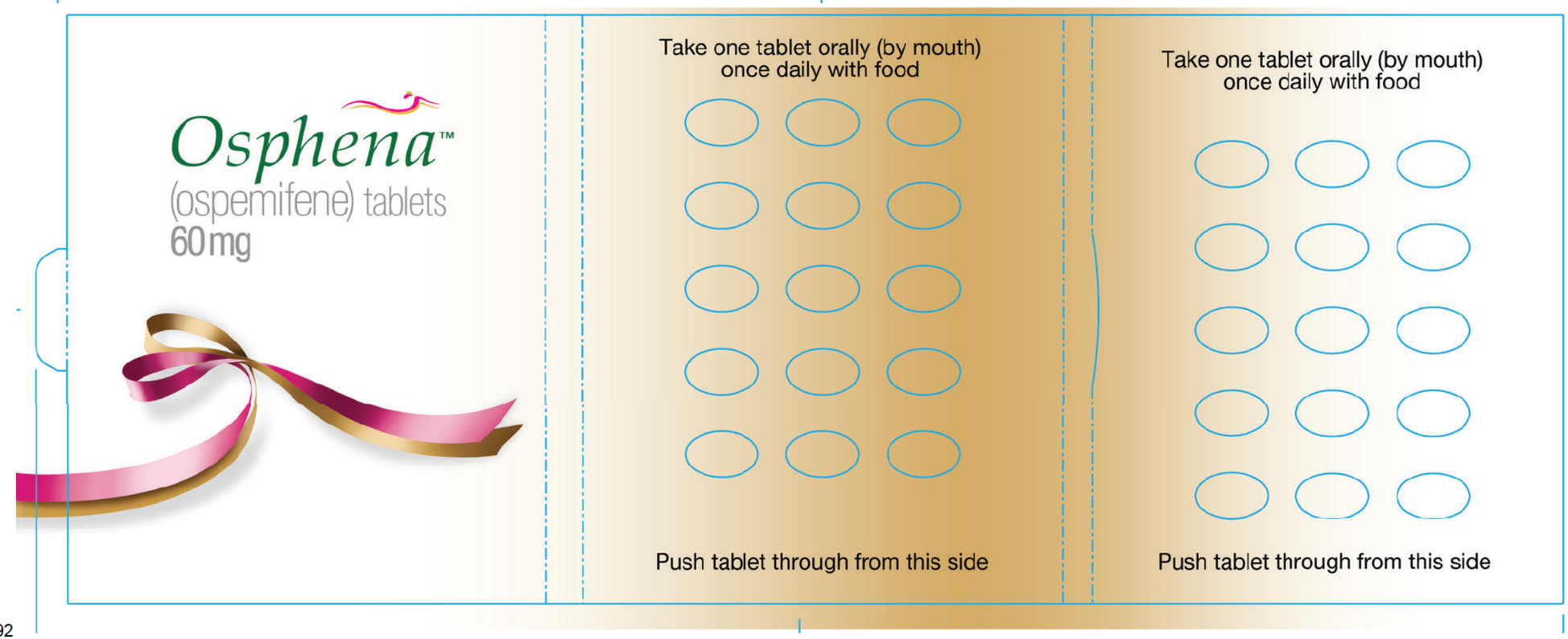
Take one tablet orally (by mouth)
once daily with food

Push tablet through from this side

Reference ID: 3267292

30 COUNT





Reference ID: 3267292

DRAFT OSPEMIFENE BOTTLE LABEL

59630-580-10

100 tablets

Osphena™
(ospemifene) tablets

60 mg

For oral use only

Rx only

SHIONOGI INC.

Each tablet contains 60 mg ospemifene.

Keep out of reach of children.

USUAL ADULT DOSAGE: See package insert for full prescribing information.

Store at 20° to 25°C (68° to 77°F); excursions permitted to 15° to 30°C (59° to 86°F) [see USP Controlled Room Temperature].

Manufactured for
Shionogi Inc.
Florham Park, NJ 07932

By
Penn Pharmaceutical Services Ltd.
23-24 Tafarnaubach Industrial Estate
Tredegar, Gwent, South Wales
NP22 3AA United Kingdom

Made in UK

OSP-TL60-01
Rev. 01/2013

FPO

3 59630 50310 9

Lot: xxxxxxxxxx

Exp: xxxxxxxxxx

Non-varnish area

Die line does not print

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

VICTORIA KUSIAK
02/26/2013