CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

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OFFICE DIRECTOR MEMO

Memorandum

Department of Health and Human Resources
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

DATE: February 26, 2013

TO: NDA 203505
Osphena (Ospemifene)
Shionogi, Inc.

FROM: Victoria Kusiak, M.D., F.A.C.C.
Deputy Director, Office of Drug Evaluation III

SUBJECT: Approval Action

Osphena is an estrogen agonist/antagonist that has tissue selective activities; a drug class commonly known as selective estrogen receptor modulators (SERMs). Osphena is chemically related to the approved drugs raloxifene, toremifene, and tamoxifen; displaying similar, but not identical pharmacological profiles to these estrogen agonist/antagonist. Osphena potently binds to both Estrogen Receptor α and ß types of nuclear receptors. In rats and monkeys, Osphena has pharmacological activities consistent with estrogen agonism in the vagina, ovary, and bone, mixed agonism/antagonism in the uterus, and antagonism in the mammary gland.

Decreases in estrogen levels after oophorectomy or spontaneous menopause leads to decreased maturation of vaginal epithelial cells; a progressive decrease in vascularity of the vaginal tissues; and decreased lubrication. The glycogen content of vaginal epithelial cells also decreases, resulting in reduced colonization by lactobacilli and increased vaginal pH. These changes result in vulvar and vaginal atrophy (VVA), clinical signs of which include vaginal dryness, redness, petechiae, pallor, and friability of the mucosa. In some postmenopausal women, these changes result in dyspareunia.

In preclinical studies, Osphena's estrogen receptor agonist activity in the vagina resulted in cellular maturation and mucification of the vaginal epithelium. In placebo controlled VVA treatment trials, Osphena therapy resulted in maturation of the vaginal mucosa, decrease in vaginal pH, and improvement in dyspareunia. None of the previously approved SERMs [1]is indicated for treatment of any of the symptoms of VVA.

[1] While the term "SERMs" will be used throughout this memorandum, product labeling will reflect the new terminology for such agents, i.e., estrogen agonist/antagonist.

Osphena is indicated for the treatment of moderate to severe dyspareunia, a symptom of vulvar and vaginal atrophy, due to menopause. The dose of Osphena is 60 mg daily, taken orally with food.

This memorandum documents my concurrence with the Division of Reproductive and Urologic Products (DRUP) recommendation to approve Osphena 60 mg, p.o. daily for the treatment of moderate to severe dyspareunia caused by VVA due to menopause.

REGULATORY HISTORY

The original sponsor (Hormos Medical Corp.) submitted [redacted] (b) (4) for Osphena on March 25, 2003. It was received April 7, 2003.

A teleconference related to the IND submission was held with the sponsor on June 10, 2003. At that teleconference, the sponsor was informed of several issues that would need to be addressed during drug development, including a recommendation that Osphena be evaluated in subjects with moderate to severe VVA symptoms. It was also noted that 2 confirmatory trials for efficacy and safety would be required for approval.

The IND was transferred to Shionogi, Inc. on June 22, 2005.

An End-of-Phase 2 meeting was held on October 4, 2005 to discuss the requirements for an NDA submission. Key clinical issues discussed during that meeting included selection of co-primary efficacy endpoints, and the definition of an adequate safety database for the VVA indication, including the need for endometrial biopsies, and a thorough QTc study.

Additionally, the Sponsor proposed two 2-year carcinogenicity bioassays, one in mice and one in rats. The protocols for these carcinogenicity studies were submitted as SPAs in September 2006. On February 2, 2007, the Division held a teleconference with the sponsor to discuss preclinical toxicities, including swelling of the urogenital area and/or abdomen and scrotal herniation, observed in male mice in the mouse carcinogenicity study after 12 weeks of dosing. These morbidities had not been observed in either the 13-week oral toxicity study in mice or in the ongoing rat carcinogenicity study. After consulting with Executive Carcinogenicity Assessment Committee (CAC), the Division issued an Advice letter on February 5, 2007, with the following recommendations:

- All male mice in the 2-year mouse carcinogenicity study may be terminated as of February 2, 2007.
- If the Sponsor can provide an explanation for the recent drug-related effects (e.g., severe swelling of the urogenital area and/or abdomen, and scrotal herniation) in all male dosing groups, and a reasonable explanation for the discrepancy between the current study and the 13-week dose range-finding study in which similar findings were not observed, then a new study in male mice will not be requested."

The Division reviewed additional clinical protocols during drug development, including protocols to establish efficacy and safety (15-50310 and 15-50821), protocols to establish bioequivalence to earlier formulations, and a protocol for a thorough QT_c study (15-50824). Design and conduct of these trials as well as other drug development issues were discussed with the sponsor through additional meetings held on March 14, 2007, April 29, 2008, September 29, 2009, and April 12, 2011. Some of the key discussions that occurred at these meetings included the following: format of the NDA for the primary disciplines, the effect of Osphena on subjects with impaired renal and hepatic function, and CMC issues.

Shionogi, Inc. submitted the NDA for Osphena on April 26, 2012 under 505(b)(1) of the Federal Food and Drug Act (FDCA). The NDA was filed on June 25, 2012 and granted a Standard Review.

CHEMISTRY MANUFACTURING and CONTROLS

There are no outstanding CMC issues. The proposed testing and acceptance criteria for both the drug substance and drug product are considered adequate to assure identity, strength, purity and quality for the requested dose strength of Osphena.

CLINICAL MICROBIOLOGY

There are no clinical microbiology issues for this application.

PRECLINICAL PHARMACOLOGY/TOXICOLOGY

Osphena demonstrated the expected pharmacology of a mixed estrogen agonist/antagonist with no unexpected nonclinical safety signals. Osphena is a reproductive toxicant and is tumorigenic in rodents at or below comparable human exposure levels; however, the reproductive findings are expected and not relevant for the indicated population of postmenopausal women. The tumor signal in rodents was expected and has been observed with other SERMs and estrogens. Most tumors observed are not relevant to humans; post-marketing experience for other SERMs has not shown an increased risk for tumors.

Osphena potently binds to both Estrogen Receptor α and ß types of nuclear receptors. In rats and monkeys, Osphena has pharmacological activities consistent with estrogen agonism in the vagina, ovary, and bone, mixed agonism/antagonism in the uterus, and antagonism in the mammary gland. There were no significant findings from a battery of safety pharmacology assays designed to evaluate neurological, cardiovascular, pulmonary and renal effects.

In toxicity studies in rats, mice, female dogs, and female monkeys, there were no unexpected toxicities noted. The main effects noted were related to exaggerated pharmacological effects of Osphena on reproductive organs. Organ weight abnormalities,

gross pathological and histopathological effects were noted in the ovary, uterus, vagina, mammary gland, liver, prostate, testis, and epididymis in most species and studies. The ovary, mammary gland, and male reproductive organs showed a predominately antagonistic profile, whereas the vagina and liver showed agonism. Some studies showed cell and tissue selective agonism. All findings were at exposures comparable to human exposure at the proposed dose

Osphena was embryotoxic and adversely affected parturition. There were developmental effects noted in the offspring of treated pregnant rats. These effects were noted at exposures significantly lower than the human exposure.

Embryofetal toxicity (EFT) studies with Osphena were conducted with rats and rabbits. In both species, significant toxicity was noted with the highest exposures obtained being only 4% of human exposure with higher doses precluded by maternal toxicities and fetal losses. No fertility and early embryonic development study was conducted or necessary given the indicated population of postmenopausal women.

The weight of evidence suggests that Osphena is not genotoxic. Osphena was negative in the Ames and mouse lymphoma cell assays and in the mouse micronucleus and the rat liver DNA assays. There were no structural alerts for Osphena or its M1 and M2 metabolites.

Osphena is carcinogenic to rodents based on the findings from the rat and mouse 2-year carcinogenicity studies. All treated rat and mouse groups had lower body weight gain and greater survival rates than control groups.

Hepatocellular and ovarian neoplasms were considered to be clearly related to drug in rats and ovarian and adrenal neoplasms were considered to be clearly related to drug in female mice. The assessment of male mice was terminated very early due to the development of swelling of the urogenital area and/or abdomen and scrotal herniation, and was not evaluable. In the carcinogenicity studies, increasing doses did not result in corresponding increases in drug blood levels and thus there was no dose response relationship for neoplastic findings. The exposure multiples in rats and mice were 1 and 5 fold respectively over clinical exposure at the proposed dose.

Except for skin, both the neoplastic and non-neoplastic treatment related effects in estrogen target organs such as testes, epididymis, ovary, uterus, mammary gland, bone, liver, adrenal, pituitary, spleen, thymus and thyroid were consistent with the established toxicology of SERMs.

Because of its reproductive toxicity profile, Osphena will be labeled Pregnancy Category X and contraindicated in pregnancy, consistent with the labeling of other SERMs. Labeling will also indicate that it is not known whether Osphena is excreted in human breast milk; it is excreted in rat milk and is detected at concentrations higher than that seen in maternal plasma. Osphena is embryotoxic in the rat and the rabbit.

CLINICAL PHARMACOLOGY

Pharmacokinetics:

The disposition of Osphena has been evaluated in 1091 postmenopausal women with VVA using a population approach. Pharmacokinetic data were also obtained in conventional clinical pharmacology studies in 394 postmenopausal women and 175 healthy subjects.

Absorption: Tmax occurs approximately 3-4 hours post oral dosing with Osphena in the fed state and 1-8 hours in the fasted state. The absolute bioavailability of Osphena has not been established. Mean Osphena Cmax and AUC(0-24 hr) were 785 ng/mL and 5448 ng**.**hr/mL, respectively after repeat doses of 60 mg Osphena once daily in the fed state.

When Osphena was administered with food, the Cmax and the AUC were 2.4 fold and 1.9 fold higher respectively, with lower variability relative to the fasting state. Therefore, Osphena should be taken with food. In healthy subjects, the absorption of Osphena is not affected by co-administration of omeprazole, a drug that increases gastric pH.

Distribution: Osphena is highly bound to serum proteins; the apparent volume of distribution is 448 L.

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

Excretion: The apparent terminal half-life of Osphena in postmenopausal women is approximately 26 hours. Following oral administration, approximately 75% and 7% of the Osphena dose was excreted in feces and urine respectively. Less that 0.2% of the Osphena was excreted unchanged in the urine.

Drug Interactions: Osphena is metabolized primarily by CYP 3A4 and CYP2C9 pathways. CYP2C19 and other pathways also contribute to its metabolism. Osphena does not inhibit the metabolism of co-administered drugs metabolized by the CYP enzymes at clinically relevant concentrations, although Osphena was a weak inhibitor for CYP2B6, CYP2C9, CYP2C19, CYP2C8, and CYP2D6 in *in vitro* studies.

The CYP3A/CYP2C9/CYP2C19 inhibitor fluconazole increased the AUC of Osphena by 174%. The CYP3A inhibitor ketaconazole increased the AUC of Osphena by 42%. The CYP3A/CYP2C9 inducer rifampin decreased the AUC of Osphena by 58%. Co-administration of omeprazole (a CYP2C19 inhibitor) increased the AUC of Osphena by 17%, which is not considered to be clinically significant.

Drug interaction studies were performed with a CYP2C9 probe (warfarin), a CYP2C19 probe and a CYP3A4 probe (omeprazole) and a CYP2B6 probe (buproprion). Osphena did not affect those enzyme activities *in vitro*.

As a result of these studies, labeling will indicate that fluconazole should not be used with Osphena; that concomitant use of rifampin and Osphena may decrease the clinical effect of Osphena; and that concomitant use of ketoconazole with Osphena may increase the risk of Osphena related adverse events.

Special Populations:

Pediatric: The pharmacokinetics of Osphena has not been evaluated in the pediatric population and it is not indicated in children.The product is indicated for postmenopausal women.

Geriatric: No differences were seen in the pharmacokinetics of Osphena with regard to age (range 40-80 years).

Renal Impairment: Severe renal impairment and end-stage renal disease did not significantly impact the systemic exposure of a single 60 mg oral dose of Osphena. In subjects with severe renal impairment and end-stage renal disease, Cmax, AUC (0-t), and AUC (0-inf) were lower by 21%, 19% and higher by 20% respectively. Half-life was the same at 34 hours in patients with severe and end-stage renal disease as it was in normal renal function subjects.

Hepatic Impairment: Subjects with normal hepatic function and patients with mild hepatic impairment had similar Cmax, AUC (0-t), and AUC (0-inf) after administration of Osphena. In patients with mild hepatic impairment, Cmax, AUC (0-t) and AUC (0-inf) were lower by 21%, 6.1% and 9.1% respectively.

Moderate hepatic impairment had a slightly greater effect on Osphena exposure compared to mild hepatic impairment. Overall, the effect of moderate hepatic impairment was not significant following a single 60 mg oral dose of Osphena. In patients with moderate hepatic impairment, Cmax was the same and AUC (0-t) and AUC (0-inf) were higher by 28% compared to subjects with normal hepatic function. These differences are not clinically significant, and therefore no dose adjustment will be recommended in labeling. Osphena has not been studied in women with severe hepatic impairment; therefore labeling will state that Osphena should not be used in these patients.

Population Pharmacokinetics: Using a two compartment model with first-order absorption processes, inter-subject variability was assessed on each of the PK parameters using the exponential error structure. Age, race, manufacturing site of drug, body weight and body mass index (BMI) were evaluated (among other parameters). No parameter was found to have a clinically relevant effect on the pharmacokinetics of Osphena.

Genetics: The Applicant excluded women who tested positive for Factor V Leiden (FVL), in whom the risk of venous thromboembolism (VTE) is 2-3 fold higher compared to non-carriers, from the Phase 3 trials. Based upon the estimated prevalence of FVL and considering the increased risk of VTE associated with FVL, few to no additional cases of VTE would have been observed if FVL carriers had been included in the Phase 3 trials.

QT prolongation: No significant effect of QT prolongation with Osphena was detected in a through QT study (TQT) (n=200). In a randomized, blinded, 4 arm parallel study, 50 healthy subjects received either Osphena 60 mg P.O. daily, Osphena 240 mg P.O. daily, placebo, or moxifloxicin 400 mg P.O. daily. They were treated for 7 days, with ECGs taken at various times relative to dose, and evaluated for QT variability using time matched change from baseline in QTc (Fredericia and Bazett).

EFFICACY

The efficacy of Osphena for treatment of VVA in postmenopausal women was evaluated in two Phase 3 clinical trials (Trial 1 and Trial 2) each of 12 weeks duration, and in one long term safety trial (Trial 3) of 52 weeks duration. In total, 1102 subjects were treated with Osphena 60 mg and 787 subjects were treated with placebo.

Trial 1

Trial 1 was a 12 week, randomized, double blind, placebo controlled, parallel group trial designed to assess the efficacy, safety, and tolerability of once daily oral doses of Osphena in the treatment of VVA. Subjects received nonhormonal vaginal lubricant to use as needed. Patients were randomized to receive Osphena 30 mg (n=282), Osphena 60 mg (n=276) or placebo (n=268). No oral, vaginal, transdermal, or injectable estrogens or progestins were allowed.

The trial enrolled generally healthy postmenopausal women 41-80 years of age (mean age=59 years) who at baseline had ≤ 5% superficial cells in the vaginal smear, a vaginal pH of >5 and moderate to severe VVA symptoms of either vaginal dryness or dyspareunia. VVA symptoms were rated on a 4 point Likert scale (0= none; 1= Mild; 2= Moderate; 4= Severe). The mean BMI of the efficacy population was 25.9 with 90.2% White, 5.5% Black, 2.0% Asian, 0.3% American or Alaska Native and 5% others. 81% of subjects had received hormone therapy within 6 months of the trial and the mean number of vaginal births was 1.7.

Mean baseline dyspareunia severity scores in both the Osphena 60 mg and placebo groups were 2.7. Mean baseline superficial cell values in both the Osphena 60 mg and placebo groups were 0.8%. Mean baseline parabasal cell values in both the Osphena 60 mg and placebo groups were 41%. Mean baseline pH values for both groups were 6.4.

Efficacy was assessed at week 12 in vaginal dryness and dyspareunia subjects separately; however, subjects were not stratified at baseline. The 4 co-primary endpoints were the change from baseline to week 12 in the following:

- Severity score for subjects having vaginal dryness as their most bothersome symptom at baseline (MBS) or severity score for subjects having dyspareunia as their MBS at baseline
- Percentage of parabasal cells in the vaginal smear
- Percentage of superficial cells in the vaginal smear
- Vaginal pH

Following completion of the 12 week Trial 1, subjects with an intact uterus were allowed to enroll in a 40 week double blind extension trial, while subjects without an intact uterus were allowed to enroll in a 52 week open label extension trial.

Osphena 60 mg statistically significantly improved the four co-primary endpoints in dyspareunia subjects (n=110, Osphena 60 mg daily; n=113, placebo) as compared to placebo for the change from baseline to week 12 in dyspareunia severity score (p =0.0012), and in vaginal dryness subjects (n=113, Osphena 60 mg daily; n=100, placebo) as to compared to placebo for the change from baseline to week 12 in vaginal dryness severity score (p = 0.0136); and in both groups in changes form baseline to week 12 in vaginal pH, % parabasal cells and % superficial cells (p= <0.0001).

Trial 2

Trial 2 was a 12-week, randomized, double-blind, placebo-controlled, parallel-group trial, designed to assess the effectiveness of once daily oral doses of Osphena 60 mg (n=463), compared to placebo (n=456), in the treatment of VVA. Two distinct cohorts, based on the moderate to severe MBS symptoms of dyspareunia or vaginal dryness, were randomized and analyzed in this trial, separately.

The efficacy population consisted of generally healthy postmenopausal women between 41 to 79 years of age (mean age = 59 years) who at baseline had ≤5.0 percent superficial cells in the vaginal smear, a vaginal pH >5.0, and moderate to severe VVA symptoms of either vaginal dryness or dyspareunia. The mean BMI of the efficacy population was 26.2 with a racial distribution of 87.9% White, 6.7% Black, 1.2% Asian, 0.2% Native Hawaiian or Other Pacific Islander, and 4.0% others.

The mean baseline dyspareunia severity scores in the efficacy population were 2.7 in both the Osphena 60 mg and the placebo group. Mean baseline superficial cell values in the efficacy population were 0.8% in both the Osphena 60 mg and the placebo group. The mean baseline parabasal cell values were 50% in the Osphena 60 mg group and 49% in the placebo group. The mean baseline pH values were 6.3 in both groups.

Primary endpoints and trial conduct were similar to those in Trial 1.

Osphena 60 mg statistically significantly improved the four co-primary endpoints in dyspareunia subjects (n=301, Osphena; n=297, placebo) as compared to placebo for the change from baseline to week 12 in dyspareunia severity score, vaginal pH, % parabasal cells and % superficial cells (p=< 0.0001).

In a separate analysis of vaginal dryness subjects (n=157, Osphena; n=150, placebo) the effect of Osphena 60 mg on vaginal dryness severity at week 12 as compared to baseline was not distinguishable from placebo (p=0.0853), but was statistically significantly different from placebo in that subset from baseline to week 12 for physiologic changes in the co-primary endpoints of % superficial cells, % parabasal cells, and pH (p= <0.0001 in all cases).

In summary, the efficacy results from the two phase 3 trials demonstrate:

- Ospemifene 60 mg once daily demonstrated a statistically significant improvement in the severity of moderate to severe dyspareunia, a symptom of vulvar and vaginal atrophy, due to menopause (p=.0012 in Trial 1 and p=<0.0001 in Trial 2).
- Ospemifene 60 mg was not consistently superior to placebo in the treatment of moderate to severe vaginal dryness, a symptom of vulvar and vaginal atrophy, due to menopause (p=0.0136 in Trial 1 and p=0.0853 in Trial 2). Therefore, efficacy of ospemifene for vaginal dryness cannot be determined based on these trials.
- Additional support that may be predictive of a positive treatment effect of ospemifene was demonstrated through statistically significant mean changes from baseline in changed in pharmacodynamic endpoints including: increases in superficial cells, decreases in parabasal cells, and increases in vaginal pH.

These efficacy results do not support the applicant's request for a vaginal dryness claim in product labeling; they do however support a claim for the treatment of moderate to severe dyspareunia, a symptom of vulvar and vaginal atrophy due to menopause.

SAFETY

The safety of Osphena has been assessed in nine Phase 2 and Phase 3 trials (n=1892) with doses ranging from 5 to 90 mg per day. The duration of treatment in these trials ranged from 6 weeks to 15 months. Most subjects (n=1370) had a treatment period of at least 12 weeks and 409 had at least 12 months of exposure.

In particular, in Phase 3 trials, Trial 3 evaluated long term safety. This trial was a 52 week, randomized, double blind, placebo controlled, long term safety trial in 426 postmenopausal women with an intact uterus. 363 subjects (85.2%) were randomized to Osphena 60 mg and 63 (14.8%) were randomized to placebo. The mean age of participants was 62.9 years in the placebo group and 61.7 years in the Osphena group.

In Phase 3 (Trials 1, 2 and 3) double blind, placebo controlled, clinical trials in patients exposed to Osphena 60 mg p.o. daily (n=1242 Osphena; 958 placebo) the adverse reactions that occurred at a frequency ≥ 1 percent and more commonly in the Osphena group were as follows: hot flushes (7.5% Osphena, 2.6% placebo); vaginal discharge (3.8% Osphena, 0.3% placebo); genital discharge (1.3% Osphena, 0.1% placebo); muscle spasms (3.2% Osphena, 0.9% placebo); and hyperhydrosis (1.6% Osphena, 0.6% placebo).

The endometrial safety of Osphena was evaluated in two ways. In Phase 2/3 clinical trials with Osphena, endometrial thickness was evaluated by ultrasound in 1229 women who took Osphena. The following numbers of women developed endometrial thickness above baseline at any time during the trial: 179 (14.6%) ≥ 4mm; 91 (7.4%) ≥5mm; 15 (1.2%) ≥8mm. The increases in endometrial thickness identified via ultrasound are consistent with the endometrial effects reported with other SERMs.

Additionally, in the two Phase 3 clinical trials, endometrial safety in women with an intact uterus was assessed by endometrial biopsy at week twelve (Osphena n=982; placebo n=469). For subjects with an intact uterus completing the Trial 3 long term extension trial (Osphena n=55; placebo n=32) endometrial safety was also assessed by endometrial biopsy at week 52. No cases of endometrial hyperplasia or endometrial carcinoma were reported at either time point. One subject in the Osphena 60 mg group was diagnosed with endometrial hyperplasia (simple hyperplasia without atypia) 88 days after the last dose of trial medication. Five subjects in the Osphena 60 mg group developed atrophic endometrial polyps.

There were no deaths reported during the Osphena development program.

In all double-blind Phase 2/3 placebo controlled trials (n=1696 Osphena; 958 placebo), serious adverse events (SAE) occurred in 39 (2.3%) Osphena treated patients and 17 (1.8) placebo treated patients. No single type of SAE occurred in more than one subject in the placebo group. In the Osphena group, SAEs that occurred in more than one subject were: osteoarthritis (3 subjects); appendicitis (2 subjects); CVA (3 subjects); diverticulitis (2 subjects); and deep vein thrombosis (DVT) (2 subjects). CVA (1 subject) and diverticulitis (1 subject) also occurred in the placebo group.

Discontinuations were similar in the two groups with 14.6% in the Osphena 60 mg group and 12.8% in the placebo group. The most common reason for discontinuation in the Osphena group (n=301) was adverse events (nausea 1%; muscle spasms 0.7%; headache 1%; hyperhydrosis 0.7%, skin rash 0.7%, and hot flushes 2%). The most common reason for discontinuation in the placebo group was “other” including withdrawal of consent, lack of efficacy, non-compliance with trial procedures and family obligations.

Potential Safety Issues:

Because Osphena has estrogen agonist activity, some of the safety concerns that are applicable to estrogens as a class are applicable to Osphena. These include the following:

Endometrial Cancer: There is an increased risk of endometrial cancer in women with a uterus who use unopposed estrogens (approximately 2-12 times greater in users versus non-users). The risk appears to be dependent upon duration of treatment and estrogen dose. Most studies show no significant increased risk with use of estrogens for less than a year. The greatest risk is associated with prolonged use, with increased risks of 15-24 fold greater for 5-10 years or more of use. This risk has been shown to persist for 8-15 years after estrogen therapy is discontinued. 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 used to rule out malignancy in postmenopausal women with undiagnosed or persistent or recurring abnormal genital bleeding.

As with other SERMs, labeling for Osphena will carry a boxed warning with regard to the potential for development of endometrial cancer.

Cardiovascular Disorders: SERMs increase the risk of venous thromboembolic events (VTE), namely DVT and pulmonary embolism (PE). Other less serious events such as superficial thrombophlebitis can occur. The greatest risk of VTE occurs during the first 4 months of treatment with SERMs, and the magnitude of risk is similar to that reported with the use of hormone therapy. In Phase 2/3 clinical trials, 2 cases of DVT versus none on placebo were reported on Osphena 60 mg; and cerebrovascular accident was reported in 1 subject on placebo, 1 subject on Osphena 30 mg and 3 subjects on Osphena 60 mg.

Because treatment with estrogen alone is known to increase the risk of stroke and VTE, the Osphena label will carry a boxed warning with regard to the risk of stroke and VTE.

ADVISORY COMMITTEE

This application was not referred to an Advisory Committee because the clinical trial design was acceptable, the application did not raise significant safety or efficacy issues, the application did not raise significant public health issues on the role of the drug in the diagnosis, cure, mitigation, treatment, or prevention of disease, and outside expertise was not necessary.

PEDIATRIC CONSIDERATIONS

Under the Pediatric Research Equity Act (PREA)(21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dose regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication in pediatric patients unless this requirement is waived, deferred, or inapplicable. Because the condition for which this product is indicated does not exist in the pediatric population (moderate to severe dyspareunia, a symptom of VVA due to menopause) the applicant is granted a full waiver with regard to this requirement.

TRADENAME REVIEW

On September 13, 2012, the Division of Medication Error Prevention and Analysis (DMEPA) in consultation with the Office of Prescription Drug Promotion concluded that the tradename “Osphena” is acceptable.

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/s/

VICTORIA KUSIAK
02/26/2013