

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

203505Orig1s000

OTHER REVIEW(S)

**Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Medical Policy Initiatives
Division of Medical Policy Programs**

PATIENT LABELING REVIEW

Date: **February 23, 2013**

To: **Hylton Joffe, M.D., Director
Division of Reproductive and Urologic Products (DRUP)**

Through: **LaShawn Griffiths, MSHS-PH, BSN, RN
Associate Director for Patient Labeling
Division of Medical Policy Programs (DMPP)**

From: **Melissa Hulett, MSBA, BSN, RN
Team Leader, Patient Labeling
Division of Medical Policy Programs (DMPP)**

Subject: **DMPP Concurrence with Submitted Patient Package Insert (PPI)**

Drug Name (established name): **Osphena (ospemifene)**

Dosage Form and Route: **Oral tablets**

Application Type/Number: **NDA 203505**

Applicant: **Shionogi, Inc.**

1 INTRODUCTION

On April 26, 2012, Shionogi submitted for the Agency's review a new drug application (NDA) for Osphe^{na} (ospemifene) oral tablets. Osphe^{na} is indicated for the treatment of vulvar and vaginal atrophy (VVA) due to menopause, including moderate to severe symptoms of dyspareunia and/or vaginal dryness and physiological changes in post-menopausal women.

The Division of Reproductive and Urologic Products (DRUP) requested the Division of Medical Policy Programs (DMPP) provide a review for the Applicant's proposed Patient Package Insert (PPI) for Osphe^{na} (ospemifene) oral tablets. The Division of Medical Policy Programs provided a PPI review to DRUP on February 14, 2013. On February 22, 2013 DMPP and DRUP concurred on the PPI and DRUP provided the PPI to the Applicant.

This memorandum documents the DMPP concurrence with DRUP on the PPI for Osphe^{na} (ospemifene) oral tablets which DRUP then provided to the Applicant on February 22, 2013.

2 MATERIAL REVIEWED

- Draft Osphe^{na} (ospemifene) oral tablets Patient Package Insert (PPI) received by DMPP on February 22, 2013

3 CONCLUSIONS

In our review, we find the PPI acceptable.

4 RECOMMENDATIONS

- Consult DMPP regarding any additional revisions made to the Prescribing Information (PI) to determine if corresponding revisions need to be made to the PPI.

Please let us know if you have any questions.

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/s/

MELISSA I HULETT
02/23/2013

SEALD Director Sign-Off Review of the End-of-Cycle Prescribing Information: Outstanding Format Deficiencies

Product Title	OSPHENA™ (ospemifene) tablets, for oral use
Applicant	Shionogi Inc.
Application/Supplement Number	NDA 203505
Type of Application	Original NDA
Indication(s)	For the treatment of moderate to severe dyspareunia, a symptom of vulvar and vaginal atrophy, due to menopause
Established Pharmacologic Class ¹	Estrogen agonist/antagonist
Office/Division	ODE III/DRUP
Division Project Manager	George Lyght
Date FDA Received Application	April 26, 2012
Goal Date	February 26, 2013
Date PI Received by SEALD	February 22, 2013
SEALD Review Date	February 22, 2013
SEALD Labeling Reviewer	Abimbola Adebowale
SEALD Division Director	Laurie Burke

PI = prescribing information

¹ The established pharmacologic class (EPC) that appears in the final draft PI.

This Study Endpoints and Labeling Development (SEALD) Director Sign-Off review of the end-of-cycle, draft prescribing information (PI) for critical format elements reveals **outstanding labeling format deficiencies that must be corrected** before the final PI is approved. After these outstanding labeling format deficiencies are corrected, the SEALD Director will have no objection to the approval of this PI.

The critical format elements include labeling regulation (21 CFR 201.56 and 201.57), labeling guidance, and best labeling practices (see list below). This review does not include every regulation or guidance that pertains to PI format.

Guide to the Selected Requirements of Prescribing Information (SRPI) Checklist: For each SRPI item, one of the following 3 response options is selected:

- **NO**: The PI **does not meet** the requirement for this item (**deficiency**).
- **YES**: The PI **meets** the requirement for this item (**not a deficiency**).
- **N/A** (not applicable): This item does not apply to the specific PI under review.

Selected Requirements of Prescribing Information

Highlights (HL)

GENERAL FORMAT

- YES** 1. Highlights (HL) must be in two-column format, with ½ inch margins on all sides and in a minimum of 8-point font.

Comment:

- YES** 2. The length of HL must be less than or equal to one-half page (the HL Boxed Warning does not count against the one-half page requirement) unless a waiver has been granted in a previous submission (i.e., the application being reviewed is an efficacy supplement).

Instructions to complete this item: If the length of the HL is less than or equal to one-half page then select “YES” in the drop-down menu because this item meets the requirement. However, if HL is longer than one-half page:

➤ **For the Filing Period (for RPMs)**

- *For efficacy supplements:* If a waiver was previously granted, select “YES” in the drop-down menu because this item meets the requirement.
- *For NDAs/BLAs and PLR conversions:* Select “NO” in the drop-down menu because this item does not meet the requirement (deficiency). The RPM notifies the Cross-Discipline Team Leader (CDTL) of the excessive HL length and the CDTL determines if this deficiency is included in the 74-day or advice letter to the applicant.

➤ **For the End-of Cycle Period (for SEALD reviewers)**

- The SEALD reviewer documents (based on information received from the RPM) that a waiver has been previously granted or will be granted by the review division in the approval letter.

Comment:

- YES** 3. All headings in HL must be presented in the center of a horizontal line, in UPPER-CASE letters and **bolded**.

Comment: *Headings are in the center of a horizontal line in Highlights (HL) however, the horizontal lines should extend to the end of text/bulleted items that appear under each heading.*

- YES** 4. White space must be present before each major heading in HL.

Comment:

- NO** 5. Each summarized statement in HL must reference the section(s) or subsection(s) of the Full Prescribing Information (FPI) that contains more detailed information. The preferred format is the numerical identifier in parenthesis [e.g., (1.1)] at the end of each information summary (e.g. end of each bullet).

Comment: *Include the cross-reference [e.g. (5.2)] at the end of the summarized labeling information in the first paragraph of the Boxed Warning in HL.*

- YES** 6. Section headings are presented in the following order in HL:

Section	Required/Optional
• Highlights Heading	Required
• Highlights Limitation Statement	Required
• Product Title	Required
• Initial U.S. Approval	Required

Selected Requirements of Prescribing Information

• Boxed Warning	Required if a Boxed Warning is in the FPI
• Recent Major Changes	Required for only certain changes to PI*
• Indications and Usage	Required
• Dosage and Administration	Required
• Dosage Forms and Strengths	Required
• Contraindications	Required (if no contraindications must state “None.”)
• Warnings and Precautions	Not required by regulation, but should be present
• Adverse Reactions	Required
• Drug Interactions	Optional
• Use in Specific Populations	Optional
• Patient Counseling Information Statement	Required
• Revision Date	Required

* RMC only applies to the Boxed Warning, Indications and Usage, Dosage and Administration, Contraindications, and Warnings and Precautions sections.

Comment:

- YES** 7. A horizontal line must separate HL and Table of Contents (TOC).

Comment:

HIGHLIGHTS DETAILS

Highlights Heading

- YES** 8. At the beginning of HL, the following heading must be **bolded** and appear in all UPPER CASE letters: “**HIGHLIGHTS OF PRESCRIBING INFORMATION**”.

Comment:

Highlights Limitation Statement

- NO** 9. The **bolded** HL Limitation Statement must be on the line immediately beneath the HL heading and must state: “**These highlights do not include all the information needed to use (insert name of drug product in UPPER CASE) safely and effectively. See full prescribing information for (insert name of drug product in UPPER CASE).**”

Comment: *The HL Limitation Statement is not on the line immediately beneath the HL heading. Delete the white space above the “Highlights Limitation Statement.”*

Product Title

- YES** 10. Product title in HL must be **bolded**.

Comment:

Initial U.S. Approval

- YES** 11. Initial U.S. Approval in HL must be placed immediately beneath the product title, **bolded**, and include the verbatim statement “**Initial U.S. Approval:**” followed by the **4-digit year**.

Comment:

Boxed Warning

- YES** 12. All text must be **bolded**.

Comment:

- YES** 13. Must have a centered heading in UPPER-CASE, containing the word “**WARNING**” (even if more than one Warning, the term, “**WARNING**” and not “**WARNINGS**” should be used) and

Selected Requirements of Prescribing Information

other words to identify the subject of the Warning (e.g., “**WARNING: SERIOUS INFECTIONS**”).

Comment:

- YES** 14. Must always have the verbatim statement “*See full prescribing information for complete boxed warning.*” in *italics* and centered immediately beneath the heading.

Comment:

- YES** 15. Must be limited in length to 20 lines (this does not include the heading and statement “*See full prescribing information for complete boxed warning.*”)

Comment:

- YES** 16. Use sentence case for summary (combination of uppercase and lowercase letters typical of that used in a sentence).

Comment:

Recent Major Changes (RMC)

- N/A** 17. Pertains to only the following five sections of the FPI: Boxed Warning, Indications and Usage, Dosage and Administration, Contraindications, and Warnings and Precautions.

Comment:

- N/A** 18. Must be listed in the same order in HL as they appear in FPI.

Comment:

- N/A** 19. Includes heading(s) and, if appropriate, subheading(s) of labeling section(s) affected by the recent major change, together with each section’s identifying number and date (month/year format) on which the change was incorporated in the PI (supplement approval date). For example, “Dosage and Administration, Coronary Stenting (2.2) --- 3/2012”.

Comment:

- N/A** 20. Must list changes for at least one year after the supplement is approved and must be removed at the first printing subsequent to one year (e.g., no listing should be one year older than revision date).

Comment:

Indications and Usage

- YES** 21. If a product belongs to an established pharmacologic class, the following statement is required in the Indications and Usage section of HL: “(Product) is a (name of established pharmacologic class) indicated for (indication)”.

Comment:

Dosage Forms and Strengths

- N/A** 22. For a product that has several dosage forms, bulleted subheadings (e.g., capsules, tablets, injection, suspension) or tabular presentations of information is used.

Comment:

Contraindications

Selected Requirements of Prescribing Information

- YES** 23. All contraindications listed in the FPI must also be listed in HL or must include the statement “None” if no contraindications are known.

Comment:

- YES** 24. Each contraindication is bulleted when there is more than one contraindication.

Comment:

Adverse Reactions

- YES** 25. For drug products other than vaccines, the verbatim **bolded** statement must be present: “**To report SUSPECTED ADVERSE REACTIONS, contact (insert name of manufacturer) at (insert manufacturer’s U.S. phone number) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch**”.

Comment:

Patient Counseling Information Statement

- YES** 26. Must include one of the following three **bolded** verbatim statements (without quotation marks):

If a product **does not** have FDA-approved patient labeling:

- “**See 17 for PATIENT COUNSELING INFORMATION**”

If a product **has** FDA-approved patient labeling:

- “**See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.**”
- “**See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.**”

Comment:

Revision Date

- NO** 27. **Bolded** revision date (i.e., “**Revised: MM/YYYY or Month Year**”) must be at the end of HL.

Comment: *Bold the revision date at the end of HL.*

Contents: Table of Contents (TOC)

GENERAL FORMAT

- YES** 28. A horizontal line must separate TOC from the FPI.

Comment:

- YES** 29. The following **bolded** heading in all UPPER CASE letters must appear at the beginning of TOC: “**FULL PRESCRIBING INFORMATION: CONTENTS**”.

Comment:

- NO** 30. The section headings and subheadings (including title of the Boxed Warning) in the TOC must match the headings and subheadings in the FPI.

Comment: *Subheading 5.3 “Severe Hepatic Impairment” in the FPI is missing from the TOC. Include in TOC.*

The title of the Boxed Warning in the TOC does not match the title in the FPI.

Selected Requirements of Prescribing Information

- NO** 31. The same title for the Boxed Warning that appears in the HL and FPI must also appear at the beginning of the TOC in UPPER-CASE letters and **bolded**.
Comment: Change the word “WARNINGS” in the title of the Boxed Warning in the TOC to “WARNING” to match the title in the HL and FPI.
- NO** 32. All section headings must be **bolded** and in UPPER CASE.
Comment: Bold all section headings in the TOC. Do not indent the section headings.
- NO** 33. All subsection headings must be indented, not bolded, and in title case.
Comment: Indent all subsection headings in the TOC.
- YES** 34. When a section or subsection is omitted, the numbering does not change.
Comment:
- NO** 35. If a section or subsection from 201.56(d)(1) is omitted from the FPI and TOC, the heading “**FULL PRESCRIBING INFORMATION: CONTENTS**” must be followed by an asterisk and the following statement must appear at the end of TOC: “*Sections or subsections omitted from the Full Prescribing Information are not listed.”
Comment: The statement “*Sections or subsections omitted from the Full Prescribing Information are not listed” appears to be included under subsection 17.2 and not at the end of TOC. Insert a white space above the statement.

Full Prescribing Information (FPI)

GENERAL FORMAT

- YES** 36. The following heading must appear at the beginning of the FPI in UPPER CASE and **bolded**: “**FULL PRESCRIBING INFORMATION**”.
Comment: Increase the type size of the “FULL PRESCRIBING INFORMATION” heading (i.e. change from 8-point to 12-point type size) to match that of the other headings in the FPI.
- YES** 37. All section and subsection headings and numbers must be **bolded**.
Comment:
- YES** 38. The **bolded** section and subsection headings must be named and numbered in accordance with 21 CFR 201.56(d)(1) as noted below. If a section/subsection is omitted, the numbering does not change.

Boxed Warning
1 INDICATIONS AND USAGE
2 DOSAGE AND ADMINISTRATION
3 DOSAGE FORMS AND STRENGTHS
4 CONTRAINDICATIONS
5 WARNINGS AND PRECAUTIONS
6 ADVERSE REACTIONS
7 DRUG INTERACTIONS
8 USE IN SPECIFIC POPULATIONS
8.1 Pregnancy
8.2 Labor and Delivery
8.3 Nursing Mothers

Selected Requirements of Prescribing Information

8.4 Pediatric Use
8.5 Geriatric Use
9 DRUG ABUSE AND DEPENDENCE
9.1 Controlled Substance
9.2 Abuse
9.3 Dependence
10 OVERDOSAGE
11 DESCRIPTION
12 CLINICAL PHARMACOLOGY
12.1 Mechanism of Action
12.2 Pharmacodynamics
12.3 Pharmacokinetics
12.4 Microbiology (by guidance)
12.5 Pharmacogenomics (by guidance)
13 NONCLINICAL TOXICOLOGY
13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
13.2 Animal Toxicology and/or Pharmacology
14 CLINICAL STUDIES
15 REFERENCES
16 HOW SUPPLIED/STORAGE AND HANDLING
17 PATIENT COUNSELING INFORMATION

Comment:

YES

39. FDA-approved patient labeling (e.g., Medication Guide, Patient Information, or Instructions for Use) must not be included as a subsection under Section 17 (Patient Counseling Information). All patient labeling must appear at the end of the PI upon approval.

Comment:

NO

40. The preferred presentation for cross-references in the FPI is the section heading (not subsection heading) followed by the numerical identifier in italics. For example, “[see *Warnings and Precautions (5.2)*]”.

Comment: Correct the Boxed Warning heading for the cross-references included with the following bulleted items in section 6:

Cardiovascular Disorders: Change the cross-reference [see Boxed warnings...] to [see Boxed Warning...]

Malignant Neoplasms: Change the cross-reference [see Boxed Warnings...] to [see Boxed Warning...]

N/A

41. If RMCs are listed in HL, the corresponding new or modified text in the FPI sections or subsections must be marked with a vertical line on the left edge.

Comment:

FULL PRESCRIBING INFORMATION DETAILS

Boxed Warning

YES

42. All text is **bolded**.

Comment:

YES

43. Must have a heading in UPPER-CASE, containing the word “**WARNING**” (even if more than one Warning, the term, “**WARNING**” and not “**WARNINGS**” should be used) and other words to identify the subject of the Warning (e.g., “**WARNING: SERIOUS INFECTIONS**”).

Selected Requirements of Prescribing Information

Comment:

YES

44. Use sentence case (combination of uppercase and lowercase letters typical of that used in a sentence) for the information in the Boxed Warning.

Comment:

Contraindications

N/A

45. If no Contraindications are known, this section must state “None”.

Comment:

Adverse Reactions

YES

46. When clinical trials adverse reactions data is included (typically in the “Clinical Trials Experience” subsection of Adverse Reactions), the following verbatim statement or appropriate modification should precede the presentation of adverse reactions:

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

Comment:

N/A

47. When postmarketing adverse reaction data is included (typically in the “Postmarketing Experience” subsection of Adverse Reactions), the following verbatim statement or appropriate modification should precede the presentation of adverse reactions:

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

Comment:

Patient Counseling Information

YES

48. Must reference any FDA-approved patient labeling, include the type of patient labeling, and use one of the following statements at the beginning of Section 17:

- “See FDA-approved patient labeling (Medication Guide)”
- “See FDA-approved patient labeling (Medication Guide and Instructions for Use)”
- “See FDA-approved patient labeling (Patient Information)”
- “See FDA-approved patient labeling (Instructions for Use)”
- “See FDA-approved patient labeling (Patient Information and Instructions for Use)”

Comment: *The statement above should not be centered in the FPI. Align left.*

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/s/

ABIMBOLA O ADEBOWALE
02/22/2013

LAURIE B BURKE
02/22/2013

*****Pre-decisional Agency Information*****

Memorandum

Date: February 22, 2012

To: George Lyght
Regulatory Project Manager
Division of Reproductive and Urologic Products (DRUP)

From: Melinda McLawhorn, PharmD, BCPS
Regulatory Review Officer
Division of Professional Drug Promotion (DPDP)
Office of Prescription Drug Promotion (OPDP)

Through: Jessica Cleck-Derenick, PhD, Regulatory Review Office (DPDP)
Mathilda Fienkeng, PharmD, Group Leader (DPDP)

CC: Carrie Newcomer, PharmD
Regulatory Review Officer
Division of Consumer Drug Promotion (DCDP)
OPDP

Subject: **NDA 203505**
OSPHENA™ (ospemifene) Tablets

Background

On March 30, 2012, DRUP consulted OPDP to review the proposed package insert (PI), patient package insert (PPI), and carton/container labeling for the original NDA submission for OSPHENA™ (ospemifene) tablets, for oral use (Osphena).

DPDP reviewed the PI from the proposed substantially complete version retrieved from the eRoom on February 14, 2013 and provide our comments below. DPDP reviewed the carton and container labeling submitted to the electronic document room on January 24, 2013 and do not have any comments. DCDP provided comments on the PPI under a separate cover on February 19, 2013.

Thank you for your consult. If you have any questions on the PI, please contact Melinda McLawhorn at 6-7559 or at Melinda.McLawhorn@fda.hhs.gov.

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/s/

MELINDA W MCLAWHORN
02/22/2013

**Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology
Office of Medication Error Prevention and Risk Management**

Labeling Memo

Date: February 20, 2013

Team Leader: Zachary Oleszczuk, PharmD, Team Leader
Division of Medication Error Prevention and Analysis

Drug Name: Ospkena (Ospemifene) Tablets, 60 mg

Application Type/Number: NDA 022090

Applicant/Sponsor: Shionogi Inc.

OSE RCM #: 2012-1048-1

*** This document contains proprietary and confidential information that should not be released to the public.***

1 INTRODUCTION

This memo responds to a request from the Division of Urology and Reproductive Products (DRUP) for review of the revised container labels for Ospheña (Ospemifene) submitted on January 24, 2013 in response to recommendations communicated to the Applicant by DMEPA.

2 MATERIAL REVIEWED

DMEPA reviewed the revised Ospheña container labels submitted January 24, 2013 (see Appendix A).

3 CONCLUSIONS AND RECOMMENDATIONS

Review of the revised container labels show that the Applicant implemented DMEPA's recommendations and we find the revisions acceptable. We have no additional recommendations at this time.

Please copy the Division of Medication Error Prevention and Analysis on any communication to the Applicant with regard to this review. If you have further questions or need clarifications on this review, please contact the OSE Regulatory Project Manager, Marcus Cato at 301-796-3903.

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/s/

ZACHARY A OLESZCZUK
02/20/2013

**FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion
Division of Consumer Drug Promotion**

*****Pre-decisional Agency Information*****

Memorandum

Date: February 19, 2013

To: George Lyght, PharmD
Regulatory Project Manager
Division of Reproductive and Urologic Products (DRUP)

From: Carrie Newcomer, PharmD
Regulatory Review Officer
Division of Consumer Drug Promotion (DCDP)
Office of Prescription Drug Promotion (OPDP)

**Subject: NDA: 203505
OSPHENA™ (ospemifene) tablets, for oral use**

Background

On July 5, 2012, DRUP consulted OPDP to review the proposed package insert (PI), patient package insert (PPI), and carton/container labeling for the original NDA submission for OSPHENA™ (ospemifene) tablets (Osphena).

DCDP notes that the Division of Medical Policy Programs (DMPP) provided comments on the draft PPI on February 14, 2013. DCDP agrees with DMPP's comments and has provided additional comments directly on DMPP's review of the PPI (please see attached document).

Please note that DCDP comments are based on the substantially complete version of the draft PI retrieved from the eRoom on February 15, 2013. The Division of Professional Promotion/OPDP will provide comments on the proposed PI and carton/container labeling under separate cover.

Thank you for your consult. If you have any questions on the PPI, please contact Carrie Newcomer at 6-1233, or carrie.newcomer@fda.hhs.gov.

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/s/

CARRIE A NEWCOMER
02/19/2013

**Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Medical Policy Initiatives
Division of Medical Policy Programs**

PATIENT LABELING REVIEW

Date: February 13, 2013

To: Hylton Joffe, M.D., Director
Division of Reproductive and Urologic Products (DRUP)

Through: LaShawn Griffiths, MSHS-PH, BSN, RN
Associate Director for Patient Labeling
Division of Medical Policy Programs (DMPP)

Melissa Hulett, RN, BSN, MSBA
Team Leader, Patient Labeling Team
Division of Medical Policy Programs

From: Robin Duer, MBA, BSN, RN
Senior Patient Labeling Reviewer
Division of Medical Policy Programs

Subject: DMPP Review of Patient Labeling (Patient Package Insert)

Drug Name (established name) Osphena (ospemifene)

Dosage Form and Route: oral tablets

Application Type/Number: NDA 203505

Applicant: Shionogi, Inc.

1 INTRODUCTION

On April 26, 2012, Shionogi submitted for the Agency's review a new drug application (NDA) for Osphe^{na} (ospemifene) oral tablets. Osphe^{na} is indicated for the treatment of vulvar and vaginal atrophy (VVA) due to menopause, including moderate to severe symptoms of dyspareunia and/or vaginal dryness and physiological changes in post-menopausal women.

This review is written in response to a request by the Division of Reproductive and Urologic Products (DRUP) for the Division of Medical Policy Programs (DMPP) to provide a review for the Applicant's proposed Patient Package Insert (PPI) for Osphe^{na} (ospemifene) oral tablets.

On January 15, 2013, DRUP requested that DMPP refer to the approved Minivelle (estradiol transdermal system) as comparator labeling for the Osphe^{na} patient labeling where appropriate.

2 MATERIAL REVIEWED

- Draft Osphe^{na} (ospemifene) oral tablets Patient Package Insert (PPI) received on April 26, 2011, and received by DMPP on February 11, 2013
- Draft Osphe^{na} (ospemifene) oral tablets Prescribing Information (PI) received on April 26, 2012, revised by the Review Division throughout the current review cycle, and received by DMPP on February 11, 2013
- Approved Minivelle (estradiol transdermal system) comparator labeling dated October 29, 2012
- Draft Guidance for Industry: Noncontraceptive Estrogen Drug Products for the Treatment of Vasomotor Symptoms and Vulvar and Vaginal Atrophy Symptoms-Recommended Prescribing Information for Health Care Providers and Patient Labeling, November 2005

3 REVIEW METHODS

To enhance patient comprehension, materials should be written at a 6th to 8th grade reading level, and have a reading ease score of at least 60%. A reading ease score of 60% corresponds to an 8th grade reading level. In our review of the PPI the target reading level is at or below an 8th grade level.

Additionally, in 2008 the American Society of Consultant Pharmacists Foundation (ASCP) in collaboration with the American Foundation for the Blind (AFB) published *Guidelines for Prescription Labeling and Consumer Medication Information for People with Vision Loss*. The ASCP and AFB recommended using fonts such as Verdana, Arial or APHont to make medical information more accessible for patients with vision loss. We have reformatted the PPI document using the Verdana font, size 11.

In our review of the PPI we have:

- simplified wording and clarified concepts where possible
- ensured that the PPI is consistent with the prescribing information (PI)
- removed unnecessary or redundant information
- ensured that the PPI meets the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)
- ensured that the PPI is consistent with the approved comparator labeling where applicable.
- ensured that the PPI is consistent with the Draft Guidance for Industry where appropriate

4 CONCLUSIONS

The PPI is acceptable with our recommended changes.

5 RECOMMENDATIONS

- Please send these comments to the Applicant and copy DMPP on the correspondence.
- Our review of the PPI is appended to this memo. Consult DMPP regarding any additional revisions made to the PI to determine if corresponding revisions need to be made to the PPI.

Please let us know if you have any questions.

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/s/

ROBIN E DUER
02/13/2013

MELISSA I HULETT
02/13/2013

LASHAWN M GRIFFITHS
02/14/2013

**Interdisciplinary Review Team for QT Studies Consultation:
Thorough QT Study Review**

NDA	203505
Brand Name	Ophena
Generic Name	Ospemifene
Sponsor	Shionogi, Inc.
Indication	Vulvar and Vaginal Atrophy (VVA)
Dosage Form	Tablet
Drug Class	Selective estrogen receptor modulator
Therapeutic Dosing Regimen	60 mg
Duration of Therapeutic Use	Acute
Maximum Tolerated Dose	
Submission Number and Date	SDN 000, 13 Dec 2012
Review Division	DRUP

Note: Any text in the review with a light background should be inferred as copied from the sponsor's document.

1 SUMMARY

1.1 OVERALL SUMMARY OF FINDINGS

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 $\Delta\Delta\text{QTcI}$ 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.

In this randomized, blinded, four-arm parallel study, 50 healthy subjects received ospemifene, placebo, and a single oral dose of moxifloxacin 400 mg. The overall summary of findings is presented in Table 1.

Table 1: The Point Estimates and the 90% CIs Corresponding to the Largest Upper Bounds for Ospemifene and the Largest Lower Bound for Moxifloxacin (FDA Analysis)

Treatment	Time	$\Delta\Delta\text{QTcI}$ (ms)	90% CI (ms)
Ospemifene 60 mg	23.5	-1.1	(-4.8, 2.6)
Ospemifene 240 mg	8	-2.2	(-5.9, 1.5)
Moxifloxacin 400 mg*	8	8.3	(4.6, 12.0)

* Multiple endpoint adjustment was not applied. The largest lower bound after Bonferroni adjustment for 4 timepoints is 3.6 ms.

The suprathreshold dose produces a C_{\max} value that is 2.9-fold the C_{\max} following the therapeutic dose. These concentrations are above the predicted worst case scenario (concomitant administration of a strong CYP3A and CYP2C9 inhibitor, such as fluconazole to hepatic impaired patients (70% increase in C_{\max})) and show that at these concentrations there are no detectable prolongations of the QT-interval.

2 QT-IRT PROPOSED LABEL

The following is recommended label language. We defer final label decision to the Division.

12.6 Cardiac Electrophysiology

At a dose 4 times the maximum recommended dose, ospemifene does not prolong QTc to any clinically relevant extent.

3 BACKGROUND

3.1 PRODUCT INFORMATION

Ospemifene is a selective estrogen receptor modulator intended to be used to alleviate vulvar and vaginal atrophy in menopausal women.

3.2 MARKET APPROVAL STATUS

Ospemifene is not approved for marketing in any country.

3.3 PRECLINICAL INFORMATION

Ospemifene and the M-1 metabolite are hERG blockers at concentrations probably irrelevantly high. There were no effects on the ECG in targeted cardiovascular safety studies in dogs and primates.

3.4 PREVIOUS CLINICAL EXPERIENCE

Over 1500 subjects have over 700 person-years of exposure to a dose of 60 mg or greater. There were no deaths and cardiovascular events were exceedingly uncommon.

3.5 CLINICAL PHARMACOLOGY

Appendix 6.1 summarizes the key features of ospemifene's clinical pharmacology.

4 SPONSOR'S SUBMISSION

4.1 OVERVIEW

The QT-IRT reviewed the protocol prior to conducting this study under IND 67216. The sponsor submitted the study report 15-50824 for ospemifene, including electronic datasets and waveforms to the ECG warehouse.

4.2 TQT STUDY

4.2.1 Title

“A Double-Blind Randomized Parallel Trial to define the ECG effects of Ospemifene using a Clinical and a Supratherapeutic Dose compared to Placebo and Moxifloxacin (a Positive Control) in Healthy Men and Women: A Thorough ECG Trial”

4.2.2 Protocol Number

15-50824

4.2.3 Study Dates

26 October 2009 – 18 December 2009

4.2.4 Objectives

Primary:

- To assess the effects of a therapeutic and a supratherapeutic dose of ospemifene on the time-matched change from baseline in QTc based on an individual correction (QTcI).

Secondary:

- To assess the effects of a therapeutic and a supratherapeutic dose of ospemifene on the time-matched change from baseline in QTc (Fridericia's [QTcF] and Bazett's [QTcB] correction methods).
- To assess the effects of a therapeutic and a supratherapeutic dose of ospemifene on heart rate, the PR interval, the QRS interval, the uncorrected QT interval, and ECG morphological patterns.
- To correlate the QTcI change from baseline with the serum concentrations of the parent drug and metabolites.
- To assess the safety and tolerability of a therapeutic and a supratherapeutic dose of ospemifene when administered for 7 days to healthy men and women.

Source: Sponsor's study report synopsis, page 1.

4.2.5 Study Description

4.2.5.1 Design

“This was a Phase 1, single-center, randomized, double-blind (except for the use of

moxifloxacin), parallel-group, active- and placebo-controlled trial designed to determine the ECG effects and safety and tolerability of ospemifene in approximately 200 healthy male and female subjects between 18 and 45 years of age. The total treatment duration was 7 days, and subjects were randomized to receive placebo daily, ospemifene 60 mg/day, ospemifene 240 mg/day, or moxifloxacin. Subjects were confined to the study clinic for a total of 10 consecutive days: Day -2 (clinic admission), Day -1 (baseline assessments), Days 1-7 (study drug treatment), and Day 8 (post-treatment assessments; AM discharge from clinic).”

Source: Sponsor’s study report, page 18.

4.2.5.2 Controls

The Sponsor used both placebo and positive (moxifloxacin) controls.

4.2.5.3 Blinding

The positive (moxifloxacin) control was not blinded.

4.2.6 Treatment Regimen

4.2.6.1 Treatment Arms

Subjects were enrolled and randomized to 1 of 4 study arms:

- Placebo
- Ospemifene 60 mg
- Ospemifene 240 mg
- Moxifloxacin 400 mg

4.2.6.2 Sponsor’s Justification for Doses

The clinical dose of ospemifene is 60 mg/day; and the selected supratherapeutic dose of 240 mg/day represents a 4-fold increase in exposure which should cover any metabolic, drug-drug interaction and QT effect modifiers.

Reviewer’s Comment: The choice of therapeutic and supratherapeutic doses is acceptable. The supratherapeutic dose produces a C_{max} value that is 2.9-fold the C_{max} following the therapeutic dose. These concentrations are above the predicted worse case scenario (concomitant administration of a strong CYP3A and CYP2C9 inhibitor, such as fluconazole to hepatic impaired patients (1.7-fold the C_{max})).

4.2.6.3 Instructions with Regard to Meals

Doses were administered after a high-fat breakfast.

Reviewer’s Comment: High fat food causes 2.8-fold the AUC and 3.6-fold the C_{max} . Therefore, administration after a high fat breakfast is acceptable.

4.2.6.4 ECG and PK Assessments

Four ECGs, approximately one minute apart were obtained at Baseline (Day -1) and Day 7 at 0.5, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 12, 16 and 23.5 hours. PK samples were obtained on Day 7 at pre-dose and at the same time points used for ECG assessment.

Reviewer's Comment: The timing of ECG/PK assessments is adequate to capture potential effects at T_{max} as well as delayed effects over 24 hours.

4.2.6.5 Baseline

The sponsor used a time-matched baseline.

Twelve-lead Holter monitoring was used to obtain digital ECGs.

4.2.7 Sponsor's Results

4.2.7.1 Study Subjects

Subjects could be men or women 18 to 45. Fifty per arm (200 total) were randomized and all completed.

4.2.7.2 Statistical Analyses

4.2.7.2.1 Primary Analysis

“The following study endpoints were defined for this analysis to compare the ECGs at baseline to those obtained on-treatment (Day 7):

- A time-matched analysis was the primary endpoint and was performed to view each of the 12 time points to define whether any subject had a delta delta (mean change from baseline and then placebo-corrected) QTcI change in which the upper 90% confidence interval (CI) 2-sided exceeded 10 ms as per ICH E14 guidance.
- The secondary analysis was a traditional time-averaged analysis of the change from mean QTcI of all baseline ECGs to the mean QTcI of all on-treatment ECG values for each subject for each ECG interval parameter (heart rate, PR, QRS, QT, and the 3 QTc [QTcI, QTcB, QTcF])
- Descriptive analysis for the time-matched and time-averaged means for the ECG interval parameters – heart rate, PR, QRS, QT, QTc (QTcF and QTcB).

“The primary analysis for the QT/QTc data in this trial was the time-matched analysis for each treatment group. This time-matched analysis was based upon a delta-delta calculation, the placebo-corrected change from baseline, which was performed to evaluate each of the 12 matched ECG time points to determine whether the upper CI of the delta delta is less than 10 ms at any of the time points. The definition of baseline is: the ECG data obtained on Day -1 in each parallel arm. For this analysis, 90% two-sided CIs were calculated using a mixed effects general linear model to include terms for treatment, time (categorical), gender and a treatment-by-time interaction. Gender effects were investigated as specified below. Had a significant gender effect been found, a treatment-by-gender interaction was also to have been included in the model.

“Subject” was included in the model as a random-effects term. CIs were calculated either using a LS Means statement or ESTIMATE statements within the SAS procedure PROC MIXED using a REML estimation method. The covariance structure used the UNSTRUCTURED option to avoid any assumptions about underlying parameter distributions. In addition, the degrees of freedom were calculated using the KENWARDROGER methodology (an option on the MODEL statement within PROC MIXED). Hypotheses were based upon the Intersection Union Test as specified below. To evaluate the drug effect, the statistical hypotheses can be stated as follows:

Ho: $\cup \{ \mu_{\text{drug}(i)} - \mu_{\text{placebo}(i)} \geq x, i = 1, 2, \dots, k \text{ and}$

HA: $\cap \{ \mu_{\text{drug}(i)} - \mu_{\text{placebo}(i)} < x, i = 1, 2, \dots, k$

where $\mu_{\text{drug}(i)}$ and $\mu_{\text{placebo}(i)}$ were the mean change from baseline of QTc for the drug and placebo at time point i for k time points, respectively. The Intersection-Union test could be applied here; therefore, no multiple endpoint adjustment was needed. Based on the ICH E14 Guidance, this hypothesis was evaluated by observing if any of the time points had a one-sided upper CI bound which was equal to or exceeded 10 ms. A QTcI change in which the upper 2-sided 90% CI exceeded 10 ms as per the E14 guidance was considered to be a positive response.”

Source: Sponsor’s study report, pages 38-39.

“In the time-averaged analysis, the QTcI placebo-corrected mean changes from baseline for the ospemifene 60 mg and 240 mg groups were -2.7 and -3.5 ms, respectively. These data show no signal for any QTc-prolonging effect of ospemifene. Assay sensitivity was reached in that the time-averaged QTcI placebo-corrected mean change from baseline values for moxifloxacin was +5.4 ms (expected 5-10 ms). The QTcI mean change from baseline for the placebo group was -2.6 ms, showing that the study was well conducted and that background QTc variability was controlled...”

“Neither of the 2 ospemifene dose groups demonstrated an upper bound that approached or exceeded 10 ms, again demonstrating no signal of any effect of this agent on cardiac repolarization.”

Source: Sponsor’s study report synopsis, pages 5-6.

Reviewer’s Comments: This reviewer’s results agree with the sponsor’s conclusions. See section 5.2 for FDA analysis.

4.2.7.2.2 Assay Sensitivity

“To establish assay sensitivity, there should be at least one time point where the mean difference of moxifloxacin and placebo was greater than 5 ms. This was evaluated by setting up the following statistical hypotheses:

Ho: $\cap \{ \mu_{\text{moxifloxacin}(i)} - \mu_{\text{placebo}(i)} < 5, i = 1, 2, \dots, k \text{ and}$

HA: $\cup \{ \mu_{\text{moxifloxacin}(i)} - \mu_{\text{placebo}(i)} \geq 5, i = 1, 2, \dots, k$

where $\mu_{\text{moxifloxacin}(i)}$ and $\mu_{\text{placebo}(i)}$ represented the mean value of a time-matched change from baseline in QTcI. K was the number of time points selected to evaluate the moxifloxacin effect.

“In an exploratory sense, the hypothesis of assay sensitivity was to have been rejected if the lower limit of the two-sided (Bonferroni-corrected) 90% CI was never above 5 ms.

However, detecting the positive control's effect would confirm the ability of the trial to detect such an effect of ospemifene.

“For purposes of determining assay sensitivity, 5 time points (the Day 7 time points 1, 2, 3, 4, and 6 hours post-dose, compared to the respectively matching Day -1 time points) were utilized for calculating the one-sided 95% (two-sided 90%) upper confidence limits. In this case, since the alternative hypothesis was that at least one of the time points was greater than or equal to 5 ms, a multiplicity adjustment was necessary. Therefore, the CIs were calculated using Bonferroni adjustment, specifically an adjusted alpha error level of $0.05/5 = 0.01$.”

Source: Sponsor's study report, pages 38-39.

“The time-matched analyses for the QTcI endpoint revealed that the moxifloxacin group generally met the assay sensitivity criteria outlined in the statistical plan and had the typical profile. The mean change in the moxifloxacin group was around 6-9 ms with upper confidence intervals of around 10 ms for all subjects, and the female subjects had a larger change than the male subjects as was expected due to women's lower mean body mass. The lower confidence interval was >5 ms at one time point (hour 8) using QTcI; at hours 3, 4, and 8 using QTcF; and also at hours 3, 4, and 8 in female subjects using QTcI. Hence, assay sensitivity was demonstrated in this trial.”

Source: Sponsor's study report synopsis, pages 5-6.

Reviewer's Comments: Our results are similar to the sponsor's results. See section 5.2.

4.2.7.3 Safety Analysis

There were no concerning cardiovascular adverse events.

4.2.7.4 Clinical Pharmacology

4.2.7.4.1 Pharmacokinetic Analysis

The PK parameter results are presented in Table 2. The concentration-time profiles are illustrated in Figure 1 and Figure 2 for the 60 mg and 240 mg doses, respectively. C_{\max} and AUC values of ospemifene in the thorough QT study were 2.9-fold and 3.4-fold higher, respectively, following administration of 240 mg compared with 60 mg ospemifene, the intended clinical dose. C_{\max} and AUC values of 4-hydroxyospemifene in the thorough QT study were 2.3-fold and 2.4-fold higher, respectively, following administration of 240 mg compared with 60 mg ospemifene. C_{\max} and AUC values of 4'-hydroxyospemifene in the thorough QT study were 1.7-fold and 1.8-fold higher, respectively, following administration of 240 mg compared with 60 mg ospemifene.

Table 2: Mean (%CV) PK Parameters for Ospemifene, 4-hydroxyospemifene and 4'-hydroxyospemifene following Administration of 60 mg and 240 mg Ospemifene Daily for 7 Days

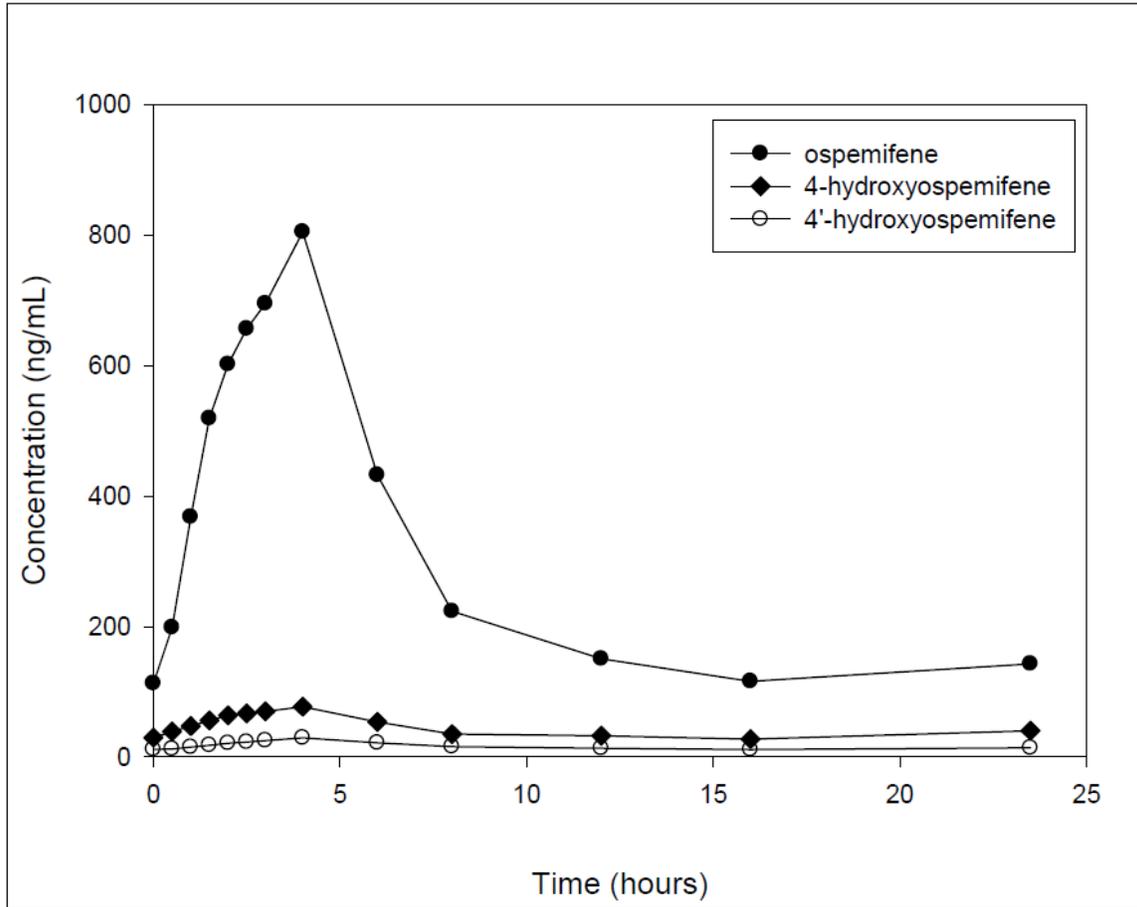
	Analyte					
	Ospemifene		4-Hydroxyospemifene		4'-Hydroxyospemifene	
	60 mg (n=50)	240 mg (n=50)	60 mg (n=50)	240 mg (n=50)	60 mg (n=50)	240 mg (n=50)
Mean (CV%)						
AUC _{0-t} (ng*hr/mL)	6175.1 (27.2)	21113.8 (20.7)	957.7 (33.0)	2252.8 (31.4)	369.6 (31.0)	653.4 (22.9)
AUC _{0-∞} (ng*hr/mL)	6691.3 (20.5) ^a	24487.9 (25.9) ^b	1532.9 ^d	-- ^e	606.9 ^d	-- ^e
AUC _{0-τ} (ng*hr/mL)	5742.2 (20.1) ^a	20573.0 (24.5) ^b	1298.2 ^d	-- ^e	490.1 ^d	-- ^e
C _{max,ss} (ng/mL)	1055.1 (31.8)	3032.7 (21.8)	84.9 (33.2)	196.9 (32.2)	30.5 (28.3)	51.0 (24.2)
C _{min,ss} (ng/mL)	112.8 (46.8)	439.9 (33.6)	29.7 (48.0)	72.8 (40.8)	11.5 (44.8)	23.3 (30.1)
C _{avg,ss} (ng/mL)	239.3 (20.1) ^a	857.2 (24.5) ^b	54.1 ^d	-- ^e	20.4 ^d	-- ^e
t _{max,ss} (hr), median (range)	4.1 (1.1-6.1)	4.1 (0.6-6.1)	3.6 (1.1-6.1)	4.1 (1.1-6.1)	4.1 (1.6-6.1)	4.1 (1.1-6.1)
PTF	9.2 (40.6) ^c	6.4 (35.3)	2.1 (46.9) ^c	1.9 (46.5)	1.9 (52.0) ^c	1.3 (44.2)
Cl/F (L/hr)	10.9 (19.5) ^a	12.4 (24.6) ^b	-- ^e	-- ^e	-- ^e	-- ^e
Vd/F (L)	99.5 (29.3) ^a	120.6 (24.1) ^b	-- ^e	-- ^e	-- ^e	-- ^e
λz (1/hr)	0.11 (15.8) ^a	0.10 (8.6) ^b	0.09 ^d	-- ^e	0.08 ^d	-- ^e
t _{1/2} (hr)	6.4 (22.9) ^a	6.8 (8.2) ^b	7.83 ^d	-- ^e	8.9 ^d	-- ^e

^an=26; ^bn=21; ^cn=49; ^dn=1.

^eNot determined due to insufficient data.

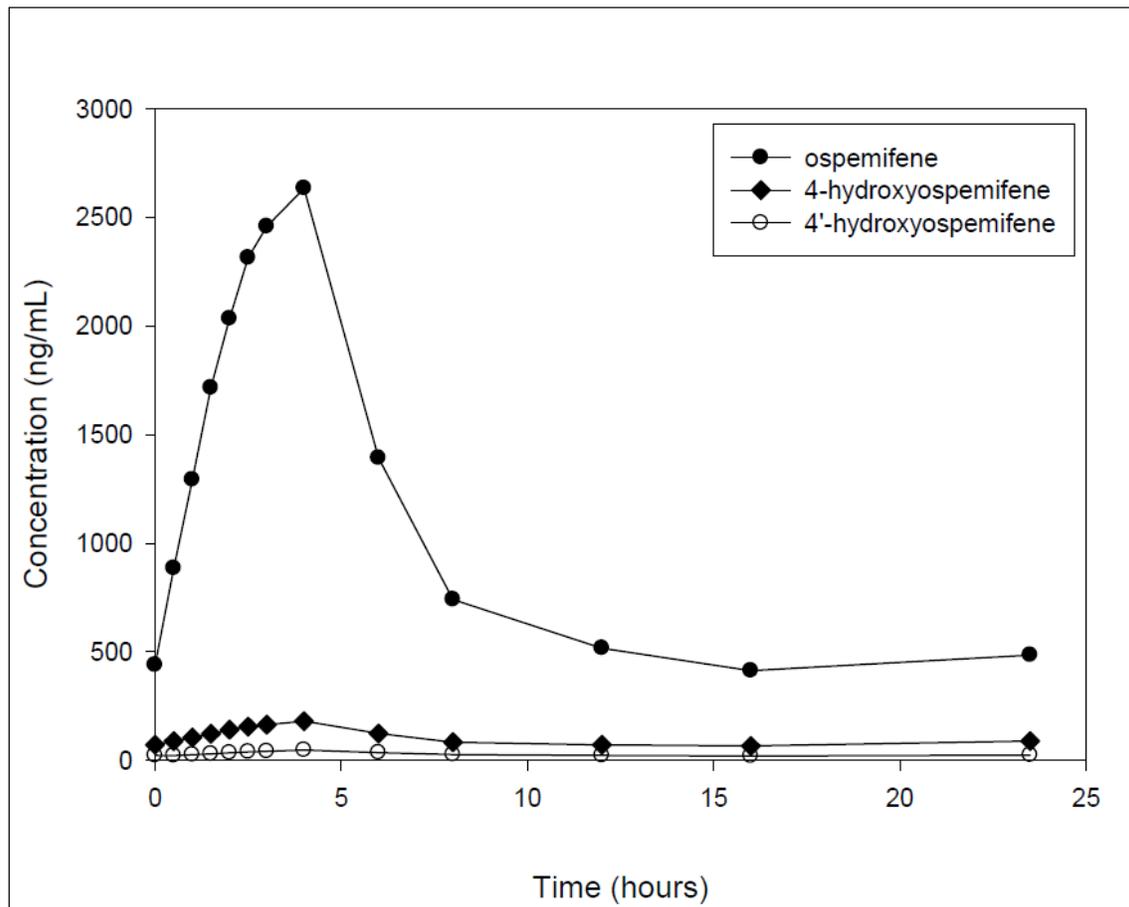
Source: Sponsor's study report, Table 8. page 58

Figure 1: Mean Ospemifene, 4-hydroxyospemifene and 4'-hydroxyospemifene Concentration-Time Profiles following 7 Days of 60 mg Ospemifene



Source: Sponsor's study report, Figure 3. page 56

Figure 2: Mean Ospemifene, 4-hydroxyospemifene and 4'-hydroxyospemifene Concentration-Time Profiles following 7 Days of 240 mg Ospemifene



Source: Sponsor's study report, Figure 4, page 57

4.2.7.4.2 Exposure-Response Analysis

A linear mixed-effects modeling approach was used to examine the relationship between the placebo-corrected change from baseline in QTc and serum concentrations of ospemifene and its major metabolites. The results indicated that the slopes for QTcI for ospemifene and its two metabolites were essentially flat.

Reviewer's Analysis: Plots of $\Delta\Delta QTcI$ vs. ospemifene, 4-hydroxyospemifene and 4'-hydroxyospemifene concentrations are presented in Figure 5, Figure 6 and Figure 7, respectively.

5 REVIEWERS' ASSESSMENT

5.1 EVALUATION OF THE QT/RR CORRECTION METHOD

We evaluated the appropriateness of the correction methods (QTcF and QTcI). Baseline values were excluded in the validation. Ideally, a good correction QTc would result in no relationship of QTc and RR intervals.

We used the mixed model of the pooled post-dose data of QTcF and QTcI distinguished by an indicator of correction method to evaluate the linear relationships between different correction methods and RR. The model included RR, correction type (QTcF or QTcI), and the interaction term of RR and correction type. The slopes of QTcF and QTcI versus RR are compared in magnitude as well as statistical significance in difference. As shown in Table 3, it appears that QTcF had smaller absolute slopes than QTcI and is a better correction method for the study data. However, this reviewer used QTcI for consistency with the sponsor's results.

Table 3: Comparison of QTcF and QTcI Using the Mixed Model

Treatment Groups	Slope of QTcF	Slope of QTcI	P-value
Ospemifene 60 mg	0.0056	0.0288	0.0000
Ospemifene 240 mg	0.0057	0.0417	0.0000
Moxifloxacin 400 mg	0.0056	0.0288	0.0000
Placebo	0.0068	0.0341	0.0000
All	0.0017	0.0340	0.0000

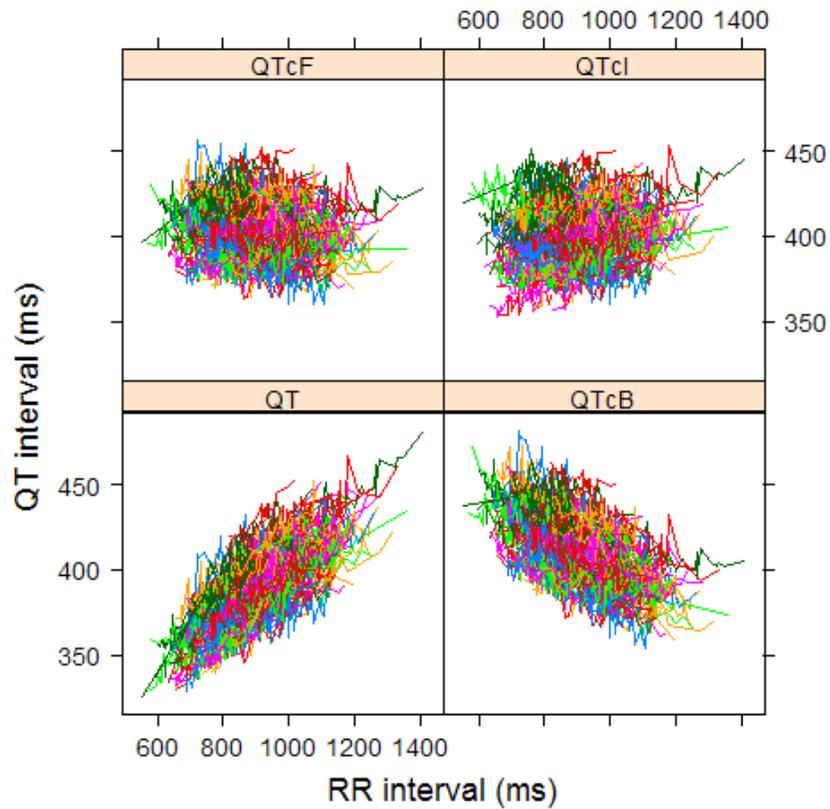
We also confirmed this conclusion by using the criterion of Mean Sum of Squared Slopes (MSSS) from individual regressions of QTc versus RR. The smaller this value is, the better the correction. Based on the results listed in Table 4, it also appears that QTcF is the best correction method. As noted above, this statistical reviewer used QTcI for the primary statistical analysis to be consistent with the sponsor's choice of QTcI for their primary analysis.

Table 4: Average of Sum of Squared Slopes for Different QT-RR Correction Methods

Treatment Group	QTcF		QTcI	
	N	MSSS	N	MSSS
Ospemifene 60 mg	50	0.0017	50	0.0035
Ospemifene 240 mg	50	0.0013	50	0.0029
Moxifloxacin 400 mg	50	0.0023	50	0.0052
Placebo	50	0.0012	50	0.0027
All	200	0.0016	200	0.0036

The relationship between different correction methods and RR is presented in Figure 3.

Figure 3: QT, QTcB, QTcF, and QTcI vs. RR (Each Subject's Data Points are Connected with a Line)



5.2 STATISTICAL ASSESSMENTS

5.2.1 QTc Analysis

5.2.1.1 The Primary Analysis for Ospemifene

The statistical reviewer used mixed model to analyze the Δ QTcI effect. The model includes treatment and sex as fixed effects and subject as a random effect. Baseline values are also included in the model as a covariate. The analysis results are listed in Table 5 and Table 6.

**Table 5: Analysis Results of Δ QTcI and $\Delta\Delta$ QTcI for Treatment Group A:
Ospemifene 60 mg x 7 days**

Time	Δ QTc: Ospemifene			Δ QTc: Placebo			$\Delta\Delta$ QTc		
	N	Mean	SD	N	Mean	SD	N	Mean	90% CI
0.5	49	-6.4	1.2	50	-3.3	1.2	49	-3.1	(-6.6, 0.5)
1	50	-6.5	1.3	50	-3.4	1.3	50	-3.0	(-6.9, 0.8)
1.5	49	-6.1	1.3	49	-2.1	1.3	49	-4.0	(-7.8, -0.3)
2	50	-6.7	1.3	50	-3.0	1.3	50	-3.7	(-7.4, 0.1)
2.5	50	-5.9	1.2	50	-2.4	1.2	50	-3.5	(-7.1, 0.1)
3	50	-4.5	1.3	50	-2.5	1.3	50	-2.0	(-5.7, 1.7)
4	50	-3.8	1.2	50	-0.9	1.2	50	-2.9	(-6.5, 0.7)
6	50	-4.0	1.2	50	-1.2	1.2	50	-2.9	(-6.4, 0.6)
8	50	-5.0	1.2	50	-2.7	1.3	50	-2.2	(-5.9, 1.5)
12	50	-3.4	1.1	50	-1.2	1.2	50	-2.2	(-5.6, 1.2)
16	50	-7.4	1.4	50	-1.8	1.4	50	-5.6	(-9.6, -1.6)
23.5	50	-3.6	1.3	50	-2.5	1.3	50	-1.1	(-4.8, 2.6)

**Table 6: Analysis Results of Δ QTcI and $\Delta\Delta$ QTcI for Treatment Group B:
Ospemifene 240 mg x 7 days**

Time	Δ QTc: Ospemifene			Δ QTc: Placebo			$\Delta\Delta$ QTc		
	N	Mean	SD	N	Mean	SD	N	Mean	90% CI
0.5	49	-7.5	1.2	50	-3.3	1.2	49	-4.1	(-7.7, -0.6)
1	49	-8.4	1.3	50	-3.4	1.3	49	-5.0	(-8.9, -1.2)
1.5	49	-7.8	1.3	49	-2.1	1.3	49	-5.8	(-9.5, -2.0)
2	49	-6.6	1.3	50	-3.0	1.3	49	-3.6	(-7.3, 0.2)
2.5	50	-5.8	1.2	50	-2.4	1.2	50	-3.4	(-7.0, 0.2)
3	50	-5.5	1.3	50	-2.5	1.3	50	-3.0	(-6.7, 0.7)
4	50	-3.9	1.2	50	-0.9	1.2	50	-3.0	(-6.6, 0.6)
6	50	-4.9	1.2	50	-1.2	1.2	50	-3.8	(-7.3, -0.3)
8	49	-4.9	1.3	50	-2.7	1.3	49	-2.2	(-5.9, 1.5)
12	50	-4.1	1.2	50	-1.2	1.2	50	-2.9	(-6.3, 0.5)
16	50	-5.2	1.4	50	-1.8	1.4	50	-3.4	(-7.4, 0.6)
23.5	50	-4.8	1.3	50	-2.5	1.3	50	-2.3	(-6.0, 1.4)

The largest upper bounds of the 2-sided 90% CI for the mean difference between Ospemifene 60 mg and placebo, and between Ospemifene 240 mg and placebo were 2.6 ms and 1.5 ms, respectively.

5.2.1.2 Assay Sensitivity Analysis

The statistical reviewer used the same statistical model to analyze moxifloxacin and placebo data. The results are presented in Table 7. The largest unadjusted 90% lower confidence interval is 4.6 ms. When considering Bonferroni multiple endpoint

adjustment, the largest lower confidence interval is 3.6 ms, which indicates that an at least 5 ms QTcI effect due to moxifloxacin was not detected in the study. However, the time profile for moxifloxacin is generally of the expected shape and shows a QT elongation effect.

Table 7: Analysis Results of Δ QTcI and $\Delta\Delta$ QTcI for Moxifloxacin

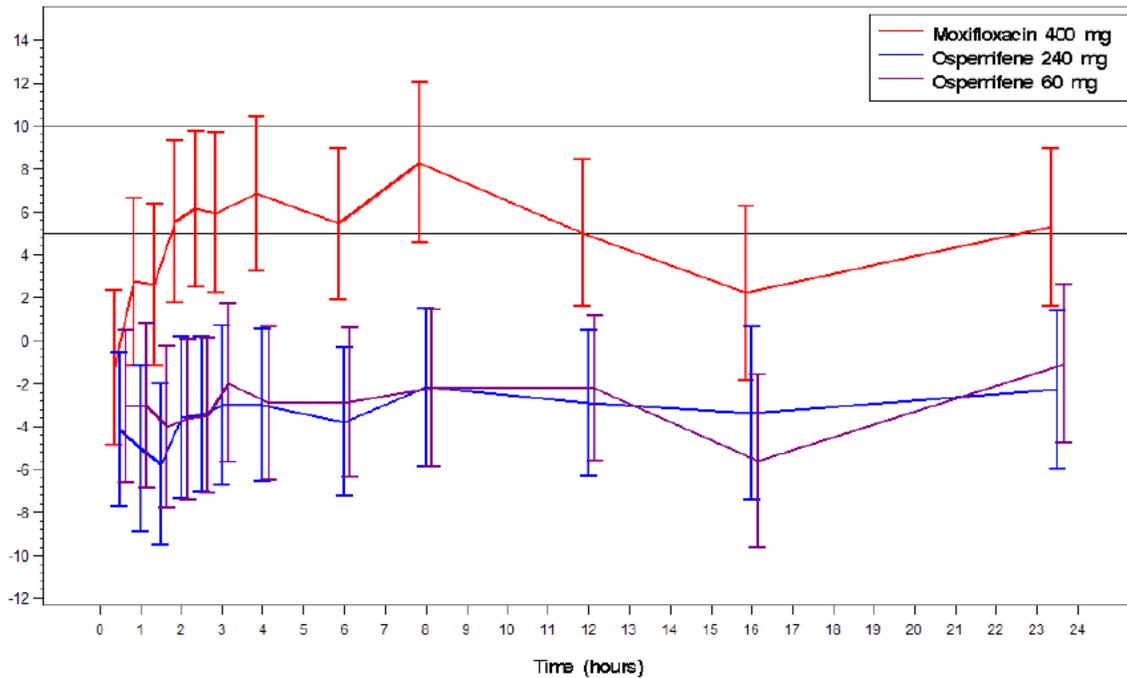
Time	Δ QTc: moxifloxacin			Δ QTc: placebo			$\Delta\Delta$ QTc			
	N	Mean	SD	N	Mean	SD	N	Mean	Unadjusted 90% CI	Adjusted* 90% CI
0.5	49	-4.6	1.2	50	-3.3	1.2	49	-1.2	(-4.8, 2.3)	(-5.8, 3.3)
1	50	-0.7	1.3	50	-3.4	1.3	50	2.7	(-1.1, 6.6)	(-2.2, 7.6)
1.5	49	0.6	1.3	49	-2.1	1.3	49	2.6	(-1.2, 6.4)	(-2.2, 7.4)
2	49	2.5	1.3	50	-3.0	1.3	49	5.5	(1.8, 9.3)	(0.7, 10.3)
2.5	49	3.7	1.2	50	-2.4	1.2	49	6.1	(2.5, 9.8)	(1.5, 10.7)
3	49	3.5	1.3	50	-2.5	1.3	49	6.0	(2.2, 9.7)	(1.2, 10.7)
4	49	5.9	1.2	50	-0.9	1.2	49	6.9	(3.2, 10.5)	(2.3, 11.4)
6	50	4.3	1.2	50	-1.2	1.2	50	5.4	(1.9, 9.0)	(1.0, 9.9)
8	49	5.6	1.3	50	-2.7	1.3	49	8.3	(4.6, 12.0)	(3.6, 13.0)
12	50	3.8	1.2	50	-1.2	1.2	50	5.0	(1.6, 8.4)	(0.7, 9.3)
16	50	0.4	1.4	50	-1.8	1.4	50	2.2	(-1.8, 6.3)	(-2.9, 7.3)
23.5	50	2.7	1.3	50	-2.5	1.3	50	5.3	(1.6, 9.0)	(0.6, 10.0)

* Bonferroni correction was applied for multiple endpoint adjustment for 4 time points.

5.2.1.3 Graph of $\Delta\Delta$ QTcI Over Time

The following figure displays the time profile of $\Delta\Delta$ QTcI for different treatment groups.

Figure 4: Mean and 90% CI $\Delta\Delta$ QTcI Timecourse



All CIs are unadjusted, including moxifloxacin.

5.2.1.4 Categorical Analysis

Table 8 lists the number of subjects as well as the number of observations whose QTcI values are ≤ 450 ms, between 450 ms and 480 ms. No subject's QTcI was above 480 ms.

Table 8: Categorical Analysis for QTcI

Treatment Group	N	Value ≤ 450 ms	450 ms < Value ≤ 480 ms	Value > 480 ms
Ospemifene 60 mg	50	50 (100%)	0 (0.0%)	0 (0.0%)
Ospemifene 240 mg	50	50 (100%)	0 (0.0%)	0 (0.0%)
Moxifloxacin 400 mg	50	50 (100%)	0 (0.0%)	0 (0.0%)
Placebo	50	49 (98.0%)	1 (2.0%)	0 (0.0%)

Table 9 lists the categorical analysis results for Δ QTcI. No subject's change from baseline was above 30 ms.

Table 9: Categorical Analysis of Δ QTcI

Treatment Group	Total N	Value \leq 30 ms	30 ms < Value \leq 60 ms
Ospemifene 60 mg	50	50 (100%)	0 (0.0%)
Ospemifene 240 mg	50	50 (100%)	0 (0.0%)
Moxifloxacin 400 mg	50	50 (100%)	0 (0.0%)
Placebo	50	50 (100%)	0 (0.0%)

5.2.2 HR Analysis

The same statistical analysis was performed based on HR. The point estimates and the 90% confidence intervals are presented in Table 10 and Table 11. The largest upper limits of 90% CI for the HR mean differences between Ospemifene 60 mg and placebo and Ospemifene 240 mg and placebo are 4.2 bpm and 4.2 bpm, respectively.

The outlier analysis results for HR are presented in Table 12.

Table 10: Analysis Results of Δ HR and $\Delta\Delta$ HR for Treatment Group A: Ospemifene 60 mg x 7 days

Time	Δ HR: Ospemifene			Δ HR: Placebo			$\Delta\Delta$ HR		
	N	Mean	SD	N	Mean	SD	N	Mean	90% CI
0.5	49	4.1	0.8	50	4.0	0.8	49	0.2	(-2.1, 2.4)
1	50	5.2	1.0	50	4.6	1.0	50	0.6	(-2.1, 3.3)
1.5	49	5.2	1.0	49	4.7	1.0	49	0.5	(-2.2, 3.2)
2	50	5.1	1.0	50	5.2	1.0	50	-0.1	(-2.7, 2.6)
2.5	50	4.0	0.9	50	4.1	0.9	50	-0.1	(-2.6, 2.5)
3	50	3.7	1.0	50	3.2	1.0	50	0.5	(-2.3, 3.3)
4	50	2.9	1.0	50	2.5	1.0	50	0.4	(-2.4, 3.2)
6	50	3.4	0.9	50	1.6	0.9	50	1.8	(-0.7, 4.2)
8	50	2.9	0.9	50	3.0	0.9	50	-0.1	(-2.6, 2.5)
12	50	3.8	0.9	50	2.5	0.9	50	1.3	(-1.1, 3.7)
16	50	3.8	0.8	50	2.9	0.8	50	0.9	(-1.2, 3.0)
23.5	50	4.7	0.9	50	3.3	0.9	50	1.3	(-1.3, 3.9)

Table 11: Analysis Results of Δ HR and $\Delta\Delta$ HR for Treatment Group B: Ospemifene 240 mg x 7 days

Time	Δ HR: Ospemifene			Δ HR: Placebo			$\Delta\Delta$ HR		
	N	Mean	SD	N	Mean	SD	N	Mean	90% CI
0.5	49	4.8	0.8	50	4.0	0.8	49	0.8	(-1.5, 3.1)
1	49	4.8	1.0	50	4.6	1.0	49	0.2	(-2.5, 2.9)
1.5	49	5.0	1.0	49	4.7	1.0	49	0.3	(-2.3, 3.0)
2	49	3.9	1.0	50	5.2	1.0	49	-1.3	(-4.0, 1.3)
2.5	50	4.5	0.9	50	4.1	0.9	50	0.4	(-2.2, 3.0)
3	50	3.4	1.0	50	3.2	1.0	50	0.2	(-2.6, 3.0)
4	50	2.4	1.0	50	2.5	1.0	50	-0.1	(-2.9, 2.7)
6	50	3.4	0.9	50	1.6	0.9	50	1.7	(-0.7, 4.2)
8	49	3.1	0.9	50	3.0	0.9	49	0.1	(-2.5, 2.7)
12	50	3.0	0.9	50	2.5	0.9	50	0.5	(-2.0, 2.9)
16	50	3.4	0.8	50	2.9	0.8	50	0.5	(-1.6, 2.6)
23.5	50	1.9	0.9	50	3.3	0.9	50	-1.4	(-4.0, 1.2)

Table 12: Categorical Analysis for HR

Treatment Group	N	HR < 100 ms	HR \geq 100 ms
Ospemifene 60 mg	50	50 (100%)	0 (0.0%)
Ospemifene 240 mg	50	49 (98.0%)	1 (2.0%)
Placebo	50	50 (100%)	0 (0.0%)

5.2.3 PR Analysis

The same statistical analysis was performed based on PR interval. The point estimates and the 90% confidence intervals are presented in Table 13 and Table 14. The largest upper limits of 90% CI for the PR mean differences between Ospemifene 60 mg and placebo and Ospemifene 240 mg and placebo are 4.4 ms and 4.3 ms, respectively.

The outlier analysis results for PR are presented in Table 15.

Table 13: Analysis Results of Δ PR and $\Delta\Delta$ PR for Treatment Group A: Ospemifene 60 mg X 7 days

Time	Δ PR: Ospemifene			Δ PR: Placebo			$\Delta\Delta$ PR		
	N	Mean	SD	N	Mean	SD	N	Mean	90% CI
0.5	49	2.5	1.2	50	1.3	1.2	49	1.2	(-2.0, 4.4)
1	50	1.4	1.1	50	0.3	1.0	50	1.1	(-1.8, 4.0)
1.5	49	1.8	1.1	49	0.5	1.1	49	1.3	(-1.6, 4.2)
2	50	0.8	1.0	50	0.3	1.0	50	0.5	(-2.1, 3.1)
2.5	50	0.5	1.0	50	0.7	1.0	50	-0.3	(-2.9, 2.4)
3	50	0.8	1.0	50	0.7	1.0	50	0.2	(-2.6, 2.9)
4	50	0.5	1.1	50	1.9	1.1	50	-1.4	(-4.5, 1.7)
6	50	1.5	1.0	50	2.9	0.9	50	-1.4	(-4.0, 1.2)
8	50	2.7	0.9	50	0.8	0.9	50	1.9	(-0.7, 4.4)
12	50	1.4	0.9	50	1.3	0.9	50	0.1	(-2.3, 2.6)
16	50	1.1	0.9	50	1.3	0.9	50	-0.2	(-2.8, 2.4)
23.5	50	-0.3	1.1	50	-1.4	1.1	50	1.1	(-2.0, 4.1)

Table 14: Analysis Results of Δ PR and $\Delta\Delta$ PR for Treatment Group B: Ospemifene 240 mg X 7 days

Time	Δ PR: Ospemifene			Δ PR: Placebo			$\Delta\Delta$ PR		
	N	Mean	SD	N	Mean	SD	N	Mean	90% CI
0.5	49	1.3	1.2	50	1.3	1.2	49	0.0	(-3.1, 3.2)
1	49	-0.3	1.1	50	0.3	1.0	49	-0.6	(-3.5, 2.3)
1.5	49	-0.4	1.1	49	0.5	1.1	49	-0.9	(-3.8, 2.0)
2	49	-0.6	1.0	50	0.3	1.0	49	-0.9	(-3.5, 1.8)
2.5	50	0.2	1.0	50	0.7	1.0	50	-0.5	(-3.2, 2.1)
3	50	0.4	1.0	50	0.7	1.0	50	-0.3	(-3.1, 2.5)
4	50	1.0	1.1	50	1.9	1.1	50	-0.9	(-4.0, 2.2)
6	50	3.6	0.9	50	2.9	0.9	50	0.7	(-1.9, 3.3)
8	49	0.5	0.9	50	0.8	0.9	49	-0.3	(-2.9, 2.3)
12	50	0.2	0.9	50	1.3	0.9	50	-1.0	(-3.5, 1.4)
16	50	-0.3	0.9	50	1.3	0.9	50	-1.6	(-4.1, 1.0)
23.5	50	-0.1	1.1	50	-1.4	1.1	50	1.3	(-1.8, 4.3)

Table 15: Categorical Analysis for PR

Treatment Group	N	PR < 200 ms	PR \geq 200 ms
Ospemifene 60 mg	50	50 (100%)	0 (0.0%)
Ospemifene 240 mg	50	49 (98.0%)	1 (2.0%)
Placebo	50	47 (94.0%)	3 (6.0%)

5.2.4 QRS Analysis

The same statistical analysis was performed based on QRS interval. The point estimates and the 90% confidence intervals are presented in Table 16 and Table 17. The largest upper limits of 90% CI for the QRS mean differences between Ospemifene 60 mg and placebo and Ospemifene 240 mg and placebo are 1.6 ms and 1.3 ms, respectively.

There are no subjects who experienced QRS interval greater than 110 ms in both Ospemifene 60-mg and Ospemifene 240-mg groups.

**Table 16: Analysis Results of Δ QRS and $\Delta\Delta$ QRS for Treatment Group A:
Ospemifene 60 mg X 7 days**

Time	Δ QRS: Ospemifene			Δ QRS: Placebo			$\Delta\Delta$ QRS		
	N	Mean	SD	N	Mean	SD	N	Mean	90% CI
0.5	49	-0.8	0.5	50	0.2	0.5	49	-1.0	(-2.4, 0.3)
1	50	-0.4	0.6	50	0.3	0.6	50	-0.7	(-2.3, 0.9)
1.5	49	-0.3	0.5	49	-0.2	0.5	49	-0.1	(-1.6, 1.3)
2	50	-1.0	0.5	50	-0.3	0.5	50	-0.7	(-2.0, 0.6)
2.5	50	-0.3	0.5	50	0.5	0.5	50	-0.8	(-2.1, 0.5)
3	50	-0.3	0.4	50	-0.1	0.4	50	-0.1	(-1.3, 1.1)
4	50	-0.2	0.4	50	0.3	0.4	50	-0.5	(-1.7, 0.7)
6	50	-0.4	0.5	50	0.1	0.5	50	-0.5	(-1.8, 0.8)
8	50	-0.3	0.5	50	-0.6	0.5	50	0.3	(-0.9, 1.6)
12	50	-0.5	0.5	50	0.4	0.5	50	-0.9	(-2.3, 0.4)
16	50	-0.6	0.5	50	0.5	0.5	50	-1.1	(-2.5, 0.3)
23.5	50	-0.5	0.5	50	0.4	0.5	50	-0.9	(-2.2, 0.4)

**Table 17: Analysis Results of Δ QRS and $\Delta\Delta$ QRS for Treatment Group B:
Ospemifene 240 mg X 7 days**

Time	Δ QRS: Ospemifene			Δ QRS: Placebo			$\Delta\Delta$ QRS		
	N	Mean	SD	N	Mean	SD	N	Mean	90% CI
0.5	49	-0.4	0.5	50	0.2	0.5	49	-0.7	(-2.0, 0.7)
1	49	-0.0	0.6	50	0.3	0.6	49	-0.3	(-1.9, 1.3)
1.5	49	-0.3	0.5	49	-0.2	0.5	49	-0.1	(-1.6, 1.3)
2	49	-0.3	0.5	50	-0.3	0.5	49	0.0	(-1.2, 1.3)
2.5	50	-1.0	0.5	50	0.5	0.5	50	-1.5	(-2.8, -0.2)
3	50	-0.6	0.4	50	-0.1	0.4	50	-0.5	(-1.7, 0.7)
4	50	-0.6	0.4	50	0.3	0.4	50	-0.9	(-2.0, 0.3)
6	50	-0.9	0.5	50	0.1	0.5	50	-1.0	(-2.3, 0.3)
8	49	-1.0	0.5	50	-0.6	0.5	49	-0.4	(-1.6, 0.9)
12	50	-0.6	0.5	50	0.4	0.5	50	-1.0	(-2.4, 0.3)
16	50	-1.4	0.5	50	0.5	0.5	50	-1.9	(-3.3, -0.5)
23.5	50	-1.1	0.5	50	0.4	0.5	50	-1.5	(-2.7, -0.2)

5.3 CLINICAL PHARMACOLOGY ASSESSMENTS

The relationship between $\Delta\Delta$ QTcI and ospemifene, 4-hydroxyospemifene and 4'-hydroxyospemifene concentrations is visualized in Figure 5, Figure 6, and Figure 7, respectively with no evident exposure-response relationship.

Figure 5: $\Delta\Delta$ QTcI vs. Ospemifene concentration

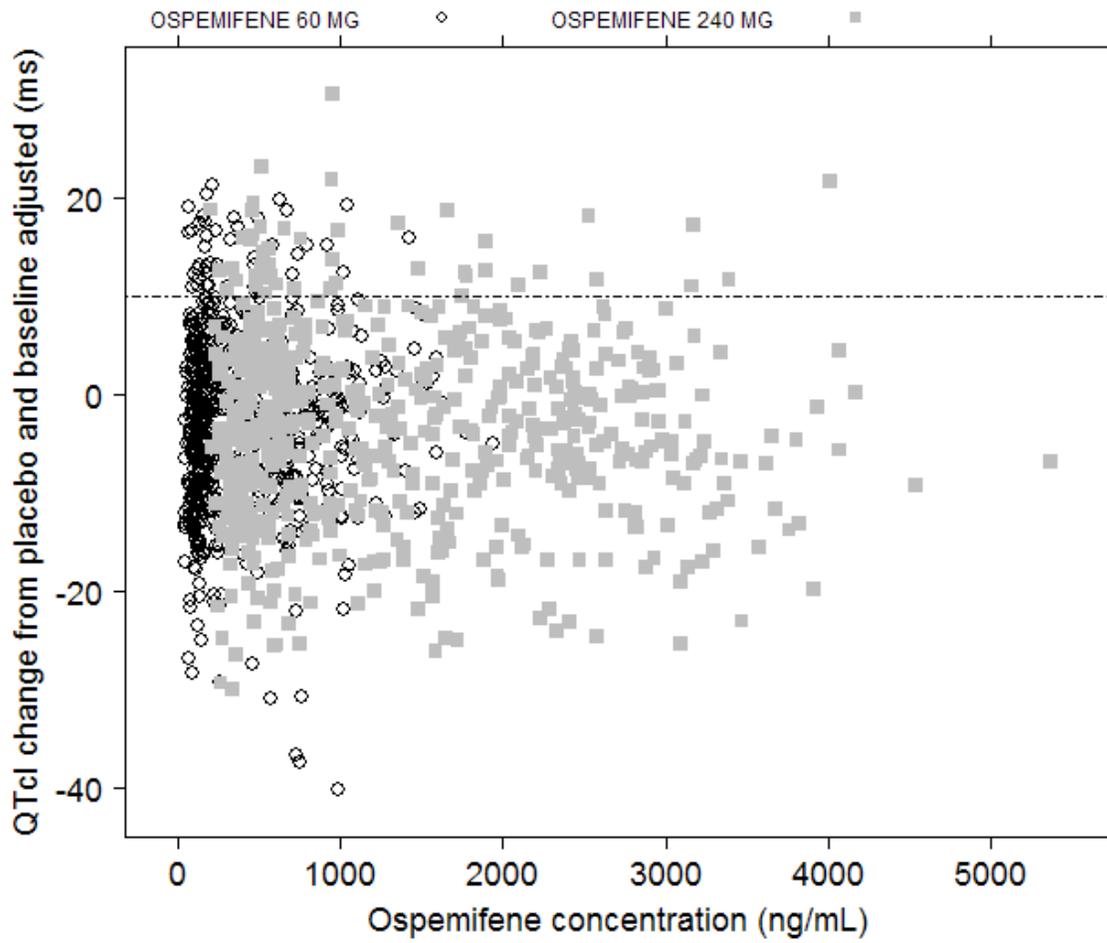


Figure 6: $\Delta\Delta$ QTcI vs. 4-Hydroxyospemifene concentration

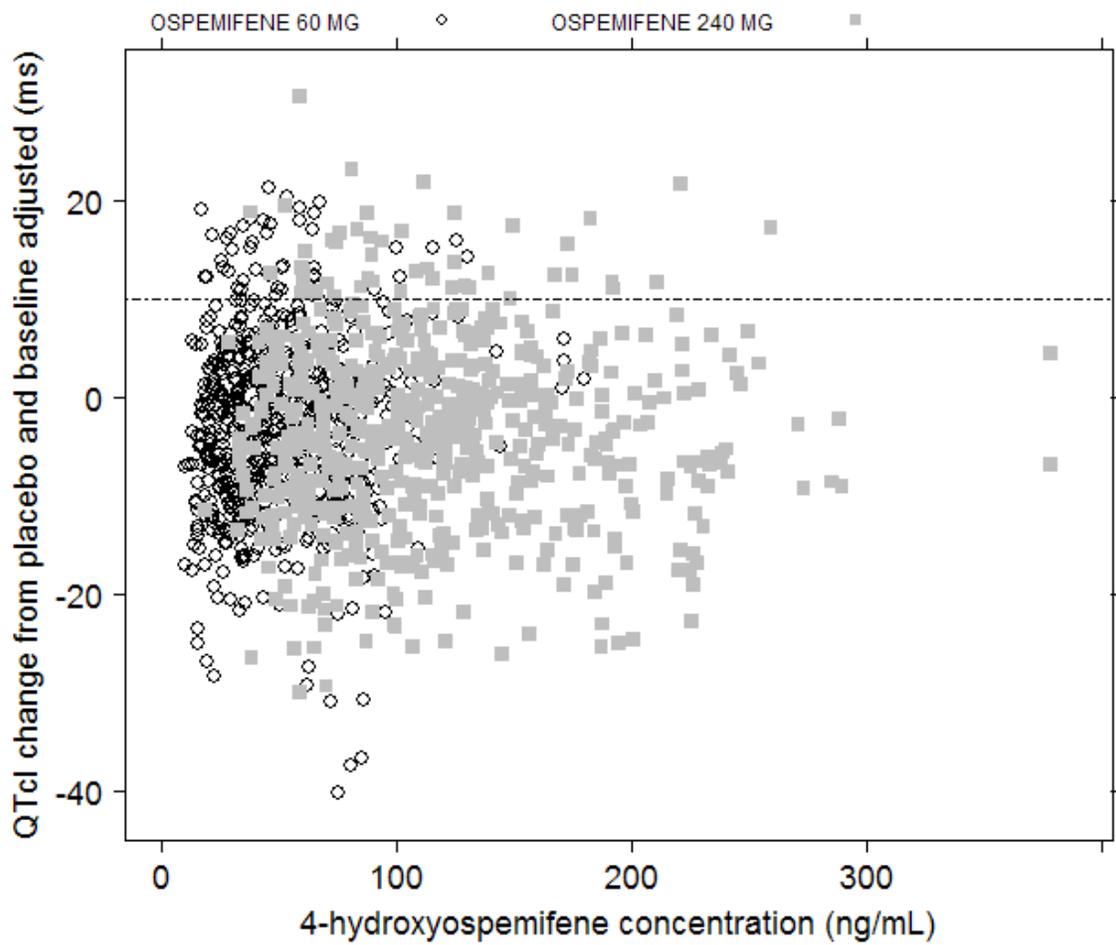
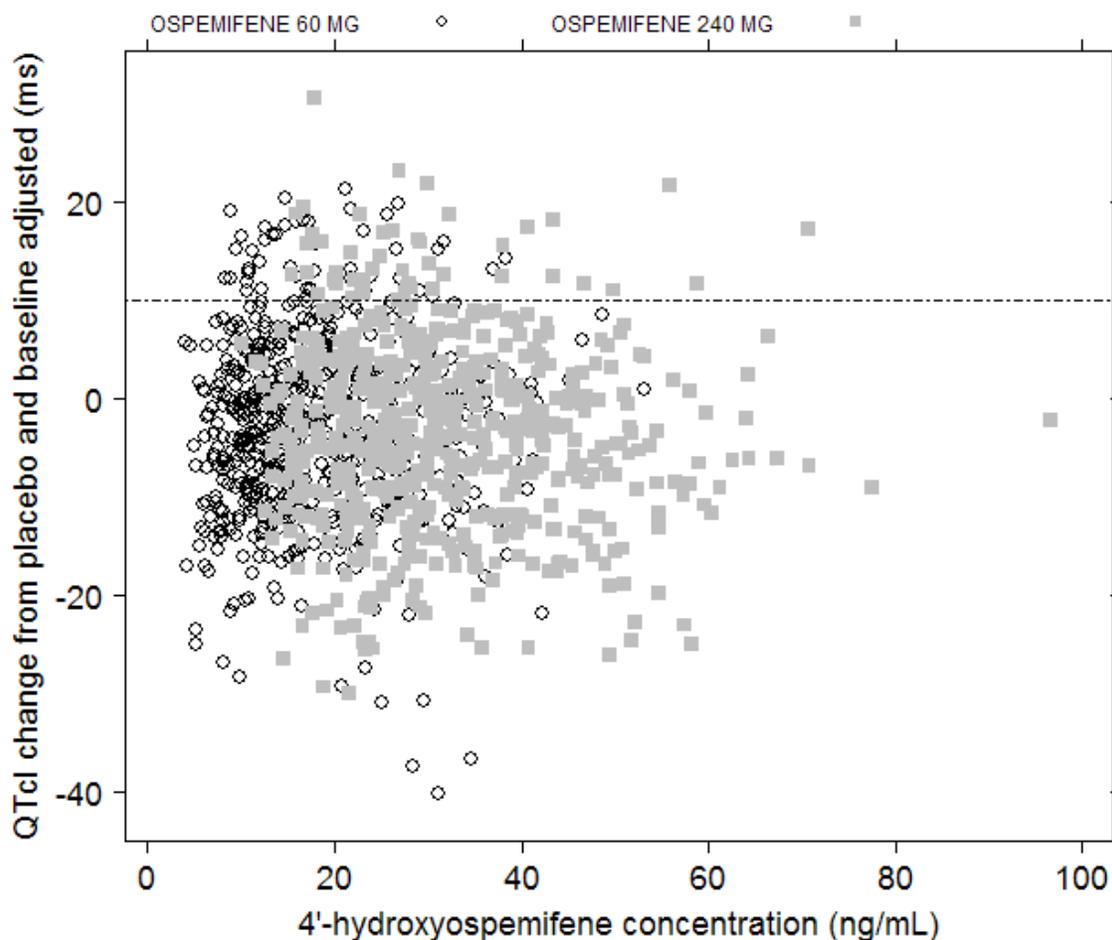


Figure 7: $\Delta\Delta$ QTcI vs. 4'-Hydroxyospemifene concentration



5.4 CLINICAL ASSESSMENTS

5.4.1 Safety assessments

None of the events identified to be of clinical importance per the ICH E 14 guidelines, i.e., syncope, seizure, significant ventricular arrhythmias or sudden cardiac death, occurred in this study.

5.4.2 ECG assessments

Waveforms from the ECG warehouse were reviewed. According to ECG warehouse statistics 99% of the ECGs were annotated in the primary lead II, and few ECGs were reported to have significant QT bias, according to the automated algorithm. Overall ECG acquisition and interpretation in this study appears acceptable.

5.4.3 PR and QRS Interval

No clinically relevant effects were seen on PR or QRS.

6 APPENDIX

6.1 HIGHLIGHTS OF CLINICAL PHARMACOLOGY

Therapeutic dose	60 mg once daily	
Maximum tolerated dose	Maximum tolerated dose has not been identified. NOAEL doses Mouse: ≥ 2000 mg/kg/day (13-week) Rat: ≥ 300 mg/kg/day (26-week) Monkey: ≥ 150 mg/kg/day (39-week)	
Principal adverse events	The most commonly reported ($\geq 3\%$) treatment emergent adverse events for ospemifene 60 mg per day in the Phase 2/3 program were: hot flush, headache, urinary tract infection, nasopharyngitis, vaginal discharge, muscle spasm, vulvovaginal candidiasis, sinusitis, back pain and vulvovaginal mycotic infection (Table 39, ISS). No dose limiting adverse events were observed with ospemifene up to a single dose of 800 mg.	
Maximum dose tested	Single Dose	800 mg
	Multiple Dose	240 mg once daily, 7 days
Exposures Achieved at Maximum Tested Dose	Single Dose	Mean (%CV) at 800 mg C_{max} : 445.5 ng/mL (64.1%) AUC: 3998 ng•hr/mL (52.8%) (3044001)
	Multiple Dose	Mean (%CV) at 240 mg once daily in females C_{max} : 3101 ng/mL (18.6%) AUC: 21590 ng•hr/mL (25.6%) (15-50824)
Range of linear PK	Up to 240 mg under the fed state	
Accumulation at steady state	Accumulation ratios (90%CI) after repeated doses of 60 mg once daily (15-50927) C_{max} : 1.222 (1.087-1.374) AUC: 1.702 (1.551-1.869)	
Metabolites	Affinities (K_i values) of ospemifene and its metabolites to estrogen receptor (ER) α and β 4-hydroxyospemifene: ER α , 270 nM; ER β , 210 nM 4'-hydroxyospemifene: ER α , 460 nM; ER β , 570 nM Ospemifene: ER α , 380 nM; ER β , 410 nM	
Absorption	Absolute/Relative Bioavailability	Absolute bioavailability has not been identified.
	T _{max}	Median (range) at 60 mg once daily at steady state: 3.0 hr (1-4) for ospemifene 3.8 hr (1.5-24) for 4-hydroxyospemifene (15-50927)
Distribution	V _d /F or V _d	Mean (%CV) of V _d /F 448 L (19.7%) (15-50920)
	% bound	>99% (15-50920)

Elimination	Route	Approximately 75% and 7% of the dose was excreted in feces and urine, respectively. Less than 0.2% of the ospemifene dose was excreted unchanged in urine. (15-50206)
	Terminal t _{1/2}	25.0 hr (20.8%) for ospemifene 29.4 hr (17.3%) for 4-hydroxyospemifene (15-50206)
	CL/F or CL	Population mean (%CV of Inter-individual variability): 9.16 L/hr (36.3%) (Population PK analysis) (CTD2.7.2.3.4)
Intrinsic Factors	Age	No age effect was identified in the population PK analysis. The mean values of Bayesian-estimated CL/F for age groups of <65 years, 65-<75 years and ≥75 years were 9.75 L/hr (N=859), 9.09 L/hr (N=211) and 9.18 L/hr (N=21), respectively. (CTD2.7.2.3.2)
	Sex	No significant pharmacokinetic differences have been observed between males and females. (15-50824)
	Race	No race effect was identified in the population PK analysis. The mean values of Bayesian estimated CL/F for Caucasian (n = 1016) and non-Caucasian (n = 75) subjects were 9.65 L/hr and 9.13 L/hr, respectively. (CTD 2.7.2.3.2)
	Hepatic & Renal Impairment	1.1% higher C _{max} and 28.6 % higher AUC in moderate hepatic impairment compared with normal hepatic functions (15-50920) 20.7% lower C _{max} and 19.6% higher AUC in severe renal impairment compared with normal renal functions (15-50921)
Extrinsic Factors	Drug interactions	Fluconazole (15-50823) Fluconazole increased C _{max} by 65.9% and AUC by 174%. Rifampin (15-50716) Rifampin decreased C _{max} by 50.7% and AUC by 58.5%. Ketoconazole (15-50716) Ketoconazole increased C _{max} by 45.7% and AUC by 42.2%. Omeprazole (15-50823) Omeprazole increased C _{max} by 20.0% and AUC by 17.1%.
	Food Effects	144% higher C _{max} and 87.1% higher AUC under the fed condition (high-fat meal) compared with the fasted condition (CTD 2.7.1.3.2)

Expected High Clinical Exposure Scenario	Worst case scenario: Concomitant administration of a strong CYP3A and CYP2C9 inhibitor (eg. fluconazole) to hepatic impaired patients. The expected fold-changes in C _{max} and AUC were 1.7 (1.011 x 1.659) and 3.5 (1.286 x 2.736), respectively, which are covered by the supra-therapeutic dose of 240 mg once daily with approximately 4-fold higher exposure compared with the therapeutic dose (60 mg).
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**Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology
Office of Medication Error Prevention and Risk Management**

Label and Labeling Review

Date: December 17, 2012

Reviewer: Manizheh Siahpoushan, PharmD
Division of Medication Error Prevention and Analysis

Team Leader: Zachary Oleszczuk, PharmD
Division of Medication Error Prevention and Analysis

Division Director: Carol Holquist, R.Ph.
Division of Medication Error Prevention and Analysis

Drug Name(s) and Strengths: Ospena (Ospemifene) Tablets, 60 mg

Application Type/Number: NDA 203505

Applicant/sponsor: Shionogi Inc.

OSE RCM #: 2012-1048

*** This document contains proprietary and confidential information that should not be released to the public.***

1 INTRODUCTION

This review evaluates the proposed container labels, carton, and insert labeling for Osphe^{na} (Ospemifene) Tablets for NDA 203505 for areas of vulnerability that could lead to medication errors. The review responds to a request from the Division of Reproductive and Urology Products (DRUP).

1.1 REGULATORY HISTORY

The Applicant submitted container labels, carton, and insert labeling for (b) (4) (Ospemifene) Tablets, 60 mg on April 26, 2012. However, the proposed proprietary name, (b) (4) was found unacceptable by DMEPA (b) (4). This concern was communicated to the Applicant during a June 18, 2012 teleconference and the firm subsequently withdrew the name from consideration on June 20, 2012.

The Applicant submitted updated labels and labeling on October 3, 2012 following receipt of DMEPA's September 14, 2012 acceptance letter for the second proposed proprietary name for this product, Osphe^{na}.

1.2 PRODUCT INFORMATION

The following product information is provided in the April 26, 2012 proprietary name submission.

- Active Ingredient: Ospemifene
- Indication of Use: 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).
- Route of administration: Oral
- Dosage form: Tablet
- Strength: 60 mg
- Dose and Frequency of Administration: One tablet orally once daily with food.
- How Supplied: Bottles of 100 and blister pack of 30 tablets containing 2 blister cards of 15 tablets each.
- Storage: Room temperature
- Container and Closure System: (b) (4), HDPE (white) plastic bottles (100 count) with a white, (b) (4) round, senior friendly, child-resistant and tamper-evident screw cap, and (b) (4) aluminum foil, push through blister packs.

2 METHODS AND MATERIALS REVIEWED

Using principles of Human Factors and Failure Mode and Effects Analysis¹, the Division of Medication Error Prevention and Analysis (DMEPA) evaluated the following:

- Container Labels submitted on October 3, 2012 (Appendix A)
- Carton Labeling (trade and professional sample blister packs) submitted on October 3, 2012 (Appendix A)
- Insert Labeling submitted on April 26, 2012 (no image)

3 DEFICIENCIES NOTED

Our evaluation of the Applicant's proposed labels noted that the proprietary name, established name, dosage form, and strength are not uniformly presented on the 100 count container label, 30-count blister pack, and the 15-count sample blister pack labeling. Additionally, the established name is not ½ the size of the proprietary name or prominently displayed, and the graphic above the proprietary name and across the blister packs is too prominent and distracts from other important information. The company logo on the 100 count container label competes in prominence with the proprietary name, and the word oral appears in the dosage form statement.

4 RECOMMENDATIONS

We recommend the following revisions be implemented prior to the approval of this NDA.

A. *General Comments for Container Labels and Carton Labeling*

1. Ensure the established name is presented in a font and prominence that is ½ the size of the proprietary name, taking into account all pertinent factors including typography, layout, contrast and other printing features so that it is in accordance with 21 CFR 201.10(g)(2).
2. Remove the word (b) (4) from the dosage form statement (b) (4) (b) (4) to be consistent with the presentation of the dosage form presentation in the insert labeling. The revised presentation would appear as:

Osphena
(Ospemifene) Tablets
60 mg

B. *Container Label (100 count)*

1. To improve readability, revise the proprietary name to title case, with only the first letter capitalized, 'Osphena'. Words set in upper and lower case

¹ Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

form recognizable shapes, making them easier to read than the rectangular shape that is formed by words set in all capital letters.

2. Decrease the prominence of the company logo on the principal display panel to ensure it does not compete with the proprietary name and product strength. Additionally, reducing the prominence of the company logo will allow for more space to be used for prominent display of the warning statement 'For oral use only'.

C. *Blister Carton Labeling (15-count sample and 30-count trade)*

1. 30-count trade only: include the statement 'Two blister cards of 15 tablets each' under the quantity statement to improve clarity. The revised presentation may appear as follows:

'30 tablets
(Two blister cards of 15 tablets)'

2. Revise the statement (b) (4) to read as follows to improve the clarity of the statement: 'Take one tablet orally (by mouth) once daily with food'. Additionally, ensure this statement appears on all blister labels.
3. Delete or reduce the prominence of the graphic that appears above the proprietary name as well as across the blister carton labeling. As currently presented, the graphic distracts attention from the proprietary name, established name, product strength, and newly added warning statement 'For oral use only'.

If you have further questions or need clarifications, please contact OSE Project Manager, Marcus Cato, at 301-796-3903.

2 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

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/s/

MANIZHEH SIAHPOUSHAN
12/17/2012

ZACHARY A OLESZCZUK
12/17/2012

CAROL A HOLQUIST
12/17/2012

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

CLINICAL INSPECTION SUMMARY

DATE: December 14, 2012

TO: George Lyght, Regulatory Project Manager
Teresa van der Vlugt, M.D., M.P.H., Medical Officer
Division of Reproductive and Urologic Products

FROM: Roy Blay, Ph.D.
Good Clinical Practice Assessment Branch
Division of Good Clinical Practice Compliance
Office of Scientific Investigations

THROUGH: Janice Pohlman, M.D., M.P.H.
Team Leader
Good Clinical Practice Assessment Branch
Division of Good Clinical Practice Compliance
Office of Scientific Investigations

Susan D. Thompson, M.D.
Acting Branch Chief
Good Clinical Practice Assessment Branch
Division of Good Clinical Practice Compliance
Office of Scientific Investigations

SUBJECT: Evaluation of Clinical Inspections

NDA: 203505

APPLICANT: Shionogi, Inc.

DRUG: Ospemifene tablets

NME: Yes

THERAPEUTIC CLASSIFICATION: Standard Review

INDICATION: Treatment of moderate to severe symptoms of vulvar and vaginal atrophy due to menopause, such as dyspareunia and/or vaginal dryness

CONSULTATION REQUEST DATE:	July 31, 2012
CLINICAL INSPECTION SUMMARY DATE:	December 19, 2012
DIVISION ACTION GOAL DATE:	February 26, 2013
PDUFA DATE:	February 26, 2013

I. BACKGROUND:

The Applicant submitted this NDA to support the use of ospemifene tablets for the treatment of moderate to severe symptoms of vulvar and vaginal atrophy due to menopause, such as dyspareunia and/or vaginal dryness

Two pivotal studies (Protocol 15-50310, entitled “Efficacy and Safety of Ospemifene in the Treatment of Vulvar and Vaginal Atrophy (VVA) in Postmenopausal Women: A 12-week, Randomized, Double-Blind, Placebo-Controlled, Parallel-Group Study Comparing Oral Ospemifene 30 mg and 60 mg Daily Doses with Placebo”, and Protocol 15-50821, entitled “Efficacy and Safety of Ospemifene in the Treatment of Moderate to Severe Vaginal Dryness and Vaginal Pain Associated with Sexual Activity, Symptoms of Vulvar and Vaginal Atrophy (VVA), Associated with Menopause: a 12-Week, Randomized, Double-Blind, Placebo-Controlled, Parallel-Group Study Comparing Oral Ospemifene 60 mg Daily Dose with Placebo in Postmenopausal Women”) were inspected in support of the indication.

The clinical sites below were selected based on their participation in the two primary 12-week safety and efficacy clinical trials submitted in support of the proposed indication for ospemifene. Each site enrolled large numbers of study participants as compared to the other clinical sites who participated in both clinical trials. All three clinical sites reported a higher number of protocol violations/deviations in the second 12-week study (Study 15-50821) than the first 12-week study (Study 15-50310).

The sponsor was also inspected consistent with OSI procedures for inspecting sponsors which submit applications for NMEs.

II. RESULTS (by Site):

Name of CI, Location	Protocol #/ Site #/ # of Subjects	Inspection Dates	Final Classification
Marina Raikhel, M.D. Torrance Clinical Research 25043 Narbonne Avenue Lomita, CA 90717	15-50310/ 1002/ 31 (enrolled)	9-16 Oct 2012	NAI
Marina Raikhel, M.D. (as above)	15-50821/ 152/ 40 (enrolled)	9-16 Oct 2012	NAI
Garn Mabey, M.D. Affiliated Clinical Research, Inc. 1881 N. Tenaya Way Las Vegas, NV 89128	15-50310/ 4633/ 65 (enrolled)	9-19 Oct 2012	VAI. Pending final classification.
Garn Mabey, M.D. (as above)	15-50821/ 108/ 33 (enrolled)	9-19 Oct 2012	VAI. Pending final classification.
R. Hal Younglove, M.D. Radiant Research 6300 Glenwood Street Bldg. 10, Suite 100 Overland Park, KS 66202	15-50310/ 1009/ 16 (enrolled)	10-13 Sep 2012	NAI
R. Hal Younglove, M.D. (as above)	15-50821/ 183/ 33 (enrolled)	10-13 Sep 2012	NAI
Shionogi USA, Inc. 300 Campus Drive, Suite 300 Florham Park, NJ 07932	(Sponsor)	4 Oct–5 Nov 2012	VAI. Pending final classification.

Key to Classifications

NAI = No deviation from regulations.

VAI = Deviation(s) from regulations.

OAI = Significant deviations from regulations. Data unreliable.

Pending = Preliminary classification based on information in Form FDA 483 or preliminary communication with the field; EIR has not been received from the field or complete review of EIR is pending.

1. Marina Raikhel, M.D.

Torrance Clinical Research
25043 Narbonne Avenue
Lomita, CA 90717

- a. What was inspected:** At this site, for Protocol 15-50310, 87 subjects were screened, 31 were enrolled, and 27 subjects completed the study. For Protocol 15-50821, 94 subjects were screened, 40 were enrolled, and 39 subjects completed the study. For both protocols, an audit of all CRFs and corresponding source documents for all randomized subjects was conducted. Signed informed consent forms for both studies were present for all subjects. Other records reviewed included, but were not limited to, screening and enrollment forms, inclusion/exclusion criteria, IRB correspondence, monitor visit logs, subject source documents including concomitant medications, protocol deviations, adverse events, and subject diaries, and case report forms (CRFs).

- b. General observations/commentary:** A Form FDA 483 was not issued at the conclusion of the inspection. Review of the records noted above revealed no significant discrepancies or regulatory violations.
- c. Assessment of data integrity:** The study appears to have been conducted adequately, and the data submitted by this site may be used in support of the respective indication.

2. Garn Mabey, M.D.

Affiliated Clinical Research, Inc.
1881 N. Tenaya Way
Las Vegas, NV 89128

- a. What was inspected:** At this site, for Protocol 15-50310, 162 subjects were screened, 65 were enrolled, and 58 subjects completed the study. For Protocol 15-50821, 61 subjects were screened, and 33 subjects were enrolled and completed the study. An audit of the records of 20 subjects in Protocol 15-50310 was conducted. The records of an additional 12 subjects were audited for Protocol 15-50821. Signed informed consent forms were present for all enrolled subjects for both protocols. Records reviewed included, but were not necessarily limited to, protocols and amendments, IRB correspondence, inclusion/exclusion criteria, source documents, monitoring logs, sponsor correspondence, randomization tables, data queries, and test article storage and accountability.
- b. General observations/commentary:** A Form FDA 483 was issued at the conclusion of the inspection. Observations for Protocol 15-50310 included five subjects whose transvaginal ultrasound (TVU) examinations were initially confirmed by a local radiology group rather than by the protocol-required central read facility. Subjects 002, 005, 007, 008, and 009, were randomized based on the local reading rather than the central reading. Subsequently, the central reader confirmed that these subjects met appropriate inclusion criteria. Ten subjects were reported as having visits outside the protocol specified time-periods. These visits were from 3 to 15 days out-of-window due to delayed diagnostic results being received from the radiology group with respect to TVU findings. Seven subjects did not sign the most recent version (4/27/06) of the informed consent form at the time of their visits which ranged from 5/2/06 through 5/11/06. The change in informed consent version was related to addition of a new radiology facility and did not contain any new safety information.

Observations for Protocol 15-50821 included Subject 026 who did not meet inclusion criterion #10 which required that subjects report moderate to severe vaginal dryness or vaginal pain associated with sexual activity as the self-reported, most bothersome (MBS) VVA symptoms at the screening and randomization visits (Visits 1 and 2). Despite not meeting an inclusion criterion, the subject was randomized to the study and completed the study. Subject 057 was randomized to the study prior to the site's receipt of documentation of a negative endometrial biopsy, a requirement for study entry. Physical examinations of at least six subjects omitted assessments of their extremities. Dr. Mabey responded adequately to the inspection findings in a letter dated October 24, 2012, in which he committed to the implementation of additional staff training and study practices to eliminate the recurrence of the findings noted above.

- c. Assessment of data integrity:** The review division may wish to consider the exclusion of the data for Subject 026 in Protocol 15-50821 as this subject met an exclusion criterion but was randomized anyway and completed the study; otherwise, the deviations noted above would not appear to have a significant effect on data quality or subject safety. Other than the deviations noted above, the study appears to have been conducted adequately, and the data generated by this site appear acceptable in support of the respective indication.

Note: The observations noted above for Dr. Mabey's clinical site are pending a final review of the Establishment Inspection Report (EIR) and sign-off on the letter to Dr. Mabey. An inspection summary addendum will be generated if conclusions change upon review of the EIR.

3. R. Hal Younglove, M.D.

Radiant Research
6300 Glenwood Street
Bldg. 10, Suite 100
Overland Park, KS 66202

- a. What was inspected:** At this site, for Protocol 15-50310, 39 subjects were screened, and 16 subjects were enrolled and completed the study. For Protocol 15-50821, 84 subjects were screened, and 33 subjects were enrolled and completed the study. For both protocols, the study records of all subjects including screen failures and randomized subjects were audited. Signed informed consent forms for both studies were present for all subjects. Other records reviewed included, but were not limited to, IRB approvals, inclusion/exclusion criteria, protocol deviations, subject files, case report forms, financial disclosure, and test article control.
- b. General observations/commentary:** A Form FDA 483 was not issued at the conclusion of the inspection. Review of the records noted above revealed no significant discrepancies or regulatory violations.
- c. Assessment of data integrity:** The study appears to have been conducted adequately, and the data generated by this site appear acceptable in support of the respective indication.

4. Shionogi USA, Inc.

300 Campus Drive, Suite 300
Florham Park, NJ 07932

- a. What was inspected:** The sponsor's oversight over the clinical trials was inspected as were the monitoring practices over the investigator sites. The monitoring files for Sites 1002, 4633, and 1009 for Protocol 15-50310 and for Sites 152, 108, and 183 for Protocol 15-50821 were reviewed. Adverse event reporting, electronic data capture (used only for Protocol 15-50821), and documentation of the final disposition of the investigational product were also reviewed.

- b. General observations/commentary:** A Form FDA 483 was issued at the conclusion of the inspection. Observations included the failure of the sponsor to obtain in writing the final disposition of all returned and unused investigational product (IP). There was no documentation regarding the final disposition of approximately 1124 bottles of the IP for Protocol 15-50310 and approximately 1296 bottles of IP for Protocol 15-50821. The sponsor responded in writing in a letter dated November 13, 2012, in which the sponsor noted that the previous sponsor did not obtain a written statement regarding the disposition of IP from the responsible CRO. The sponsor submitted updated SOPs that should address the need for written documentation of IP disposition for future studies.
- c. Assessment of data integrity:** 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.

Note: 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 summary addendum will be generated if conclusions change upon review of the EIR.

III. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

The clinical investigator sites of Drs. Raikehl, Mabey, and Younglove were inspected in support of this NDA. Drs. Raikehl and Younglove were not issued Form FDA 483s. Dr. Mabey was issued a Form FDA 483. The review division may wish to exclude the data from Subject 026 at Dr. Mabey's site for the reason noted above. 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.

Note: The observations noted above for Dr. Mabey and the sponsor, Shionogi, are based on reviews of draft Establishment Inspection Reports (EIRs). An inspection summary addendum will be generated if conclusions change upon receipt and review of the final EIRs.

{See appended electronic signature page}

Roy Blay, Ph.D.
Good Clinical Practice Assessment Branch
Division of Good Clinical Practice Compliance
Office of Scientific Investigations

CONCURRENCE:

{See appended electronic signature page}

Janice Pohlman, M.D., M.P.H.
Team Leader
Good Clinical Practice Assessment Branch
Division of Good Clinical Practice Compliance
Office of Scientific Investigations

CONCURRENCE:

{See appended electronic signature page}

Susan D. Thompson, M.D.
Acting Branch Chief
Good Clinical Practice Assessment Branch
Division of Good Clinical Practice Compliance
Office of Scientific Investigations

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/s/

ROY A BLAY
12/18/2012

JANICE K POHLMAN
12/18/2012

SUSAN D THOMPSON
12/18/2012

DGCPC/OSI CONSULT: Request for Clinical Inspections

Date: July 31, 2012

To:
Susan Thompson, M.D., Acting Branch Chief, GCPAB
CDER OSI PM Track
Roy Blay, Ph.D., OSI Reviewer
Division of Good Clinical Practice Compliance
Office of Scientific Investigations
Office of Compliance/CDER

Through: Shelley R. Slaughter, M.D., Ph.D.,
Clinical Team Leader
Division of Reproductive and Urologic Products (DRUP)

Through: Theresa van der Vlugt, M.D., M.P.H.
Medical Officer
DRUP

From: George Lyght, R.Ph, PharmD.
Sr. Regulatory Health Project Manager
DRUP

Subject: Request for Clinical Site Inspections

I. General Information

Application#: NDA 203505
IND#: 067216

Shionogi USA, Inc.
Ting Chen, M.S., Director, Regulatory Affairs
300 Campus Drive
Florham Park, NJ 07932
Telephone (973) 966-6900
Fax (973) 966-2820
tchen@shionogi.com

Drug Proprietary Name: TBD
Generic Drug Name: ospemifene
NME: Yes
DGCPC/OSI Consult
version: 07/9/2012

Review Priority: Standard

Study Population includes < 17 years of age : No

Is this for Pediatric Exclusivity: Yes

Proposed New Indication(s): The treatment of vulvar and vaginal atrophy

PDUFA: February 26, 2013

Action Goal Date: February 26, 2013

Inspection Summary Goal Date: December 5, 2012

II. Protocol/Site Identification

Include the Protocol Title or Protocol Number for all protocols to be audited. Complete the following table (Note: ALL items listed are required, to process inspection request. Failure to provide complete information will result in delay of inspection process).

Site # Name Address (Contact Information: Ph. No., E-mail, Fax #, etc.)	Protocol #	# of subjects (enrolled)	Indication
Site #1002 Marina Rackhel, M.D. Torrance Clinical Research 25043 Narbonne Avenue Lomita, CA 90717 (310) 373-8120	15-50310	31	VVA
Site #152 Marina Rackhel, M.D. (as above)	15-50821	40	VVA
Site # 4633 Garn Mabey, M.D. Affiliated Clinical Research, Inc. 1881 N. Tenaya Way Las Vegas, NV 89128 DRRGMABEY@lvresearch.com (702) 242-8800	15-50310	65	VVA
Site #108 Garn Mabey, M.D. (as above)	15-50821	33	VVA
Site #1009 R. Hal Younglove, M.D. Radiant Research 6300 Glenwood Street Bldg. 10, Suite 100 Overland Park, KS 66202 (913) 599-3333	15-50310	16	VVA
Site #183 R. Hal Younglove, M.D. (as above)	15-50821	33	VVA

III. Site Selection/Rationale

The 3 identified clinical sites included in this Request for Clinical Inspections are all sites in the US who participated in the two primary 12-week safety and efficacy clinical trials submitted in support of the proposed indication for ospemifene. Each site enrolled large numbers of study participants (collectively) as compared to the other clinical sites who participated in both clinical trials. All three clinical sites reported a higher number of protocol violations/deviations in the second 12-week study (Study 15-50821) than the first 12-week study (Study 15-50310). No concerns about site-specific efficacy data was identified.

Domestic Inspections:

Reasons for inspections (please check all that apply):

- Enrollment of large numbers of study subjects
- High treatment responders (specify):
- Significant primary efficacy results pertinent to decision-making
- There is a serious issue to resolve, e.g., suspicion of fraud, scientific misconduct, significant human subject protection violations or adverse event profiles.
- Other (specify):

International Inspections:

Reasons for inspections (please check all that apply):

- There are insufficient domestic data
- Only foreign data are submitted to support an application
- Domestic and foreign data show conflicting results pertinent to decision-making
- There is a serious issue to resolve, e.g., suspicion of fraud, scientific misconduct, or significant human subject protection violations.
- Other (specify) (Examples include: Enrollment of large numbers of study subjects and site specific protocol violations. This would be the first approval of this new drug and most of the limited experience with this drug has been at foreign sites, it would be desirable to include one foreign site in the DSI inspections to verify the quality of conduct of the study).

Five or More Inspection Sites (delete this if it does not apply):

We have requested these sites for inspection (international and/or domestic) because of the following reasons: *state reason(s) and prioritize sites.*

Note: International inspection requests or requests for five or more inspections require sign-off by the OND Division Director and forwarding through the Director, DG CPC.

IV. Tables of Specific Data to be Verified (if applicable)

If you have specific data that needs to be verified, please provide a table for data verification, if applicable.

Should you require any additional information, please contact George Lyght, R.Ph., PharmD. at 301-796-0948 or Theresa van der Vlugt, M.D., Medical Officer at 301-796-1014.

Concurrence: (as needed)

Shelley R. Slaughter, M.D., Ph.D. Medical Team Leader
Theresa van der Vlugt, M.D., M.P.H., Medical Reviewer
_____ Division Director (for foreign inspection requests or requests for 5
or more sites only)

*****Things to consider in decision to submit request for OSI Audit**

- *Evaluate site specific efficacy. Note the sites with the greatest efficacy compared to active or placebo comparator. Are these sites driving the results?*
- *Determine the sites with the largest number of subjects. Is the efficacy being driven by these sites?*
- *Evaluate the financial disclosures. Do sites with investigators holding financial interest in the sponsor's company show superior efficacy compared to other sites?*
- *Are there concerns that the data may be fraudulent or inconsistent?*
 - *Efficacy looks too good to be true, based on knowledge of drug based on previous clinical studies and/or mechanism of action*
 - *Expected commonly reported AEs are not reported in the NDA*
- *Evaluate the protocol violations. Are there a significant number of protocol violations reported at one or more particular sites? Are the types of protocol violations suspicious for clinical trial misconduct?*
- *Is this a new molecular entity or original biological product?*
- *Is the data gathered solely from foreign sites?*
- *Were the NDA studies conducted under an IND?*

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/s/

GEORGE A LYGHT
07/31/2012

DGCPC/OSI CONSULT: Request for Clinical Inspections

Date: July 13, 2012

To:
Susan Thompson, M.D., Acting Branch Chief, GCPAB
CDER OSI PM Track
Roy Blay, Ph.D., OSI Reviewer
Division of Good Clinical Practice Compliance
Office of Scientific Investigations
Office of Compliance/CDER

Through: Shelley R. Slaughter, M.D., Ph.D.,
Clinical Team Leader
Division of Reproductive and Urologic Products (DRUP)

Through: Theresa van der Vlugt, M.D., M.P.H.
Medical Officer
DRUP

From: George Lyght, R.Ph, PharmD.
Sr. Regulatory Health Project Manager
DRUP

Subject: **Request for Clinical Site Inspections**

I. General Information

Application#: NDA 203505
IND#: 067216

Shionogi USA, Inc.
Ting Chen, M.S., Director, Regulatory Affairs
300 Campus Drive
Florham Park, NJ 07932
Telephone (973) 966-6900
Fax (973) 966-2820
tchen@shionogi.com

Drug Proprietary Name: TBD
Generic Drug Name: ospemifene
NME: Yes
DGCPC/OSI Consult
version: 07/9/2012

Review Priority: Standard

Study Population includes < 17 years of age : No

Is this for Pediatric Exclusivity: Yes

Proposed New Indication(s): The treatment of vulvar and vaginal atrophy

PDUFA: February 26, 2013

Action Goal Date: February 26, 6013

Inspection Summary Goal Date: November 5, 2012

II. Protocol/Site Identification

Include the Protocol Title or Protocol Number for all protocols to be audited. Complete the following table (Note: ALL items listed are required, to process inspection request. Failure to provide complete information will result in delay of inspection process).

Site # (Name,Address, Phone #, e-mail, Fax #)	Protocol ID	Number of Subjects	Indication
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<p>Marina Rackhel, MD Torrance Clinical Research 25043 Narbonne Avenue Lomita, CA 90717 (310) 373-8120</p> <p>Site # 1002 for Study 15-50310</p> <p>Site # 152 for Study 15-50821</p>	<p>Protocol 15-50310: Efficacy and safety of Ospemifene in the Treatment of Vulvar and Vaginal Atrophy (VVA) in Postmenopausal Women: A 12-week, Randomized, Double- Blind, Placebo- Controlled, Parallel- Group Study Comparing Oral Ospemifene 30 MG and 60 MG Daily Doses with Placebo</p> <p>Protocol 15-50821: Efficacy and safety of Ospemifene in the Treatment of Moderate to Severe Vaginal Dryness and Vaginal Pain Associated with Sexual Activity, Symptoms of Vulvar and Vaginal Atrophy (VVA), Associated with Menopause: a 12- Week, Randomized, Double-Blind, Placebo- Controlled, Parallel- Group Study Comparing Oral Ospemifene 60 MG Daily Dose with Placebo in Postmenopausal Women</p>	<p>Study 15-50310</p> <p>30 mg: 282</p> <p>60 mg: 276</p> <p>Placebo: 268</p> <p>Study 15-50821</p> <p>60 mg: 463</p> <p>Placebo: 456</p>	<p>Treatment of vulvar and vaginal due to menopause, including moderate to severe symptoms of dyspareunia and/or vaginal dryness and physiological changes (parabasal cells, superficial cells and pH).</p> <p>Treatment of vulvar and vaginal due to menopause, including moderate to severe symptoms of dyspareunia and/or vaginal dryness and physiological changes (parabasal cells, superficial cells and pH).</p>
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<p>Garn Mabey, MD Affiliated Clinical Research, Inc. 1881 N. Tenaya Way Las Vegas, NV 89128 DRRGMABEY@lvresearch.com (702) 242-8800</p> <p>Site # 4633 for Study 15-50310</p> <p>Site #108 for Study 15-50821</p>	<p>Same as above</p>	<p>Same as above</p>	<p>Same as above</p>
<p>R. Hal Younglove, MD Radiant Research 6300 Glenwood Street Bldg. 10, Suite 100 Overland Park, KS 66202 (913) 599-3333</p> <p>Site # 1009 for Study 15-50310 Co-Investigator: Monica Pierson, MD</p> <p>Site # 183 for Study 15-50821</p>	<p>Same as above</p>	<p>Same as above</p>	<p>Same as above</p>

III. Site Selection/Rationale

Summarize the reason for requesting OSI consult and then complete the checklist that follows your rationale for site selection. Medical Officers may choose to consider the following in providing their summary for site selection.

Summarize the reason for requesting OSI consult, then complete the checklist that follows your rationale for site selection. Medical Officers may choose to consider the following in providing their summary for site selection.

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Rationale for OSI Audits

- *A specific safety concern at a particular site based on review of AEs, SAEs, deaths, or discontinuations*
- *A specific efficacy concern based on review of site specific efficacy data*
- *Specific concern for scientific misconduct at one or more particular sites based on review of financial disclosures, protocol violations, study discontinuations, safety and efficacy results*

*See*** at end of consult template for OSI's thoughts on things to consider in your decision making process*

Domestic Inspections:

Reasons for inspections (please check all that apply):

- Enrollment of large numbers of study subjects
- High treatment responders (specify):
- Significant primary efficacy results pertinent to decision-making
- There is a serious issue to resolve, e.g., suspicion of fraud, scientific misconduct, significant human subject protection violations or adverse event profiles.
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- Other (specify) (Examples include: Enrollment of large numbers of study subjects and site specific protocol violations. This would be the first approval of this new drug and most of the limited experience with this drug has been at foreign sites, it would be desirable to include one foreign site in the DSI inspections to verify the quality of conduct of the study).

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If you have specific data that needs to be verified, please provide a table for data verification, if applicable.

Should you require any additional information, please contact George Lyght, R.Ph., PharmD. at 301-796-0948 or Theresa van der Vlugt, M.D., Medical Officer at 301-796-1014.

Concurrence: (as needed)

Shelley R. Slaughter, M.D., Ph.D. Medical Team Leader
Theresa van der Vlugt, M.D., M.P.H., Medical Reviewer
_____ Division Director (for foreign inspection requests or requests for 5 or more sites only)

*****Things to consider in decision to submit request for OSI Audit**

- *Evaluate site specific efficacy. Note the sites with the greatest efficacy compared to active or placebo comparator. Are these sites driving the results?*
- *Determine the sites with the largest number of subjects. Is the efficacy being driven by these sites?*
- *Evaluate the financial disclosures. Do sites with investigators holding financial interest in the sponsor's company show superior efficacy compared to other sites?*
- *Are there concerns that the data may be fraudulent or inconsistent?*
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 - *Expected commonly reported AEs are not reported in the NDA*
- *Evaluate the protocol violations. Are there a significant number of protocol violations reported at one or more particular sites? Are the types of protocol violations suspicious for clinical trial misconduct?*
- *Is this a new molecular entity or original biological product?*
- *Is the data gathered solely from foreign sites?*
- *Were the NDA studies conducted under an IND?*

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/s/

GEORGE A LYGHT
07/13/2012

RPM FILING REVIEW

(Including Memo of Filing Meeting)

To be completed for all new NDAs, BLAs, and Efficacy Supplements [except SE8 (labeling change with clinical data) and SE9 (manufacturing change with clinical data)]

Application Information		
NDA # 203505 BLA#	NDA Supplement #:S- BLA Supplement #	Efficacy Supplement Type SE-
Proprietary Name: TBD Established/Proper Name: ospemifene Dosage Form: tablets Strengths: 60 mg		
Applicant: Shionogi Inc. Agent for Applicant (if applicable):		
Date of Application: April 26, 2012 Date of Receipt: April 26, 2012 Date clock started after UN:		
PDUFA Goal Date: February 26, 2013	Action Goal Date (if different):	
Filing Date: June 25, 2012	Date of Filing Meeting: June 19, 2012	
Chemical Classification: (1,2,3 etc.) (original NDAs only) 1 (NME)		
Proposed indication(s)/Proposed change(s): The treatment of vulvar and vaginal atrophy		
Type of Original NDA: AND (if applicable) Type of NDA Supplement:	<input checked="" type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2) <input type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2)	
<i>If 505(b)(2): Draft the "505(b)(2) Assessment" review found at: http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/UCM027499 and refer to Appendix A for further information.</i>		
Review Classification:	<input checked="" type="checkbox"/> Standard <input type="checkbox"/> Priority <input type="checkbox"/> Tropical Disease Priority Review Voucher submitted	
<i>If the application includes a complete response to pediatric WR, review classification is Priority.</i>		
<i>If a tropical disease priority review voucher was submitted, review classification is Priority.</i>		
Resubmission after withdrawal? <input type="checkbox"/>	Resubmission after refuse to file? <input type="checkbox"/>	
Part 3 Combination Product? <input type="checkbox"/>	<input type="checkbox"/> Convenience kit/Co-package <input type="checkbox"/> Pre-filled drug delivery device/system (syringe, patch, etc.) <input type="checkbox"/> Pre-filled biologic delivery device/system (syringe, patch, etc.) <input type="checkbox"/> Device coated/impregnated/combined with drug <input type="checkbox"/> Device coated/impregnated/combined with biologic <input type="checkbox"/> Separate products requiring cross-labeling <input type="checkbox"/> Drug/Biologic <input type="checkbox"/> Possible combination based on cross-labeling of separate products <input type="checkbox"/> Other (drug/device/biological product)	
<i>If yes, contact the Office of Combination Products (OCP) and copy them on all Inter-Center consults</i>		

<input type="checkbox"/> Fast Track <input type="checkbox"/> Rolling Review <input type="checkbox"/> Orphan Designation <input type="checkbox"/> Rx-to-OTC switch, Full <input type="checkbox"/> Rx-to-OTC switch, Partial <input type="checkbox"/> Direct-to-OTC Other:	<input type="checkbox"/> PMC response <input type="checkbox"/> PMR response: <input type="checkbox"/> FDAAA [505(o)] <input type="checkbox"/> PREA deferred pediatric studies [21 CFR 314.55(b)/21 CFR 601.27(b)] <input type="checkbox"/> Accelerated approval confirmatory studies (21 CFR 314.510/21 CFR 601.41) <input type="checkbox"/> Animal rule postmarketing studies to verify clinical benefit and safety (21 CFR 314.610/21 CFR 601.42)			
Collaborative Review Division (<i>if OTC product</i>):				
List referenced IND Number(s):				
Goal Dates/Product Names/Classification Properties	YES	NO	NA	Comment
PDUFA and Action Goal dates correct in tracking system? <i>If no, ask the document room staff to correct them immediately. These are the dates used for calculating inspection dates.</i>	X			
Are the proprietary, established/proper, and applicant names correct in tracking system? <i>If no, ask the document room staff to make the corrections. Also, ask the document room staff to add the established/proper name to the supporting IND(s) if not already entered into tracking system.</i>	X			
Is the review priority (S or P) and all appropriate classifications/properties entered into tracking system (e.g., chemical classification, combination product classification, 505(b)(2), orphan drug)? <i>For NDAs/NDA supplements, check the New Application and New Supplement Notification Checklists for a list of all classifications/properties at: http://inside.fda.gov:9003/CDER/OfficeofBusinessProcessSupport/ucm163969.htm</i> <i>If no, ask the document room staff to make the appropriate entries.</i>	X			
Application Integrity Policy	YES	NO	NA	Comment
Is the application affected by the Application Integrity Policy (AIP)? <i>Check the AIP list at: http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm</i>		X		
If yes, explain in comment column.				
If affected by AIP, has OC/OMPQ been notified of the submission? If yes, date notified:			X	
User Fees	YES	NO	NA	Comment
Is Form 3397 (User Fee Cover Sheet) included with authorized signature?	X			

<p><u>User Fee Status</u></p> <p><i>If a user fee is required and it has not been paid (and it is not exempted or waived), the application is unacceptable for filing following a 5-day grace period. Review stops. Send Unacceptable for Filing (UN) letter and contact user fee staff.</i></p>	<p>Payment for this application:</p> <p><input checked="" type="checkbox"/> Paid <input type="checkbox"/> Exempt (orphan, government) <input type="checkbox"/> Waived (e.g., small business, public health) <input type="checkbox"/> Not required</p>																			
<p><i>If the firm is in arrears for other fees (regardless of whether a user fee has been paid for this application), the application is unacceptable for filing (5-day grace period does not apply). Review stops. Send UN letter and contact the user fee staff.</i></p>	<p>Payment of other user fees:</p> <p><input checked="" type="checkbox"/> Not in arrears <input type="checkbox"/> In arrears</p>																			
<p>505(b)(2) (NDAs/NDA Efficacy Supplements only)</p>	<p>YES</p>	<p>NO</p>	<p>NA</p>	<p>Comment</p>																
<p>Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA?</p>																				
<p>Is the application for a duplicate of a listed drug whose only difference is that the extent to which the active ingredient(s) is absorbed or otherwise made available to the site of action is less than that of the reference listed drug (RLD)? [see 21 CFR 314.54(b)(1)].</p>																				
<p>Is the application for a duplicate of a listed drug whose only difference is that the rate at which the proposed product's active ingredient(s) is absorbed or made available to the site of action is unintentionally less than that of the listed drug [see 21 CFR 314.54(b)(2)]?</p> <p><i>If you answered yes to any of the above questions, the application may be refused for filing under 21 CFR 314.101(d)(9). Contact the (b)(2) review staff in the Immediate Office of New Drugs</i></p>																				
<p>Is there unexpired exclusivity on the active moiety (e.g., 5-year, 3-year, orphan, or pediatric exclusivity)? Check the <i>Electronic Orange Book</i> at: http://www.accessdata.fda.gov/scripts/cder/ob/default.cfm</p> <p>If yes, please list below:</p> <table border="1" data-bbox="203 1451 1349 1587"> <thead> <tr> <th>Application No.</th> <th>Drug Name</th> <th>Exclusivity Code</th> <th>Exclusivity Expiration</th> </tr> </thead> <tbody> <tr> <td> </td> <td> </td> <td> </td> <td> </td> </tr> <tr> <td> </td> <td> </td> <td> </td> <td> </td> </tr> <tr> <td> </td> <td> </td> <td> </td> <td> </td> </tr> </tbody> </table>	Application No.	Drug Name	Exclusivity Code	Exclusivity Expiration																
Application No.	Drug Name	Exclusivity Code	Exclusivity Expiration																	
<p><i>If there is unexpired, 5-year exclusivity remaining on the active moiety for the proposed drug product, a 505(b)(2) application cannot be submitted until the period of exclusivity expires (unless the applicant provides paragraph IV patent certification; then an application can be submitted four years after the date of approval.) Pediatric exclusivity will extend both of the timeframes in this provision by 6 months. 21 CFR 314.108(b)(2). Unexpired, 3-year exclusivity will only block the approval, not the submission of a 505(b)(2) application.</i></p>																				
<p>Exclusivity</p>	<p>YES</p>	<p>NO</p>	<p>NA</p>	<p>Comment</p>																
<p>Does another product (same active moiety) have orphan exclusivity for the same indication? <i>Check the Orphan Drug Designations and Approvals list at:</i> http://www.accessdata.fda.gov/scripts/opdlisting/opd/index.cfm</p>		<p>X</p>																		

<p>If another product has orphan exclusivity, is the product considered to be the same product according to the orphan drug definition of sameness [see 21 CFR 316.3(b)(13)]?</p> <p><i>If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy</i></p>			X	
<p>Has the applicant requested 5-year or 3-year Waxman-Hatch exclusivity? (<i>NDAs/NDA efficacy supplements only</i>)</p> <p>If yes, # years requested:</p> <p><i>Note: An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.</i></p>		X		
<p>Is the proposed product a single enantiomer of a racemic drug previously approved for a different therapeutic use (<i>NDAs only</i>)?</p>		X		
<p>If yes, did the applicant: (a) elect to have the single enantiomer (contained as an active ingredient) not be considered the same active ingredient as that contained in an already approved racemic drug, and/or (b): request exclusivity pursuant to section 505(u) of the Act (per FDAAA Section 1113)?</p> <p><i>If yes, contact Mary Ann Holovac, Director of Drug Information, OGD/DLPS/LRB.</i></p>			X	

Format and Content				
<p><i>Do not check mixed submission if the only electronic component is the content of labeling (COL).</i></p>	<input type="checkbox"/> All paper (except for COL) <input checked="" type="checkbox"/> All electronic <input type="checkbox"/> Mixed (paper/electronic) <input checked="" type="checkbox"/> CTD <input type="checkbox"/> Non-CTD <input type="checkbox"/> Mixed (CTD/non-CTD)			
<p>If mixed (paper/electronic) submission, which parts of the application are submitted in electronic format?</p>				
Overall Format/Content	YES	NO	NA	Comment
<p>If electronic submission, does it follow the eCTD guidance?¹ If not, explain (e.g., waiver granted).</p>	X			
<p>Index: Does the submission contain an accurate comprehensive index?</p>	X			
<p>Is the submission complete as required under 21 CFR 314.50 (<i>NDAs/NDA efficacy supplements</i>) or under 21 CFR 601.2 (<i>BLAs/BLA efficacy supplements</i>) including:</p>	X			

1

<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072349.pdf>

<input type="checkbox"/> legible <input checked="" type="checkbox"/> English (or translated into English) <input type="checkbox"/> pagination <input type="checkbox"/> navigable hyperlinks (electronic submissions only)				
If no, explain.				
BLAs only: Companion application received if a shared or divided manufacturing arrangement?				
If yes, BLA #				
Forms and Certifications				
<i>Electronic forms and certifications with electronic signatures (scanned, digital, or electronic – similar to DARRTS, e.g., /s/) are acceptable. Otherwise, paper forms and certifications with hand-written signatures must be included. Forms include: user fee cover sheet (3397), application form (356h), patent information (3542a), financial disclosure (3454/3455), and clinical trials (3674); Certifications include: debarment certification, patent certification(s), field copy certification, and pediatric certification.</i>				
Application Form	YES	NO	NA	Comment
Is form FDA 356h included with authorized signature per 21 CFR 314.50(a)?	X			
<i>If foreign applicant, a U.S. agent must sign the form [see 21 CFR 314.50(a)(5)].</i>				
Are all establishments and their registration numbers listed on the form/attached to the form?	X			
Patent Information (NDAs/NDA efficacy supplements only)	YES	NO	NA	Comment
Is patent information submitted on form FDA 3542a per 21 CFR 314.53(c)?	X			
Financial Disclosure	YES	NO	NA	Comment
Are financial disclosure forms FDA 3454 and/or 3455 included with authorized signature per 21 CFR 54.4(a)(1) and (3)?	X			
<i>Forms must be signed by the APPLICANT, not an Agent [see 21 CFR 54.2(g)].</i>				
<i>Note: Financial disclosure is required for bioequivalence studies that are the basis for approval.</i>				
Clinical Trials Database	YES	NO	NA	Comment
Is form FDA 3674 included with authorized signature?	X			
<i>If yes, ensure that the application is also coded with the supporting document category, "Form 3674."</i>				
<i>If no, ensure that language requesting submission of the form is included in the acknowledgement letter sent to the applicant</i>				
Debarment Certification	YES	NO	NA	Comment
Is a correctly worded Debarment Certification included with authorized signature?	X			

<p><i>Certification is not required for supplements if submitted in the original application; If foreign applicant, both the applicant and the U.S. Agent must sign the certification [per Guidance for Industry: Submitting Debarment Certifications].</i></p> <p><i>Note: Debarment Certification should use wording in FD&C Act Section 306(k)(1) i.e., “[Name of applicant] hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application.” Applicant may not use wording such as, “To the best of my knowledge...”</i></p>				
Field Copy Certification (NDAs/NDA efficacy supplements only)	YES	NO	NA	Comment
<p>For paper submissions only: Is a Field Copy Certification (that it is a true copy of the CMC technical section) included?</p> <p><i>Field Copy Certification is not needed if there is no CMC technical section or if this is an electronic submission (the Field Office has access to the EDR)</i></p> <p><i>If maroon field copy jackets from foreign applicants are received, return them to CDR for delivery to the appropriate field office.</i></p>			X	

Controlled Substance/Product with Abuse Potential	YES	NO	NA	Comment
<p><u>For NMEs:</u> Is an Abuse Liability Assessment, including a proposal for scheduling, submitted per 21 CFR 314.50(d)(5)(vii)?</p> <p><i>If yes, date consult sent to the Controlled Substance Staff:</i></p> <p><u>For non-NMEs:</u> <i>Date of consult sent to Controlled Substance Staff:</i></p>			X	

Pediatrics	YES	NO	NA	Comment
<p><u>PREA</u></p> <p>Does the application trigger PREA?</p> <p><i>If yes, notify PeRC RPM (PeRC meeting is required)²</i></p> <p><i>Note: NDAs/BLAs/efficacy supplements for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration trigger PREA. All waiver & deferral requests, pediatric plans, and pediatric assessment studies must be reviewed by PeRC prior to approval of the application/supplement.</i></p>	X			
<p>If the application triggers PREA, are the required pediatric assessment studies or a full waiver of pediatric studies included?</p>		X		

² <http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/PediatricandMaternalHealthStaff/ucm027829.htm>

If studies or full waiver not included , is a request for full waiver of pediatric studies OR a request for partial waiver and/or deferral with a pediatric plan included? <i>If no, request in 74-day letter</i>	X			
If a request for full waiver/partial waiver/deferral is included , does the application contain the certification(s) required by FDCA Section 505B(a)(3) and (4)? <i>If no, request in 74-day letter</i>	X			
BPCA (NDAs/NDA efficacy supplements only): Is this submission a complete response to a pediatric Written Request? <i>If yes, notify Pediatric Exclusivity Board RPM (pediatric exclusivity determination is required)³</i>		X		
Proprietary Name	YES	NO	NA	Comment
Is a proposed proprietary name submitted? <i>If yes, ensure that the application is also coded with the supporting document category, "Proprietary Name/Request for Review."</i>	X			
REMS	YES	NO	NA	Comment
Is a REMS submitted? <i>If yes, send consult to OSE/DRISK and notify OC/OSI/DSC/PMSB via the CDER OSI RMP mailbox</i>		X		
Prescription Labeling	<input type="checkbox"/> Not applicable			
Check all types of labeling submitted.	<input checked="" type="checkbox"/> Package Insert (PI) <input checked="" type="checkbox"/> Patient Package Insert (PPI) <input type="checkbox"/> Instructions for Use (IFU) <input type="checkbox"/> Medication Guide (MedGuide) <input checked="" type="checkbox"/> Carton labels <input checked="" type="checkbox"/> Immediate container labels <input type="checkbox"/> Diluent <input type="checkbox"/> Other (specify)			
	YES	NO	NA	Comment
Is Electronic Content of Labeling (COL) submitted in SPL format? <i>If no, request applicant to submit SPL before the filing date.</i>	X			
Is the PI submitted in PLR format? ⁴	X			

³ <http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/PediatricandMaternalHealthStaff/ucm027837.htm>

⁴ <http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/StudyEndpointsandLabelingDevelopmentTeam/ucm025576.htm>

If PI not submitted in PLR format , was a waiver or deferral requested before the application was received or in the submission? If requested before application was submitted , what is the status of the request? <i>If no waiver or deferral, request applicant to submit labeling in PLR format before the filing date.</i>			X	
All labeling (PI, PPI, MedGuide, IFU, carton and immediate container labels) consulted to OPDP?	X			
MedGuide, PPI, IFU (plus PI) consulted to OSE/DRISK? (send WORD version if available)	X			
Carton and immediate container labels, PI, PPI sent to OSE/DMEPA and appropriate CMC review office (OBP or ONDQA)?	X			
OTC Labeling	<input checked="" type="checkbox"/> Not Applicable			
Check all types of labeling submitted.	<input type="checkbox"/> Outer carton label <input type="checkbox"/> Immediate container label <input type="checkbox"/> Blister card <input type="checkbox"/> Blister backing label <input type="checkbox"/> Consumer Information Leaflet (CIL) <input type="checkbox"/> Physician sample <input type="checkbox"/> Consumer sample <input type="checkbox"/> Other (specify)			
	YES	NO	NA	Comment
Is electronic content of labeling (COL) submitted? <i>If no, request in 74-day letter.</i>				
Are annotated specifications submitted for all stock keeping units (SKUs)? <i>If no, request in 74-day letter.</i>				
If representative labeling is submitted, are all represented SKUs defined? <i>If no, request in 74-day letter.</i>				
All labeling/packaging, and current approved Rx PI (if switch) sent to OSE/DMEPA?				
Other Consults	YES	NO	NA	Comment
Are additional consults needed? (e.g., IFU to CDRH; QT study report to QT Interdisciplinary Review Team) <i>If yes, specify consult(s) and date(s) sent:</i>		X		
Meeting Minutes/SPAs	YES	NO	NA	Comment
End-of Phase 2 meeting(s) Date(s): Oct. 4, 2005 <i>If yes, distribute minutes before filing meeting</i>	X			

Pre-NDA/Pre-BLA/Pre-Supplement meeting(s)? Date(s): Sept. 29, 2009 <i>If yes, distribute minutes before filing meeting</i>	X			
Any Special Protocol Assessments (SPAs)? Date(s): Oct. 19, 2006 & Feb. 2, 2007 T-con <i>If yes, distribute letter and/or relevant minutes before filing meeting</i>	X			Toxicology SPA

ATTACHMENT

MEMO OF FILING MEETING

DATE: June 19, 2012

NDA #: 203505

PROPRIETARY NAME:

ESTABLISHED/PROPER NAME: ospemifene

DOSAGE FORM/STRENGTH: tablets 60 mg

APPLICANT: Shionogi, Inc.

PROPOSED INDICATION(S)/PROPOSED CHANGE(S): Treatment of vulvar and vaginal atrophy.

BACKGROUND: The IND for ospemifene was opened in 2003. This new molecular entity (NME) is a selective estrogen- receptor modulator (SERM). If approved, this product would be first-in-class for this indication.

REVIEW TEAM:

Discipline/Organization	Names		Present at filing meeting? (Y or N)
Regulatory Project Management	RPM:	George Lyght Kimberly Shiley	N Y
	CPMS/TL:	Margaret Kober	Y
Cross-Discipline Team Leader (CDTL)			
Clinical	Reviewer:	Phill Price & Theresa van der Vlugt	Y Y
	TL:	Shelley Slaughter	Y
Social Scientist Review (<i>for OTC products</i>)	Reviewer:		
	TL:		
OTC Labeling Review (<i>for OTC products</i>)	Reviewer:		
	TL:		
Clinical Microbiology (<i>for antimicrobial products</i>)	Reviewer:		
	TL:		

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APPEARS THIS WAY ON ORIGINAL



Clinical Pharmacology	Reviewer:	LaiMing Lee Jiang Liu Kareen Riviere	Y Y Y
	TL:	Myong-Jin Kim	Y
Biostatistics	Reviewer:	Xin Fang	Y
	TL:	Mahboob Sobhan	
Nonclinical (Pharmacology/Toxicology)	Reviewer:	Leslie McKinney	Y
	TL:	Alexander Jordan	N
Statistics (carcinogenicity)	Reviewer:		
	TL:		
Immunogenicity (assay/assay validation) (<i>for BLAs/BLA efficacy supplements</i>)	Reviewer:		
	TL:		
Product Quality (CMC)	Reviewer:	Hitesh Shroff	Y
	TL:	Donna Christner	Y
Quality Microbiology (<i>for sterile products</i>)	Reviewer:		
	TL:		
CMC Labeling Review	Reviewer:		
	TL:		
Facility Review/Inspection	Reviewer:		
	TL:		
OSE/DMEPA (proprietary name)	Reviewer:	David Moeny	Y
	TL:	Zachary Oleszczuk	
OSE/DRISK (REMS)	Reviewer:	Manizheh Siahpoushan	Y
	TL:	Adrienne Rothstein	Y
OC/OSI/DSC/PMSB (REMS)	Reviewer:	Roy Blay	Y
	TL:		

Bioresearch Monitoring (OSI)	Reviewer:		
	TL:		
Controlled Substance Staff (CSS)	Reviewer:		
	TL:		
Other reviewers			
Other attendees	Julie Beitz, MD, Director ODEIII Victoria Kusiak, MD, Deputy Director, ODEIII Hylton Joffe, MD, Director DRUP Maria Walsh, Assoc. Dir, Reg Affairs, ODEIII	Y Y Y Y	

FILING MEETING DISCUSSION:

GENERAL	
<ul style="list-style-type: none"> 505(b)(2) filing issues? <p>If yes, list issues:</p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> Per reviewers, are all parts in English or English translation? <p>If no, explain:</p>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> Electronic Submission comments <p>List comments:</p>	<input type="checkbox"/> Not Applicable
CLINICAL	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input checked="" type="checkbox"/> Review issues for 74-day letter
<ul style="list-style-type: none"> Clinical study site(s) inspections(s) needed? <p>If no, explain:</p>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> Advisory Committee Meeting needed? <p>Comments:</p>	<input type="checkbox"/> YES Date if known: <input checked="" type="checkbox"/> NO <input type="checkbox"/> To be determined

<p><i>If no, for an original NME or BLA application, include the reason. For example:</i></p> <ul style="list-style-type: none"> ○ <i>this drug/biologic is not the first in its class</i> ○ <i>the clinical study design was acceptable</i> ○ <i>the application did not raise significant safety or efficacy issues</i> ○ <i>the application did not raise significant public health questions on the role of the drug/biologic in the diagnosis, cure, mitigation, treatment or prevention of a disease</i> 	<p>Reason: The application did not raise significant safety or efficacy issues.</p>
<ul style="list-style-type: none"> • Abuse Liability/Potential <p>Comments:</p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<ul style="list-style-type: none"> • If the application is affected by the AIP, has the division made a recommendation regarding whether or not an exception to the AIP should be granted to permit review based on medical necessity or public health significance? <p>Comments:</p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> YES <input type="checkbox"/> NO
<p>CLINICAL MICROBIOLOGY</p> <p>Comments:</p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<p>CLINICAL PHARMACOLOGY</p> <p>Comments:</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input checked="" type="checkbox"/> Review issues for 74-day letter
<ul style="list-style-type: none"> • Clinical pharmacology study site(s) inspections(s) needed? 	<input type="checkbox"/> YES <input checked="" type="checkbox"/> NO
<p>BIOSTATISTICS</p> <p>Comments:</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<p>NONCLINICAL (PHARMACOLOGY/TOXICOLOGY)</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter

Comments:	
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APPEARS THIS WAY ON ORIGINAL



<p>IMMUNOGENICITY (BLAs/BLA efficacy supplements only)</p> <p>Comments:</p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<p>PRODUCT QUALITY (CMC)</p> <p>Comments:</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<p><u>Environmental Assessment</u></p> <ul style="list-style-type: none"> • Categorical exclusion for environmental assessment (EA) requested? <p>If no, was a complete EA submitted?</p> <p>If EA submitted, consulted to EA officer (OPS)?</p> <p>Comments:</p>	<input type="checkbox"/> Not Applicable <input type="checkbox"/> YES <input type="checkbox"/> NO <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO <input type="checkbox"/> YES <input checked="" type="checkbox"/> NO
<p><u>Quality Microbiology (for sterile products)</u></p> <ul style="list-style-type: none"> • Was the Microbiology Team consulted for validation of sterilization? (NDAs/NDA supplements only) <p>Comments:</p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> YES <input type="checkbox"/> NO
<p><u>Facility Inspection</u></p> <ul style="list-style-type: none"> • Establishment(s) ready for inspection? ▪ Establishment Evaluation Request (EER/TBP-EER) submitted to OMPQ? <p>Comments:</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO <input type="checkbox"/> YES <input type="checkbox"/> NO
<p><u>Facility/Microbiology Review (BLAs only)</u></p> <p>Comments:</p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter

<u>CMC Labeling Review</u>	
Comments:	<input type="checkbox"/> Review issues for 74-day letter
REGULATORY PROJECT MANAGEMENT	
Signatory Authority: Victoria Kusiak, M.D., Deputy Director, ODEIII	
21st Century Review Milestones (see attached) (listing review milestones in this document is optional):	
Comments:	
REGULATORY CONCLUSIONS/DEFICIENCIES	
<input type="checkbox"/>	The application is unsuitable for filing. Explain why:
<input checked="" type="checkbox"/>	The application, on its face, appears to be suitable for filing. <u>Review Issues:</u> <input type="checkbox"/> No review issues have been identified for the 74-day letter. <input checked="" type="checkbox"/> Review issues have been identified for the 74-day letter. List (optional): <u>Review Classification:</u> <input checked="" type="checkbox"/> Standard Review <input type="checkbox"/> Priority Review
ACTIONS ITEMS	
<input type="checkbox"/>	Ensure that any updates to the review priority (S or P) and classifications/properties are entered into tracking system (e.g., chemical classification, combination product classification, 505(b)(2), orphan drug).
<input type="checkbox"/>	If RTF, notify everybody who already received a consult request, OSE PM, and Product Quality PM (to cancel EER/TBP-EER).
<input type="checkbox"/>	If filed, and the application is under AIP, prepare a letter either granting (for signature by Center Director) or denying (for signature by ODE Director) an exception for review.
<input type="checkbox"/>	BLA/BLA supplements: If filed, send 60-day filing letter
<input type="checkbox"/>	If priority review: <ul style="list-style-type: none"> • notify sponsor in writing by day 60 (For BLAs/BLA supplements: include in 60-day filing letter; For NDAs/NDA supplements: see CST for choices)

<input type="checkbox"/>	<ul style="list-style-type: none"> • notify OMPQ (so facility inspections can be scheduled earlier)
<input checked="" type="checkbox"/>	Send review issues/no review issues by day 74
<input checked="" type="checkbox"/>	Conduct a PLR format labeling review and include labeling issues in the 74-day letter
<input type="checkbox"/>	<p>BLA/BLA supplements: Send the Product Information Sheet to the product reviewer and the Facility Information Sheet to the facility reviewer for completion. Ensure that the completed forms are forwarded to the CDER RMS-BLA Superuser for data entry into RMS-BLA one month prior to taking an action [These sheets may be found in the CST eRoom at: http://erom.fda.gov/eRoom/CDER2/CDERStandardLettersCommittee/0_1685f]</p>
<input type="checkbox"/>	Other

Appendix A (NDA and NDA Supplements only)

NOTE: The term "original application" or "original NDA" as used in this appendix denotes the NDA submitted. It does not refer to the reference drug product or "reference listed drug."

An original application is likely to be a 505(b)(2) application if:

- (1) it relies on published literature to meet any of the approval requirements, and the applicant does not have a written right of reference to the underlying data. If published literature is cited in the NDA but is not necessary for approval, the inclusion of such literature will not, in itself, make the application a 505(b)(2) application,
- (2) it relies for approval on the Agency's previous findings of safety and efficacy for a listed drug product and the applicant does not own or have right to reference the data supporting that approval, or
- (3) it relies on what is "generally known" or "scientifically accepted" about a class of products to support the safety or effectiveness of the particular drug for which the applicant is seeking approval. (Note, however, that this does not mean *any* reference to general information or knowledge (e.g., about disease etiology, support for particular endpoints, methods of analysis) causes the application to be a 505(b)(2) application.)

Types of products for which 505(b)(2) applications are likely to be submitted include: fixed-dose combination drug products (e.g., heart drug and diuretic (hydrochlorothiazide) combinations); OTC monograph deviations (see 21 CFR 330.11); new dosage forms; new indications; and, new salts.

An efficacy supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2).

An efficacy supplement is a 505(b)(1) supplement if the supplement contains all of the information needed to support the approval of the change proposed in the supplement. For example, if the supplemental application is for a new indication, the supplement is a 505(b)(1) if:

- (1) The applicant has conducted its own studies to support the new indication (or otherwise owns or has right of reference to the data/studies),
- (2) No additional information beyond what is included in the supplement or was embodied in the finding of safety and effectiveness for the original application or previously approved supplements is needed to support the change. For example, this would likely be the case with respect to safety considerations if the dose(s) was/were the same as (or lower than) the original application, and.
- (3) All other "criteria" are met (e.g., the applicant owns or has right of reference to the data relied upon for approval of the supplement, the application does not rely

for approval on published literature based on data to which the applicant does not have a right of reference).

An efficacy supplement is a 505(b)(2) supplement if:

- (1) Approval of the change proposed in the supplemental application would require data beyond that needed to support our previous finding of safety and efficacy in the approval of the original application (or earlier supplement), and the applicant has not conducted all of its own studies for approval of the change, or obtained a right to reference studies it does not own. For example, if the change were for a new indication AND a higher dose, we would likely require clinical efficacy data and preclinical safety data to approve the higher dose. If the applicant provided the effectiveness data, but had to rely on a different listed drug, or a new aspect of a previously cited listed drug, to support the safety of the new dose, the supplement would be a 505(b)(2),
- (2) The applicant relies for approval of the supplement on published literature that is based on data that the applicant does not own or have a right to reference. If published literature is cited in the supplement but is not necessary for approval, the inclusion of such literature will not, in itself, make the supplement a 505(b)(2) supplement, or
- (3) The applicant is relying upon any data they do not own or to which they do not have right of reference.

If you have questions about whether an application is a 505(b)(1) or 505(b)(2) application, consult with your OND ADRA or OND IO.

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/s/

GEORGE A LYGHT
07/05/2012

MARGARET M KOBER
07/05/2012