CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

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SUMMARY REVIEW

Deputy Division Director Summary Review

Date	February 26, 2013
From	Audrey Gassman, MD
NDA #	203505
Applicant name	Shionogi, Inc
Date of receipt of original submission	April 26, 2013
PDUFA goal date	February 26, 2013
Proprietary name/established name	Osphena/ospemifene
Dosage Form/strength	Tablets/60 mg
Proposed Indication	Treatment of moderate to severe dyspareunia, a symptom of vulvar and vaginal atrophy, due to menopause
Action	Approval

Material reviewed/consulted	Names of discipline reviewers
CDTL Review	Shelley R. Slaughter, MD, PhD
Medical Officer Review	Theresa van der Vlugt, MD
Statistical Review	Xin Fang, PhD Mahboob Sobhan, PhD
Pharmacology/Toxicology Review	Jeffrey Bray, PhD Alex Jordan, PhD Abigail Jacobs, PhD
Clinical Pharmacology Review	LaiMing Lee, PhD Myong-Jin Kim, PhD
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CDTL=Cross-Discipline Team Leader
OND=Office of New Drugs
DMEPA=Division of Medication Error Prevention and Analysis
ONDQA=Office of New Drug Quality Assessment
DMPP=Division of Medical Policy Programs
OPDP=Office of Prescription Drug Promotion
DPP=Division of Professional Promotion
DDTCP=Division of Direct-to-Consumer Promotion
OSI=Office of Scientific Investigations
SEALD=Study Endpoints and Labeling Development Team

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1. Introduction

Shionogi, Inc. submitted an NDA (203-505) for a new molecular entity (NME) containing an estrogen agonist/antagonist in a tablet formulation designated as ospemifene (tradename Osphena). Each ospemifene tablet contains 60 mg of the active ingredient to be taken once daily orally with food. The Applicant's proposed indication in the application reads, "(b) (4) (the original proposed tradename) is an estrogen receptor agonist/antagonist for the treatment of vulvar and vaginal atrophy due to menopause, including moderate to severe symptoms of dyspareunia and/or vaginal dryness and physiological changes (parabasal cells, superficial cells and pH)." Vulvar and vaginal atrophy (VVA) is a condition associated with declining estrogen levels that occur during menopause and initially results in decreased vaginal lubrication, but over time can lead to clinical symptoms including vaginal dryness, burning/irritation/itching, and dyspareunia. These VVA symptoms can lead to vulvovaginal pain and sexual dysfunction.

If approved, ospemifene will be the first estrogen agonist/antagonist approved for the treatment of any of the symptoms of VVA. There are three estrogen agonist/antagonists in the same pharmacologic class that are currently approved by the Agency: tamoxifen, raloxifene, and toremifene. Tamoxifen (Nolvadex®, NDA 017970) and toremifene (Fareston®, NDA 020497) are approved for the treatment of breast cancer. Raloxifene (Evista®, NDA 020815) is approved for the treatment and prevention of osteoporosis in postmenopausal women. None of these are approved for treatment of VVA symptoms. Approved treatments for symptoms of VVA include tablets, topically applied transdermal products and vaginally applied products that contain estrogen as well as estrogen and progestin.

Ospemifene is classified as an estrogen agonist/antagonist; it binds to human estrogen receptors (ERα and ERβ). Ospemifene and its main metabolites (4-hydroxyospemifene [M1] and 4'-hydroxyospemifene [M2]) cause estrogen-like effects on vaginal epithelium. Ospemifene is primarily metabolized by CYP3A4 and CYP2C9 and has a terminal half-life of approximately 26 hours. The biological action of ospemifene is mediated through

binding to estrogen receptors. The proposed dosing regimen that the Applicant is seeking approval for is one 60 mg film coated tablet orally once daily with food. None of the tested extrinsic or intrinsic factors require dose adjustment.

To support approval of this NDA, the Applicant conducted a total of 30 clinical studies that included 21 clinical pharmacology trials and 9 phase 2/3 clinical trials. In the phase 2 and 3 studies, a total of 1,892 postmenopausal subjects, with and without a uterus, were exposed to at least one dose of ospemifene. Of the 1,892 subjects in the phase 2 and 3 trials, 1546 (approximately 80%) received the 60 mg or higher dose. Among ospemifene-treated subjects, 1370 had at least 12 weeks exposure, 659 had a least 6 months exposure and 409 subjects had at least 1 year of exposure, with a maximum exposure of 89 weeks.

The clinical data for 12-week Phase 2 Trial 15-50717, 12-week Phase 3 Trials 15-50310 and 15-50821, 52-week Phase 3 Trial 15-50718, the 40-week safety extension Trial 15-50310X, and the 52-week safety extension Study 15-50312 provide the primary support for the safety and efficacy of 60 mg ospemifene for the treatment of moderate to severe vaginal dryness and moderate to severe dyspareunia, symptoms of vulvar and vaginal atrophy, due to menopause.

From an efficacy perspective, the Applicant supported the 60 mg ospemifene dose with two randomized, double-blind, parallel-group, placebo-controlled phase 3 trials (trials 15-50310 and 15-50821). A third phase 3 trial (15-50718) did not assess the change from baseline to week 12 in the individual self-identified most bothersome symptom, and therefore was not included in the efficacy evaluation for ospemifene. The treatment duration in the two controlled phase 3 trials was 12 weeks with efficacy data collected as recommended by the Agency's 2003 draft Guidance for Industry entitled, "Estrogen and estrogen/progestin drug products to treat vasomotor symptoms and vulvar and vaginal atrophy symptoms – recommendations for clinical evaluation". The co-primary efficacy outcomes for the phase 3 studies included:

- Percent parabasal cells from the vaginal smear
- Percent superficial cells from the vaginal smear
- Vaginal pH
- Severity of the most bothersome VVA symptom (vaginal dryness or vaginal pain associated with sexual activity)

In the two primary phase 3 trials, treatment with ospemifene 60 mg once daily resulted in a statistically significant improvement over placebo in the severity of moderate to severe dyspareunia due to menopause ($p=.0012$ in Trial 15-50310) and $p<0.0001$ in Trial 15-50821). However, substantial evidence of effectiveness was not established for the treatment of moderate to severe vaginal dryness due to the failure to demonstrate statistically significant improvement in both phase 3 trials (mITT analysis: $p=0.0136$ in Trial 15-50310 and $p=0.0853$ in Trial 15-50821). Only one secondary efficacy endpoint was evaluated during this review, "frequency of lubricant use (non-hormonal) and sexual activity". The Applicant evaluated the effect of any lubricant use versus no lubricant use in subjects complaining of dyspareunia and vaginal dryness. The Medical Officer and

Statistical reviewer concluded that use of any lubricant did not influence the effectiveness of ospemifene to relieve moderate to severe dyspareunia.

From a safety perspective, the review focused on several different data sources including: 1) the Integrated Safety Summary, 2) the thorough QT study (15-50824), and 3) selected data from the controlled phase 2 and 3 studies, data from the extension studies [15-50821 and the extensions of Trial 15-50310 in women with uteri (15-50310X) and without uteri (15-50312) and two 12-week trials (1506001 and 1506002)] that evaluated bone, vascular and lipid metabolism. Key safety issues that the clinical review team evaluated based on the known safety profile of other estrogen agonist/antagonist products included evaluation of endometrial and uterine safety, venous and arterial thrombotic events, and breast adverse events. Other potential safety issues of interest included evaluation of other reproductive system adverse events (including pelvic organ prolapse, vulvovaginal infections and vaginal bleeding/spotting).

Comment: The Applicant's original proposed indication included (b) (4)

These were designated as co-primary endpoints. The positive statistical outcomes for these endpoints were supportive of the key clinical outcome of most bothersome symptom of VVA; however, changes in these pharmacodynamic endpoints are not, by themselves, clinically meaningful. After discussion with the Applicant, the final agreed upon indication supported by ospemifene's clinical trial data is: "Osphena is indicated for the treatment of moderate to severe dyspareunia, a symptom of vulvar and vaginal atrophy, due to menopause."

2. Background

The original Applicant initiated discussions on the development of ospemifene for the treatment of moderate to severe vaginal dryness and moderate to severe dyspareunia, symptoms of vulvar and vaginal atrophy (VVA), due to menopause with the Division of Reproductive and Urologic Products (DRUP) through IND 67,216. This IND was opened on March 25, 2003, with a protocol for a phase 3 randomized, multi-center, double-blind, parallel-group study of 2 doses of ospemifene (60 mg and 90 mg). A teleconference related to the IND submission was held with this 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 ospemifene be evaluated in subjects with moderate to severe VVA symptoms.

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

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. These two protocols were reviewed by the Division's pharmacology/toxicology reviewers and presented to the Executive Carcinogenicity Assessment Committee (CAC). On February 2, 2007, the Division held a teleconference with the Applicant 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 the CAC, the Division issued an Advice letter on February 5, 2007 and concurred with termination of the carcinogenicity study in male mice. A follow-up submission on the findings in the mouse carcinogenicity study was submitted on July 18, 2008 and reviewed by the Division. The Pharmacology/Toxicology review team subsequently determined that no further carcinogenicity studies were required in male mice as they were not a pertinent model for the stated indication in women.

The Division also reviewed other clinical protocols during drug development, including protocols to establish efficacy and safety (15-50310 and 15-50821), protocols to establish bioequivalence to earlier formulations (such as between the to-be-marketed product and the product used in the phase 3 clinical trials - Trial 15-51031), and a protocol for a thorough QT study (15-50824). Design and conduct of these trials as well as other drug development issues were discussed with the Applicant 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: format of the NDA for the primary disciplines, the effect of ospemifene on subjects with impaired renal function, and CMC issues.

NDA 203-505 was submitted on April 26, 2012, to support the efficacy and safety of ospemifene with the proposed indication of moderate to severe dyspareunia and moderate to severe vaginal dryness, symptoms of vulvar and vaginal atrophy, due to menopause. Efficacy for ospemifene was based on the two phase 3 studies conducted in the United States in postmenopausal subjects with moderate to severe vulvar and vaginal atrophy (15-50310 and 15-50821).

Other studies were reviewed as supportive safety studies and included 3 key phase 2 dose-finding trials (1506001, 1506002 and 15-50717) and 21 phase 1 pharmacokinetic and pharmacodynamic studies. The phase 1 trials consisted of five drug-drug interaction studies that included a study of the effect of ospemifene on warfarin (15-50614), two food effect trials (15-50208 and 15-50208-02), hepatic and renal impairment trials (15-50820, 15-50920 and 15-50921), a thorough QT study (15-50824) and several bioequivalence trials. In addition, the Applicant completed 3 long term trials (2 double blind, placebo-controlled safety trials [extension trial 15-50310X and 15-50718] and one uncontrolled safety extension trial [15-50312]).

3. ONDQA

Osphena tablets contain 60 mg of the active ingredient, ospemifene, exclusively in the Z-isomer conformation with a chemical designation of Z-2-[4-(4-chloro-1,2-diphenylbut-1-

enyl)phenoxy]ethanol. Other inactive ingredients in Osphena tablets include: pregelatinized starch, mannitol, povidone, sodium starch glycolate, microcrystalline cellulose, colloidal silicon dioxide, magnesium stearate. There are no novel excipients in this drug product and all ingredients are compendial. The tablets are (b) (4) and are manufactured (b) (4) Tablets will be supplied in two container closure systems: plastic bottles with a screw cap and blister packs that have an aluminum foil push through.

A memorandum was entered by the Division of Pharmaceutical Analysis (DPA) regarding Methods Validation. The Summary Report from DPA, entered on September 27, 2012, classified the validation methods for ospemifene as acceptable for control and regulatory purposes.

The Chemistry Review (ONDQA) team made the following initial recommendation in their review dated December 12, 2012, "The NDA has provided sufficient information to assure identity, strength, purity and quality of the drug product. However, the label/labeling issues are still not satisfactorily resolved. Also, a site recommendation from the Office of Compliance has not been made as of the date of this review. Therefore, from the ONDQA perspective, this NDA is not recommended for approval per 21CFR 314.125(b)(6) in its present form until the issue delineated in the "List of Deficiencies" (see p. 85) is satisfactorily resolved."

In an addendum to the December, 2012, ONDQA review, finalized on February 20, 2013, the ONDQA reviewer concluded that the Office of Compliance has made an overall "Acceptable" recommendation for the facilities involved in the NDA and that labeling had been adequately addressed and stated that, "From the ONDQA perspective, this NDA is now recommended for "Approval" with an expiration dating period of 24 months."

The ONDQA Biopharmaceutics Review team evaluated the acceptability of the proposed dissolution and acceptance criteria methodology. The Biopharmaceutics team concluded on December 11, 2012, that, "Osphena (ospemifene) 60 mg strength immediate release tablets are recommended for approval from a Biopharmaceutics standpoint.

- The following dissolution method and acceptance criterion is recommended for both strengths:
    i. Dissolution method: Apparatus II, 50 rpm agitation rate, 900 mL media volume, 37 °C, 2% SDS in water.
    ii. Dissolution acceptance criterion: Q = (b) (4) at 60 minutes."

Comment: There are no outstanding CMC, Biopharmaceutics or Method Validation issues. I concur with the Approval recommendation of the ONDQA review team.

4. Nonclinical Pharmacology/Toxicology

Nonclinical data submitted to support approval of ospemifene included assessments of nonclinical pharmacology, pharmacokinetic and toxicology. The pharmacology/toxicology reviewer, Dr. Jeffrey Bray, classified ospemifene as a mixed

estrogen receptor agonist/antagonist. Of note, previously these products were classified as selective estrogen receptor modulators or SERMs. He stated that, "Ospemifene demonstrated the expected pharmacology of a mixed estrogen agonist/antagonist with no unexpected nonclinical safety signals. Ospemifene is a reproductive toxicant and is tumorigenic in rodents (see below) at or below comparable human exposure levels. However, the reproductive findings are expected and not relevant for the indicated population and the tumor signal in rodents was expected and was 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."

Nonclinical studies using ospemifene demonstrated that it has pharmacologic activities in rats and monkeys consistent with estrogen agonism in the vagina, ovary and bone, mixed agonism/antagonism in the uterus, and antagonism in the mammary glands. The nonclinical reviewer concluded that there were no significant findings in the safety pharmacology assays of concern. He also concluded that studies in rats, mice, female dogs and female monkeys did not show any unexpected toxicities. Ospemifene was not genotoxic or mutagenic in in vitro studies. Ospemifene was carcinogenic in rodents; although findings in the two carcinogenicity studies were similar to those reported for other products in this class and are likely species specific. The findings of morbidities in males in the mouse carcinogenicity study were noted in his review, but the pharmacology/toxicology reviewer stated that, "The indication (for ospemifene) is for females only, so male mouse data is not essential for risk assessment".

The nonclinical reproductive toxicology studies demonstrated that ospemifene was embryotoxic and adversely affected partitution. In rabbits, a decreased number of live fetuses and increased post-implantation losses were reported. In rats, there was increased maternal mortality, increased total litter loss and clinical adverse signs of difficult partition at exposures significantly less than clinical exposures. The Pharmacology/Toxicology group determined, based on these findings, that the Pregnancy Category for ospemifene should be an "X".

In conclusion, the pharmacology/toxicology reviewer stated in his review dated January 15, 2013, that, "The nonclinical findings support Approval for the treatment of moderate to severe VVA in post-menopausal women at a daily oral dose of 60 mg." No postmarketing commitments or requirements were recommended by the pharmacology/toxicology review team.

On January 15, 2013, the Associate Director for Pharmacology/Toxicology also finalized a brief memo stating her concurrence that there were no outstanding pharmacology/toxicology issues.

Comments:

1. *I concur with the Approval recommendation of the pharmacology/toxicology review team from a pharmacology/toxicology perspective. There are no outstanding pharmacology/toxicology issues.*
2. *I also concur with the Pharmacology/Toxicology reviewer that the reported morbidities in male mice identified in the mouse carcinogenicity study are not likely to be relevant to the intended postmenopausal female patient population.*

5. Clinical Pharmacology

The Clinical Pharmacology review team evaluated data from healthy male subjects, healthy postmenopausal female subjects and subjects who had hepatic and renal impairment. In addition, data was collected from nonclinical in vitro studies (in vitro metabolite profiling, CYP inhibition and induction and P-gp substrate evaluation). The phase 1 program consisted of 7 biopharmaceutics and 21 clinical pharmacology studies. During the clinical development program, there were several formulations (solution, capsule, and tablets) evaluated with multiple manufacturing sites ((b) (4) Penn Pharmaceuticals in the United Kingdom, (b) (4) for the tablet formulations. Ospemifene 30 (Lot 0248A) and 60 mg tablets (Lot 0249A) were manufactured by Penn Pharmaceuticals for Phase 3 Trial 15-50310. Ospemifene 60 mg tablets (Lot A07006) were manufactured by (b) (4) for Phase 3 Trial 15-50821. The to-be-marketed ospemifene 60 mg tablets will be manufactured Penn Pharmaceuticals. The sponsor demonstrated bioequivalence under fasting conditions between the two formulations of 60 mg ospemifene used in the two Phase 3 studies. Key findings from the clinical pharmacology studies included:

- Following oral administration of a single 60 mg ospemifene tablet (an early development tablet formulation) in healthy male subjects, T_{max} was approximately 2 hours (range: 1 to 4 hours) after a high fat meal (Study 15-50208). Under fasted condition with the to-be-marketed tablets, Tmax was approximately 2 hours (range: 1 to 8 hours) and terminal $t_{½}$ was approximately 25 hours in postmenopausal women.
- In two food effect studies (Studies 15-50208 and 15-50208-02) in healthy male subjects using an early development tablet formulation, 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.
- To assess the effect of food on the to-be-marketed ospemifene tablets in postmenopausal women, the Clinical Pharmacology reviewer conducted a cross-study comparison using PK data gathered from 5 bioequivalence studies (1 under fed condition and 4 under fasted condition (Studies 15-50926, 15-51028, 15-51030 and 15-51031 under fasted condition were compared to Study 15-51029 under fed condition). A single 60 mg ospemifene to-be-marketed 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.

- In the two pivotal Phase 3 clinical trials (Trials 15-50310 and 15-50821) and long-term endometrial safety study (Trial 15-50718) ospemifene was administered with food (no specific type indicated). The label will include instructions for patients to take ospemifene with food.
- Pharmacokinetic steady state is attained approximately 7 days after the start of repeated doses of ospemifene and there is extensive (>99%) binding to serum proteins.
- In vivo studies showed that ospemifene is metabolized primarily by CYP3A4 and CYP2C9 enzymes. CYP2C19 and other pathways contribute to the metabolism of ospemifene.

Based on the data from these pharmacokinetic studies, the Applicant conducted the phase 3 studies using a dosing regimen of ospemifene as one tablet once daily with food without regard to the type of food. The Applicant is seeking approval of only one tablet strength of ospemifene, 60 mg and did not propose any dosing adjustment. As the target population of patients with vulvar and vaginal atrophy is likely to be older, the Applicant performed studies to characterize the pharmacokinetics of ospemifene in special populations. These special population studies included 2 studies in subjects with impaired hepatic function, 1 study in subjects with impaired renal function and 7 drug-drug interaction studies. In addition, a thorough QT study was also performed in healthy males and females. Clinical Pharmacology findings from these special population studies included:

1. Key clinical pharmacology studies identified the following issues:
    - Drug-drug interactions:
        - Key interactions with CYP inducers and inhibitors: (Trials 15-50716 and 15-50823): CYP3A inhibitor ketoconazole increased the AUC of ospemifene by 42%. A CYP3A/CYP2C9 inducer, rifampin, decreased the AUC of ospemifene by 58%. A CYP3A/CYP2C9/ CYP2C19 inhibitor, fluconazole, increased the AUC of ospemifene by 174%. As a result of these studies, labeling will note that patients should not use fluconazole or rifampin concomitantly with ospemifene. Labeling will also reflect that co-administration of ospemifene with ketoconazole or a drug known to inhibit CYP3A4 and CYP2C9 isoenzymes may increase the risk of ospemifene-related adverse events.
        - Ospemifene is >99% bound to plasma protein. Labeling will reflect that concomitant use with other highly bound protein drugs (such as bedaquiline, for example) should be considered with caution.
    - Hepatic impairment:
        - Mild (Trial 15-50820): No significant differences in the pharmacokinetic profile between subjects with mild hepatic impairment and healthy subjects were noted, so no dose adjustment will be recommended for this population.
        - Moderate (Trials 15-50820 and 15-50920): A 28% increase in ospemifene exposure was reported in subjects with moderate

hepatic impairment, although this finding was not considered by the Applicant or the Clinical Pharmacology team to be clinically significant. Therefore, no dose adjustment for patients with moderate hepatic failure will be recommended in labeling.
        - No evaluation was conducted in patients with severe hepatic impairment; as a result, labeling will state ospemifene should not be used in women with severe hepatic impairment.
    - Renal impairment:
        - Severe (Trial 15-50921): No significant pharmacokinetic differences in subjects with severe renal impairment compared to healthy subjects were observed. Therefore, no dose adjustment will be recommended for this population in labeling.
2. Other clinical pharmacology studies reported the following special population information:
    - The thorough QT study (Study 15-50824) did not identify a major signal of clinical concern, at therapeutic or supratherapeutic doses. The Clinical and Interdisciplinary QT team agreed that there was no significant QTc prolongation effect reported for ospemifene.

Comment: Drug-drug interactions studies were reviewed by the Clinical Pharmacology team (See Clinical Pharmacology review of Individual Studies dated February 22, 2013). The Clinical Pharmacology team agreed with the Applicant and concluded that the dose (60 mg) and dosage regimen (once daily with food), were acceptable. In addition, results of extrinsic and intrinsic factor studies (such as hepatic and renal impairment), and drug-drug interaction studies will be labeled where appropriate.

On January 15, 2013, the Interdisciplinary Review Team (IRT) for QT Studies provided a consult regarding the Applicant's thorough QT study (Study 15-50824) and made the following recommendation, "No significant QTc prolongation effect of ospemifene was detected in this TQT study. The largest upper bounds of the 2-sided 90% CI for the mean difference between ospemifene and placebo were below 10 ms, the threshold for regulatory concern as described in ICH E14 guidelines. The largest lower bound of the two-sided 90% CI for the ΔΔQTcI for moxifloxacin was not greater than 5 ms, but the moxifloxacin profile over time is adequately demonstrated in Figure 4, indicating that assay sensitivity was established."

Comment: I concur with the IRT review team and the Applicant that Study 15-50824 was sufficient to demonstrate that there was no serious QT signal of concern was identified at the proposed 60 mg dose of ospemifene.

The Clinical Pharmacology review team evaluated data from the clinical development program related to the pharmacokinetics and special populations. The Clinical Pharmacology reviewer, Dr. LaiMing Lee, made the following overall recommendation in her review dated January 11, 2013, that, "The Office of Clinical Pharmacology/Division of Clinical Pharmacology 3 (OCP/DCP3) has reviewed NDA 203505 for ospemifene 60 mg oral tablets submitted to the Agency on April 29, 2012.

We found this NDA acceptable from a Clinical Pharmacology perspective provided that an agreement is reached between the sponsor and the Division regarding the labeling language." No postmarketing commitments or requirements were recommended by the Clinical Pharmacology review team.

Comment: I concur with the overall Approval recommendation of the Clinical Pharmacology review team. At this time, labeling text for the Clinical Pharmacology section has been agreed to with the Applicant. Therefore, there are no outstanding Clinical Pharmacology issues.

6. Clinical Microbiology

A consult to the Clinical Microbiology team was not required for this application.

7. Efficacy/Statistics

The two Phase 3 trials (15-50310 and 15-50821) provided the primary support for the efficacy of ospemifene for the treatment of moderate to severe dyspareunia in women with vulvar and vaginal atrophy (VVA) due to menopause. In Trial 15-50310, two doses of ospemifene were evaluated, 30 and 60 mg against placebo. In Trial 15-50821, only the 60 mg dose was evaluated against placebo. The Applicant requested consideration of the 60 mg dose only in this submission; therefore, the focus of the clinical efficacy was on the findings of the 60 mg dose.

These two phase 3 clinical trials were similar in design and conduct. Both trials were randomized double-blind, placebo-controlled and conducted entirely in the United States. The treatment period for both trials was 12 weeks. Subjects were to take 1 tablet of study medication each morning with food and were instructed to apply a vaginal lubricant (K-Y® Brand Jelly) as needed and to record its use in the daily medication diary. The primary objective of these phase 3 trials was to assess the efficacy, safety, and tolerability of ospemifene versus placebo in the treatment of VVA in postmenopausal women.

Comment: Trial 15-50718 was included in the Applicant's submissions as a phase 3 trial, but did not assess the change from baseline to week 12 in the self-identified most bothersome moderate to severe symptom of vulvar and vaginal atrophy (the third recommended primary endpoint for a VVA indication). In addition, this study used a 6:1 randomization scheme for 60 mg ospemifene to placebo. Based on these design issues, the MO and CDTL recommended against use of data from this trial to support the effectiveness of the 60 mg dose in labeling. I concur with their assessment and therefore this trial is supportive solely of the safety profile of ospemifene.

A brief overview of the two key phase 3 clinical trials is outlined in the Table below:

Table 1: Overview of phase 3 trials*:

Trial #/ Study completion date	Total # centers/ Total # subjects enrolled	Design and control type	Dose regimen and administration route	Subject numbers and type	Duration of Treatment
15-50310 November 2007	83/76** 826 subjects	Randomized, multicenter, double-blind, parallel-group, placebo-controlled. Phase 3	Treatment groups: 1) Placebo, 2) 30 mg daily or; 3) 60 mg daily; given orally with food without regard to the type of food	Randomized: 30 mg = 282 60 mg = 276 Placebo = 268 Completed: 30 mg = 225 60 mg =234 Placebo = 230	12 weeks Postmenopausal women 40 to 80 years of age with vaginal pH >5.0, ≤ 5% superficial cells in vaginal smear, and self-reported MBS of VVA
15-50821 July 2009	119/112*** 919 subjects	Randomized, multicenter, double-blind, parallel-group, placebo-controlled, stratified. Phase 3	Treatment groups: 1) Placebo Or; 2) 60 mg daily; given orally with food without regard to the type of food	Randomized: 60 mg = 463 Placebo = 456 Completed: 60 mg =416 Placebo = 403	12 weeks Postmenopausal women 40 to 80 years of age with vaginal pH > 5, ≤ 5% superficial cells in vaginal smear, and self-reported MBS of VVA

*Adapted from Table 25 of the Medical Officer's review dated February 25, 2013.
** Only 76 sites randomized at least one subject into this trial
*** Only 112 sites randomized at least one subject into this trial

Comment: The population studied in these phase 3 trials was determined by the clinical and statistical review teams to be adequate and to represent the target population for the purposes of efficacy review.

Efficacy assessments in the two phase 3 trials:

The Division recommended the Applicant follow the 2003 draft guidance entitled, "Estrogen and Estrogen/Progestin Drug Products to Treat Vasomotor Symptoms and Vulvar and Vaginal Atrophy Symptoms — Recommendations for Clinical Evaluation", which outlines the following primary efficacy endpoints for two phase 3 trials seeking an indication of treatment of moderate to severe symptoms of vulvar and vaginal atrophy including:

1. Mean change from baseline to week 12 in the moderate to severe symptom that has been identified by the patient as most bothersome to her.
2. Mean change from baseline to week 12 in vaginal pH
3. Mean change from baseline to week 12 in vaginal maturation index (parabasal and superficial cells)

These efficacy endpoints were obtained using the following methodologies:

Most bothersome symptom to the patient (i.e. MBS): To obtain the most bothersome symptom, a 4-point scale (none [0], mild [1], moderate [2], or severe [3]) was used where each subject self-identified one of two moderate to severe symptoms as was most bothersome to her:

- Vaginal pain associated with sexual atrophy (dyspareunia)
- Vaginal dryness

Vaginal pH: The vaginal pH measurement was obtained by pressing a pH indicator strip against the middle third of the vaginal wall. The subjects entering the study were required to have a vaginal pH value greater than 5.0 at Screening. The subjects were advised not to have sexual intercourse and to refrain from using vaginal lubricant within 24 hours prior to the measurement.

Maturation Index: To obtain the Maturation Index, vaginal smear samples were taken from the middle third of the lateral vaginal wall to determine the proportion of superficial and parabasal cells in the vaginal epithelium. The vaginal smear samples were evaluated at the central pathology laboratory by a qualified pathologist and included the identification of any underlying infection or condition and its impact on the validity of the Maturation Index. The central pathologist performed the cell count for each sample. The subjects entering the study were required to have 5% or less superficial cells at screening.

Comment: During drug development, the Division discussed with the Applicant analyses of the symptom identified by patients as most bothersome, inclusion of only patients with either vaginal dryness or dyspareunia as their most bothersome symptom, and allowing the use of lubricant as needed. The key statistical analyses for primary efficacy endpoints in these phase 3 trials reflect these discussions.

The Applicant evaluated multiple secondary efficacy endpoints in the phase 3 trials including assessment of changes in physiologic status and other symptoms at weeks 4 and 12. The clinical team assessed these secondary endpoints, but concluded that only one of these endpoints was clinically relevant. This endpoint, "frequency of lubricant application" is discussed below in the section "Secondary efficacy endpoint considerations".

<u>Key inclusion – exclusion criteria for the phase 3 trials:</u>

Key entry criteria common to the two phase 3 trials:

- A woman 40 to 80 years of age at the time of Randomization.
- Postmenopausal defined as:
  - at least 12 months since the last spontaneous menstrual bleeding (if uncertain, confirmed with FSH level > 40 IU/L)
  - had a hysterectomy with ovaries intact and a FSH level of > 40 IU/L

- at least 6 weeks since bilateral oophorectomy with or without hysterectomy

➢ Had the following criteria for vulvar and vaginal atrophy (VVA): 5% or fewer superficial cells confirmed by maturation index in the vaginal smear, vaginal pH greater than 5.0, and moderate to severe vaginal dryness or dyspareunia as the self-reported most bothersome symptom (MBS).

Subjects with or without an intact uterus were eligible for enrollment.

Demographics and patient characteristics in the pivotal phase 3 trials:

In general, the study population in the ospemifene trials generally represented the intended population in the US. A brief summary of key demographics in these two trials is outlined in the Table below:

Table 2: Key demographics in the ITT cohorts obtained in the phase 3 trials*:

Category	Trial 15-50310		Trial 15-50821	
	Placebo	Ospemifene 60 mg	Placebo	Ospemifene 60 mg
	N=268	N=282	N=456	N=463
Age (Years)				
Mean (SD)	58.9 (6.0)	58.6 (6.3)	58.5(6.4)	58.7 (6.6)
Median	58.0	58.0	58.0	58.0
(Min, Max)	(43, 79)	(42, 80)	(41, 79)	(40, 78)
Body Mass Index (kg/m^2)				
Mean (SD)	26.1 (4.4)	26.0 (4.4)	26.2(4.3)	26.2 (4.3)
Median	25.3	25.4	25.9	25.7
(Min, Max)	(17.4, 38.0)	(15.7, 48.6)	(16.5, 38.7)	(16.7, 37.0)
Weight (kg)				
Mean (SD)	69.0 (12.9)	68.4 (12.1)	69.38(12.4)	68.98 (12.4)
Median	67.7	66.8	68.35	67.70
(Min, Max)	(43.1, 113.4)	(37.6, 106.6)	(29.6, 111.8)	(40.7, 108.1)
Race				
African-American	14 (5.2%)	18 (6.5%)	35 (7.7%)	28 (6.0%)
Asian	6 (2.2%)	4 (1.4%)	3 (0.7%)	8 (1.7%)
Caucasian	242 (90.3%)	249 (90.2%)	396 (86.8%)	409 (88.3%)
Hispanic	17 (6.0%)	24 (9.0%)	NA**	NA**
Other	4 (1.5%)	2 (0.7%)	22 (4.8%)	16 (3.5%)

*Adapted from Tables 3 and 4 of the Medical Officer's review dated February 8, 2013.
** NA – Demographic characteristic not recorded in Trial 15-50821

The Medical Officer concluded that demographics were similar between treatment groups within studies and also that, "….demographic characteristics in Study 15-50821 are similar to Phase 3 Study 15-50310." (See Medical Officer's review dated February 8, 2013)

Subject disposition in the two phase 3 trials:

For Trial 15-50301, a total of 826 eligible subjects were randomly assigned in a 1:1:1 ratio to receive placebo, ospemifene 30 mg, or ospemifene 60 mg orally daily for 12 weeks. Randomization was stratified by uterine status (intact or hysterectomized). The

proportion of subjects who discontinued treatment was similar across treatment groups, ranging from 14% to 20%. The primary reasons for discontinuation across all treatment groups were adverse event and consent withdrawal.

For Trial 15-50821, trial design was similar in some aspects to Trial 15-50310, but had some differences. In this trial, a total of 919 eligible subjects were randomly assigned in a 1:1 ratio to receive placebo or ospemifene 60 mg orally daily for 12 weeks. The proportion of patients that discontinued the trial was similar across the two treatment groups (11.6% and 10.2% for placebo and ospemifene 60 mg, respectively). The most frequently cited reason for discontinuation was adverse event.

Comments:

1. *In her review dated February 8, 2013, the Medical Officer concluded that the subject disposition for the individual phase 3 trial was acceptable, and determined that the rates and reasons for discontinuations were balanced across treatment groups and would not be expected to bias trial outcomes. I concur with the Medical Officer's conclusions.*
2. *The similarities between 15-50310 and 15-50821 included that the inclusion/exclusion criteria and co-primary efficacy endpoints were identical. The primary difference between the two trials was in the randomization of subjects with dyspareunia and vaginal dryness. Trial 15-50310 recruited postmenopausal women with any VVA symptomatology, although only those with dyspareunia and vaginal dryness were assessed in the mITT analyses. In Trial 15-50821, subjects were specifically recruited and randomized (1:1) to either the dyspareunia stratum or the dryness stratum.*

Efficacy results from the phase 3 trials:

The co-primary efficacy variables were:

- Change from baseline (Randomization) to Week 12 in most bothersome VVA symptom (hereafter referred to as the MBS) of vaginal dryness and vaginal pain associated with sexual activity (hereafter referred to as dyspareunia).
- Change from baseline (Screening) to Week 12 in the percentage of parabasal cells in maturation index of the vaginal smear.
- Change from baseline (Screening) to Week 12 in the percentage of superficial cells in maturation index of the vaginal smear.
- Change from baseline (Screening) to Week 12 in vaginal pH.

The primary analysis population was the ITT population, which included all randomized patients who received at least one dose of study drug (placebo or ospemifene 60 mg). In both phase 3 trials, as per the statistical analysis plan (SAP), changes in superficial cells, parabasal cells, and vaginal pH were to be analyzed using an ANCOVA model where change from baseline was the response variable, the baseline value was the covariate, and the treatment, uterine status and study center were the fixed effects. Per the application, the ANCOVA assumptions were severely violated in Trial 15-50310, thus a nonparametric approach (rank-based analysis of variance method) that had been pre-

specified was used, stratifying by study center and by uterine status separately. The change from Baseline to Week 12 in the severity of the MBS (dryness stratum or dyspareunia stratum) was analyzed using a CMH row mean scores test controlling for study center. As compared to Trial 15-50310, where subjects were enrolled and then subsequently analyzed by most bothersome symptom, Trial 15-50821, enrolled subjects into two efficacy strata (vaginal dryness or dyspareunia) and analyzed each stratum separately. Trial 15-50821 did not pre-specify that the two strata needed to enroll equivalent numbers of subjects. Analyses were conducted on the combined data for the 2 strata for all safety variables.

In addition, in both phase 3 trials, small centers were pooled by geographical location. The last-observation-carried-forward (LOCF) approach was used to handle missing values for the primary efficacy analyses. If the subject had no post-baseline assessments during treatment, baseline assessments were carried forward.

In a teleconference with the Applicant on June 27, 2012, DRUP repeated its previous advice to the Applicant that the determination of efficacy would be based on data from subjects who met all 3 inclusion criteria: ≤ 5% superficial cells on a vaginal smear, a vaginal pH > 5.0, and a most bothersome moderate to severe symptom (vaginal dryness or dyspareunia). The data submitted in the individual phase 3 trials were not from subjects who met all of the three recommended inclusion criteria.

Comment: Trials 15-50310 and 15-0821 included subjects who did not meet all of the inclusion criteria for vulvar and vaginal atrophy (VVA) outlined in the draft 2003 guidance. Therefore, the Division requested that the Applicant re-analyze both trials using an modified ITT (mITT) population, which was defined as including only subjects who, at baseline, met the inclusion criteria of ≤ 5% superficial cells on a vaginal smear, had a vaginal pH > 5.0, and at least 1 symptom of VVA (vaginal dryness or dyspareunia) that was designated as moderate or severe and most bothersome. The efficacy analyses for the phase 3 trials based on the mITT population were submitted on July 9, 2012, as an addendum to the NDA. The total number of subjects in the mITT population was slightly decreased as compared to the ITT population (approximately 1-7% lower), with most subjects removed due to unmet MBS criteria.

Each trial was analyzed separately for efficacy and results of the co-primary efficacy endpoints for the phase 3 trials are summarized below in Tables 3, 4 and 5.

For Trial 15-50310, the co-primary efficacy outcomes are summarized in Table 3:

Table 3: Mean Change from Baseline to Week 12/LOCF in Trial 15-50310; mITT Population*

	Ospemifene 60 mg	**Placebo**
Subjects who reported moderate to severe dyspareunia		
Dyspareunia - Mean Change from baseline (SD) - p-value for treatment comparison[a]	N = 110 -1.39 (0.11) 0.0012	N = 113 -0.89 (0.11) -
Vaginal pH _Mean Change from baseline (SD) -p-value for treatment comparison[b]	N=110 -0.97(0.09) <0.0001	N = 113 -0.002 (0.09) -
% Superficial Cells -Mean change from baseline (SD) -p-value for treatment comparison[b]	N = 110 10.88 (1.27) <0.0001	N = 113 2.73 (1.27) -
% Parabasal Cells - Mean change from baseline (SD) - p-value for treatment comparison[b]	N = 110 -34.44 (2.44) <0.0001	N = 113 5.84(2.44) -
Subjects who reported moderate to severe vaginal dryness		
Vaginal dryness - Mean Change from baseline (SD) - p-value for treatment comparison[a]	n = 113 -1.29 (0.09) 0.0136	n = 100 -0.92 (0.10) -
Vaginal pH _Mean Change from baseline (SD) -p-value for treatment comparison[b]	n =113 -0.92(0.09) <0.0001	n = 100 -0.16 (0.09) -
% Superficial Cells -Mean change from baseline (SD) -p-value for treatment comparison[b]	n = 113 11.16 (1.19) <0.0001	n = 100 2.33 (1.25) -
% Parabasal Cells - Mean change from baseline (SD) - p-value for treatment comparison[b]	n = 113 -26.65 (2.35) <0.0001	n = 100 0.12(2.47) -

*Adapted from Tables 5 and 10 of the Statistical review dated February 11, 2013. Based mITT population of subjects who met all three baseline inclusion criteria: ≤ 5% superficial cells on a vaginal smear, a vaginal pH greater than 5.0, and a most bothersome moderate to severe vaginal symptom (vaginal dryness or dyspareunia).

[a]p-value was computed using Cochran-Mantel-Haenszel row mean score test controlling for uterus status (intact or not) and center.

[b]p-value was computed using ANCOVA where change from baseline is response variable, Baseline assessment is the covariate, and treatment, uterus status (intact or not), and center are fixed effects.

Definitions: LOCF = last observation carried forward, mITT = modified intent-to-treat, SD = standard deviation.

As shown in Table 3, in Trial 15-50310, the 60 mg ospemifene dose demonstrates statistically significantly greater improvement over placebo from baseline to week 12 in the mITT population in the key clinical outcomes of:

- decrease in the severity of the MBS of dyspareunia ($p=0.0012$)
- decrease in the severity of the MBS of vaginal dryness ($p=0.0136$)

In addition, 60 mg ospemifene daily dose demonstrates a statistically improvement when compared to placebo in mean change from baseline to week 12 in the physiologic outcomes of:

- increase of number of superficial epithelial cells ($p<0.0001$)
- decrease in number of parabasal epithelial cells ($p<0.0001$)
- decrease in vaginal pH ($p<0.0001$)

For Trial 15-50821, the co-primary efficacy outcomes are summarized in Tables 4 and 5:

The Applicant stratified subjects in trial 15-50821 into two strata (dryness or dyspareunia) and analyzed each stratum separately for the purposes of efficacy claims. The outcomes of dryness stratum and dyspareunia stratum from Trial 15-50821 are outlined in the tables below:

Table 4: Mean Change from Baseline to Week 12/LOCF (Dryness Stratum) in Trial 15-50821; mITT Population*

	Ospemifene 60 mg	**Placebo**
Vaginal Dryness -Mean Change from baseline (SD) -p-value for treatment comparison[a]	n = 157 -1.3 (1.1) 0.0853	n = 150 -1.1 (1.0) -
% Superficial cells -Mean Change from baseline (SD) - p-value for treatment comparison[b]	n =157 12.5 (15.4) <0.0001	n = 150 3.5 (9.0) -
% Parabasal cells -Mean Change from baseline (SD) -p-value for treatment comparison[b]	n = 157 -31.7 (37.2) <0.0001	n =150 -3.9 (30.2) -
Vaginal pH -Mean Change from baseline (SD) -p-value for treatment comparison[b]	n = 157 -0.95 (0.07) <0.0001	n= 150 -0.25(0.07) -

*Adapted from Table 14 of the Medical Officer's review dated February 8, 2013 and Table 10 of the Statistical review dated February 11, 2013. Based on subjects who met all three baseline inclusion criteria: ≤ 5% superficial cells on a vaginal smear, a vaginal pH greater than 5.0, and a most bothersome moderate to severe vaginal symptom (vaginal dryness or dyspareunia).

[a]p-value was computed using Cochran-Mantel-Haenszel row mean score test controlling for center.

[b]p-value was computed using ANCOVA where change from baseline is response variable, Baseline assessment is the covariate, and treatment and center are fixed effects.

Definitions: LOCF = last observation carried forward, mITT = modified intent-to-treat, SD = standard deviation, SE = standard error.

For dryness stratum, Table 4 provides an overview of the analyses of change for physiologic parameters (vaginal cellular and pH changes) from baseline to Week 12/LOCF for the mITT population. These analyses show that ospemifene treatment conferred a statistically significant pharmacodynamic effect compared to placebo. However, analyses of change from baseline to Week 12/LOCF in the clinical endpoint of severity of vaginal dryness (Dryness Stratum) for the mITT population as outlined in Table 4 failed to show a statistically significant benefit for ospemifene over placebo (p=0.0853).

Table 5: Mean Change from Baseline to Week 12/LOCF (Dyspareunia Stratum) in Trial 15-50821: mITT Population*

	Ospemifene 60 mg	Placebo
Vaginal Dyspareunia -Mean Change from baseline (SD) -p-value for treatment comparison[a]	n = 301 -1.5 (1.009) <0.0001	n = 297 -1.2 (1.13) -
% Superficial cells- -Mean Change from baseline (SD) -p-value for treatment comparison[b]	n =301 12.4 (14.76) <0.0001	n = 297 1.7 (6.93) -
% Parabasal cells -Mean Change from baseline (SD) -p-value for treatment comparison[b]	n = 301 -40.4 (38.84) <0.0001	n =297 0.0 (30.25) -
Vaginal pH -Mean Change from baseline (SD) -p-value for treatment comparison[b]	n = 301 -0.95 (1.014) <0.0001	n = 297 -0.07 (0.809) -

*Adapted from Table 17 of the Medical Officer's review dated February 8, 2013. Based on subjects who met all three baseline inclusion criteria: ≤ 5% superficial cells on a vaginal smear, a vaginal pH greater than 5.0, and a most bothersome moderate to severe vaginal symptom (vaginal dryness or dyspareunia).

[a]p-value was computed using Cochran-Mantel-Haenszel row mean score test controlling for center.

[b]p-value was computed using ANCOVA where change from baseline is response variable, Baseline assessment is the covariate, and treatment and center are fixed effects.

Definitions: LOCF = last observation carried forward, mITT = modified intent-to-treat, SD = standard deviation, SE = standard error.

For the dyspareunia stratum, the table above provides an overview of the analyses of change for key physiologic parameters from baseline to Week 12/LOCF in the mITT population. These analyses show statistically significant pharmacodynamic changes when comparing ospemifene to placebo. These changes were considered positive responses from a statistical perspective (p<0.0001), but were not considered as directly clinically meaningful outcomes. Analyses of change from baseline to Week 12/LOCF in the severity of the MBS of dyspareunia (Dyspareunia Stratum) for the mITT population as outlined in the table above show that ospemifene treatment resulted in statistically significant improvement compared to placebo (p=<0.0001).

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 15-50310 and p=<0.0001 in Trial 15-50821).
- 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 15-50310 and p=0.0853 in Trial 15-50821). 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 increases in pharmacodynamic endpoints including: superficial cells, decreases in parabasal cells, and increases in vaginal pH.

Secondary efficacy endpoint consideration:

A non-hormonal lubricant was provided to all subjects in both phase 3 trials with instructions to use it as needed. The Agency provided recommendations to the Applicant regarding non-hormonal lubricant use that would demonstrate that ospemifene achieved efficacy above the non-hormonal lubricant alone, but did not intend that the Applicant would recommend concomitant use of ospemifene with a non-hormonal lubricant. In addition, lubricant use was captured differently in Trials 15-50310 and 15-0821 (daily versus weekly). After review, the Clinical team concluded that use of lubricant did not alter the efficacy of ospemifene 60 mg daily and the trials were not adequately designed to demonstrate superiority with concomitant use. Therefore, the Clinical Team did not recommend that any labeling claims related to lubricant use be allowed in labeling for ospemifene.

Comments:

1. *I concur with the Clinical review team that the 60 mg dose demonstrated efficacy for moderate to severe dyspareunia symptoms of VVA through Trials 15-50310 and 15-50821*
2. *Data from these trials related to non-hormonal lubricant use was not sufficient for the purposes of labeling claims.*

Statistical review of the primary efficacy results for the pivotal phase 3 trials:

The statistical review for this NDA was primarily based on the two phase 3 trials, 15-50310 and 15-50821. The statistical reviewer stated that there were no statistical issues identified in this submission. In a review dated February 12, 2013, the statistical reviewer stated that, "From a statistical perspective, data from the two submitted studies provided statistical evidence in support of ospemifene 60 mg in the treatment of moderate to severe VVA symptom of dyspareunia in post-menopausal women at 12 weeks."

Comment: I concur with the Statistical review team that the 60 mg dose demonstrated efficacy through Trials 15-50310 and 15-50821.

Third phase 3 trial (15-50718) submitted to support efficacy findings:
The clinical review team evaluated a third Phase 3 trial (15-50718) that evaluated the effect of ospemifene at the 60 mg dose in postmenopausal women with intact uteri in 426 subjects. The efficacy measurements in this trial were limited to vaginal pH and the percentage of superficial and parabasal cells on the Maturation Index. The Medical Officer concluded that, "Because Study 15-50718 did not assessed the change from Baseline to Week 12 in the individual self-identified most bothersome moderate to severe symptom of vulvar and vaginal atrophy, a third recommended co-primary endpoint for a VVA indication, the results for the proportion of superficial/parabasal cells in the Maturation Index, and vaginal pH in Study 15-50718 are not included in this reviewer's decision regarding the effectiveness of the 60 mg ospemifene dose to relieve moderate to severe vaginal dryness or dyspareunia." (See Medical Officer review dated February 8, 2013).

Comments: Findings from the pharmacodynamic evaluations (changes in superficial and parabasal cells and vaginal pH) of Trial 50718 were incorporated into labeling where appropriate. I concur with the Medical Officer's conclusion that Trial 15-50718 can not be included in labeling for efficacy purposes because of the lack of pre-identification for the clinically meaningful endpoint of self-reported most bothersome symptom of VVA.

Efficacy summary:

The main objective of the Applicant's NDA submission was to demonstrate that Osphena ospemifene) was effective in the treatment of moderate to severe vaginal dryness and moderate to severe dyspareunia, symptoms of vulvar and vaginal atrophy, due to menopause. The Medical Officer summarized her findings of the efficacy outcomes in her February 8, 2013, review as follows, "The data presented in the application for 2 double-blind, placebo controlled 12-week clinical trials support the approval of ospemifene 60 mg, taken orally daily, for the treatment of moderate to severe dyspareunia, a symptom of vulvar and vaginal trophy, due to menopause (mITT analysis: $p=0.0012$ in Trial 15-50310 and $p<0.0001$ in Trial 15-50821).

The data presented in the application do not consistently support the approval of ospemifene 60 mg, taken orally daily, for the treatment of moderate to severe vaginal dryness, a symptom of vulvar and vaginal atrophy, due to menopause (mITT analysis: $p=0.0136$ in Trial 15-50310 and $p=0.0853$ in Trial 15-50821). Therefore, approval of moderate to severe vaginal dryness, a symptom of vulvar and vaginal atrophy, due to menopause is not recommended."

In her review dated, February 25, 2013, the CDTL further concluded that, "Confirmatory evidence for efficacy in both Study 15-50310 and Study 15-50821 was obtained only for the 60 mg dose of ospemifene for the indication of treatment of moderate to severe dyspareunia, a symptom of vulvar and vaginal atrophy, due to menopause. Confirmatory evidence was not obtained for the efficacy of any dose of ospemifene for the indication of treatment of moderate to severe vaginal dryness."

I agree with the clinical reviewer and CDTL that substantial evidence of effectiveness of ospemifene has been demonstrated for treatment of moderate to severe dyspareunia, but not for moderate to severe vaginal dryness, due to menopause. Therefore, I concur with the recommendations of the clinical review team, statistical review team and Cross-Discipline Team Leader that there are no outstanding efficacy concerns for this new estrogen agonist/antagonist product.

8. Safety

The data supporting the safety of ospemifene for the treatment of vulvar and vaginal atrophy come from 30 phase 1, 2 and 3 clinical trials contained in this NDA submission. The Applicant provided several safety cohorts for evaluation and an integrated safety

summary (ISS) containing all safety data obtained from all doses of ospemifene evaluated during the clinical development program ranging from 10 mg to 800 mg.

The clinical review team focused their analysis of safety on several cohorts including: 1) the Integrated Safety Summary (ISS) that included data from all subjects who received at least one dose of ospemifene, 2) the cohort from the nine phase 2 and 3 trials, 3) the cohort from the safety extension trials that included two controlled trials (15-50718 and extension trial 15-50310X) and one uncontrolled extension trial (15-50312), 4) the subjects in selected phase 1 studies including those in the thorough QT study (15-50824) and five drug-drug interaction studies (Studies 15-50823 [fluconazole and omeprazole] and 15-50716 [ketoconazole and rifampin]). An additional safety analysis was also conducted by the Office of Clinical Pharmacology, Genomics Group to assess whether "1) the risk estimation for venous thrombotic event (VTE) was biased due to exclusion of factor V Leiden (FVL) carriers in Phase 2 and 3 trials and 2) whether screening for FVL was indicated in patients who are eligible for ospemifene therapy".

The primary safety database consisted of a total of 2654 subjects who were exposed to at least one dose of study medication (ospemifene or placebo) in seven double-blind, placebo-controlled phase 2 and 3 trials (referred to hereafter as the "double-blind, phase 2/3 population"). The median exposure to ospemifene was 85 days with a minimum/maximum exposure time to ospemifene (all dose groups) of 1/395 days, respectively. Of these subjects:

- A total of 1242 received the proposed ospemifene dose of 60 mg
- Of 1242 subjects receiving the 60 mg ospemifene dose, 384 subjects had ≥ 24 weeks of exposure, 353 subjects had ≥ 48 weeks of exposure and 191 had ≥ 52 weeks of exposure

Other cohorts that were evaluated by the clinical reviewers to assess the safety of ospemifene were defined as follows:

1. The Integrated Summary of Safety population, which consisted of 2741 study participants in 30 phase 1, 2, and 3 clinical trials who received at least one dose of ospemifene. This population included 1583 subjects with symptoms of vulvar and vaginal atrophy as well as 309 subjects with other postmenopausal symptoms who were treated with ospemifene.
2. The entire Phase 2/3 population (referred to as the "All Phase 2/3 study cohort" which consisted of 2 additional phase 2/3 studies for a total of nine trials. In this cohort, a total of 1892 subjects received at least one dose of ospemifene, of which 409 had ≥ 52 weeks (1 year) of exposure.
3. The long-term controlled population – consisted of all subjects who enrolled in long-term safety trial 15-50718 and safety extension trial 15-50310X. Both of these studies evaluated safety and tolerability in postmenopausal women with symptoms of vulvar and vaginal atrophy in women receiving treatment for 1 year.

Comment: As previously stated, the clinical review was primarily obtained from subjects enrolled in the seven controlled Phase 2 and 3 trials and also on those subjects enrolled

and treated in the long-term extension trials (Trial 15-50718 and 15-50310X). The clinical review team focused their safety review on subjects who received ospemifene 60 mg dose as proposed for the intended population. Other safety databases, such as the Integrated Safety Summary (ISS) population and the "All Phase 2/3 study cohort" were also reviewed to provide additional safety information as needed by the review team.

Primary safety cohort (double-blind phase 2/3 population):
The primary safety analysis focused on data from the 1696 subjects in the seven double-blind, placebo-controlled trials who received ospemifene or placebo in the controlled phase 2 and 3 trials. Of these subjects, 958 received placebo, 33 received 5 mg ospemifene, 29 received 15 mg ospemifene, 352 received 30 mg ospemifene, 1242 received the proposed 60 mg ospemifene and 40 received 90 mg ospemifene. An overview of trials obtained from this phase 2/3 safety population are outlined in the table below:

Table 6: Overview of double-blind phase 2/3 population*:

Trial ID - Number of Sites - Number Enrolled	Trial Design	Route and Regimen	Indication	Number of Subjects (Randomized/ Completed)	Treatment Duration Main Criteria for Inclusion
1506002 - 2 - 159	Randomized, multicenter, double-blind, parallel-group, placebo-controlled. Phase 2	Oral capsules 30 mg 60 mg 90 mg Placebo	Effects on bone, vascular endothelium, lipid metabolism and endometrium	Randomized: 30 mg = 40 60 mg = 40 90 mg = 40 Placebo = 40 Completed: 30 mg = 39 60 mg = 36 90 mg = 37 Placebo = 37	12 weeks Postmenopausal women 45 to 65 years of age with an intact uterus
15-50615 - 11 - 198	Randomized, multicenter, double-blind, parallel-group, placebo-controlled. Phase 2	Oral tablets 60 mg Placebo	Vasomotor symptoms	Randomized: 60 mg =100 Placebo = 98 Completed: 60 mg = 93 Placebo =92	6 weeks Postmenopausal women 40 to 70 years of age with ≥ 7 moderate, severe or very severe hot flashes per day or 50 per week
15-50717 - 9 - 126	Randomized, multicenter, double-blind, parallel-group, placebo-controlled. Phase 2	Oral Tablets 5 mg 15 mg 30 mg Placebo	VVA	Randomized: 5 mg = 33 15 mg = 29 30 mg = 30 Placebo = 34 Completed: 5 mg = 29 15 mg = 28 30 mg = 27 Placebo = 33	12 weeks Postmenopausal women 40 to 80 years of age with vaginal pH >5.0 and ≤ 5% superficial cells in vaginal smear

15-50310 - 83[a] - 826	Randomized, multicenter, double-blind, parallel-group, placebo-controlled. Phase 3	Oral Tablet 30 mg 60 mg Placebo	VVA	Randomized: 30 mg = 282 60 mg = 276 Placebo = 268 Completed: 30 mg = 225 60 mg =234 Placebo = 230	12 weeks Postmenopausal women 40 to 80 years of age with vaginal pH >5.0, ≤ 5% superficial cells in vaginal smear, and self-reported MBS of VVA
15-50310X - 51 - 180	Randomized, multicenter, double-blind, parallel-group, placebo-controlled, long-term safety extension of Trial 15-50310, women with an intact uterus Phase 3	Oral Tablet 30 mg 60 mg Placebo	VVA	Randomized: 30 mg = 62 60 mg = 60 Placebo = 49 Completed: 30 mg = 44 60 mg =51 Placebo = 31	40 weeks Subjects with an intact uterus that completed Trial 15-50310 without clinically significant abnormal findings
15-50821 - 119[b] - 919	Randomized, multicenter, double-blind, parallel-group, placebo-controlled, stratified. Phase 3	Oral Tablet 60 mg Placebo	Moderate to severe vaginal dryness and pain associated with sexual activity, symptoms of VVA associated with menopause	Randomized: 60 mg = 463 Placebo = 456 Completed: 60 mg =416 Placebo = 403	12 weeks Postmenopausal women 40 to 80 years of age with vaginal pH > 5, ≤ 5% superficial cells in vaginal smear, and self-reported MBS of VVA
15-50718 - 23 - 426	Randomized, multicenter, double-blind, parallel-group, placebo-controlled. Phase 3	Oral Tablet 60 mg Placebo	VVA	Randomized: 60 mg = 363 Placebo = 63 Completed: 60 mg = 294 Placebo = 55	52 weeks Postmenopausal women 40 to 80 years of age with an intact uterus with vaginal pH > 5 and ≤ 5% superficial cells in vaginal smear

Adapted from Table 25 of the Medical Officer's review dated February 8, 2013.
a Only 76 sites randomized at least 1 subject into the trial.
b Only 112 sites randomized at least 1 subject into the trial.
Definitions: VVA = vulvar and vaginal atrophy.

Long-term trials (15-50718, 15-50310X, and 15-50312):
Two (2) of the 7 double-blind, placebo-controlled trials had durations longer than 12-weeks. Trial 15-50310X was a 40-week extension of 12-week parent Trial 15-50310. In Trial 15-50310X, the mean duration of exposure (not including the 12-week exposure in parent phase 3 trial 15-50310) is as follows:

- 30 mg ospemifene group = 266.0 ± 98.01 days
- 60 mg ospemifene group = 253.6 ± 69.81 days
- Placebo group = 232.4 ± 92.99

Trial 15-50718 was a 52-week long-term trial with a mean duration of exposure of:

- 60 mg ospemifene group = 321.5 ± 97.06 days
- Placebo group = 339.3 ± 74.88 days

One additional 52-week long-term safety extension study (Study 15-50312) is included in the application. Study 15-50312 entitled, "Long term Safety of Ospemifene 60 mg Oral Daily Dose for the Treatment of Vulvar and Vaginal Atrophy (VVA) in Postmenopausal Women without a Uterus: A 52-Week Open-Label Follow-up to Protocol 15-50310" enrolled 301 subjects who did not have a uterus and who completed 12-week parent Trial 15-50310 to receive a once-daily dose of 60 mg ospemifene. The mean duration of exposure (not including the 12-week exposure in parent Trial 15-50310) in Study 15-50312 was 309.2 days.

The Medical Officer reviewed the total population exposure data (See Medical Officer's review dated February 8, 2013) and did not identify any issues regarding the adequacy of the safety database for the proposed 60 mg dose.

Comment: I concur with the Medical Officer that the safety database was adequate to characterize the safety profile of ospemifene for the proposed 60 mg dose.

Deaths, Serious Adverse Events and Discontinuations due to Adverse Events:

Deaths: No deaths occurred during the ospemifene development program.

Non-fatal Serious Adverse Events (SAE):

In the double-blind phase 2/3 population, SAEs were reported by 56 subjects: 39/1696 subjects (2.3%) in the ospemifene group, 7/352 (2.0%) in ospemifene 30 mg/day, 32/1242 (2.6%) in ospemifene 60 mg/day and 17/958 subjects (1.8%) in the placebo group. A similar percentage of SAEs occurred at the 30 mg and 60 mg ospemifene dosage strengths (2.0%, 7 of 352 subjects at the 30 mg ospemifene dose and 2.6%, 32 of 1242 subjects at the 60 mg dose). Overall, few SAEs were reported in more than one ospemifene-treated subject and included: appendicitis (2 subjects compared to none in the placebo treated group), cerebrovascular accident (CVA, 2 subjects in the 60 mg ospemifene group; 1 subject with a thalamic hemorrhage and 1 subject with the term CVA compared to 1 subject in the placebo treated group), diverticulitis (2 subjects compared to 1 subject in the placebo treated group), and deep vein thrombosis (DVT, 2 subjects compared to no subjects in the placebo treated group). All other SAEs in ospemifene-treated subjects occurred in 1 subject only (incidence 0.1%).

Discontinuations for adverse events:

A total of 155 subjects experienced an adverse event that led to discontinuation from the double-blind, Phase 2/3, placebo-controlled trials: 121/1696 subjects (7.1%) in all ospemifene treatment groups and 35/958 subjects (3.7%) in the placebo group; the percentage of subjects that discontinued due to adverse events was slightly higher in the

all ospemifene group compared with the placebo group. There was no dose-related increase in adverse events that led to discontinuation; the incidences were 6.5, 6.0, 7.6, 2.5, and 7.1% for the ospemifene ≤15 mg/day, 30 mg/day, 60 mg/day, and 90 mg/day groups, respectively. The most common adverse events leading to discontinuation in the ospemifene groups in these studies included hot flushes, headaches and nausea.

Comments:

1. *The Medical Officer reviewed narratives of non-fatal serious adverse events and stated in her February, 2013, review that, "Overall, the incidence of SAEs is low (2.7%) across all Phase 2/3 studies. This reported incidence of all SAEs does not raise safety concerns for 60 mg ospemifene." I concur with her assessment.*
2. *The Medical Officer also evaluated the discontinuations for adverse events. She noted that the largest percentage of discontinuations occurred in the 30 mg group, and the majority of subjects across the dose groups withdrew because of adverse events. In her February 2013 review she concluded that the discontinuations for adverse events did not raise new safety concerns for use of the proposed 60 mg ospemifene dose.*

Treatment Emergent Adverse Events (TEAEs)

In the double-blind phase 2/3 population, a clear difference was noted between the occurrence of hot flashes between ospemifene treated and placebo treated subjects. In addition, there were also differences noted in the occurrence of vaginal discharge and hyperhydrosis (excessive sweating) in ospemifene treated subjects as compared to placebo treated subjects. An overview of the rates of adverse events seen in the double-blind phase 2/3 trials in the ospemifene and placebo treated groups is outlined in the table below:

Table 7: Summary of number (%) of subjects with TEAEs in ≥1% in the double-blind phase 2/3 population*

Preferred Term	Placebo N=958	Number (%) of Subjects Ospemifene-Treated				
		≤ 15 mg N=62	30 mg n-352	60 mg N=1242	90 mg N=40	All N=1696
Any Treatment-Related AE	157 (16.4)	19 (30.6)	111 (31.5)	378 (30.4)	8 (20.0)	516 (30.4)
- Hot flush	25 (2.6)	6 (9.7)	28 (8.0)	93 (7.5)	1 (2.5)	128 (7.5)
- Vaginal discharge	3 (0.3)	2 (3.2)	13 (3.7)	47 (3.8)	0	62 (3.7)
- Headache	23 (2.4)	4 (6.5)	15 (4.3)	30 (2.4)	4 (10.0)	53 (3.1)
- Muscle spasms	9 (0.9)	0	7 (2.0)	40 (3.2)	0	47 (2.8)
- Genital discharge	1 (0.1)	2 (3.2)	9 (2.6)	16 (1.3)	2 (5.0)	29 (1.7)
- Hyperhidrosis	6 (0.6)	0	4 (1.1)	20 (1.6)	2 (5.0)	26 (1.5)
- Weight increased	5 (0.5)	0	7 (2.0)	11 (0.9)	0	18 (1.1)

*Adapted from Table 43 of the Medical Officer's review dated February 8, 2013.

Comment: After review of the adverse event data from double-blind, phase 2/3 population, the Medical Officer concluded that, "These reported treatment-related AEs do not raise safety concerns for 60 mg ospemifene tablets." I agree with the Medical Officer's assessment that the majority of adverse events related to ospemifene were only modestly increased as compared to placebo users and that there was no clear dose

relationship from the reported adverse events. In addition, the reproductive-system related AEs reported in these trials were expected based on the mechanism of action of ospemifene on vaginal epithelium. Therefore, the rates of these TEAEs provided further support that the safety profile for ospemifene was acceptable.

Vital Sign and Laboratory Findings

The Medical Officer performed a focused evaluation of laboratory parameters that were previously identified as potential safety signals based on data from other estrogen agonist/antagonist products. This safety evaluation included evaluation of mean changes in vital signs, lipid and coagulation parameters. In her February 8, 2013, review, the Medical Officer stated that he did not identify any trends of concern related to either vital sign changes (including systolic and diastolic blood pressure measurements as well as mean increase in weight at 12 months) or coagulation values. Two specific laboratory parameters that required additional review included:

- QT issues: A dedicated TQT study [Study 15-50824] showed that, according to ICH E14 (2005) criteria, ospemifene did not cause individually corrected QT interval (QTcI) prolongation at the proposed therapeutic dose of 60 mg nor at the supratherapeutic dose of 240 mg, a dose which increased Cmax and AUCtau by approximately 2.9 fold the C_{max} relative to the proposed therapeutic dose of 60 mg. At both doses, the upper bound of the 1-sided 95% CI of corrected QT interval (QTc) interval did not exceed 10 msec, which is the threshold for regulatory concern described in ICH E14 guidelines.

  Both the Medical Officer and the Interdisciplinary Review Team for QT Studies Consultation reviewed the results of the thorough QT study (TQT). The QT review team concluded in their review dated January 15, 2013, that, "No significant QTc prolongation effect of ospemifene was detected in this TQT study." The Medical Officer concurred with the QT review team's assessment.

- Assessment of exclusion of Factor V Leiden carriers: .

  The Applicant screened subjects in all phase 2/3 trials for Factor V Leiden (FVL) at baseline and excluded any subject that was positive. The OCP Genomic Group reviewer was asked to assess whether: "1) the risk estimation for venous thrombotic event (VTE) was biased due to exclusion of FVL carriers in Phase 2 and Phase 3 trials and 2) whether screening for FVL is indicated for patients who are eligible for ospemifene therapy."

  The OCP Genomics Group reviewer provided a risk estimate for the VTE incidence for ospemifene from the data obtained from the Applicant's clinical trials of approximately 2.12 VTEs/1000 patient years. He stated that this incidence of VTEs observed in the ospemifene trials is within the range of what has been observed with other estrogen agonists/antagonist products used for other indications.

In the January 12, 2013, Clinical Pharmacology Review, the OCP Genomic Group reviewer concluded the following:

> "…Based on the estimated prevalence of FVL and considering the increased risk associated with FVL, few/no additional VTE cases would have been observed if FVL carriers were included in Phase 2/3 trials. Therefore, current risk estimates are reasonable. Additionally, screening for FVL in patients being considered for ospemifene is not recommended given estimates that more than 1000 patients would need to be screened in order to prevent a single VTE."

The Medical Officer reviewed the OCP Genomic's group consult and conclusions and concurred that the risk estimates of venous thrombosis for ospemifene therapy were reasonable and that there was no reason to perform routine screening for FVL in patients who will receive ospemifene.

Comment: I concur with the conclusions of the QT review team, OCP Genomic Group and the clinical review team that there are no outstanding issues related to QT, vital signs or other laboratory parameters that were evaluated in the ospemifene drug development program.

Other Significant Safety Issues Identified:

The clinical review team identified specific safety issues during drug development and also during the review of the submission. Their safety review included assessment of endometrial and uterine safety, venous and arterial thrombotic events, breast adverse events, and data on other reproductive adverse events including vaginal bleeding/spotting and pelvic organ prolapse. These issues were discussed with the Applicant and these were addressed through labeling and included:

1. Endometrial and uterine safety:

As previously discussed, the clinical review team had concerns related to the endometrial and uterine safety of ospemifene as these reproductive adverse events were reported with use of other estrogen agonist/antagonist products. All subjects with an intact uterus received evaluation of their endometrial lining and uterus as part of routine monitoring through baseline and end-of-study transvaginal ultrasound (TVU) measurements and endometrial biopsy. Evaluation of endometrial biopsies was performed using standard criteria (Blaustein's) as outlined in the 2003 draft guidance, although the assessments were not performed as recommended in the guidance (i.e. the Applicant did not have three independent expert pathologists review each endometrial biopsy slide). Endometrial biopsies were performed as part of routine monitoring or could be performed "for cause" if vaginal bleeding and/or spotting occurred.

The clinical review team assessed the transvaginal ultrasound (TVU) measurements, endometrial histology, and adverse events that were obtained during the phase 2/3 trials.

For all women with an intact uterus, TVU measurements and endometrial biopsies were performed. For the double-blind phase 2/3 trials:

- Endometrial thickness via TVU: A thickness ≥ 4mm at any time post-baseline was reported in 16.6% of the ospemifene 60 mg group as compared to 5.1% of the placebo group. In the double-blind, phase 2/3 trials, there was a slight increase in mean endometrial thickness over time in all ospemifene treated groups as compared to little to no increase in endometrial thickness in the placebo treated group.
- Endometrial biopsies: No reports of hyperplasia or carcinoma were reported in ospemifene or placebo treated subjects at 12 months. One subject in the 60 mg ospemifene treated group had an endometrial biopsy with simple hyperplasia without atypia; however, this biopsy occurred 3 months after the last dose of ospemifene.
- Uterine polyps: The Medical Officer identified a total of 13 reports of "uterine polyps" (11 subjects who received ospemifene and 2 subjects who received placebo treatment) who were reported to have a possible uterine polyp. For the 60 mg treated group 10/881 subjects (1.1%) had a report of a polyp as compared to 2/570 (0.35%) in the placebo treated group.

After review, the Medical Officer noted that the transvaginal ultrasound measurements and histologic findings were, in the majority of ospemifene treated subjects, consistent with findings in a postmenopausal population. Regarding the reports of uterine polyps, she stated in her February 2013, review that, "Overall, the incidence of uterine polyps in the ospemifene development program is low and does not raise concerns for the 60 mg ospemifene tablet. The occurrence of polyps supports, however, the estrogenic agonistic effect of 60 mg ospemifene on the uterus."

In her review dated February 25, 2013, regarding the histology findings, the CDTL stated that, "Overall, the endometrial histology findings, particularly with respect to the percentage of proliferative type endometrium and endometrial hyperplasia is not unlike the findings seen in the evaluation of very low dose estrogen products. The endometrial histology findings along with the transvaginal ultrasound findings with respect to endometrial thickness for ospemifene are consistent with a stimulatory or estrogen agonistic effect on the endometrium."

Comments:

1. *From a clinical perspective, I believe that the Applicant's evaluation of endometrial and uterine safety for ospemifene was acceptable for the purposes of review, although the reading of the histology slides was not performed as outlined in the 2003 draft guidance.*

2. *The safety data indicate that ospemifene has a potential stimulatory effect on the endometrium as evidenced by the increase in endometrial thickness measurements and increase in reports of uterine polyps in treated subjects. Therefore, I support the Medical Officer and CDTL's recommendation that labeling for ospemifene reflect the available data on endometrial safety and also include a warning that women with endometrial cancer not use ospemifene.*

2. Venous and arterial thrombotic events:

Safety information from other estrogen agonist/antagonists in the same pharmacologic class has raised concerns about an increased risk of thrombotic events. In the ospemifene trials, adverse events for all cerebral and cardiovascular adverse events were evaluated and did not appear to exceed background rates in the general population.

Thrombotic reports included:

- One subject in the Phase 1 trials who was treated with ospemifene had a thrombotic event (transient cerebral ischemic event). This subject was discontinued from the trial and had known previous risk factors for cerebral thrombosis.
- Seven subjects (7/1892 [0.4%] in the phase 2/3 population who were treated with ospemifene had a thrombotic event. Of these 7 CV-related events, 1 occurred in the 30 mg ospemifene treatment group (0.3%, 1 of 381 subjects treated with 30 mg of ospemifene in all Phase 2/3 studies), 1 occurred in the placebo treatment group (0.1%, 1 in 958 placebo-treated subjects in all Phase 2/3 studies), and 5 occurred in the 60 mg ospemifene treatment group (0.4%, 5 of 1379 subjects treated with 60 mg ospemifene in all Phase 2/3 studies). The events included cerebrovascular accidents (2 subjects), deep vein thrombosis (2 subjects), acute myocardial infarction (1 subject), cerebral hemorrhage (1 subject) and hemorrhagic stroke (1 subject).

As previously stated, the OCP Genomics group and the Medical Officer evaluated the risk of thrombotic events. Both the OCP Genomics group and Medical Officer concluded that the incidence rates for thrombotic stroke is approximately 1.06 per 1000 ospemifene treated subjects and for hemorrhagic strokes it is approximately 1.45 per 1000 ospemifene treated women. Neither the OCP Genomics group nor the Medical Officer determined that these rates represented a thrombotic risk above background rates for ospemifene users. In her February 2013, review, the Medical Officer concluded that, "The occurrence of these reported cardiovascular/cerebrovascular/thrombotic events, at the incidence rates calculated, do not raise any overall safety concerns for the 60 mg ospemifene dose. This reviewer recommends that the incidence rates for these reported cardiovascular/cerebrovascular/ thrombotic events, either the rate for all ospemifene treated subjects in all Phase 2/3 studies or the incidence rate only for

the 60 mg ospemifene dose or both incidence rates, be included in a Boxed Warning in the ospemifene labeling and under Section 5 Warnings and Precautions, Subsection 5.1 Cardiovascular Disorders. The intent is to advise healthcare providers of the increased risk of DVT with estrogen containing drug products, and to inform them of the rates obtained in the clinical trials with ospemifene, an estrogen agonist/antagonist."

Comment: I concur with the Medical Officer and CDTL's recommendations that labeling reflect the available data on this signal of thrombosis. I also agree that these data suggest that the risk of thrombosis with ospemifene will be similar to other estrogen agonist/antagonist products, and therefore, no further trials or data are necessary.

3. Breast adverse events:

Because of the potential negative impact of estrogen agonist/antagonist products on breast tissue, the Medical Officer evaluated all serious breast-related adverse events that were reported in the double-blind phase 2/3 population. In this population, 63 of a total of 2297 subjects (0.3%) reported a breast-related adverse event. Of the breast-related events of interest, one event of breast cancer (1 metastatic breast cancer) was identified in ospemifene treatment groups and 2 events (both in situ breast cancers) were reported in subjects receiving placebo treatment.

In her Medical Officer review dated February 8, 2013, the Medical Officer concluded that, "No breast cancers were reported in the 60 mg ospemifene treatment group. The single reported case of metastatic breast cancer of unknown primary location (MRI of breast showed no primary cancer) in the 30 mg ospemifene group does not raise safety concerns. Further, there were 2 cases of breast cancer in placebo-treated subjects."

Comment: I concur that the events of breast adverse cancer were rare and similar to those reported in placebo treated subjects I believe that these data do not indicate a new safety trend or signal for these estrogen agonist/antagonist products and agree that no further trials or data are necessary for ospemifene.

4. Other reproductive adverse events:

As previously stated, because of the concerns of estrogen-agonism with ospemifene use, other reproductive adverse events were also evaluated by the Applicant and the review team. These adverse events of interest included:

- Vaginal bleeding/spotting: In the double-blind, phase 2/3 population, a total of 22 subjects with an intact uterus reported vaginal bleeding and/or spotting (17 ospemifene-treated subjects [1.5%] and 5 placebo-treated subjects [0.9%]). Ten (10) of the 17 ospemifene-treated subjects were

treated with 60 mg ospemifene (1.2%, 10 of 851 subjects with an intact uterus). None of the vaginal bleeding and/or spotting adverse events led to discontinuations.

- Urinary symptoms/infections: In the double-blind, phase 2/3 population, a total of 221 subjects reported a UTI-related TEAE (161 ospemifene-treated subjects [9.5%) and 60 placebo-treated subjects [6.3%]). The most common UTI-related TEAE (greater than 1%) in both the ospemifene and placebo groups were urinary tract infection (6.4% versus 4.8%, respectively), cystitis (1.5% versus 0.6%, respectively), and bacterial UTI (1.0% versus 0.6%, respectively). In the all Phase 2/3 studies, 23 additional subjects reported UTIs and 1 additional subject reported cystitis. Overall, only 1 subject discontinued with a UTI-related TEAE in all Phase 2/3 studies.
- Pelvic organ prolapse: In all phase 2/3 studies: 3 ospemifene treated subjects and 1 placebo treated subject experienced a pelvic organ prolapse.

In her Medical Officer review dated February 8, 2013, she stated that, "The application only includes narratives for women with a uterus who reported vaginal bleeding/spotting. Therefore, limited information is available for women without an intact uterus who reported vaginal bleeding/spotting. No safety concerns result for the information presented, however, regarding vaginal bleeding and/or spotting for 60 mg ospemifene." In addition, her review did not identify any safety issues of concern regarding urinary symptoms or pelvic organ prolapse with use of ospemifene.

Comment: The types and nature of the reproductive adverse events above do not indicate a new safety signal for ospemifene, although these reported events will be included in labeling.

5. Postmarketing data summary:

Ospemifene has not been approved in any country and, therefore, postmarketing data are not available for review.

Safety summary:

The safety database for ospemifene tablets was determined by the Clinical review team to be sufficient and supports approval for the treatment of moderate to severe dyspareunia, a symptom of vaginal and vulvar atrophy, due to menopause. The clinical review team, the Applicant and CDER consultants have analyzed adverse events through evaluations of the entire clinical trial database, database from the primary phase 3 trials and the extension trials database. The relevant safety issues identified have been sufficiently addressed in labeling, including the risk of arterial and venous thrombotic events and the risks of endometrial and other reproductive adverse events.

In summary, the Medical Officer concluded the following on the safety of ospemifene in her review dated February 8, 2013: "The safety of 60 mg ospemifene tablets, taken orally daily, is not a concern. The review of the original safety data in the application, the Safety Update Report received on August 24, 2012, and the additional safety data received on November 2, 2012 did not demonstrate any overall safety concerns for 60 mg ospemifene."

The Cross-Discipline Team Leader (CDTL) concurred with the primary Medical Officer's assessment of the safety issues identified with Osphena in her CDTL review (dated February 25, 2013).

I concur with the recommendations of the primary Medical Officer and CDTL that there are no remaining safety concerns that preclude approval of this NDA.

9. Advisory Committee Meeting

The first estrogen agonist/antagonist, Nolvadex (tamoxifen citrate) was initially approved in 1977 for treatment of breast cancer in women. Since then, other estrogen agonist/antagonists have been approved in the US and are used in current clinical practice. Safety issues associated with these estrogen agonist/antagonist products are known and can be adequately labeled. In addition, no new safety concerns were identified for ospemifene. Therefore, no Advisory Committee was convened.

10. Pediatrics

The Applicant requested a full waiver of pediatric studies in patients from birth through 18 years as the condition only occurs in adults. The Division concurred with the Applicant's request, and the Pediatric Review Committee (PeRC) granted the full waiver.

11. Other Relevant Regulatory Issues

Division of Medical Policy Programs (DMPP):

DMPP reviewed the Patient Package Insert (PPI) on February 14, 2013, and found it to be acceptable with several recommended changes. The Division discussed several of the recommendations with DMPP, and after editing, the agreed to recommendations were implemented. The revised PPI submitted by the Applicant was reviewed by DMPP and determined to be acceptable on February 23, 2013.

Office of Prescription Drug Promotion (OPDP):

OPDP reviewed the Prescribing Information and the Patient Package Insert. OPDP completed their review of the PPI on February 19, 2013 and of the PI on February 22, 2013. The Division discussed several of the recommendations with OPDP, and after editing, the agreed to recommendations were implemented.

Office of Scientific Investigations (OSI):

OSI conducted inspections of three clinical sites (Drs. Raikhel, Mabey, and Younglove) and the Applicant (Shionogi USA, Inc) in support of this NDA. After these inspections were conducted and assessed by OSI, the Clinical Inspection Summary stated that, "The clinical investigator sites of Drs. Raikehl, Mabey, and Younglove were inspected in support of this NDA. Drs. Raikhel and Younglove were not issued Form FDA 483s. Dr. Mabey was issued a Form FDA 483 (as a result of failure to meet study inclusion criteria for moderate to severe VVA symptoms). The review division may wish to exclude the data from Subject 026 at Dr. Mabey's site for the reason noted above." (See OSI Clinical Inspection Summary dated December 18, 2012 and VAI letter to Dr. Mabey and OSI Summary finalized on February 21, 2013).

The clinical reviewer considered the issue regarding subject 026 and determined that, "This reviewer does not recommend exclusion of the data for Subject 026 in Study 15-50821. VVA effectiveness is evaluated by mean change from baseline in the self-reported MBS. A review of the efficacy data reported for Subject 026 does not raise any concerns." (See Medical Officer's review dated February 8, 2013)

OSI also completed an inspection of Shionigi USA, Inc. and noted in their Clinical Inspection Summary dated December, 2012, that, "The sponsor was issued a Form FDA 483 for failure to document the disposition of returned or unused IP. Other than the deviations noted, the data generated by these clinical sites and submitted by the sponsor appear adequate in support of the respective indication."

The Applicant responded in writing to the 483 in a letter dated November 13, 2012. Per the Applicant, "the previous sponsor did not obtain a written statement regarding the disposition of IP from the responsible CRO." Updated SOPs have been submitted by the Applicant that "should address the need for written documentation of IP disposition for future studies." "Other than the deficiency regarding documentation of the disposition of IP as noted above, the studies appear to have been conducted adequately, and the data submitted by the sponsor appear acceptable in support of the respective indication. The observations noted above for Shionogi are pending a final review of the Establishment Inspection Report (EIR) and sign-off on the letter to the firm. An inspection addendum will be generated if conclusions change upon review of the EIR."

Comment: In an Email dated February 15, 2013, OSI confirmed that the response from the Applicant was acceptable. Based on this Email, it is my understanding that no other outstanding issues from the OSI perspective require additional investigation or response.

Division of Medication Error Prevention and Analysis (DMEPA):

The DMEPA review team assessed the proposed tradename "Osphena" on September 14, 2012, and found it acceptable. DMEPA reassessed the tradename on November 29, 2012, and did not identify any new concerns. Therefore, DMEPA had no objections to the proprietary name.

In addition, the DMEPA review team provided reviews on December 17, 2012 and February 20, 2013, of carton and container labels for areas of vulnerability that could lead to medication errors. DMEPA's recommendations were implemented.

Financial Disclosures**:**

The clinical review team did not identify any issues of serious concern related to financial disclosures for the phase 3 studies (See Medical Officer review dated February 8, 2013).

Study Endpoints and Labeling Development Team (SEALD)**:**

The SEALD review team reviewed the label in a review dated February 22, 2013, and provided recommendations. These recommendations were implemented.

12. Labeling

Labeling discussions are complete. Labeling for Osphena (ospemifene) was acceptable to the review teams. Labeling was also evaluated by the following groups:

- Office of Medical Policy Programs (DMPP) reviewed the label and the Patient Package Insert and their recommendations were considered during labeling negotiations with the Applicant.
- Office of Prescription Drug Promotion (OPDP) reviewed the label and the Patient Package Insert and their recommendations were considered during labeling negotiations with the Applicant.

Labeling was reviewed by the Study Endpoints and Label Development (SEALD) Team. An edited version of the label was sent to the Applicant. The Applicant accepted the requested edits from SEALD. No additional labeling review by SEALD was required.

13. Decision/Action/Risk Benefit Assessment

Decision:

I agree with the Cross-Discipline Team Leader, Medical Officer, and the Clinical Pharmacology, Pharmacology/Toxicology, CMC, and Statistical review teams that the Osphena (ospemifene) tablet application should receive an Approval action.

Risk Benefit Assessment:

Efficacy and safety data from the two adequately controlled phase 3 trials (15-50310 and 15-50821) using accepted endpoints have demonstrated that ospemifene 60 mg tablets were effective in the treatment of moderate to severe dyspareunia, a symptom of vulvar and vaginal atrophy, due to menopause. The results from these two trials for this clinical benefit were consistently statistically significant in the pivotal trials and are clinically meaningful.

Efficacy of ospemifene 60 mg was not consistently demonstrated for the treatment of moderate to severe vaginal dryness, a symptom of vulvar and vaginal atrophy due to menopause.

No significant safety concerns were identified in the safety database of ospemifene that preclude approval. The size and scope of the safety database were sufficient to adequately characterize the safety profile of ospemifene. Specific safety concerns identified included risks of arterial and venous thrombotic events and endometrial adverse events; these risks are known to the class of estrogen agonist/antagonist products. These risks and other adverse reactions will be addressed in labeling. Finally, other reproductive-system adverse events, such as vaginal, genital and breast adverse events were evaluated and did not raise new safety concerns for ospemifene.

In my opinion, the risk/benefit assessment favors approval of Osphena (ospemifene) for the treatment of moderate to severe dyspareunia, a symptom of vulvar and vaginal atrophy, due to menopause.

Post-Marketing Requirement/Commitment and Risk Evaluation and Mitigation Strategies (REMS):

- The review teams determined that a REMS was not necessary for this product.
- The review teams also determined that no postmarketing requirements or commitments were necessary for this product

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

/s/

AUDREY L GASSMAN
02/26/2013