MEMORANDUM
REVIEW OF REVISED LABEL AND LABELING
Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

Date of This Memorandum: July 16, 2018
Requesting Office or Division: Division of Bone, Reproductive, and Urologic Products (DBRUP)
Application Type and Number: NDA 210450
Product Name and Strength: Orilissa (elagolix sodium) tablets 150 mg and 200 mg
Applicant/Sponsor Name: AbbVie Inc.
FDA Received Date: July 12, 2018
OSE RCM #: 2017-1760-3
DMEPA Safety Evaluator: Briana Rider, PharmD
DMEPA Team Leader: Lolita White, PharmD

1 PURPOSE OF MEMORANDUM
The Division of Bone, Reproductive, and Urologic Products requested that we review the revised container labels and carton labeling for Orilissa (Appendix A) to determine if they are acceptable from a medication error perspective. The revisions are in response to recommendations that we made during a previous label and labeling review.a

2 OVERALL ASSESSMENT OF THE MATERIALS REVIEWED
We reviewed the revised container labels and carton labeling for areas of vulnerability which could lead to medication error.

We previously advised that the carton labeling (month’s supply) and the container label (week supply) could not have the same NDC package code (last 1-2 digits of the NDC number) per 21 CFR 207.33. After discussion and agreement with the CDER Electronic Drug Registration and

Listing System (EDRLS) team, AbbVie has elected not to include the NDC number on the weekly wallet container label. We find this to be acceptable.

We also previously advised AbbVie to add the product’s linear barcode to each individual weekly wallet container label as required per 21 CFR 201.25(c)(2). AbbVie indicates that, because they removed the NDC number from the weekly wallet container labels, for consistency they will not add a barcode to the weekly wallet container labels. We note that per the barcode rule (21 CFR 201.25), a linear barcode must appear on the drug’s label as defined by section 201(k) of the Federal Food, Drug, and Cosmetic Act. However, the barcode rule also indicates that the linear barcode must contain, at a minimum, the appropriate NDC number and there is no associated NDC number for the weekly wallet container labels.

Our current review finds the proposed Orilissa (elagolix sodium) tablet packaging configuration includes an outer carton which contains four weekly wallet blister packs. We note the labeling on the outer carton includes a linear barcode and NDC number. We also note the weekly wallet blister packs are not intended to be dispensed separately from the carton. We considered the risk for medication error to occur due to the lack of a linear barcode on the weekly wallet container label and find that it does not pose a significant safety concern. For the aforementioned reasons, we find AbbVie’s proposal not to include a linear barcode on the weekly wallet container labels to be acceptable.

3 CONCLUSION

The revised container labels and carton labeling for Orilissa are acceptable from a medication error perspective. We have no further recommendations at this time.
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/s/

BRIANA B RIDER
07/16/2018

LOLITA G WHITE
07/17/2018
Memorandum

Date: July 5, 2018

To: Maria Wasilik, Regulatory Project Manager
Division of Bone, Reproductive, and Urologic Products (DBRUP)

From: Lynn Panholzer, PharmD, Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

CC: Matthew Falter, PharmD, Team Leader, OPDP

Subject: OPDP Labeling Comments for ORILISSA (elagolix) tablets, for oral use

NDA: 210450

In response to DBRUP’s consult request dated October 24, 2017, OPDP has reviewed the proposed product labeling (PI), Medication Guide, and carton and container labeling for the original NDA submission for ORILISSA (elagolix) tablets, for oral use.

**PI and Medication Guide:** OPDP’s comments on the proposed PI are based on the draft PI retrieved from DBRUP’s sharepoint site on June 22, 2018, and are provided below.

A combined OPDP and Division of Medical Policy Programs (DMPP) review of the Medication Guide was completed, and comments on the proposed Medication Guide were sent under separate cover on July 2, 2018.

**Carton and Container Labeling:** OPDP has reviewed the attached proposed carton and container labeling submitted by the applicant to the electronic document room on May 21, 2018, and our comments are provided below.

Thank you for your consult. If you have any questions, please contact Lynn Panholzer at (301) 796-0616 or lynn.panholzer@fda.hhs.gov.

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/s/

LYNN M PANHOLZER
07/05/2018
Date: July 2, 2018

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

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

From: Sharon W. Williams, MSN, BSN, RN
   Senior Patient Labeling Reviewer
   Division of Medical Policy Programs (DMPP)
   Lynn Panholzer, PharmD
   Regulatory Review Officer
   Office of Prescription Drug Promotion (OPDP)

Subject: Review of Patient Labeling: Medication Guide (MG)

Drug Name (established name): ORILISSA (elagolix)

Dosage Form and Route: tablets, for oral use

Application Type/Number: NDA 210450

Applicant: AbbVie Inc.
1 INTRODUCTION
On August 23, 2017, AbbVie Inc. submitted for the Agency’s review a New Drug Application (NDA) for elagolix, tablets for oral use indicated for the management of endometriosis with associated pain. On October 23, 2017, the Division of Medication Error Prevention and Analysis (DMEPA) approved the submitted tradename ORLISSA for the application.

This collaborative review is written by the Division of Medical Policy Programs (DMPP) and the Office of Prescription Drug Promotion (OPDP) in response to a request by the Division of Bone, Reproductive, and Urology Products (DBRUP) on October 24, 2017, for DMPP and OPDP to review the Applicant’s proposed MG for elagolix (ORLISSA), tablets for oral use.

2 MATERIAL REVIEWED
- Draft elagolix (ORLISSA) tablets, for oral use MG received on August 23, 2017, and received by DMPP and OPDP on June 22, 2018.
- Draft elagolix (ORLISSA) tablets, for oral use Prescribing Information (PI) received on August 23, 2017, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on June 22, 2018.

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.

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.

In our collaborative review of the MG we have:
- simplified wording and clarified concepts where possible
- ensured that the MG is consistent with the Prescribing Information (PI)
- removed unnecessary or redundant information
- ensured that the MG is free of promotional language or suggested revisions to ensure that it is free of promotional language
- ensured that the MG meets the Regulations as specified in 21 CFR 208.20
- ensured that the MG meets the criteria as specified in FDA’s Guidance for Useful Written Consumer Medication Information (published July 2006)
4 **CONCLUSIONS**
The MG is acceptable with our recommended changes.

5 **RECOMMENDATIONS**
- Please send these comments to the Applicant and copy DMPP and OPDP on the correspondence.
- Our collaborative review of the MG is appended to this memorandum. Consult DMPP and OPDP regarding any additional revisions made to the PI to determine if corresponding revisions need to be made to the MG.

Please let us know if you have any questions.
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/s/

SHARON W WILLIAMS
07/02/2018

LYNN M PANHOLZER
07/02/2018

LASHAWN M GRIFFITHS
07/02/2018
Department of Health and Human Services  
Public Health Service  
Food and Drug Administration  
Center for Drug Evaluation and Research  
Office of Surveillance and Epidemiology Review (OSE)  
Office of Pharmacovigilance and Epidemiology (OPE)

Epidemiology: Review of postmarketing requirement study protocol synopses

Date: May 15, 2018
Reviewer: Wei Liu, PhD, MSc  
Division of Epidemiology II
Team Leader: Jie (Jenni) Li, PhD  
Division of Epidemiology II
Division Director: CAPT David Moeny, RPh, MPH, USPHS  
Division of Epidemiology II
Subject: Review of the sponsor’s protocol synopses for postmarketing requirement studies to evaluate adverse pregnancy outcomes following in utero exposure to elagolix
Drug Name(s): Elagolix
Application Type/Number: NDA 210450
Sponsor: AbbVie
OSE RCM #: 2017-2302

Reference ID: 4265959
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EXECUTIVE SUMMARY

Elagolix is a novel gonadotropin-releasing hormone (GnRH) receptor antagonists used to treat endometriosis-related pain. The new drug application (NDA) review of this drug identified a possible safety concern regarding adverse pregnancy outcomes. Because the number of patients with in utero exposure to elagolix identified in the preapproval trials is small, during the Late-cycle Meeting, the FDA required the Sponsor to conduct a prospective pregnancy registry study and a retrospective cohort study in an electronic healthcare database with maternal-infant record linkage to further assess the signal. On April 10, 2018, the Sponsor submitted protocol synopses for the required postmarketing requirement (PMR) studies. The sponsor seeks input from the agency regarding the required postmarketing observational studies.

After reviewing the protocol synopses, Division of Epidemiology (DEPI) concluded that basic design features outlined in the protocol synopses generally align with the PMR language communicated to the sponsor during the Late-cycle Meeting. DEPI provides additional comments in the end of this review for sponsor to address in the full protocol submission.

In addition, the FDA refers the sponsor to the following FDA Guidances for the development of the full study protocol:


1 INTRODUCTION

Endometriosis is a chronic inflammatory disease that affects mainly women of reproductive age. There is no cure for endometriosis and the treatment goal set for endometriosis focuses on resolving pain or improving fertility. Currently, the first-line medical treatment for endometriosis-related pain include use of hormone therapy or pain relievers. Gonadotropin-releasing hormone (GnRH) analogues are considered as secondary-line therapies. Currently FDA-approved GnRH antagonists such as garelix acetate are peptide analogs of the GnRH and therefore cannot be taken orally as the protein structure of the molecule undergoes proteolysis in the gastrointestinal tract before absorption. Elagolix is the first of a class of novel GnRH receptor antagonists due to its non-peptide nature and oral bioavailability.

Elagolix is contraindicated in pregnant women because the safe use of elagolix during pregnancy in humans has not been established. However, pregnancies are expected to occur because ovulation is not completely suppressed. Women may inadvertently take elagolix till pregnancy is recognized. In clinical development trials, patients were required to use dual non-hormonal contraception during the run-in period, treatment period, and the first 3 months of the post-treatment follow-up period. Despite this, 69 on-treatment pregnancies (e.g., a pregnancy with a conception date that occurred during the treatment period with elagolix or within 30 days after the last dose) were reported, including 49 reported in the elagolix group and the rest of them from the placebo group. For the elagolix group, 23 out of the 49 pregnancies had an outcome of live birth. Other pregnancy outcomes included elective termination, spontaneous abortion and lost to follow-up. Two major congenital malformations (MCMs) were reported in subjects treated with elagolix during pregnancy in elagolix phase 2 endometriosis studies.

The number of patients becoming pregnant during elagolix treatment in phase 2 or 3 clinical trials was small, and therefore does not allow a firm conclusion to be drawn about maternal and fetal safety of elagolix use. During the Late-cycle Meeting held on February 12, 2018, the FDA recommended the sponsor to conduct postmarketing surveillance to evaluate pregnancy outcomes possibly associated with in utero elagolix exposure. On April 10, 2018, the sponsor submitted protocol synopses for two postmarketing requirement (PMR) studies. The sponsor seeks input from the agency regarding the required postmarketing observational studies.

The Division of Bone, Reproductive and Urologic Products (DBRUP) consulted the Division of Epidemiology (DEPI) to review the protocol synopses and provide recommendations for the sponsor to prepare detailed full protocol for both PMR studies.

2 REVIEW MATERIAL

- Amendment to original NDA 210450 (\CDSESUB\evsprod\NDA210450\0036)
- Protocol synopsis for a prospective registry to evaluate pregnancy outcomes in women treated with elagolix (b)(4)
- Protocol synopsis for pregnancy surveillance study in women with endometriosis treated with elagolix (b)(4)
3 REVIEW RESULTS

3.1 Protocol synopsis for a prospective registry to evaluate pregnancy outcomes in women treated with elagolix
3.2 Protocol synopsis for pregnancy surveillance study in women with endometriosis treated with elagolix
4 DISCUSSION

DEPI reviewed the basic study design features of both PMR studies outlined by the sponsor. We concluded that the synopses generally align with PMR language in the elagolix Late-cycle Meeting minutes. However, the brief description of basic design elements hinders our ability to provide
definitive advice for the sponsor. Thus, we offer the following recommendations for the sponsor’s development of full study protocol:

**Elagolix Pregnancy Exposure Registry (PMR1)**
Electronic database study (PMR2)
5 CONCLUSIONS

Basic design features outlined by the sponsor in its protocol synopses generally align with PMR language in the elagolix Late-cycle Meeting minutes. However, because the sponsor provided only a brief summary, FDA cannot make a final decision about adequacy of design elements that respond to the PMRs for postmarketing observational studies.

6 COMMENTS TO THE SPONSOR

Basic design features outlined in the synopses generally align with FDA’s PMR requirements. However, a determination of the suitability of the protocol to meet the PMR requirements is contingent upon review of the full protocol for each study. Based upon our review of your study synopses, we have the following recommendations for development of the full protocols.

Pregnancy Exposure Registry (PMRI):
Electronic database study (PMR2):
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/s/

WEI LIU
05/21/2018

JIE J LI
05/21/2018

DAVID G MOENY
05/22/2018

Reference ID: 4265959
Division of Pediatric and Maternal Health Review

Date: 05-17-2018

From: Leyla Sahin, M.D.
Medical Officer, Maternal Health
Division of Pediatric and Maternal Health

Through: Lynne P. Yao, M.D.
Director,
Division of Pediatric and Maternal Health

To: Division of Bone, Reproductive, and Urology Products

Drug: Elagolix; NDA 210450

Applicant: AbbVie

Proposed Indication: Endometriosis with associated moderate to severe pain

Subject: Post-marketing Requirement (PMR) protocol synopses to assess safety in pregnancy

Materials Reviewed: • Study protocol synopses
• Summary of Clinical Safety document submitted as part of NDA

Consult Question: Please assist with PMRs and review of PMR protocol synopses
INTRODUCTION
The applicant submitted an original new molecular entity NDA on 8-23-2017 for elagolix, for the management of endometriosis with associated moderate to severe pain. The Division of Bone, Reproductive, and Urology Products (DBRUP) consulted the Division of Pediatric and Maternal Health (DPMH) on 11-7-2017, to assist with assessing the need for a Post-marketing Requirement (PMR) to assess safety in pregnancy, and to review the PMR draft study protocols submitted on 4-10-2018. DPMH discussed pregnancy safety PMRs at meetings with DBRUP, the Division of Epidemiology II (DEPI II), and the applicant, and discussed the protocol synopses at a meeting with DBRUP and DEPI II on 4-25-2018.

BACKGROUND
Product Background
• orally administered, short-acting, selective, non-peptide small molecule gonadotropin releasing hormone (GnRh) receptor antagonist that blocks endogenous GnRH signaling by binding competitively to GnRH receptors in the pituitary gland
• results in dose-dependent suppression of luteinizing hormone (LH) and follicle-stimulating hormone (FSH) levels, leading to decreased blood levels of the ovarian sex hormones, estradiol and progesterone
• half-life: 4-6 hours
• Nonclinical studies: (The reader is referred to the review by Dr. Leslie McKinney)
  o no structural abnormalities in the fetuses at exposures up to 40 and 12 times the maximum recommended human dose (MRHD) for the rat and rabbit, respectively
  o spontaneous abortion and total litter loss was observed in rabbits at doses 7 and 12 times the MRHD
  o post implantation loss was observed in pregnant rats at doses 20 times the MRHD.
• Clinical development program:
  o 49 pregnancies among 3,564 exposed women:
    ▪ 23 live births; 5 spontaneous abortions
    ▪ 2 major malformations: cleft palate, tracheoesophageal fistula
    ▪ 15 elective terminations
    ▪ 6 lost to follow-up

DISCUSSION
Intended and unintended exposures during pregnancy will likely occur because endometriosis commonly occurs in females of reproductive potential. Safety data regarding exposure during pregnancy are lacking because pregnant women were excluded during the elagolix clinical development program, and limited outcome data are available on the women who became pregnant in the clinical trials. In addition, the mechanism of action of
elagolix may increase the risk for spontaneous abortion. Therefore, post-approval studies to assess outcomes following exposure in pregnancy are important to help characterize the safety of elagolix in pregnancy. A prospective pregnancy exposure registry is the Agency’s preferred method for post-marketing data collection in pregnant women because such prospective registry decrease bias related to retrospective data collection, and generally include a control group (e.g., unexposed pregnant population with the disease or condition), which allows for evaluation of drug-related and/or disease-related events. In addition, pregnancy registries allow collection of patient level detailed information on exposures and potential confounding factors, and confirmation of outcomes with medical records. However, pregnancy registries are limited in their ability to assess incidence of specific (rare) birth defects because such studies would require decades to accrue sufficient number of patients in many cases. As discussed by the expert panel at the 2014 FDA public meeting on pregnancy registries and other post-approval safety studies in pregnant women, combining two study methods addresses limitations inherent to each study design. Combining a pregnancy registry with a complementary study with a different study design that relies on large databases may address the potential low enrollment in a registry. Examples of complementary study designs include a retrospective cohort study using electronic medical record or claims data or a case control study. However, database studies are often limited by their inability to capture non-livebirth outcomes, especially spontaneous and elective abortions, and stillbirths.

DPMH recommends the following Post Marketing Requirement (PMR)

For a more detailed description of the PMR, the reader is referred to the Appendix A.

REVIEW OF PROTOCOLS
Pregnancy Registry Protocol Synopsis
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/s/

LEYLA SAHIN
05/17/2018

LYNNE P YAO
05/18/2018
MEMORANDUM
REVIEW OF REVISED LABEL AND LABELING
Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

Date of This Memorandum: May 8, 2018
Requesting Office or Division: Division of Bone, Reproductive, and Urologic Products (DBRUP)
Application Type and Number: NDA 210450
Product Name and Strength: Orilissa (elagolix sodium) tablets 150 mg and 200 mg
Applicant/Sponsor Name: AbbVie Inc.
FDA Received Date: March 5, 2018 and April 12, 2018
OSE RCM #: 2017-1760-1
DMEPA Safety Evaluator: Briana Rider, PharmD
DMEPA Team Leader: Lolita White, PharmD

1 PURPOSE OF MEMORANDUM
The Division of Bone, Reproductive, and Urologic Products requested that we review the revised container labels and carton labeling for Orilissa (Appendix A) to determine if they are acceptable from a medication error perspective. The revisions are in response to recommendations that we made during a previous label and labeling review.¹

2 CONCLUSION
We note that the Sponsor no longer proposes to from the proposed labeling will not pose a risk of medication errors. However, the revised container labels and carton labeling are unacceptable from a medication error perspective. Our review of the revised container labels and carton labeling identified the following areas of needed improvement that may contribute to medication errors:

- The format for the expiration date is not defined.

¹ Fava W. Label and Labeling Review for Orilissa (NDA 210450). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2018 MAR 15. RCM No.: 2017-1760.
The middle digits of the NDC product code numbers (i.e., 0038 and 0039) are sequential which is not an effective differentiating feature.

The strength is not presented with space between the numeral dose and unit of measure which poses risk of misinterpretation.

It is not immediately clear that the designated strength is per one tablet on the blister pack/wallet.

3 RECOMMENDATIONS FOR ABBVIE INC.

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

A. General Comments for Container Labels and Carton Labeling
   1. As currently presented, the format for the expiration date is not defined. To minimize and reduce the risk for deteriorated drug medication errors, identify the format you intend to use. We recommend using a format like either:
      - DDMMMYYYY (e.g., 31JAN2013)
      - MMMYYYY (e.g., JAN2013)
      - YYYY-MMM-DD (e.g., 2013-JAN-31)
      - YYYY-MM-DD (e.g., 2013-01-31)

   2. Assignment of sequential numbers for the middle digits of the NDC product code numbers (i.e., 0038 and 0039) is not an effective differentiating feature. Postmarketing experience indicates that similarity of the NDC product code numbers has led to selecting and dispensing the wrong strength. The middle 3-4 digits are traditionally used by healthcare providers to check the correct product, strength, and formulation. Please revised the middle digits so they are not sequential. If for some reason the middle digits cannot be revised, increase the prominence of the middle digits by increasing their size in comparison to the remaining digits in the NDC number or put them in bold type. For example:
      XXXX-XXXX-XX

   3. The statement of strength is not presented with space between the numerical dose and unit of measure (i.e., 150mg and 200mg). The “m” in mg when placed too close to the numeric strength is sometimes mistaken as a zero or two zeros and my contribute to wrong dose medication errors.\textsuperscript{b} We recommend you place adequate space between the numerical dose and unit of measure (i.e., 150 mg and 200 mg).

B. Container Labels (blister pack/wallet)
   1. It is not immediately clear that the designated strength (i.e., 150 mg and 200 mg) is per unit (one tablet). The product strength should describe the amount of drug per single unit so there is no confusion as to how much product is contained in a

single unit as compared to the total contents of the entire blister card. Revise the strength statement on the principal display panel (i.e., 150 mg in yellow box and 200 mg strength in blue box) to state “150 mg per tablet” and “200 mg per tablet”, respectively.

APPENDIX A. IMAGES OF LABEL AND LABELING RECEIVED ON MARCH 5, 2018 AND APRIL 12, 2018

Container labels

**Commercial packaging**
- 150 mg weekly blister pack/wallet
  - 150 mg blister pack/wallet foil label and puck
- 200 mg weekly blister pack/wallet
  - 200 mg blister pack/wallet foil label and puck

**Professional Sample**
- 150 mg weekly blister pack/wallet
  - 150 mg blister pack/wallet foil label and puck
- 200 mg weekly blister pack/wallet
  - 200 mg blister pack/wallet foil label and puck

Carton labeling

**Commercial packaging**
- 150 mg carton
- 200 mg carton

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/s/

BRIANA B RIDER
05/08/2018

LOLITA G WHITE
05/08/2018
Consult Response

TO: Christina Chang, MD
   Clinical Team Leader
   Division of Bone, Reproductive, and Urologic Products
   (DBRUP)

FROM: Robert Shibuya, MD
      Clinical Team Leader
      Division of Anesthesia, Analgesia, and Addiction Products
      (DAAAP)

THROUGH: Ellen Fields, MD, MPH
          Deputy Director
          DAAAP

THROUGH: Sharon Hertz, MD
          Director
          DAAAP

SUBJECT: Consult Response

SOURCE DOCUMENTS: DBRUP consult dated February 22, 2018, follow up teleconference
                  with Dr. Chang (2/28/18) and relevant internal documents and
                  submissions to NDA 201450 and IND

DATE of REQUEST: February 22, 2018

DATE of RESPONSE: March 21, 2018
Consult Request:
The Division of Bone, Reproductive, and Urologic Products (DBRUP) has requested:

Please comment on the applicant’s proposed labeling related to analgesic use:
- Under Section 2.2:
- Under Section 14, (with DBRUP’s preliminary edits)

Background
Endometriosis is a chronic disease characterized by implants of endometrium-like tissue outside the uterus. The ectopic tissue is responsive to estrogen and clinically manifests as pain and, in some instances, infertility. A rating instrument known as the Composite Pelvic Signs and Symptoms Score (CPSSS) subclassifies manifestations of endometriosis as dysmenorrhea (DYS), nonmenstrual pelvic pain (NMPP), and dyspareunia (DYSP) among other assessments. Current therapies for endometriosis-related pain include nonsteroidal anti-inflammatory drugs (NSAIDs), oral contraceptives, gonadotropin-releasing hormone (GnRH) agonists, other hormones, and surgical ablation or excision of the lesions. Opioid analgesics are used as second-line treatment for the pain of endometriosis.

Elagolix sodium is a novel oral GnRH antagonist. In August of 2017, AbbVie submitted a NDA, currently under review in DBRUP for “management of endometriosis with associated pain.” Two Phase 3 studies were submitted to support a finding of efficacy, Study M12-665 (Study 665) and Study M12-671 (Study 671) which were of identical design. The substantive difference between studies is the location of the study sites and the choice of the opioid rescue medication. Study 665 was conducted in North America and Study 671 was global; the differences in rescue will be described later in this consult. During development of this drug, AbbVie submitted the protocol for Study 665 for Special Protocol Assessment (SPA). While there is no documentation of an approved SPA, AbbVie and DBRUP continued to negotiate and it appears that issues had been resolved informally by 2014.

During the SPA negotiations, DAAAP was consulted once, in April 2012 (consult response May 21, 2012). The consultation pertained to a Type A meeting with AbbVie to discuss the SPA. DAAAP was asked about the use of rescue analgesics in the proposed primary efficacy endpoint (PEP). The proposed PEP was the difference in the proportion of responders (which required a clinically meaningful difference in pain from baseline AND no increase in use of rescue analgesics [15%]) at Month 3. Pain was to be assessed daily with both DYS and NMPP and a statistically significant difference had to be observed for both scales for the study to be
considered positive. The scoring system for DYS and NMPP was to be categorical (none, mild, moderate, severe) which was to correlate with numerical scores of 0, 1, 2, and 3.

AbbVie proposed an unusual methodology to define a clinically meaningful difference in pain. Each month, patients were also to be asked to complete a 7-point categorical Patient Global Impression of Change (PGIC) that ranged from “Very much worse” to “Very much improved.” Using Receiver Operating Characteristic (ROC) curve methodology, AbbVie proposed to determine the difference in the DYS and NMPP that would be considered clinically meaningful. In the ROC curve, “Very much improved” and “Much improved” were to be considered positive responses and the less favorable responses of “minimally improved” and below were considered negative responses. We note that, in a consult dated February 27, 2014, the Study Endpoints and Labeling Development group at CDER opined that “The PGIC is not a well-defined and reliable measure of endometriosis-associated pain in the proposed context of use…” With regard to rescue analgesics, patients were to be considered non-responders if there was a 15% increase in days of use or a 15% increase in the average daily dose.

DAAAP did not limit its consult response to the rescue analgesic. Key advice in the consult around the efficacy endpoints included:

1. With regard to the threshold for a responder for DYS and NMPP, DAAAP does not have experience with the proposed approach to define a responder (ROC methodology). However, the definition should be clinically relevant and based on what is known about an acceptable response to treatment in patients with endometriosis.

   DAAAP expressed concern that the Sponsor proposed to define clinically meaningful.

2. DAAAP did not specifically address whether the proposed 15% increase in rescue analgesics was appropriate but opined that the change in rescue medication use be clinically relevant for this population.

3. DAAAP opined that, since rescue is to be part of the responder definition, it is appropriate to include that fact in labeling. However, DAAAP stated that inclusion of other information around use of rescue was inappropriate for labeling unless it was associated with a meaningful change in toxicity associated with the rescue.

Key comments (including post-meeting comments) from the Type A SPA meeting of April 24, 2012 include:

1. Subjects identified as responders on the basis of the receiver operating characteristic (ROC) analysis of pain scores would be reclassified as nonresponders if they had a 15% or greater increase in average daily dose of rescue analgesic.

2. There would be no threshold (as described above) for increased use; however, the Sponsor is free to use such a threshold as a sensitivity analysis. The Division would consider this information, particularly if the results of the primary analysis failed to show a compelling difference in treatment effect between treatment groups. In that case, it would be a review decision as to whether the sensitivity analysis provided a more reasonable assessment of whether any increased analgesia use was actually clinically meaningful.
3. An additional secondary analysis could evaluate the proportion of subjects in each treatment arm who experience improvement in pain ranging from 0 to 100%, as a cumulative distribution.

4. Other pain trials have included in responder definitions such criteria as “a stable or decreasing regimen of concurrent opioid analgesics” and “no change in the type of concurrent opioid analgesics.” The Division continues to believe that if elagolix is effective, subjects should not demonstrate an increase in concomitant use of analgesics. The subjects should be optimized on their rescue regimen during the baseline period, and if the Sponsor is concerned about variability in analgesic use, it may wish to obtain a longer baseline.

5. The Sponsor indicated that it may not want to engage in another SPA review cycle but would consider reconciling differences with DBRUP informally.

An internal memo dated 5/28/13 indicates that the Sponsor modified the definition of non-responder for analgesic use to a 15% or greater increase in the average daily dose as requested in the Type A meeting. The rescue analgesics were limited to naproxen, 500 mg or an opioid. The opioid to be used varied by country/region and was hydrocodone (HC)/APAP, 5/300-325 or codeine/APAP, 30/300-500 mg. Hydrocodone/APAP was used in the United States. At this time (2013), AbbVie reported that 22% of patients used neither rescue at baseline, thus any use of naproxen or opioid would result in a non-responder classification. As will be shown in the results of these studies, this unexpectedly high rate of patients who did not require analgesics was not sustained as the trials progressed.

The Pre-NDA meeting (12/9/16) minutes do not include questions or a discussion relevant to this consult.

**Study 665 (Amendment 3, August 4, 2014)**

Relevant features of the protocol are summarized following.

**Title:** A Randomized, Double-Blind, Placebo-Controlled Study to Evaluate the Safety and Efficacy of Elagolix in Subjects with Moderate to Severe Endometriosis-Associated Pain

**Design:**
Randomized, double-blind, placebo-controlled, parallel group
Primary Objectives:
Safety, tolerability, and efficacy of elagolix for moderate to severe endometriosis-associated pain and to evaluate the effect of elagolix on analgesic use (emphasis added)

Population:
875 women with endometriosis and a composite Pelvic Signs and Symptoms Score ≥6 with a score of at least 2 for DYS AND 2 for NMPP. The scoring system for DYS and NMPP is a 4-point categorical scale (0=none, 1=mild, 2=moderate, 3=severe).

Treatment Groups:
Elagolix 150 mg QD (n=250)
Elagolix 200 mg BID (n=250)
Placebo (n=375)

Rescue analgesics:
The rescue was to be prescribed at the time of screening “taking into consideration the subject's preference and/or historical use of analgesics.” As noted previously, the rescue was limited to naproxen or a combination opioid/APAP that differed by country/region. Use of rescue was captured in an e-Diary.

Source: Protocol, Study 665, Amendment 3, Figure 1
Key Outcome Measures (daily):
- DYS
- NMPP
- Numerical pain rating scale (appears to be an 11-point numeric)
- Use of rescue (~monthly pill counts and daily diary)
- Patient Global Impression of Change (PGIC) (not daily - Months 1, 2, 3, 4, 5, 6)

Primary Efficacy Endpoint:
The co-primary efficacy endpoints were to be the proportion of responders at Month 3 based upon the mutually-exclusive scales for daily assessment of DYS and NMPP. The complete definition of responder is described in the Pertinent Results section.

Pertinent Results (Studies 665 and 671)

Disposition: 871 and 815 patients were randomized (3:2:2 [Placebo:low dose;high dose]) in Studies 665 and 671, respectively and overall 75% and 78% completed these six-month studies.

Pain at Baseline:
Table 17 from both CSRs shows that, for DYS, approximately 50% reported moderate and 50% reported severe symptoms for both studies. For NMPP, 63-65% reported moderate symptoms (35-37% severe). The average NRS for pain was 5.5 and 5.3 for Studies 665 and 671, respectively (Table 18 in both CSRs).

Prior Analgesic Use:
Analgesics for endometriosis used prior to screening are summarized below:

<table>
<thead>
<tr>
<th>Analgesic</th>
<th>Study 665</th>
<th>Study 671</th>
</tr>
</thead>
<tbody>
<tr>
<td>None</td>
<td>8.7%</td>
<td>9.6%</td>
</tr>
<tr>
<td>NSAID only</td>
<td>32.3%</td>
<td>30.3%</td>
</tr>
<tr>
<td>Opioid only</td>
<td>19.4%</td>
<td>14.4%</td>
</tr>
<tr>
<td>NSAID + opioid</td>
<td>39.6%</td>
<td>45.8%</td>
</tr>
</tbody>
</table>

Source: Table 20, both CSRs

There was no washout of analgesics prior to randomization.

Key Efficacy Analyses:

The final definition of responder was:
- Reduction of X or greater from baseline in pain where X will be determined on a ROC analysis
- No increased analgesic use for endometriosis-associated pain
  - The average pill count of analgesics during the screening period will be summarized over the last 35 days prior to the first dose of study medication.
For the primary endpoints of DYS and NMPP, subjects will be considered non-responders if they have a 15% or greater increase in average pill count of rescue analgesics.

The co-primary endpoints were the proportion of responders at Month 3 for both DYS and NMPP.

**Summary Primary Endpoint (proportion of responders), Study 665 (source CO p 33/96)**

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>Placebo</th>
<th>Elagolix 150 QD</th>
<th>Elagolix 200 BID</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>%</td>
<td>%</td>
<td>P-value</td>
</tr>
<tr>
<td>DYS M3</td>
<td>19.6</td>
<td>46.4</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>NMPP M 3</td>
<td>36.5</td>
<td>50.4</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

**Summary Primary Endpoint (proportion of responders), Study 671 (source CO p 34/96)**

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>Placebo</th>
<th>Elagolix 150 QD</th>
<th>Elagolix 200 BID</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>%</td>
<td>%</td>
<td>P-value</td>
</tr>
<tr>
<td>DYS M3</td>
<td>22.7</td>
<td>43.4</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>NMPP M 3</td>
<td>36.5</td>
<td>49.8</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

The analysis of change for the NPRS follows:

<table>
<thead>
<tr>
<th>Study</th>
<th>Placebo</th>
<th>Elagolix 150 BID</th>
<th>Elagolix 200 BID</th>
</tr>
</thead>
<tbody>
<tr>
<td>665</td>
<td>5.6</td>
<td>5.7</td>
<td>5.5</td>
</tr>
<tr>
<td>LS mean change from BL at Month 3</td>
<td>-1.09</td>
<td>-1.74</td>
<td>-2.39</td>
</tr>
<tr>
<td>671</td>
<td>5.6</td>
<td>5.7</td>
<td>5.3</td>
</tr>
<tr>
<td>LS mean change from BL at Month 3</td>
<td>-1.33</td>
<td>-2.28</td>
<td>-2.87</td>
</tr>
</tbody>
</table>

**Rescue Analgesic Use:**

Rescue analgesics were prescribed at the time of screening and were supposed to remain either naproxen or a fixed combination opioid/APAP solid oral dosage form. From the CSRs, it is unclear how many patients switched rescue analgesics while on study. At each visit (approximately monthly), a bottle pill count was conducted. The Applicant defined “average pill count” as the total number of pills of rescue analgesic used divided by the number of days in the interval. Thus, apparently, an average daily rescue pill count of 1.0 would reflect 30 pills used in a 30-day period. This metric does not allow an understanding of whether all pills were used in a few days or one pill was used per day. On the basis of the tables submitted, it is also not possible to know if any particular patient had a large increase or decrease in rescue use.
Summary tables (Tables 40 and 39 for Studies 665 and 671, respectively) for changes average pill count for any rescue follow.

### Table 40. Change from Baseline to Month 3 and Month 6 in Average Daily Rescue Analgesic (NSAID or Opioid) Pill Count During the Treatment Period Using Repeated Measures Analysis – Observed Cases

<table>
<thead>
<tr>
<th>Time Point/Treatment Group</th>
<th>N</th>
<th>Baseline Mean (SD)</th>
<th>LS Mean Change (SE)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Baseline</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Placebo</td>
<td>374</td>
<td>0.87 (0.872)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Elagolix 150 mg QD</td>
<td>249</td>
<td>0.87 (0.937)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Elagolix 200 mg BID</td>
<td>248</td>
<td>0.85 (0.891)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Month 3</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Placebo</td>
<td>329</td>
<td>−0.29 (0.052)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Elagolix 150 mg QD</td>
<td>226</td>
<td>−0.29 (0.039)</td>
<td>0.910</td>
<td></td>
</tr>
<tr>
<td>Elagolix 200 mg BID</td>
<td>213</td>
<td>−0.55 (0.040)</td>
<td>&lt; 0.001</td>
<td></td>
</tr>
<tr>
<td><strong>Month 6</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Placebo</td>
<td>288</td>
<td>−0.27 (0.036)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Elagolix 150 mg QD</td>
<td>198</td>
<td>−0.35 (0.043)</td>
<td>0.185</td>
<td></td>
</tr>
<tr>
<td>Elagolix 200 mg BID</td>
<td>182</td>
<td>−0.56 (0.045)</td>
<td>&lt; 0.001</td>
<td></td>
</tr>
</tbody>
</table>

**Note:** Average pill count is the total number of pills of rescue analgesic type divided by the length of window (usually 35 days). P values for the difference between each elagolix treatment group and placebo (as well as LS mean and SE) were derived using a mixed effects model using repeated measures with treatment as the main effect, visit number as the repeated measure, baseline value as a covariate, and an interaction between treatment and visit.

### Table 39. Change from Baseline to Month 3 and Month 6 in Average Daily Rescue Analgesic (NSAID or Opioids) Pill Count During the Treatment Period Using Repeated Measures Analysis – Observed Cases

<table>
<thead>
<tr>
<th>Time Point/Treatment Group</th>
<th>N</th>
<th>Baseline Mean (SD)</th>
<th>LS Mean Change (SE)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Baseline</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Placebo</td>
<td>360</td>
<td>0.80 (1.006)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Elagolix 150 mg QD</td>
<td>226</td>
<td>0.85 (1.151)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Elagolix 200 mg BID</td>
<td>229</td>
<td>0.73 (0.962)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Month 3</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Placebo</td>
<td>312</td>
<td>−0.31 (0.028)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Elagolix 150 mg QD</td>
<td>204</td>
<td>−0.36 (0.035)</td>
<td>0.260</td>
<td></td>
</tr>
<tr>
<td>Elagolix 200 mg BID</td>
<td>209</td>
<td>−0.49 (0.034)</td>
<td>&lt; 0.001</td>
<td></td>
</tr>
<tr>
<td><strong>Month 6</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Placebo</td>
<td>273</td>
<td>−0.32 (0.030)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Elagolix 150 mg QD</td>
<td>185</td>
<td>−0.40 (0.038)</td>
<td>0.088</td>
<td></td>
</tr>
<tr>
<td>Elagolix 200 mg BID</td>
<td>187</td>
<td>−0.52 (0.037)</td>
<td>&lt; 0.001</td>
<td></td>
</tr>
</tbody>
</table>

P values for the difference between each elagolix treatment group and placebo (as well as LS mean and SE) were derived using a mixed effects model using repeated measures with treatment as the main effect, visit number as the repeated measure, baseline value as a covariate, and an interaction between treatment and visit.
The Applicant summarized the median percentage of days of use of any rescue analgesic in Tables 41 and 41 for Studies 665/671, following.

Table 41. Average Percentage of Days of Any Rescue Analgesic (NSAID or Opioid) Usage at Month 3 and Month 6 During the Treatment Period – LOCF

<table>
<thead>
<tr>
<th>Time Point/Treatment Group</th>
<th>N</th>
<th>Median %</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Baseline</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Placebo</td>
<td>374</td>
<td>37.1</td>
</tr>
<tr>
<td>Elagolix 150 mg QD</td>
<td>249</td>
<td>37.1</td>
</tr>
<tr>
<td>Elagolix 200 mg BID</td>
<td>248</td>
<td>34.3</td>
</tr>
<tr>
<td><strong>Month 3</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Placebo</td>
<td>373</td>
<td>17.1</td>
</tr>
<tr>
<td>Elagolix 150 mg QD</td>
<td>248</td>
<td>11.4</td>
</tr>
<tr>
<td>Elagolix 200 mg BID</td>
<td>244</td>
<td>5.5</td>
</tr>
<tr>
<td><strong>Month 6</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Placebo</td>
<td>372</td>
<td>14.3</td>
</tr>
<tr>
<td>Elagolix 150 mg QD</td>
<td>247</td>
<td>8.8</td>
</tr>
<tr>
<td>Elagolix 200 mg BID</td>
<td>243</td>
<td>2.9</td>
</tr>
</tbody>
</table>

Table 40. Median Percentage of Days of Any Rescue Analgesic (NSAID or Opioids) Usage at Month 3 and Month 6 During the Treatment Period – LOCF

<table>
<thead>
<tr>
<th>Time Point/Treatment Group</th>
<th>N</th>
<th>Median %</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Baseline</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Placebo</td>
<td>360</td>
<td>28.6</td>
</tr>
<tr>
<td>Elagolix 150 mg QD</td>
<td>226</td>
<td>32.9</td>
</tr>
<tr>
<td>Elagolix 200 mg BID</td>
<td>229</td>
<td>25.7</td>
</tr>
<tr>
<td><strong>Month 3</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Placebo</td>
<td>353</td>
<td>14.3</td>
</tr>
<tr>
<td>Elagolix 150 mg QD</td>
<td>221</td>
<td>8.6</td>
</tr>
<tr>
<td>Elagolix 200 mg BID</td>
<td>225</td>
<td>2.9</td>
</tr>
<tr>
<td><strong>Month 6</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Placebo</td>
<td>355</td>
<td>14.3</td>
</tr>
<tr>
<td>Elagolix 150 mg QD</td>
<td>221</td>
<td>5.7</td>
</tr>
<tr>
<td>Elagolix 200 mg BID</td>
<td>225</td>
<td>0</td>
</tr>
</tbody>
</table>
Last, the Applicant separated out the average pill count by NSAID or opioid, following:

### Study 665 NSAIDs

Table 42. Change from Baseline to Month 3 and Month 6 in Average Daily NSAID Pill Count During the Treatment Period Using Repeated Measures Analysis – Observed Cases

<table>
<thead>
<tr>
<th>Time Point/ Treatment Group</th>
<th>N</th>
<th>Baseline Mean (SD)</th>
<th>LS Mean Change (SE)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Baseline</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Placebo</td>
<td>374</td>
<td>0.50 (0.616)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Elagolix 150 mg QD</td>
<td>249</td>
<td>0.46 (0.639)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Elagolix 200 mg BID</td>
<td>248</td>
<td>0.43 (0.496)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Month 3</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Placebo</td>
<td>329</td>
<td>−0.18 (0.018)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Elagolix 150 mg QD</td>
<td>226</td>
<td>−0.22 (0.021)</td>
<td>0.121</td>
<td></td>
</tr>
<tr>
<td>Elagolix 200 mg BID</td>
<td>213</td>
<td>−0.33 (0.022)</td>
<td>&lt; 0.001</td>
<td></td>
</tr>
<tr>
<td><strong>Month 6</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Placebo</td>
<td>288</td>
<td>−0.19 (0.022)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Elagolix 150 mg QD</td>
<td>198</td>
<td>−0.24 (0.026)</td>
<td>0.102</td>
<td></td>
</tr>
<tr>
<td>Elagolix 200 mg BID</td>
<td>182</td>
<td>−0.32 (0.027)</td>
<td>&lt; 0.001</td>
<td></td>
</tr>
</tbody>
</table>

### Study 671 NSAIDs

Table 41. Change from Baseline to Month 3 and Month 6 in Average Daily NSAID Pill Count During the Treatment Period Using Repeated Measures Analysis – Observed Cases

<table>
<thead>
<tr>
<th>Time Point/ Treatment Group</th>
<th>N</th>
<th>Baseline Mean (SD)</th>
<th>LS Mean Change (SE)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Baseline</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Placebo</td>
<td>360</td>
<td>0.46 (0.694)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Elagolix 150 mg QD</td>
<td>226</td>
<td>0.49 (0.708)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Elagolix 200 mg BID</td>
<td>229</td>
<td>0.40 (0.476)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Month 3</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Placebo</td>
<td>312</td>
<td>−0.18 (0.017)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Elagolix 150 mg QD</td>
<td>204</td>
<td>−0.23 (0.021)</td>
<td>0.067</td>
<td></td>
</tr>
<tr>
<td>Elagolix 200 mg BID</td>
<td>209</td>
<td>−0.29 (0.021)</td>
<td>&lt; 0.001</td>
<td></td>
</tr>
<tr>
<td><strong>Month 6</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Placebo</td>
<td>273</td>
<td>−0.20 (0.019)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Elagolix 150 mg QD</td>
<td>185</td>
<td>−0.24 (0.024)</td>
<td>0.247</td>
<td></td>
</tr>
<tr>
<td>Elagolix 200 mg BID</td>
<td>187</td>
<td>−0.31 (0.024)</td>
<td>&lt; 0.001</td>
<td></td>
</tr>
</tbody>
</table>
### Study 665 Opioids

Table 44. Change from Baseline to Month 3 and Month 6 in Average Daily Opioid Pill Count During the Treatment Period Using Repeated Measures – Observed Cases

<table>
<thead>
<tr>
<th>Time Point/Treatment Group</th>
<th>N</th>
<th>Baseline Mean (SD)</th>
<th>LS Mean Change (SE)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Baseline</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Placebo</td>
<td>374</td>
<td>0.37 (0.588)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Elagolix 150 mg QD</td>
<td>249</td>
<td>0.42 (0.674)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Elagolix 200 mg BID</td>
<td>248</td>
<td>0.42 (0.721)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Month 3</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Placebo</td>
<td>329</td>
<td>–0.10 (0.024)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Elagolix 150 mg QD</td>
<td>226</td>
<td>–0.07 (0.029)</td>
<td>0.424</td>
<td></td>
</tr>
<tr>
<td>Elagolix 200 mg BID</td>
<td>213</td>
<td>–0.22 (0.029)</td>
<td>0.002</td>
<td></td>
</tr>
<tr>
<td><strong>Month 6</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Placebo</td>
<td>288</td>
<td>–0.08 (0.025)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Elagolix 150 mg QD</td>
<td>198</td>
<td>–0.11 (0.031)</td>
<td>0.558</td>
<td></td>
</tr>
<tr>
<td>Elagolix 200 mg BID</td>
<td>182</td>
<td>–0.24 (0.032)</td>
<td>&lt; 0.001</td>
<td></td>
</tr>
</tbody>
</table>

### Study 671 Opioids

Table 43. Change from Baseline to Month 3 and Month 6 in Average Daily Opioid Pill Count During the Treatment Period Using Repeated Measures – Observed Cases

<table>
<thead>
<tr>
<th>Time Point/Treatment Group</th>
<th>N</th>
<th>Baseline Mean (SD)</th>
<th>LS Mean Change (SE)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Baseline</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Placebo</td>
<td>360</td>
<td>0.34 (0.603)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Elagolix 150 mg QD</td>
<td>226</td>
<td>0.36 (0.829)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Elagolix 200 mg BID</td>
<td>229</td>
<td>0.33 (0.736)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Month 3</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Placebo</td>
<td>312</td>
<td>–0.12 (0.019)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Elagolix 150 mg QD</td>
<td>204</td>
<td>–0.12 (0.024)</td>
<td>0.968</td>
<td></td>
</tr>
<tr>
<td>Elagolix 200 mg BID</td>
<td>209</td>
<td>–0.21 (0.023)</td>
<td>0.007</td>
<td></td>
</tr>
<tr>
<td><strong>Month 6</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Placebo</td>
<td>273</td>
<td>–0.12 (0.020)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Elagolix 150 mg QD</td>
<td>185</td>
<td>–0.16 (0.024)</td>
<td>0.152</td>
<td></td>
</tr>
<tr>
<td>Elagolix 200 mg BID</td>
<td>187</td>
<td>–0.22 (0.024)</td>
<td>&lt; 0.001</td>
<td></td>
</tr>
</tbody>
</table>
Discussion:

Question 1 of the consult asks whether dosing recommendations should contain language

Subgroup analyses by baseline analgesic use may inform this question. I accessed Tables 14.2.6.1.1 and 14.2.6.2.1 from both studies. These studies are titled “PROPORTION OF SIMULTANEOUS PAIN AND ANALGESIC RESPONDERS USING CHANGE FROM BASELINE FOR [DYSMENORRHEA or] NON-MENSTRUAL PELVIC PAIN AT MONTH 3 DURING THE TREATMENT PERIOD SUBGROUP ANALYSIS (MODIFIED INTENT-TO-TREAT SET).” I have reformatted the relevant statistics to facilitate comparison in the table below.

<table>
<thead>
<tr>
<th>Study</th>
<th>DYS/NMPP</th>
<th>Baseline Analgesic</th>
<th>Placebo</th>
<th>Elagolix 150</th>
<th>Elagolix 200</th>
<th>Difference in responders (200-150)</th>
</tr>
</thead>
<tbody>
<tr>
<td>665</td>
<td>DYS</td>
<td>None</td>
<td>29.6</td>
<td>55.9</td>
<td>78.6</td>
<td>22.7</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Narcotic-only</td>
<td>19.7</td>
<td>46.7</td>
<td>82.7</td>
<td>36.0</td>
</tr>
<tr>
<td></td>
<td></td>
<td>NSAID-only</td>
<td>22.2</td>
<td>60.9</td>
<td>75.9</td>
<td>15.0</td>
</tr>
<tr>
<td></td>
<td></td>
<td>NSAID+narcotic</td>
<td>15.0</td>
<td>34.3</td>
<td>71.7</td>
<td>37.4</td>
</tr>
<tr>
<td>665</td>
<td>NMPP</td>
<td>None</td>
<td>44.4</td>
<td>50.0</td>
<td>64.3</td>
<td>14.3</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Narcotic-only</td>
<td>25.4</td>
<td>53.3</td>
<td>46.2</td>
<td>-7.1</td>
</tr>
<tr>
<td></td>
<td></td>
<td>NSAID-only</td>
<td>43.7</td>
<td>59.4</td>
<td>57.0</td>
<td>-2.4</td>
</tr>
<tr>
<td></td>
<td></td>
<td>NSAID+narcotic</td>
<td>33.6</td>
<td>43.8</td>
<td>55.6</td>
<td>11.8</td>
</tr>
<tr>
<td>671</td>
<td>DYS</td>
<td>None</td>
<td>18.2</td>
<td>42.9</td>
<td>68.2</td>
<td>25.3</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Narcotic-only</td>
<td>16.4</td>
<td>51.5</td>
<td>75.0</td>
<td>23.5</td>
</tr>
<tr>
<td></td>
<td></td>
<td>NSAID-only</td>
<td>20.0</td>
<td>56.6</td>
<td>71.0</td>
<td>14.4</td>
</tr>
<tr>
<td></td>
<td></td>
<td>NSAID+narcotic</td>
<td>27.3</td>
<td>29.7</td>
<td>73.6</td>
<td>43.9</td>
</tr>
<tr>
<td>671</td>
<td>NMPP</td>
<td>None</td>
<td>30.3</td>
<td>38.1</td>
<td>63.6</td>
<td>25.5</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Narcotic-only</td>
<td>29.1</td>
<td>66.7</td>
<td>53.6</td>
<td>-13.1</td>
</tr>
<tr>
<td></td>
<td></td>
<td>NSAID-only</td>
<td>37.0</td>
<td>55.3</td>
<td>62.3</td>
<td>7.0</td>
</tr>
<tr>
<td></td>
<td></td>
<td>NSAID+narcotic</td>
<td>40.0</td>
<td>41.8</td>
<td>54.7</td>
<td>12.9</td>
</tr>
</tbody>
</table>

The table shows that, for the DYS endpoint, the higher dose appears to offer more benefit for patients on baseline opioids-only compared to NSAIDs-only. The results are the opposite for the NMPP endpoint. However, this analysis would also support the use of the high dose over the low dose in patients with no prior analgesic therapy over all other baseline therapies for the NMPP endpoint. The subgroup analyses do not reveal a clear and consistent pattern.

Question 2 in the consult pertains to claims requested by AbbVie.
Response to DBRUP’s questions:

1. Under Section 2.2:

   **DAAAP Response:** We are limiting our response to the portion of the prose pertaining to opioid use. As described in the Discussion section, we do not believe that the subgroup analyses support the language recommending the 200 mg BID regimen for patients

2. Under Section 14, **(with DBRUP’s preliminary edits)**

   **DAAAP Response:** We advise against inclusion of the proposed language into labeling
This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

----------------------------------------
ROBERT B SHIBUYA
03/21/2018

SHARON H HERTZ
03/22/2018
# HUMAN FACTORS VALIDATION LABEL COMPREHENSION RESULTS REVIEW

Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

*** This document contains proprietary information that cannot be released to the public***

<table>
<thead>
<tr>
<th>Date of This Review:</th>
<th>March 15, 2018</th>
</tr>
</thead>
<tbody>
<tr>
<td>Requesting Office or Division:</td>
<td>Division of Bone, Reproductive, and Urologic Products (DBRUP)</td>
</tr>
<tr>
<td>Application Type and Number:</td>
<td>NDA 210450</td>
</tr>
<tr>
<td>Product Name and Strength:</td>
<td>Orilissa (elagolix sodium) Tablets 150 mg and 200 mg</td>
</tr>
<tr>
<td>Product Type:</td>
<td>Single Ingredient</td>
</tr>
<tr>
<td>Rx or OTC:</td>
<td>Rx</td>
</tr>
<tr>
<td>Applicant/Sponsor Name:</td>
<td>Abbvie Inc.</td>
</tr>
<tr>
<td>Submission Date:</td>
<td>August 23, 2017, February 22, 2018</td>
</tr>
<tr>
<td>OSE RCM #:</td>
<td>2017-1760</td>
</tr>
<tr>
<td>DMEPA Primary Reviewer:</td>
<td>Walter Fava, RPh., MSEd.</td>
</tr>
<tr>
<td>DMEPA Team Leader:</td>
<td>Lolita White, PharmD.</td>
</tr>
<tr>
<td>DMEPA Associate Director for Human Factors:</td>
<td>QuynhNhu Nguyen, MS.</td>
</tr>
</tbody>
</table>
1 REASON FOR REVIEW
The Division of Bone, Reproductive, and Urologic Products (DBRUP) requested that DMEPA evaluate the human factors (HF) label comprehension study report submitted on August 23, 2017 for NDA 210450 to determine if the results support the safe and effective use of the proposed product for the intended users.

2 PRODUCT INFORMATION
Orilissa (elagolix sodium) is a gonadotropin-releasing hormone receptor antagonist indicated for the management of endometriosis with associated pain. The proposed product is available as a 150 mg and 200 mg tablet and is taken orally as 150 mg once a day or 200 mg twice a day, with or without food. It is packaged in blister wallets with 7 tablets of 150 mg per wallet for the once daily dosage and 14 tablets of 200 mg per wallet for the twice daily dosing. The tablets are supplied in 4 weekly wallets per carton. The 150 mg once daily weekly blister wallet label uses a calendarized blister label and also further labels an AM and PM dose. The Applicant states the packaging was designed to facilitate patient adherence to the long term maintenance regimen for this chronic condition. The tablets are stored at .

3 MATERIALS REVIEWED
We considered the materials listed in Table 1 for this review. The Appendices provide the methods and results for each material reviewed.

<table>
<thead>
<tr>
<th>Material Reviewed</th>
<th>Appendix Section (for Methods and Results)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Product Information/Prescribing Information</td>
<td>A</td>
</tr>
<tr>
<td>Previous DMEPA Reviews</td>
<td>B</td>
</tr>
<tr>
<td>Human Factors Label Comprehension Study</td>
<td>C</td>
</tr>
<tr>
<td>ISMP Newsletters</td>
<td>D</td>
</tr>
<tr>
<td>FDA Adverse Event Reporting System (FAERS)*</td>
<td>E (N/A)</td>
</tr>
<tr>
<td>Other -IR to provide an updated URRA</td>
<td>F</td>
</tr>
<tr>
<td>Labels and Labeling</td>
<td>G</td>
</tr>
</tbody>
</table>

N/A=not applicable for this review
*We do not typically search FAERS for our label and labeling reviews unless we are aware of medication errors through our routine postmarket safety surveillance

4 OVERALL ASSESSMENT OF THE MATERIALS REVIEWED

4.1 HUMAN FACTORS LABEL COMPREHENSION VALIDATION STUDY METHODOLOGY
We reviewed the labeling comprehension study results, blister label, prescribing information and carton labeling for the proposed product. The label comprehension validation study focused on label and labeling assessment and included thirty (30) participants were representative of the intended elagolix user population (e.g. patients
diagnosed with endometriosis). The participants were further divided into two user groups; fifteen participants were assigned to the 150 mg once daily group and fifteen participants were assigned to the 200 mg twice daily group. The participants received no training and were asked to imagine they had just received the medication from the pharmacy and to simulate the experience of administering the medication for the first two doses (150 mg daily) or the first three doses (200 mg twice daily). Participants were then asked to point to the remaining doses and tell the moderator when they would take each remaining tablet without removing them from the blister package.

4.2 **HUMAN FACTORS LABEL COMPREHENSION VALIDATION STUDY RESULTS**

Our review of the human factors label comprehension validation study results identify failures and confusion with the calendarized blister labels which may lead to medication error of underdose, overdose or dose omission. Specifically, within the study results, we note use errors in the use task to remove the correct tablet for all use scenarios (e.g. dose 1, dose 2 and dose 3). Although, none of the reported failures in this study resulted in a wrong dose medication error (e.g. underdose, overdose, dose omission), we note the reported feedback of confusion posing a risk of medication error to occur. In further review of the use-related risk analysis, we noted the analysis did not adequately address or discuss risk mitigation strategies for the user who is confused with the calendarized blister label and removes the tablet from the incorrect blister. As such, on February 20, 2018 an Information Request (IR) was sent for the Sponsor to provide further clarification on the risk associated with this failure. The Sponsor updated the URRA to address the risk.

The Sponsor concluded that the risk of this failure is not associated with harm or clinical impact because the correct dose is still taken. They further state that the risk has been mitigated to the greatest extent possible and no additional strategies are likely to reduce risk further (see appendix F). We find their response to be acceptable.

Our detailed assessment of the human factors (HF) label comprehension validation study results is as follows. Table 2 provide a summary of the number of use errors occurred during the study. Table 3 provides a detailed assessment provided by the Sponsor as well as DMEPA.
### Table 2: Summary of Critical Task Use Errors and Close Calls

<table>
<thead>
<tr>
<th>Critical Tasks Description</th>
<th>150 mg daily use scenario</th>
<th>200 mg twice daily use scenario</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Use Errors</td>
<td>Close Calls</td>
<td>Use Errors</td>
</tr>
<tr>
<td>Understand pre-use requirements for medicine (e.g. dose timing and circumstances under which the medication should not be taken) [Knowledge Assessment]</td>
<td>0</td>
<td>0</td>
<td>4</td>
</tr>
<tr>
<td>Take first dose according to patient instructions – select the correct tablet for dose 1 [Observation]</td>
<td>1</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Take second dose according to patient instructions - select the correct tablet for dose 2 [Observation]</td>
<td>2</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Take third dose according to patient instructions – select the correct tablet for dose 3 (200 mg BiD only) [Observation]</td>
<td>N/A</td>
<td>N/A</td>
<td>1</td>
</tr>
<tr>
<td>Critical Tasks Description</td>
<td>Description of Use Errors</td>
<td>Participant Subjective Feedback</td>
<td>Applicant’s Root Cause Analysis</td>
</tr>
<tr>
<td>----------------------------</td>
<td>---------------------------</td>
<td>---------------------------------</td>
<td>--------------------------------</td>
</tr>
<tr>
<td>Select the correct tablet for dose 1 (150 mg daily) (n=1)</td>
<td>The participant should have</td>
<td>One participant when prompted to go through the steps to take the first dose of medication, she</td>
<td>The Applicant attributes this use error to insufficient guidance – the participant did not notice the labels on the blister pack which</td>
</tr>
<tr>
<td>(n=1)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Administering the correct dose is a critical task. Although an intended user may
Select correct tablet for dose 2 (150 mg daily) (n=2)

The participant took her second dose. Participant removed the One participant stated all the tablets are 150 mg so it makes no difference to take them out of order. The participant states the labeling of the pills did not matter as long as she was taking one per day and that she would keep track of when she started taking pills so she would know if she forgot a dose or had skipped a day. The participant stated she became aware of the labels after she removed her first dose. She further stated if she was at home she would have approached the dosing schedule the same way.

One participant removed the. The Applicant provided a root cause analysis of Intentional misuse for both use errors. The Applicant states the participant purposefully ignored the blister labels and took the tablet out of the intended order. The use related risk analysis from the Applicant recognizes failure to fully read instructions about proper administration to be a common use error related to similar packages for other pharmaceutical products. The Applicant states this failure is not associated with clinical harm due to the fact the participants would still have taken the correct dose in the correct intervals. The Applicant did not propose any mitigations for this use error.

The Applicant provided a root cause analysis of Intentional misuse for both use errors. The Applicant states the participant purposefully ignored the blister labels and took the tablet out of the intended order. The use related risk analysis from the Applicant recognizes failure to fully read instructions about proper administration to be a common use error related to similar packages for other pharmaceutical products. The Applicant states this failure is not associated with clinical harm due to the fact the participants would still have taken the correct dose in the correct intervals. The Applicant did not propose any mitigations for this use error.

No root cause was provided for participant.
No additional subjective feedback was provided for this use error.

| Select correct tablet for dose 1 (200 mg bid) (n=1) | Participant selected the wrong tablet for dose 1. | One participant stated that she would take her first dose. | The Applicant’s root cause analysis attributed this error to participant inattentiveness. The participant did not pay attention during the session.

This was exacerbated by the simulated nature of this study. The Applicant includes the failure to fully read instructions about proper administration as a known use error for similarly packaged pharmaceuticals and did not propose additional mitigations for this use error. |

| Select correct tablet for dose 2 (200 mg bid) (n=1) Select the correct tablet for dose 3 (200 mg bid) (n=1) | Participant selected the wrong tablet for dose 2. Participant took the wrong tablet for dose 3. | One participant who incorrectly took the | The Applicant contributes this use error to the Participant inattentiveness to dosing labels at the beginning of the regimen. According to the Applicant, this was exacerbated by the simulated use hypothetical nature of the study. According to the Applicant, this failure is not associated with clinical harm due to the fact the participant would have taken the correct dose in the correct |
intervals (one tablet twice a day). The Applicant includes the failure to fully read instructions about proper administration as a known use error for similarly packaged pharmaceuticals and did not propose additional mitigations for this use error. The Applicant attributes this use failure to the participant inattentiveness related to inattentiveness to dosing labels at the beginning of the regimen. According to the Applicant, this was exacerbated by the simulated use hypothetical nature of the study. The Applicant states this failure is not associated with clinical harm due to the fact that the participant would have taken the correct dose in the correct intervals. The Applicant includes the failure to fully read instructions about proper administration as a known use error for similarly packaged pharmaceuticals and did not propose additional mitigations for this use error.

<table>
<thead>
<tr>
<th>Knowledge</th>
<th>Participant</th>
<th>One participant did not</th>
<th>The Applicant contributes this</th>
<th>We reviewed the participants’</th>
</tr>
</thead>
</table>

Reference ID: 4234866
<table>
<thead>
<tr>
<th>Assessment (Are there any circumstances you shouldn’t take this medication) (n=2)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Participant was unable to provide an answer to this question.</td>
</tr>
<tr>
<td>Participant partially answered this knowledge assessment and stated, ‘if pregnant but did not provide the rest of the answer. When asked why she had not provided the full answer, she stated that she combined “pregnant”</td>
</tr>
<tr>
<td>One participant made a guess that if she was a</td>
</tr>
</tbody>
</table>

**Incomplete answer to Mental model – participant’s experience with other medications and the associated warning labels.** The participant’s mental model that.

**Subjective feedback, the Applicants root cause analysis and agree that both of the use errors are attributed to participant’s experience with using similar medications. In our review of the use error for the second participant it appears from the description of this knowledge error, the participant did not see the instruction and had to look for it, and even after finding it she did not completely read the full instruction aloud for her response. Our review of the carton labeling identified the first statement under ‘Important Information’ to state: ‘DO NOT take Orilissa if you are pregnant, ...’ We find this warning statement is clearly and prominently placed. We have no additional recommendations to further mitigate the risk of this knowledge error.**

The Applicant attributed this failure to fully answer the question to “mental model”. The participant disregarded the information due to the fact the instruction were not relevant to her particular situation. The...
<table>
<thead>
<tr>
<th>Knowledge assessment (Is this medication a contraceptive?) (n=1)</th>
<th>Participant was unable to locate the answer for this question on the package and was unable to provide the correct answer for the question.</th>
<th>The participant stated, ‘That’s the only thing I didn’t see because there was nothing to give me more information, there is just whatever is in the box’. The participant pointed out that you should check with your doctor if your bone health...if you have problems with your bones. The participant said she expected to find this under important information. The participant did reference the blank PI and stated she expected the information to be there. The USPI was intentionally left blank as part of the study protocol.</th>
<th>The Applicant’s root cause analysis states that the participant answered that the information was not there prior to looking for it. When the information was pointed out to her by the moderator, she stated she did not initially see this information because she only read the first part of each section. Because the information was on the second line, she skipped it. The Applicant categorizes this error as insufficiently prominent guidance for this participant. The Applicant states in a real world situation, had the participant looked for the information in the USPI, it is possible she would have been able to find the information there. There will also be a medication guide included in the package, which clearly states that the drug does not prevent pregnancy and you need to use effective methods of birth control while on this</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Participant was unable to locate the answer for this question on the package and was unable to provide the correct answer for the question.</td>
<td>The participant stated, ‘That’s the only thing I didn’t see because there was nothing to give me more information, there is just whatever is in the box’. The participant pointed out that you should check with your doctor if your bone health...if you have problems with your bones. The participant said she expected to find this under important information. The participant did reference the blank PI and stated she expected the information to be there. The USPI was intentionally left blank as part of the study protocol.</td>
<td>The Applicant’s root cause analysis states that the participant answered that the information was not there prior to looking for it. When the information was pointed out to her by the moderator, she stated she did not initially see this information because she only read the first part of each section. Because the information was on the second line, she skipped it. The Applicant categorizes this error as insufficiently prominent guidance for this participant. The Applicant states in a real world situation, had the participant looked for the information in the USPI, it is possible she would have been able to find the information there. There will also be a medication guide included in the package, which clearly states that the drug does not prevent pregnancy and you need to use effective methods of birth control while on this</td>
</tr>
</tbody>
</table>

Our review of the participant’s subjective information notes that the participant looked for that information within the PI, however, the PI was intentionally left blank as part of the study. We agree this information is usually found within the PI. Our review of the important information section on the carton and wallet labeling identified the second statement under important information is, We find this labeling statement acceptable and have no additional recommendations to further mitigate this knowledge task failure.
| Knowledge assessment (According to the package, imagine that one day you weren’t experiencing endometriosis symptoms. What would you do in regards to this medication?) (n=1) | The participant was unable to immediately locate the answer to this question | The participant stated she saw the answer somewhere, however she was not able to locate it when looking at both the carton and wallet. The participant stated she saw the first part of the bullet point, but did not fully read the sentence. The participant was able to answer the question with assistance from the moderator. The participant did not suggest any mitigation. | The Applicant’s root cause analysis for this knowledge assessment difficulty was was insufficient prominent guidance and inattentiveness and proposed no additional mitigations for this knowledge assessment difficulty. | Our review of the participant’s subjective feedback notes the participant had difficulty finding the information immediately when asked. However, we find that since the participant did see it and answered the question correctly, but could not remember where it was stated, we find this failure is acceptable. Our review of the carton and wallet labeling identified the third bullet under important information states to take the product even if symptom free. We find this statement acceptable and have no additional recommendations to further mitigate the risk of this knowledge assessment difficulty. |
4.3 CARTON LABELING AND PRESCRIBER INFORMATION

We reviewed the proposed labeling comprehension study results, blister label, prescribing information and carton labeling for the proposed product for vulnerability to medication error and areas of needed improvement. We note the submitted blister labels and carton labeling contain revisions in response to recommendations that we made during a previous human factors protocol review. Our review of the proposed labels and labeling identified the following areas of needed improvement that may contribute to medication errors:

- The blister label does not indicate the expiration date.
- The established name is not commensurate with the proprietary name.
- The dosage and administration section of the prescribing information includes the error prone abbreviations QD and BID.

We provide recommendations regarding these areas below in Section 5.1 and Section 5.2 in order to help minimize the potential for medication errors to occur with the use of the product.

5 CONCLUSION & RECOMMENDATIONS

The results of the human factors label comprehension study identified some use errors however, our assessment of the errors, subjective feedback and root cause analyses indicated that the user interface has been optimized to the greatest extent possible. However, we note areas of improvement within the PI to minimize the risk of medication errors to meet Agency regulation. Specifically, the use of error prone abbreviations in the PI, lack of expiration date on the blister label and the presentation of the established name on the labels and labeling could benefit from further improvements. We advise these recommendations are implemented prior to the approval of this application. Please see our recommendation in Section 5.1 for the division and Section 5.2 for Abbvie Inc.

5.1 RECOMMENDATIONS AND COMMENTS FOR THE DIVISION

1. To prevent confusion in the dosage and administration section of the prescribing information, we recommend removing the abbreviations, ‘QD’ and ‘BID’ throughout the labeling and replacing them with their corresponding meanings, ‘once daily’ and ‘twice daily’.

5.2 RECOMMENDATIONS AND COMMENTS FOR ABBVIE INC.

---

5.2.1 Human Factors Label Comprehension

We find the results of your human factors label comprehension study and revised use related risk analysis acceptable and have no additional recommendations at this time.

5.2.2 Label and Labeling

1. As currently presented, the foil blister card contains the established name, strength and lot number however does not include an expiration date. The expiration date is required on the immediate container per 21 CFR 201.17. To align with regulations, we recommend you include the expiration date on the foil blister label. Please ensure that there are no other numbers located in close proximity to the expiration date where it can be mistaken as the expiration date.

2. The established name lacks prominence commensurate with the proprietary name. Increase the prominence of the established name taking into account all pertinent factors, including typography, layout, contrast, and other printing features in accordance with 21 CFR 201.10(g)(2).
### APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

<table>
<thead>
<tr>
<th>Table 2. Relevant Product Information for</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Initial Approval Date</strong></td>
<td>N/A</td>
</tr>
<tr>
<td><strong>Active Ingredient</strong></td>
<td>elagolix sodium</td>
</tr>
<tr>
<td><strong>Indication</strong></td>
<td>Endometriosis and associated pain</td>
</tr>
<tr>
<td><strong>Route of Administration</strong></td>
<td>Oral</td>
</tr>
<tr>
<td><strong>Dosage Form</strong></td>
<td>Tablets</td>
</tr>
<tr>
<td><strong>Strength</strong></td>
<td>150 mg and 200 mg</td>
</tr>
<tr>
<td><strong>Dose and Frequency</strong></td>
<td>150 mg by mouth once daily or 200 mg by mouth twice daily</td>
</tr>
<tr>
<td><strong>How Supplied/ Container Closure</strong></td>
<td>Blister wallets contain a one week supply per wallet with four wallets in a carton.</td>
</tr>
<tr>
<td><strong>Storage</strong></td>
<td><em>(b)(4)</em></td>
</tr>
</tbody>
</table>
APPENDIX B. PREVIOUS DMEPA REVIEWS

B.1 Methods
On December 21, 2017 we searched the L:drive and AIMS using the term, elagolix to identify reviews previously performed by DMEPA.

B.2 Results
Our search identified three previous reviews\(^1\),\(^2\),\(^3\) and we confirmed that our previous recommendations communicated to the Applicant thus far have been implemented.

APPENDIX F. INFORMATION REQUEST RESPONSE FROM SPONSOR FOR UPDATED USE RELATED RISK ANALYSIS FEBRUARY 22, 2018 SUBMISSION

EDR Link found in 1.14.1.4 submitted February 22, 2018:

\cdsesub1\evsprod\nda210450\0026\m1\us\114-labeling\draft\comprehension-studies\patient-summative-rpt.pdf
APPENDIX G. LABELS AND LABELING
G.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,\(^{e}\) along with postmarket medication error data, we reviewed the following Orilissa labels and labeling submitted by Abbvie Inc. August 23, 2017.

- Carton labeling
- Blister label
- Prescribing Information (no image)

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

/s/

----------------------------------------
WALTER L FAVA
03/15/2018

----------------------------------------
LOLITA G WHITE
03/15/2018

----------------------------------------
QUYNHNHU T NGUYEN
03/16/2018

Reference ID: 4234866
Clinical Inspection Summary

Date From 03/01/2018
Jenn Sellers, M.D., Ph.D.
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations (OSI)

To
Maria Wasilik, RPM
Gerald Willett, Medical Officer
Abby Anderson, Medical Officer
Christina Chang, Clinical Team Leader
Division of Bone, Reproductive, and Urologic Products (DBRUP)

NDA # 210450
Applicant AbbVie, Inc.
Drug Elagolix
NME Yes
Therapeutic Classification Gonadotropin-releasing Hormone Receptor Antagonist
Proposed Indication Management of Endometriosis with Associated Pain
Consultation Request Date October 13, 2017
Summary Goal Date March 1, 2018
Action Goal Date April 23, 2018
PDUFA Date April 23, 2018

I. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

The clinical sites of Drs. Osborn, Simon, Somasundaram, Wilk, and Young were inspected in support of this NDA. The studies appear to have been conducted adequately, and the data generated by these sites appear acceptable in support of the respective indication. Although regulatory violations were noted at Drs. Simon’s, Wilk’s, and Young’s sites, the findings are unlikely to significantly impact data reliability.

The final compliance classification of the inspection of Dr. Somasundaram was No Action Indicated (NAI). The preliminary classification of the inspection of Dr. Osborn was NAI, and the preliminary classifications of the inspections of Drs. Simon, Wilk, and Young were Voluntary Action Indicated (VAI).

II. BACKGROUND

The Applicant submitted this NDA to support the use of elagolix for the treatment of moderate to severe endometriosis-associated pain. Inspections were requested for the following protocols in support of this application:
Protocol M12-665, “A Randomized, Double-Blind, Placebo-Controlled Study to Evaluate the Safety and Efficacy of Elagolix in Subjects with Moderate to Severe Endometriosis-Associated Pain”

This study took place in 151 sites in the United States and Canada, beginning May 22, 2012 and ending September 28, 2015. A total of 871 subjects were randomized.

This was a phase 3, multicenter, double-blind, placebo-controlled, randomized study to assess the safety and efficacy of 2 doses of elagolix (150 mg QD and 200 mg BID) versus placebo in premenopausal women 18 to 49 years of age with moderate to severe endometriosis-associated pain.

The study objectives were to:

- Evaluate the safety, tolerability, and efficacy of elagolix, administered as 150 mg once daily (QD) or 200 mg twice daily (BID) for 3 months in the management of moderate to severe endometriosis-associated pain and to evaluate the effect of elagolix treatment on analgesic use for endometriosis-associated pain
- Evaluate the persistence of efficacy of elagolix at 6 months
- Assess other endometriosis-related symptoms like dyspareunia, analgesic use, as well as quality of life endpoints

The coprimary efficacy endpoints were the proportion of responders at Month 3 based on assessment of dysmenorrhea and non-menstrual pelvic pain as measured by the daily e-Diary ratings.

Protocol M12-671, “A Randomized, Double-Blind, Placebo-Controlled Study to Evaluate the Safety and Efficacy of Elagolix in Subjects with Moderate to Severe Endometriosis-Associated Pain”

This study took place in 187 sites in Argentina, Austria, Australia, Brazil, Czech Republic, Hungary, Italy, New Zealand, Poland, South Africa, Spain, the United States, and the United Kingdom, beginning September 09, 2013 and ending December 19, 2016. A total of 815 subjects were randomized. The study design and endpoints were identical to Protocol M12-665.

Rationale for Site Selection

A site selection tool was used to identify sites for inspection. The sites of Drs. Osborn, Simon and Somasundaram were selected due to high enrollment. Dr. Wilk’s site was selected due to the highest risk rank, high enrollment, low discontinuation and low protocol violations, and high treatment effect. Dr. Young’s site was selected due to high enrollment and high treatment effect.
### III. RESULTS (by site):

<table>
<thead>
<tr>
<th>Site #/Name of CI/Address</th>
<th>Protocol#/# of Enrolled Subjects</th>
<th>Inspection Dates</th>
<th>Classification</th>
</tr>
</thead>
<tbody>
<tr>
<td>Site #45069 Osborn, Alvadore, D.O. 5950 University Avenue West Des Moines, Iowa 50266</td>
<td>Protocol: M12-665 Subjects: 14</td>
<td>11-14 Dec 2017</td>
<td>NAI*</td>
</tr>
<tr>
<td>Site #17011 Simon, James, M.D. 1850 M. Street, NW Washington, DC 20036</td>
<td>Protocol: M12-671 Subjects: 13</td>
<td>04-07, 11 Dec 2017</td>
<td>VAI*</td>
</tr>
<tr>
<td>Site #53501 Somasundaram, Shivkamini, M.D. 3600 Olentangy River Road Columbus, Ohio 43214</td>
<td>Protocol: M12-671 Subjects: 22</td>
<td>04-08 Dec 2017 11-13, 18 Dec 2017</td>
<td>NAI</td>
</tr>
<tr>
<td>Site #51673 Wilk, Krzysztof, M.D., Ph.D. VITA LONGA Sp. z.o.o. ul. Uniczowska 6 Katowice 40-748 Poland</td>
<td>Protocol: M12-671 Subjects: 30</td>
<td>22-26 Jan 2018</td>
<td>VAI*</td>
</tr>
</tbody>
</table>

Key to Compliance 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 483 or preliminary communication with the field; EIR has not been received from the field, and complete review of EIR is pending. Final classification occurs when the post-inspectional letter has been sent to the inspected entity.
1. **Osborn, Alvadore, D.O.**

At this site for Protocol M12-665, 20 subjects were screened, 14 were enrolled, and 13 completed the study. One subject was discontinued due to a diagnosis of bipolar disorder which was made while she was on the study. The inspection reviewed all consent forms for all screened; and the eligibility, the primary and the secondary efficacy endpoints, AEs, and protocol deviations for 14 enrolled subjects. Both the primary and secondary efficacy endpoint data were verifiable. There was no evidence of under-reporting of AEs.

2. **Simon, James, M.D.**

At this site for Protocol M12-671, 34 subjects were screened, 13 were enrolled, and 9 completed the study. The reasons for discontinuation of 4 subjects were: withdrawal of consent (2), pregnancy (1), and site transfer (1). The inspection reviewed the source records, drug accountability, subject's e-Diary entries, consent forms, and clinical trial administration documents for all enrolled subjects.

The primary efficacy endpoint data were verifiable. There was no evidence of under-reporting of AEs.

A Form FDA 483, Inspectional Observations, was issued at the conclusion of the inspection for an eligibility violation. Specifically, Subject # (in the elagolix 200 mg BID group) was enrolled and completed the study, even though she did not meet the inclusion criteria #14, which required an eligible subject to have "moderate" or "severe" pain for dysmenorrhea and non-menstrual pelvic pain using the Monthly Assessment of Endometriosis Pain on Treatment Day 1. Subject # had “mild” pain for non-menstrual pelvic pain.

Dr. Simon responded to the inspection finding in a letter dated 12/20/2017.

*Reviewer’s comment: This protocol violation was reported to FDA.*

3. **Somasundaram, Shivkamini, M.D.**

At this site for Protocol M12-671, 39 subjects were screened, 23 enrolled, 6 withdrew the study and 17 completed the study. A complete record review of 11 enrolled subjects’ records was performed.

The primary efficacy endpoint data were verifiable. There was no evidence of under-reporting of AEs.

A Form FDA 483, Inspectional Observation, was issued to the investigator at the conclusion of the inspection and preliminarily classified as VAI. The inspection findings included 1) failure to list study coordinator, the cardiologist performing the ECGs, and the ultrasound and DEXA technicians as sub-investigators; 2) no documented training for the cardiologist, the ultrasound and DEXA technicians; 3) failure to report a SAE of hospitalization to rule out appendicitis promptly to the institutional review board (IRB), etc. However, after reviewing the Form FDA
483 and the establishment inspection report (EIR), the classification was downgraded to NAI because the findings listed on the Form FDA 483 were not regulatory violations. FDA does not require the investigator to list those who did not make a direct and significant contribution to the study data on Form FDA 1572. FDA does not specifically require that the investigator keep training logs if those he has delegated study responsibilities are qualified by training and/or experience. The investigator only need to report to IRB if SAEs were unexpected, serious, and would have implications for the conduct of the study. The investigator did not need to report the hospitalization to rule out appendicitis to IRB. Dr. Somasundaram adequately responded to the inspection findings in a letter dated December 27, 2017.

4. Wilk, Krzysztof, M.D., Ph.D.

At this site for Protocol M12-671, 47 subjects were screened, 30 were enrolled and 27 completed the study. The inspection reviewed all consent forms for all screened; and the eligibility, endpoints, AEs, concomitant medications, and protocol deviations for the 14 enrolled subjects.

The primary efficacy endpoint data were verifiable. There was no evidence of underreporting of AEs.

A Form FDA 483, Inspectional Observation, was issued at the conclusion of the inspection for an eligibility violation. Specifically, Subject #  (in elagolix 150 mg QD group) was enrolled and treated with study drug despite the subject meeting exclusion criterion #12 (subject who has had any major surgery within 6 months or any minor surgery within 3 months prior to Treatment Day 1). This subject had thyroid surgery 5 weeks prior to Treatment Day 1.

Dr. Wilk adequately responded to the inspection finding in a letter dated 02/14/2018.

Reviewer’s comment: This ineligible subject should not have been included in the study. The subject likely did not have an impact on the efficacy or safety results of the study. This protocol violation was not reported to FDA.

5. Young, David, D.O.

At this site for Protocol M12-665, 24 subjects were screened, 14 were enrolled and 7 completed the study. A review of 13 subject records were performed.

The primary efficacy endpoint data were verifiable. There was no evidence of under-reporting of AEs.

A Form FDA 483, Inspectional Observations, was issued at the conclusion of the inspection for several protocol violations. For example:

a. Subject # (placebo) did not meet inclusion criterion #9 (subjects must have at least two menstrual cycles within the Screening Period prior to Day 1). This subject was enrolled, treated and completed the study even though she only had one menstrual cycle in the Screening Period.
Reviewer’s comment: This ineligible subject should not have been included in the study. This subject likely did not have an impact on the efficacy or safety results of the study. The sponsor approved the subject to continue in the study per Dr. Young’s response letter dated January 10, 2018. This protocol violation was reported to FDA.

b. Subject # (in Elagolix 200 mg BID group) documented the use of hydrocodone/acetaminophen 500mg oral PRN from April 22 to May 26, 2013 for the pain in shoulder, neck and back associated with a car accident. This concomitant medication was not recorded in the Concomitant Medication log or the eCRF.

Reviewer’s comment: Per Dr. Young’s response letter dated January 10, 2018, there was a possible mistake in subject ID during the inspection. It was Subject # (placebo group), not Subject #, who used hydrocodone/acetaminophen 500 mg oral PRN from April 22 to May 26, 2013. The protocol violation was reported to FDA. This protocol violation of a single subject likely did not have an impact on the efficacy or safety results of the study.

{See appended electronic signature page}

Jenn W. Sellers, M.D.
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

CONCURRENCE:

{See appended electronic signature page}

Phillip Kronstein, M.D.
Team Leader,
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
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CONCURRENCE:

{See appended electronic signature page}

Kassa Ayalew, M.D., M.P.H
Branch Chief
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations
cc:
Central Doc. Rm. NDA 210450
DBRUP/Project Manager/Maria Wasilik
DBRUP/Medical Officer/Gerald Willett
DBRUP/Medical Officer/Abby Anderson
DBRUP/Clinical Team Leader/Christina Chang
OSI/Office Director/David Burrow
OSI/DCCE/Division Director/Ni Khin
OSI/DCCE/Branch Chief/Kassa Ayalew
OSI/DCCE/Team Leader/Phillip Kronstein
OSI/DCCE/GCP Reviewer/Jenn Sellers
OSI/GCP Program Analysts/Joseph Peacock/Yolanda Patague
OSI/Database PM/Dana Walters
This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

JENN W SELLERS
03/01/2018

PHILLIP D KRONSTEIN
03/01/2018

KASSA AYALEW
03/01/2018

Reference ID: 4228294
Date: February 13, 2018

From: CDER DCRP QT Interdisciplinary Review Team

Through: Christine Garnett, Pharm.D.
Clinical Analyst
Division of Cardiovascular and Renal Products /CDER

To: Maria Wasilik, RPM
DBRUP

Subject: QT-IRT Consult to NDA 210450

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

This memo responds to your consult to us dated 02/09/2018 regarding the QT related labeling recommendation for elagolix. The QT-IRT reviewed the following materials:

- Sponsor’s proposed labeling;
- Summary of clinical pharmacology;
- CSR for Study M12-790:
- Previous QT-IRT review for TQT study (M12-661) under IND 64802 dated 09/23/2015 in DARRTS.

1. QT-IRT Responses
The Sponsor included the following language in the proposed label:

12.2 Pharmacodynamics
Effect of TRADENAME on QT Interval

Reference ID: 4221151
The following is QT-IRT's proposed labeling language, which is a suggestion only. We defer final labeling decisions to the Division.

### 12.2 Pharmacodynamics

**Cardiac Electrophysiology**

The effect of elagolix on the QTc interval was evaluated in a Phase 1 randomized, placebo and positive controlled, open-label, single-dose, crossover thorough QTc study in 48 healthy adult premenopausal female subjects. At a single dose that produces 17-fold the concentrations with highest recommended therapeutic dose, elagolix did not prolong the QTc interval to any clinically relevant extent.

### 2. BACKGROUND

We have previously reviewed the TQT study for elagolix under IND 64802. As per the review, no significant QTc prolongation effect of elagolix (300 mg and 1200 mg) was detected in the TQT study and the supratherapeutic dose (1200 mg) adequately covers the worst case exposure scenario.

The therapeutic dosing proposed in the sponsor’s label in the current NDA submission is 150 mg once daily (QD) or 200 mg twice daily (BID).

The supratherapeutic dose (1200 mg) in the TQT study produced mean $C_{max}$ of 13229 ng/mL which is ~17-fold the mean $C_{max}$ (774 ng/mL on Day 21) at the highest recommended therapeutic dosing of 200 mg BID (see Table 1 and Table 2 below).

#### Table 1: Mean Pharmacokinetic Parameters of Elagolix (TQT Study M12-661)

<table>
<thead>
<tr>
<th>Pharmacokinetic Parameters (units)</th>
<th>C: Elagolix 300 mg (N = 46)</th>
<th>D: Elagolix 1200 mg (N = 47)</th>
</tr>
</thead>
<tbody>
<tr>
<td>$C_{max}$ (ng/mL)</td>
<td>1356 ± 751</td>
<td>13229 ± 4218</td>
</tr>
<tr>
<td>$T_{max}$ (hr)</td>
<td>1.0 (0.5 − 2.0)</td>
<td>2.0 (0.6 − 2.0)</td>
</tr>
<tr>
<td>$AUC_1$ (ng·hr/mL)</td>
<td>3507 ± 1650</td>
<td>49055 ± 18409</td>
</tr>
<tr>
<td>$AUC_{\infty}$ (ng·hr/mL)</td>
<td>3514 ± 1652</td>
<td>49070 ± 18414</td>
</tr>
<tr>
<td>$t_{1/2}$ (hr)</td>
<td>7.13 ± 3.65</td>
<td>6.06 ± 2.28</td>
</tr>
<tr>
<td>$C_{max}$/Dose (ng/mL)/mg</td>
<td>4.52 ± 2.50</td>
<td>11.0 ± 3.5</td>
</tr>
<tr>
<td>$AUC_1$/Dose (ng·hr/mL)/mg</td>
<td>11.7 ± 5.5</td>
<td>40.9 ± 15.3</td>
</tr>
<tr>
<td>$AUC_{\infty}$/Dose (ng·hr/mL)/mg</td>
<td>11.7 ± 5.5</td>
<td>40.9 ± 15.4</td>
</tr>
</tbody>
</table>

*Source: Summary of clinical pharmacology, Table 28, page 56 of 122*
Table 2: Mean Pharmacokinetic Parameters of Elagolix (Study M12-790)

<table>
<thead>
<tr>
<th>Pharmacokinetic Parameter (units)</th>
<th>100 mg BID N = 7</th>
<th>150 mg QD N = 6</th>
<th>200 mg BID N = 7</th>
<th>300 mg BID N = 8</th>
<th>400 mg BID N = 6</th>
</tr>
</thead>
<tbody>
<tr>
<td>( T_{\text{max}} ) (hr)</td>
<td>1.2 ± 0.4</td>
<td>1.3 ± 0.3</td>
<td>1.1 ± 0.3</td>
<td>1.2 ± 0.4</td>
<td>1.3 ± 0.5</td>
</tr>
<tr>
<td>( C_{\text{max}} ) (ng/mL)</td>
<td>285 ± 89.2</td>
<td>507 ± 207</td>
<td>712 ± 362</td>
<td>1479 ± 740</td>
<td>1928 ± 783</td>
</tr>
<tr>
<td>( \text{AUC}_{\text{t}} ) (ng( \cdot )hr/mL)</td>
<td>787 ± 288</td>
<td>1331 ± 487</td>
<td>1813 ± 876</td>
<td>3509 ± 1556</td>
<td>4918 ± 2070</td>
</tr>
<tr>
<td>( C_{\text{trough}} ) (ng/mL)c</td>
<td>4.58 ± 4.67</td>
<td>0.88 ± 0.32</td>
<td>6.52 ± 3.20</td>
<td>9.97 ± 3.45</td>
<td>17.6 ± 10.3</td>
</tr>
<tr>
<td>( C_{\text{max}}/\text{Dose} )</td>
<td>2.85 ± 0.89</td>
<td>3.38 ± 1.38</td>
<td>3.56 ± 1.81</td>
<td>4.93 ± 2.47</td>
<td>4.82 ± 1.96</td>
</tr>
<tr>
<td>( \text{AUC}_{\text{t}}/\text{Dose} )</td>
<td>7.87 ± 2.88</td>
<td>8.87 ± 3.25</td>
<td>9.07 ± 4.38</td>
<td>11.7 ± 5.19</td>
<td>12.3 ± 5.17</td>
</tr>
<tr>
<td>( T_{\text{max}} ) (hr)</td>
<td>1.0 ± 0.4</td>
<td>0.9 ± 0.2</td>
<td>1.1 ± 0.4</td>
<td>1.2 ± 0.4</td>
<td>1.2 ± 0.4</td>
</tr>
<tr>
<td>( C_{\text{max}} ) (ng/mL)</td>
<td>278 ± 131</td>
<td>574 ± 164</td>
<td>774 ± 530</td>
<td>1200 ± 544</td>
<td>1758 ± 308</td>
</tr>
<tr>
<td>( \text{AUC}_{\text{t}} ) (ng( \cdot )hr/mL)</td>
<td>779 ± 373</td>
<td>1292 ± 403</td>
<td>1725 ± 990</td>
<td>2826 ± 1231</td>
<td>3716 ± 592</td>
</tr>
<tr>
<td>( t_{1/2} ) (hr)b</td>
<td>4.65 ± 2.54</td>
<td>6.42 ± 3.20</td>
<td>4.29 ± 0.47</td>
<td>5.32 ± 1.52</td>
<td>5.62 ± 1.82</td>
</tr>
<tr>
<td>( R_{\text{sc}} ) d</td>
<td>0.98 ± 0.15</td>
<td>0.98 ± 0.07</td>
<td>0.89 ± 0.17</td>
<td>0.78 ± 0.09</td>
<td>0.84 ± 0.29</td>
</tr>
<tr>
<td>( C_{\text{trough}} ) (ng/mL)c</td>
<td>5.06 ± 4.25</td>
<td>0.84 ± 0.58</td>
<td>5.92 ± 4.05</td>
<td>9.78 ± 4.68</td>
<td>11.9 ± 5.52</td>
</tr>
<tr>
<td>( \text{CL/F} ) (L/hr)</td>
<td>163 ± 91.1</td>
<td>123 ± 26.1</td>
<td>144 ± 61.5</td>
<td>126 ± 58.0</td>
<td>110 ± 16.6</td>
</tr>
<tr>
<td>( \text{Vd/F} ) (L)</td>
<td>1499 ± 1709</td>
<td>1674 ± 1570</td>
<td>881 ± 335</td>
<td>977 ± 327</td>
<td>1026 ± 512</td>
</tr>
<tr>
<td>( C_{\text{max}}/\text{Dose} )</td>
<td>2.78 ± 1.32</td>
<td>3.83 ± 1.09</td>
<td>3.87 ± 2.65</td>
<td>4.00 ± 1.81</td>
<td>4.40 ± 0.77</td>
</tr>
<tr>
<td>( \text{AUC}_{\text{t}}/\text{Dose} )</td>
<td>7.79 ± 3.73</td>
<td>8.61 ± 2.68</td>
<td>8.62 ± 4.95</td>
<td>9.42 ± 4.10</td>
<td>9.29 ± 1.48</td>
</tr>
</tbody>
</table>

Source: [CSR for Study M12-790](https://www.fda.gov), Table 13, page 102 of 719

Thank you for requesting our input into the development of this product. We welcome more discussion with you now and in the future. Please feel free to contact us via email at cderdcrpqqt@fda.hhs.gov
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/s/

DHANANJAY D MARATHE
02/13/2018

CHRISTINE E GARNETT
02/13/2018
DATE: January 16, 2018

TO: Hylton Joffe, M.D., M.M.Sc.
    Director
    Division of Bone, Reproductive and Urologic Products (DBRUP)
    Office of Drug Evaluation III (ODE III)
    Office of New Drugs

FROM: Srinivas R. Chennamaneni, Ph.D.
    Staff Fellow
    Division of New Drug Bioequivalence Evaluation (DNDBE)
    Office of Study Integrity and Surveillance (OSIS)
    Office of Translational Sciences

THROUGH: Charles Bonapace, Pharm.D.
    Director
    Division of New Drug Bioequivalence Evaluation (DNDBE)
    Office of Study Integrity and Surveillance (OSIS)
    Office of Translational Sciences

SUBJECT: Routine inspection of AbbVie Clinical Pharmacology Research Unit, Grayslake, IL.

**Inspection Summary:**

The Office of Study Integrity and Surveillance (OSIS) arranged an inspection of AbbVie Clinical Pharmacology Research Unit, Grayslake, IL.

No objectionable conditions were observed and Form FDA 483 was not issued at the inspection close-out. However, two items were discussed with management at the inspection close-out meeting. The final inspection classification is No Action Indicated (NAI).

After reviewing the inspectional findings, I conclude the data from the audited studies (Studies M15-817 & M13-995) are reliable. Thus, I recommend that the data from Studies M15-817 & M13-995 be accepted for further Agency review. In addition, the data from other studies of similar design conducted at AbbVie.
Clinical Pharmacology Research Unit before the end of the current Surveillance Interval should be accepted for review without an inspection.

**Studies audited during the inspection:**

**NDA 210450**

**Study Number 1:** M15-817  
**Study Title:** “A Bioequivalence and Food Effect Study of Elagolix Tablets in Healthy Premenopausal Female Subjects”  
**Dates of conduct:** March 09, 2016 – September 01, 2016

**Study Number 2:** M13-995  
**Study Title:** “A Comparative Bioavailability and Food Effect Study of Elagolix Tablets in Healthy Premenopausal Females”  
**Dates of conduct:** April 05, 2013 – June 28, 2013

**Clinical Site:** AbbVie Clinical Pharmacology Research Unit  
480 South U.S. Highway 45  
Grayslake, IL 60030

ORA investigator Leighton K. Ngai, ORA, BIMO Division 2 (West), inspected AbbVie Clinical Pharmacology Research Unit, Grayslake, IL from November 27 – December 1, 2017.

The inspection included a thorough examination of subject selection criteria, subject records, informed consent, protocol compliance and deviations, study subject files, IRB and Institutional Ethics Committee approvals and correspondence, sponsor correspondence, adverse events, case report forms, safety parameters, comparing source documents with the study report submitted to the agency, test article accountability and storage, and discussions with the firm’s management and staff.

At the conclusion of inspection, investigator Ngai did not observe any objectionable conditions and Form FDA 483 was not issued to the clinical site. However, two items were discussed with AbbVie Clinical Pharmacology Research Unit’s management. The discussion items and my evaluation follow.
Discussion item #1:
About 5 out of 54 subjects enrolled in Study M15-817, and 2 out of 23 subjects enrolled in Study M13-995 were initially consented with an outdated ICF.

OSIS Evaluation:
For study M15-817, subjects [REDACTED] and for study M13-995, subjects [REDACTED] were initially consented with preceding ICF version. However, all five subjects in study M15-817 and both subjects in study M13-995 were reconsented with the approved ICF version prior to randomization and drug administration. Therefore, this discussion item does not have any impact on the study outcome.

Discussion item #2:
For study M13-995, an inaccurate case history was presented for subject [REDACTED]. A discrepancy was seen in reporting safety assessments, where source record entries did not match the information presented in the study report.

OSIS Evaluation:
For study M13-995, safety assessments using 12-lead ECG (ECG tracing paper record) for subject [REDACTED] resulted in an abnormal reading, detailed as “right ventrical conduction delay” whereas the source document entry showed the result as normal. This appears to be a transcription error and an isolated incident. The firm migrated from the manual entry of data into Phase 1 Management System (PIMS) to automatically transfer data from its ECG machine to PIMS via E-Scribe. Thus, the firm’s new procedure of direct transfer of ECG data to PIMS should prevent the recurrence of such errors in future studies. This discussion item is not likely to impact the integrity of the study data.

Conclusion:
After reviewing the inspectional findings, I conclude the data from the audited studies are reliable. Therefore, I recommend that the data from studies M15-817 & M13-995 (NDA 210450) be accepted for further review. In addition, studies of similar design conducted at Clinical Pharmacology Research Unit, Grayslake, IL before the end of the current Surveillance Interval should also be accepted for review by the Agency without an inspection.
Final Classification:

NAI- AbbVie Clinical Pharmacology Research Unit, Grayslake, IL
FEI#: 3013956469

CC:
OTS/OSIS/Kassim/Choe/Haidar/Fenty-Stewart/Nkah
OTS/OSIS/DNDBE/Bonapace/Dasgupta/Ayala/Biswas/Chennamaneni
OTS/OSIS/DGDBE/Cho/Kadavil/Choi/Skelly/Au

Draft: SRC 1/10/2018
Edit: GB 1/11/2018; CB 1/16/2018

ECMS: Cabinets/CDER_OC/OSI/Division of Bioequivalence & Good Laboratory Practice Compliance/INSPECTIONS/BE Program/Clinical Sites/AbbVie, Clinical Pharmacology Research Unit, Grayslake, IL, USA/NDA 210450_Elagolix IR Tablet, & 200 mg

OSIS File #: BE 7679 (NDA 210450)
FACTS: 11793442
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/s/

SRINIVAS RAO N CHENNAMANENI
01/16/2018

GOPA BISWAS
01/16/2018

CHARLES R BONAPACE
01/16/2018
DATE: 11/6/2017

TO: Division of Bone, Reproductive and Urologic Products
Office of Drug Evaluation III

FROM: Division of New Drug Bioequivalence Evaluation (DNDBE)
Office of Study Integrity and Surveillance

SUBJECT: Recommendation to accept data without an on-site inspection

RE: NDA 210450 S001
NDA 210450 S002

The Division of New Drug Bioequivalence Evaluation (DNDBE) within the Office of Study Integrity and Surveillance (OSIS) recommends accepting data without an on-site inspection. The rationale for this decision is noted below.

Rationale

Although the last inspection was classified as a VAI, based on the inspectional outcome and our recommendation to the review division, an inspection is not needed at this time.

Inspection Site

<table>
<thead>
<tr>
<th>Facility Type</th>
<th>Facility Name</th>
<th>Facility Address</th>
</tr>
</thead>
<tbody>
<tr>
<td>Analytical</td>
<td>AbbVie</td>
<td>Drug Analysis Department, 1 North Waukegan Road, North Chicago, IL</td>
</tr>
</tbody>
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/s/

SHILA S NKAH
11/07/2017