**FOR IMMEDIATE RELEASE**

SHIONOGI INC.

# SHIONOGI RECEIVES FDA APPROVAL FOR OSPHENA™ (OSPEMIFENE) FOR THE TREATMENT OF DYSPAREUNIA, A SYMPTOM OF VULVAR AND VAGINAL ATROPHY (VVA), DUE TO MENOPAUSE

**FLORHAM PARK, NJ (February 26, 2013) –** Shionogi Inc., the United States (U.S.)-based company of Shionogi & Co., Ltd., today announced that the U.S. Food and Drug Administration (FDA) has approved Osphena™ (ospemifene) tablets for the treatment of moderate to severe dyspareunia (painful intercourse), a symptom of vulvar and vaginal atrophy (VVA), due to menopause.[1]

Osphena™, as an estrogen agonist/antagonist with tissue selective effects, is the first and only oral treatment alternative to vaginal or oral steroidal estrogens for women with dyspareunia due to menopause.[2,3] Its biological actions are mediated through binding to estrogen receptors, which results in activation of estrogenic pathways in some tissues (agonism) and blockade of estrogenic pathways in others (antagonism).[4] The efficacy and safety of Osphena™ was demonstrated in three clinical trials. Osphena™ demonstrated significant improvements in dyspareunia (painful intercourse) as well as on the physical changes of the vagina associated with menopause. These improvements include increased superficial cells and decreased parabasal cells and vaginal pH.[5,6]

"While more than half of all women in the U.S. will experience symptoms of VVA at some time in their postmenopausal life, the vast majority of women with VVA are not being treated with a prescription medication because women and their healthcare professionals are not proactively discussing the condition, and its associated symptoms," said David J. Portman, M.D., OB/GYN and Director of the Columbus Center for Women's Health Research.[7,8] "Osphena™ received approval based on a clinical development program in postmenopausal women with dyspareunia, a symptom of VVA.[9,10] As an oral medication taken once-daily, Osphena™ is a convenient way for postmenopausal women to help treat dyspareunia."

"The FDA approval of Osphena™ represents an important advancement in the treatment of dyspareunia, providing an alternative treatment option for the millions of women living with this condition," said John Keller, Ph.D., President and Chief Executive Officer, Shionogi Inc. "We look forward to building our product portfolio in women's health by advancing important therapies, such as Osphena™."

Shionogi obtained exclusive global marketing rights to Osphena™ under a license agreement entered into between Shionogi and QuatRx Pharmaceuticals Company in 2010.

Osphena™ is an estrogen agonist/antagonist with tissue selective effects. Serious risks of estrogen-alone therapy can include increased risk of endometrial cancer, stroke, and deep vein thrombosis (DVT). Osphena™ should be prescribed for the shortest duration consistent with treatment goals for the individual woman. Women considering treatment for dyspareunia are encouraged to discuss the potential risks and benefits of Osphena™ with their healthcare provider. Please click here for additional Important Safety Information.

**Osphena™ Clinical Trials**

The FDA approval of Osphena™ was supported by three Phase 3 placebo-controlled clinical trials involving approximately 1,800 postmenopausal women with VVA receiving either Osphena™ 60 mg (N=1102) or placebo (N=787).[9] Two of the clinical trials were of 12 weeks duration and the third clinical trial was a 52-week long-term safety study.[10]

In the first and second clinical trials, Osphena™ demonstrated a statistically significant improvement from Baseline to Week 12 in moderate to severe dyspareunia (1st clinical trial p=0.0012, 2nd trial p<0.0001), compared to placebo.[11] 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 from Baseline to Week 12 was also statistically significant (p<0.0001).[12]

In clinical studies, the more commonly reported adverse reactions (greater than or equal to 1 percent) in patients treated with Osphena™ 60 mg compared to placebo were: hot flush (7.5 percent vs. 2.6 percent), vaginal discharge (3.8 percent vs. 0.3 percent), muscle spasms (3.2 percent vs. 0.9 percent), hyperhidrosis (1.6 percent vs. 0.6 percent), and genital discharge (1.3 percent vs. 0.1 percent).[13]

**Important Safety Information for Osphena™ (ospemifene) tablets**

**Boxed WARNING: Endometrial Cancer and Cardiovascular Disorders**

**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 estrogen therapy. Adding a progestin to estrogen therapy has been shown to reduce the risk of endometrial hyperplasia, which may be a precursor to endometrial cancer. 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.**

**The Women's Health Initiative (WHI) estrogen-alone substudy reported an increased risk of stroke and deep vein thrombosis (DVT) in postmenopausal women (50 to 79 years of age) during 7.1 years of treatment with daily oral conjugated estrogens (CE) [0.625 mg], relative to placebo. Osphena™ 60 mg had cerebral thromboembolic and hemorrhagic stroke incidence rates of 0.72 and 1.45 per thousand women vs. 1.04 and 0 per thousand women for placebo and a DVT incidence rate of 1.45 vs. 1.04 per thousand women for placebo. Osphena™ should be prescribed for the shortest duration consistent with treatment goals and risks for the individual woman.**

**Contraindications**

- Undiagnosed abnormal genital bleeding
- Known or suspected estrogen-dependent neoplasia
- Active deep vein thrombosis (DVT), pulmonary embolism (PE) or a history of these conditions
- Active arterial thromboembolic disease (for example, stroke and myocardial infarction), or a history of these conditions
- In women who are or may become pregnant, as Osphena™ may cause fetal harm

**Warnings and Precautions**

**Cardiovascular Disorders:** In Osphena™ clinical trials of up to 15 months the incidence rates compared to placebo for cerebral thromboembolic and hemorrhagic stroke were 0.72 Osphena™ 60 mg vs. 1.04

placebo and 1.45 Osphena™ 60 mg vs. 0 placebo per thousand women. Should thromboembolic or hemorrhagic stroke occur or be suspected, Osphena™ should be discontinued immediately.

***Coronary Heart Disease:*** In clinical trials, a single MI occurred in a woman receiving Osphena™ 60 mg.

***Venous Thromboembolism:*** Incidence rate of DVT was 1.45 Osphena™ vs. 1.04 placebo per thousand women. Should a VTE occur or be suspected, Osphena™ should be discontinued immediately. Osphena™ should be discontinued at least 4 to 6 weeks before surgery with increased risk of thromboembolism or during periods of prolonged immobilization.

***Malignant Neoplasms***

***Endometrial Cancer:*** Osphena™ is an estrogen agonist/antagonist with tissue selective effects. In the endometrium Osphena™ has agonistic effects. In Osphena™ clinical trials, no cases of endometrial cancer were seen with exposure up to 52 weeks.

***Breast Cancer:*** Osphena™ has not been adequately studied in women with breast cancer; therefore Osphena™ should not be used in women with known or suspected breast cancer or with a history of breast cancer.

**Severe Hepatic Impairment:** Do not use Osphena™ in women with severe hepatic impairment as it has not been studied.

**Adverse Reactions:** In clinical studies, the more commonly reported adverse reactions (greater than or equal to 1 percent) in patients treated with Osphena™ 60 mg compared to placebo were: hot flush (7.5 percent vs. 2.6 percent), vaginal discharge (3.8 percent vs. 0.3 percent), muscle spasms (3.2 percent vs. 0.9 percent), hyperhidrosis (1.6 percent vs. 0.6 percent), and genital discharge (1.3 percent vs. 0.1 percent).

**Drug Interactions**

- Do not use estrogens or estrogen agonists/antagonists or fluconazole concomitantly with Osphena™.
- Coadministration of Osphena™ with drugs that inhibit CYP3A4 and CYP2C9 may increase the risk of Osphena™ related adverse reactions.

Click here for Full Prescribing Information for Osphena™ (ospemifene) tablets, including **Boxed WARNING** and Patient Information. For more information, please visit www.Osphena.com.

## Indications and Usage for Osphena™ (ospemifene) tablets

Osphena™ (ospemifene) is indicated for the treatment of moderate to severe dyspareunia, a symptom of vulvar and vaginal atrophy, due to menopause.

### About Dyspareunia and VVA

Dyspareunia (painful intercourse) is one of the most common symptoms of vulvar and vaginal atrophy (VVA), a chronic and progressive condition due to menopause.[14,15] Declining estrogen levels during menopause can cause tissues of the vaginal lining to grow thinner and to lose elasticity, a condition known as vaginal atrophy.[16] Menopause also causes increases in vaginal pH.[17] These changes can lead to dyspareunia. While approximately 32 million postmenopausal women in the U.S. experience symptoms of VVA, 93 percent are not being treated with a prescription medication.[18] Women who may be experiencing dyspareunia due to menopause should consult with their healthcare professional to discuss appropriate treatment options. Prescription therapies are often required for symptomatic women.[19]

**About Shionogi**

Shionogi Inc. is the U.S.-based subsidiary of Shionogi & Co., Ltd., headquartered in Osaka, Japan. Shionogi & Co., Ltd. is a major research-driven pharmaceutical company dedicated to placing the highest value on patients. Shionogi's research and development currently targets three therapeutic areas: infectious diseases, pain, and metabolic syndrome. In addition, Shionogi is engaged in new research areas such as allergy and cancer. Contributing to the health of patients around the world through development in these therapeutic areas is Shionogi's primary goal. For more details, please visit www.shionogi.co.jp. For more information on Shionogi Inc., headquartered in Florham Park, NJ, please visit www.shionogi.com.

***Forward Looking Statement***

*This announcement contains forward-looking statements. These statements are based on expectations in light of the information currently available, assumptions that are subject to risks and uncertainties which could cause actual results to differ materially from these statements. Risks and uncertainties include general domestic and international economic conditions such as general industry and market conditions, and changes of interest rate and currency exchange rate. These risks and uncertainties particularly apply with respect to product-related forward-looking statements. Product risks and uncertainties include, but are not limited to, completion and discontinuation of clinical trials; obtaining regulatory approvals; claims and concerns about product safety and efficacy; technological advances; adverse outcome of important litigation; domestic and foreign healthcare reforms and changes of laws and regulations. Also for existing products, there are manufacturing and marketing risks, which include, but are not limited to, inability to build production capacity to meet demand, unavailability of raw materials and entry of competitive products. The company disclaims any intention or obligation to update or revise any forward-looking statements whether as a result of new information, future events or otherwise.*

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## References


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