# CENTER FOR DRUG EVALUATION AND RESEARCH

***APPLICATION NUMBER:***

# 210450Orig1s000

# PRODUCT QUALITY REVIEW(S)

**Recommendation:** ***Approval***

# NDA 210450
# Review # 1

# ORILISSA (elagolix) Tablets

| | |
|---|---|
| Drug Name/Dosage Form | Elagolix Tablets, film-coated immediate-release |
| Strength | 150 mg and 200 mg elagolix (equivalent to 155.2 mg and 207.0 mg elagolix sodium, respectively) |
| | Oral |
| Rx/OTC Dispensed | Rx |
| Applicant | AbbVie Inc. |
| US agent, if applicable | - |

| SUBMISSION(S) REVIEWED (seq. no.) | DOCUMENT DATE | DISCIPLINE(S) AFFECTED |
|---|---|---|
| Original (0000) | 08/23/17 | Multi-discipline |
| (0003) | 09/25/17 | Facilities |
| (0006) | 11/15/17 | Product Labeling |
| (0009) | 12/08/17 | Biopharmaceutics; Process/Micro; |
| (0011) | 12/15/17 | Biopharmaceutics; Product |
| (0014) | 01/02/18 | Product |
| (0017) | 01/12/18 | Process |
| (0023) | 02/20/18 | Product Labeling |
| (0029) | 03/05/18 | Product Labeling |
| (0032) | 03/12/18 | EA |
| (0033) | 03/14/18 | Product |
| (0037) | 04/12/18 | Product Labeling |
| (0040) | 05/21/18 | Product Labeling |
| (0041) | 06/07/18 | Product Labeling |
| (0042) | 06/15/18 | Product Labeling |
| (0044) | 06/29/18 | EA |
| (0046) | 07/12/18 | Product Labeling |
| (0047) | 07/13/18 | Product Labeling |

**Quality Review Team**

| DISCIPLINE | REVIEWER | DIVISION / BRANCH |
|---|---|---|
| Drug Substance | Debasis Ghosh | ONDP/DNDPAPI/BII |
| Drug Product / Labeling | Hamid Shafiei | ONDP/DBRUP/BV |
| Process / Microbiology | Zhao (Joe) Wang | OPF/DPAII/BV |
| Facility | Carl Lee | OPF/DIA/BIII |
| Biopharmaceutics | Peng (Vincent) Duan / Vidula Kolhatkar | ONDP/DB/BII |
| RBPM | Bamidele (Florence) Aisida | OPRO/DRBPMI/BI |
| Application Technical Lead | Mark Seggel | ONDP/DNDPII/BV |
| Laboratory (OTR) | Laura Pogue | OTR/DPA |
| Environmental Analysis (EA) | Jim Laurenson | ONDP/EA Team |

# Quality Review Data Sheet

## 1. RELATED/SUPPORTING DOCUMENTS

### A. DMFs:

| DMF # | Type | Holder | Item Referenced | Status | Date Review Completed | Comments |
|---|---|---|---|---|---|---|
| (b) (4) | III | | (b) (4) | N/A | | |
| | III | | | N/A | | |
| | III | | | N/A | | |
| | III | | | N/A | | |
| | III | | | N/A | | |

N/A: There is enough data in the application, therefore the DMF did not need to be reviewed.

### B. Other Documents: *IND, RLD, or sister applications*

| DOCUMENT | APPLICATION NUMBER | DESCRIPTION |
|---|---|---|
| IND submissions and associated reviews | **IND 64802**, IND (b) (4) and IND (b) (4) | AbbVie INDs for investigational use of elagolix |

## 2. CONSULTS

| DISCIPLINE | STATUS | RECOMMENDATION | DATE | REVIEWER |
|---|---|---|---|---|
| Biostatistics | na | | | |
| Pharmacology/Toxicology | na | | | |
| CDRH | na | | | |
| Clinical | na | | | |
| Other | na | | | |

na: not applicable

# Executive Summary

## I. Recommendations and Conclusion on Approvability

AbbVie Inc.'s 505(b)(1) new drug application for Orilissa (elagolix) Tablets, 150 mg and 200 mg, is recommended for APPROVAL from the OPQ perspective.

Sufficient information and supporting data have been provided in accordance with 21 CFR 314.50 to ensure the identity, strength, quality, purity, potency and bioavailability of the drug product. The revised drug product labeling as submitted on July 12, 2018 and July 13, 2018 is accurate, complete and complies with the requirements under 21 CFR 201.

The drug substance and drug product manufacturing, packaging and testing facilities have acceptable CGMP status.

Based on AbbVie's Environmental Assessment submitted June 29, 2018, A Finding of No Significant Impact (FONSI) has been filed.

## II. Summary of Quality Assessments

### A. Product Overview

| | |
|---|---|
| **Proposed Indication(s) including Intended Patient Population** | ORILISSA is a gonadotropin-releasing hormone (GnRH) receptor antagonist indicated for the management of endometriosis with associated moderate to severe pain. |
| **Duration of Treatment** | 150 mg once daily: No longer than 24 months<br>200 mg twice daily: No longer than 6 months |
| **Maximum Daily Dose** | ORILISSA Tablets may be taken orally as 150 mg once daily or 200 mg twice daily, with or without food. |
| **Alternative Methods of Administration** | No applicable. |

Endometriosis is a "chronic, estrogen-dependent, inflammatory condition affecting 6% to 10% of women of reproductive age." The pain associated with endometriosis is frequently debilitating. Current non-surgical treatment options include NSAIDs, estrogen-progestin contraceptives, high-dose progestins (e.g., medroxyprogesterone acetate), GnRH agonists (e.g., leuprolide acetate), and androgenic compounds. These drugs are not without limitations and have potentially significant side effects.

Elagolix (as elagolix sodium) is a novel, oral, short-acting, nonpeptide gonadotropin-releasing hormone (GnRH) receptor antagonist. It is formulated as film-coated

immediate-release tablets in 150 mg and 200 mg strengths. Elagolix tablets will be supplied in foil/film blister packs.

The proposed dosage regimens allow flexibility in modulating estrogen suppression to maximize efficacy and minimize adverse effects (e.g., decrease in bone mineral density).

Orilissa (elagolix) Tablets are a relatively stable, easily administered product with minimal risks associated with product quality. The product offers another alternative to current surgical and nonsurgical options.

## B. Quality Assessment Overview

Drug Substance:

The active ingredient (API) in Orilissa Tablets is elagolix sodium, a small, nonpeptide gonadotropin releasing hormone (GnRH) receptor antagonist.

The chemistry, manufacturing and controls (CMC) for elagolix sodium is documented in NDA 210450.

Elagolix sodium is a small synthetic molecule chemically known as Sodium 4-({(1R)-2-[5-(2-fluoro-3-methoxyphenyl)-3-{[2-fluoro-6-(trifluoromethyl) phenyl]methyl}-4-methyl -2,6-dioxo-3,6-dihydropyrimidin-1(2H)-yl]-1-phenylethyl} amino)butanoate. The structure was confirmed by mass spectrometry, infrared spectroscopy, nuclear magnetic resonance.

Elagolix sodium is isolated as a hygroscopic, amorphous white to off-white to light yellow powder. Note that the strength of Orilissa Tablets is (b) (4) elagolix (the active moiety).

Elagolix contains one chiral center (b) (4) (b) (4) (b) (4) Based on extensive polymorphic screening studies, elagolix did not show polymorphism. (b) (4)

(b) (4)

At either the 150 mg or the 200 mg dose, elagolix is highly soluble per the biopharmaceutics classification system (BCS) throughout the physiological pH range.

The proposed specification for elagolix sodium includes tests for identity, assay, impurities, residual solvents, (b) (4) (b) (4) Limits for individual known impurities range from (b) (4)% to (b) (4)%. Individual unspecified impurities are limited to (b) (4)%, while total impurities are controlled to not more than (NMT) (b) (4)%. (b) (4) impurities are controlled on a ppm level, the total of which is limited to (b) (4) ppm.

Numerous impurities have been identified in the drug substance. A comprehensive list of impurities was provided which includes justification for inclusion or exclusion of mutagenic or non-mutagenic impurities in elagolix. An extensive toxicology assessment of the impurities was conducted by Dr. Leslie McKinney (see Dr. McKinney's review dated May 10, 2018 for details). All impurities specified in the drug substance specification are qualified by toxicology studies.

The management of the impurities in the drug substance was thoroughly evaluated by AbbVie. (b) (4) (b) (4) (b) (4) Despite the large number of potential impurities, the process control strategy adequately controls the impurities in drug substance.

Based on the available long term and accelerated stability data, the proposed retest period of (b) (4) when stored (b) (4)°C (with excursion permitted at or (b) (4)°C) is granted.

From the drug substance CMC perspective, the NDA is recommended for APPROVAL. (See IQA Chapter 1 for details).

Drug Product:

Orilissa (elagolix) Tablets are a film-coated, immediate-release formulation containing the equivalent of 150 mg and 200 mg elagolix. (b) (4) (b) (4) (b) (4)

Drug (salt form) loading is (b) (4). Inactive ingredients (b) (4) include mannitol, pre-gelatinized starch, povidone, sodium carbonate and magnesium stearate. (b) (4) (b) (4) polyvinyl alcohol, titanium dioxide, polyethylene glycol / (b) (4) talc, and either carmine or iron oxide

red. All inactive ingredient in the finished dosage form are of suitable quality for the intended use.

The 150 mg tablets are oblong, light pink with the imprint 'EL 150' on one side. The slightly larger 200 mg tablets are light orange and have the imprint 'EL 200' on one side. The tablets are not scored.

Elagolix tablets are packaged in (b) (4) film with aluminum foil lidding. (b) (4)

The drug product specification includes tests for appearance, identification, assay, uniformity of dosage units (weight variation), (b) (4), microbiological quality, dissolution and degradation products. Limits for specified, known degradation products range from NMT (b) (4) % to NMT (b) (4) %. Individual unspecified degradants are limited to NMT (b) (4) %, and total degradants to NMT (b) (4) %. the degradation products are adequately qualified at the proposed levels.

The analytical procedures have been adequately described and validated, and are suitable for the control of product quality.

Drug product stability has been evaluated under conditions ranging from -20°C to 40°C/75% RH. Long term storage was conducted at 30°C/75% to support product registration outside of the U.S. An expiration dating period of 24 months was proposed. Overall, the data support storage at 2°C to 30°C for 24 months; a 24-month expiry is granted.

Overall, the chemistry, manufacturing and controls are sufficient to ensure the identity, strength, quality, purity, potency, and bioavailability of the drug product. The NDA is, therefore, recommended for APPROVAL from the drug product review perspective.

Environmental Analysis:

Elagolix is a gonadotropin releasing hormone (GnRH) receptor antagonist. Because of the potential endocrine-related environmental effects from elagolix, AbbVie prepared an Environmental Assessment (EA) in support of this NDA. The final EA was submitted via a June 29, 2018 amendment.

Dr. James Laurenson, OPQ/ONDP Environmental Assessment Officer concluded:

> "The EA is adequate. It contains sufficient information to enable FDA to tentatively determine whether the proposed action may significantly affect the quality of the human environment. Based on an evaluation of the information provided in the EA and additional reports, and on the scientific validity of the conclusions of the EA, no significant adverse environmental impacts are expected from the approval of this NDA.

> FDA recommends a prudent use of label language that provides guidance regarding environmentally protective disposal practices. Based on the information available to date, a FONSI is recommended for this portion of the application."

See IQA Chapter III for details. A Finding of No Significant Impact (FONSI) was filed in Panorama on July 11, 2018.

Labeling:

The initial review of CMC-related aspects of the package insert and container (blister) and carton labels identified several deficiencies including missing active moiety expression of strength with equivalency statements in Section 3, Dosage Form and Strengths, Section 11, Description, and Section 16, How Supplied. Pharmacological / therapeutic class information and route of administration, among others, were also missing from Section 11. Identifying information was missing form Section 16. The proposed storage statement in Section 16 was also considered unsatisfactory at the time.

Deficiencies with the blister and carton labels included missing active moiety expression of strength with equivalency statements, missing expiration date, and an unsatisfactory storage statement. See IQA Chapter IV, Labeling for details.

The proposed storage statement, 'Store at 2°C to 30°C (36°F to 86°F)' was considered unacceptable from the drug product reviewer's perspective, in part because the stability package had minimal data at 5°C±3°C and the stability commitment did not provide for long term testing at 5°. Nevertheless, there is precedent for such a storage statement for solid oral dosages forms (especially immediate-release tablets) even when there is minimal data at 5°C and with products that applicants plan to market in other climate zones where stability studies at 30°C are required. AbbVie subsequently agreed to conduct long term stability testing at 5°C on a limited number of batches as part of the revised stability commitment (see 03/14/18 amendment). The initially propose storage statement is thus acceptable.

The other deficiencies have been conveyed to the Applicant and the labeling and labels have been through several versions.

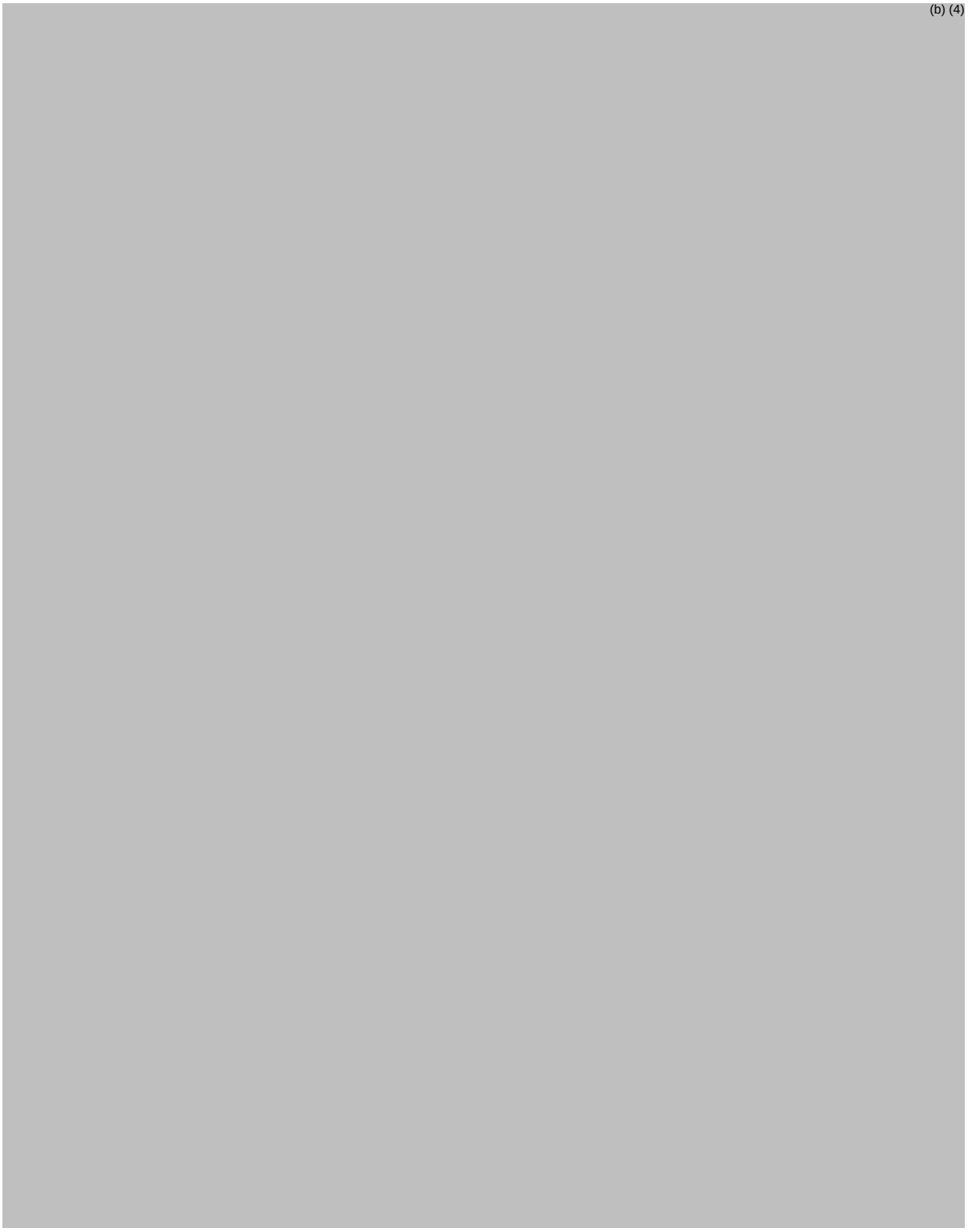
From the CMC perspective, the blister and carton labels as submitted on July 12, 2018 are accurate and complete. The Prescribing Information and Medication Guide are, as submitted July 13, 2018, accurate and complete.

As requested by the Environmental Assessment Team, the labels and labeling now include the reminder, 'Do not flush (b) (4).'

Process:

(b) (4)

(b) (4)



Facilities:

Drug substance for commercial tablets is manufactured by AbbVie Singapore Pte. Ltd. While this facility initially appeared to be high risk, it was subsequently found acceptable

to carry out the proposed functions described in the NDA. (b) (4)

The drug product is manufactured by AbbVie Ireland and packaged at AbbVie, N. Waukegan Rd., Chicago. Release and stability testing are performed at the AbbVie Sheridan Rd. facility. All three facilities have been found "acceptable for the functions and responsibilities listed in the application."

An Overall Inspection Recommendation of APPROVE was issued on January 9, 2018.

Biopharmaceutics:

The drug product dissolution test method and acceptance criteria for the 150 mg and 200 mg tablets were evaluated. The proposed dissolution test method uses USP Apparatus 2 (paddle) at 50 rpm, with a dissolution medium of 900 mL of 0.05 M sodium phosphate (pH 6.8) at 37°C. The method is supported by the dissolution method development report and is acceptable from the biopharmaceutics perspective.

AbbVie initially proposed acceptance criteria (b) (4) Subsequently AbbVie amended the NDA with a request to revise the acceptance criterion for the 200 mg tablet to NLT (b) (4)% (Q) in 45 minutes because a number of tested units failed to meet the original acceptance criterion. To support this change, AbbVie provided additional stability data and physiologically-based pharmacokinetic (PBPK) modeling data. Based on this new information it was determined that the wider dissolution acceptance criterion of NLT (b) (4)% (Q) in 45 minutes would still ensure consistent quality and clinical performance of the 200 mg drug product.

In addition to the dissolution test and acceptance criteria, AbbVie's biowaiver request for the 150 mg tablet was evaluated. The formulation of 150 mg and 200 mg to-be-marketed tablets is compositionally proportional, with the difference in formulation in the color of film coating, which contributes to (b) (4) the total formulation. The dissolution profiles of 150 mg and 200 mg tablets are similar in all three dissolution media tested. Therefore, the biowaiver request for the lower strength 150 mg tablets is acceptable.

From the biopharmaceutics perspective the NDA, as amended, is recommended for APPROVAL. See IQA Chapter VII for details.

Refer to the Office of Clinical Pharmacology review of bioequivalence studies conducted to bridge various formulations and manufacturing processes.

Microbiology:

The chemically synthesized drug substance is (b) (4) material. Although the drug substance is hygroscopic, (b) (4) Microbial limits testing (MLT) is conducted at release (b) (4)

The drug product is film-coated tablet for oral administration. The manufacturing (b) (4) (b) (4) Nevertheless, stability batches have met USP acceptance criteria for MLT.

The firm states that MLT will be performed for release test only, not for stability testing. Based on MLT (b) (4) data of exhibit batches and MLT data for stability batches provided in 3.2.P.8.3, the risk for microbial growth is low. Therefore, the firm's proposal of waiving MLT for stability testing is acceptable.

From the product quality microbiology review perspective, this NDA is recommended for approval. See IQA Chapter V, Process, for details.

Analytical Methods Verification:

Verification of HPLC methods for the drug substance and drug product by the (b) (4) was requested for this NME. Specifically, analytical methods (b) (4): Determination of Assay, Identification, and Impurities in Elagolix Drug Substance by HPLC and (b) (4): Determination of Assay, Identification, and Degradation Products in Elagolix Tablets by HPLC were evaluated. Both methods were found acceptable for quality control and regulatory purposes. See Methods Verification Report Summary dated February 21, 2018.

**C. Special Product Quality Labeling Recommendations**

Not Applicable

**D. Final Risk Assessment (see Attachment I)**

## OVERALL ASSESSMENT AND SIGNATURES:

***Application Technical Lead Name:***
Mark R. Seggel, Ph.D.
CMC Lead (acting)

*{see electronic signature page}*

# CHAPTERS: Primary Quality Assessment

CHAPTER I: Drug Substance
CHAPTER II: Drug Product
CHAPTER III: Environmental Assessment
CHAPTER IV: Labeling
CHAPTER V: Process
CHAPTER VI: Facilities
CHAPTER VII: Biopharmaceutics
CHAPTER VIII: Microbiology (see Chapter V, Process)
Attachment I: Final Risk Assessment / Life Cycle Management
Attachment II: List of Deficiencies for Complete Response (*Not Applicable*)

# ATTACHMENT I: Final Risk Assessments

A. Final Risk Assessment and Lifecycle Knowledge Management for NDA 210450 Elagolix Tablets, 150 and 200 mg (film-coated, immediate-release tablets)***

| From Initial Risk Identification | | | Review Assessment | | |
|---|---|---|---|---|---|
| **Attribute/ CQA** | **Factors that can impact the CQA** | **Initial Risk Ranking*** | **Risk Mitigation Approach** | **Final Risk Evaluation** | **Lifecycle Considerations/ Comments**** |
| Appearance | • Process<br>• Stability | L | (b) (4) | Acceptable | Tablet is not scored. (b) (4) film-coat. |
| Identification | • CGMPs | L | | Acceptable | |
| Assay | • Formulation<br>• Container closure<br>• Raw materials<br>• Process parameters<br>• Scale/equipment<br>• Site | L | (b) (4) | Acceptable | |
| Related Substances Impurities/ Degradants | • Formulation<br>• Process parameters<br>• CCS | L | | Acceptable | |
| Solid-State Form | • API Properties<br>• Process<br>• Storage | L | | Acceptable | Amorphous API<br>Tg ca. 108 C |
| (b) (4) | | | | | |
| Uniformity of Dosage Units | • API Properties<br>• Formulation<br>• Process<br>• Scale/equipment<br>• Site | L | | Acceptable | Drug (salt) load: (b) (4) %w/w |
| Dissolution | • Formulation<br>• Raw materials<br>• Process parameters<br>• Scale/equipment<br>• Site | L | (b) (4)<br>PBPK modeling. | Acceptable | Elagolix is highly soluble per the biopharmaceutics classification system throughout the physiological range |
| Microbial limits | • Raw materials<br>• Equipment and handling<br>• CCS<br>(b) (4) | L | MLT will be performed for release test only, Based on MLT (b) (4) of exhibit batches and MLT data for stability batches, the risk for microbial growth is low. Firm's proposal of waiving MLT for stability testing is acceptable. | Acceptable | |

*Risk ranking applies to product attribute/CQA
**For example, critical controls, underlying control strategies assumptions, post marketing commitment, knowledge management post approval, etc.
*** See Chapter V, Process, for risk assessments for each of the major unit operations.

Additional Lifecycle Management Considerations (per Process review)
• The firm should perform stratified content uniformity test if there is manufacturing site change or process change. A statement is provided in 3.2.P 3.4.
• The firm does not propose any hold time for process (b) (4). However, per 3.2.P.3.1, the commercial manufacturing site is AbbVie Ireland NL B.V.. The primary packaging site is in North Chicago IL USA.

######

Mark
Seggel

Digitally signed by Mark Seggel
Date: 7/17/2018 05:02:00PM
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| BIOPHARMACEUTICS REVIEW FOR NDA AMENDMENT<br>Office of New Drug Products | | | |
|---|---|---|---|
| **Application No.:** | 210450 | **Primary Reviewer:** Vincent (Peng) Duan, Ph.D.<br><br>**Acting Quality Assessment Lead:** Vidula, Ph.D. | |
| **Submission Date:** | 12/15/2017 | | |
| **Applicant:** | Abbvie | | |
| **Trade Name:** | Elagolix sodium | **Date Assigned:** | 12/15/2018 |
| **Generic Name:** | Elagolix sodium (ABT-620) | **Date of Review:** | 01/15/2018 |
| **Indication:** | For the management of endometriosis with associated pain | **Type of Submission:** Amendment to original NDA 210450, quality information amendment | |
| **Formulation/strengths:** | Tablets 150 mg and 200 mg | | |
| **Route of Administration:** | Oral | | |

**Background:** This quality information amendment is referred to NDA 210450 elagolix, 150 mg and 200 mg tablets, submitted by the Applicant on 08/23/2017 for the management of endometriosis with associated pain. The Applicant was amending NDA 210450 to revise the dissolution acceptance criteria for the 200 mg elagolix tablet from Q = (b)(4)% in (b)(4)minutes to Q = (b)(4)% in 45 minutes. (b) (4)

**Submission:** To support the proposed the change in dissolution acceptance criterion of 200 mg tablets, the Applicant submitted the following information:

- Updated stability data for:
  - Elagolix tablets, 200 mg primary stability batches 15-006116, 15-006118, and 15-006119 at 30°C/75% relative humidity (RH)
  - Elagolix tablets, 200 mg commercial site specific stability batches 1000167108, 1000167111, and 1000167319 at 30°C/75%RH and 40°C/75%RH
- A PBPK model for elagolix was submitted to demonstrate that the slow in vitro dissolution would not affect the drug exposure

**Review:** Consistent with dissolution data submitted in original NDA submission, based on the submitted dissolution data for release of two commercial batches and additional long-term stability batches, a significant number of tested units from 200 mg tablets failed to meet the originally proposed dissolution acceptance criterion of NLT (b)(4)% (Q) in (b) (4)min at Stage 1, while all of them passed dissolution acceptance criterion of NLT (b)(4)% (Q) in 45 min. To demonstrate that those units failed to release more than (b)(4)% at (b)(4)min would not significantly affect clinical performance of drug product compared to clinical batches, the Applicant modified the submitted PBPK model supporting DDI and verified it with additional PK data from dose ascending study and food effect study. Overall, the submitted PBPK model is acceptable from Biopharmaceutics perspective. This PBPK model predicted a similar elagolix exposure for batches with slower dissolution rate compared to the clinical batches. Therefore, a wider dissolution acceptance criterion of NLT (b) (4)% (Q) in 45 min would still ensure a consistent quality and clinical performance of drug product.

**Recommendation:** The proposed dissolution acceptance criterion of NLT (b)(4)% (Q) in 45 min for 200 mg strength is acceptable. From Biopharmaceutics perspective, NDA 210450 as amended is recommended for approval.

| **Signature** | **Signature** |
| --- | --- |
| **Vincent (Peng) Duan, Ph.D.**<br>**Biopharmaceutics Reviewer**<br>**Office of new Drug Products** | **Vidula Kolhatkar, Ph.D.**<br>**Biopharmaceutics Quality Assessment Lead**<br>**Office of New Drug Products** |
| cc. TGhosh; PSeo | |

On Dec 08, 2017, the Applicant submitted an amendment for NDA 210450 to the dissolution acceptance criterion of 200 mg elagolix tablet and proposed a new dissolution acceptance criterion of NLT (b) (4)% (Q) in 45 min (b) (4) To support the proposed change, the Applicant submitted the following information and analysis:

1. Dissolution results from two additional commercial scale batches and stability test
2. A PBPK model to support the conclusion that a slower dissolution would not affect in vivo exposure of elagolix

**Amendment Review**

**1. Additional dissolution results from stability test and commercial batches**

Figure 1A is an updated dissolution data (refer to Figure 6B in Biopharm review for NDA 210450) with additional dissolution data from two commercial batches (1000208714 and 1000188407). Figure 1B is dissolution of individual units from these two commercial batches (12 units from 1000208714 and 24 units from 1000188407). (b) (4)

**Figure 1A. Dissolution Profiles of Elagolix Tablets, 200 mg from Clinical Batches (b) (4) a, Primary Stability Batches (PSB), Commercial Site Specific Batches (SSB), and Commercial Scale Batches (Commer)**

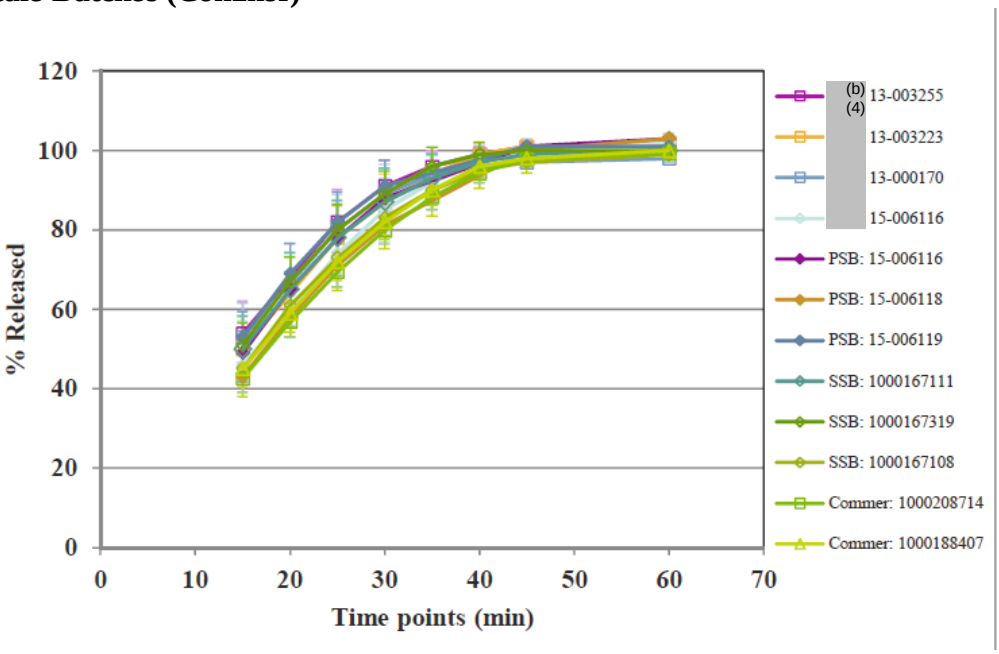
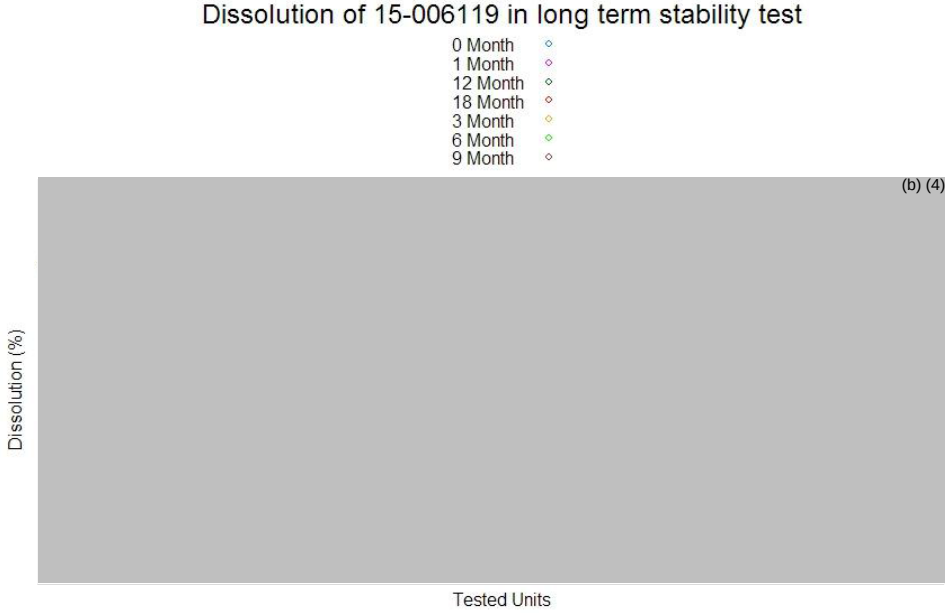


**Figure 1B. Reviewer's Plot on Dissolution Profiles of Elagolix Tablets, 200 mg from commercial batches 1000208714 and 1000188407**

The Applicant also submitted new stability data for batch 15-006119 at long term room temperature up to 18 Months. The acceptability of these stability data will be evaluated and determined by the drug product reviewer. Like data the Applicant submitted previously (refer to Biopharm review for NDA 210450), dissolution data generated during stability test shown in Figure 2 below, indicated no significant trend in dissolution during long term stability test. Significant numbers of units failed to meet (b) (4) % of release at (b) (4) min.

**Figure 2. Reviewer's plot on dissolution of batch 15-006119 (Packaged in Blister (b) (4)) at long term stability test**



Consistent with dissolution data submitted in original NDA submission, the new dissolution data from additional commercial batches and stability test indicated that the original proposed dissolution acceptance criterion of NLT (b)(4)% (Q) in (b)(4)min resulted in a high failure rate at Stage 1 for 200 mg strength. Although they may pass it at Stage 2, the high failure rate may bring in unnecessary burden for Stage 2 or Stage 3 test, if batches failing to meet NLT (b)(4)% (Q) in (b)(4)min might have similar clinical performance as the clinical batches. All the batches would pass at Stage 1 if the dissolution acceptance criterion is NLT (b)(4)% (Q) in 45 min. To demonstrate slower dissolution rate would not affect in vivo exposure of elagolix, the Applicant submitted a PBPK model incorporated in vitro dissolution data generated by QC method.

## 2. Physiologically-Based Pharmacokinetic (PBPK) Modeling Review

### 2.1 Objective:

The objective of this PBPK model is to:

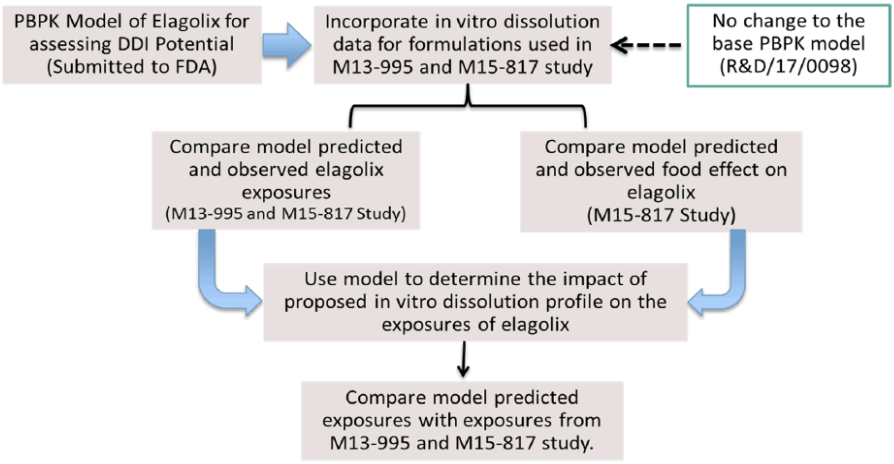
- To evaluate the predictive ability of a physiologically based pharmacokinetics (PBPK) model of elagolix that incorporates in vitro dissolution data to predict the exposures of elagolix after administration of commercial 200 mg immediate release (IR) elagolix tablets.
- To determine the impact of changing the in vitro dissolution profile on the exposures of elagolix using a PBPK modeling approach.

### 2.2 Model Development

The PBPK model was developed by SimCYP (Certara Inc.) V15. The submitted PBPK model was developed based on the PBPK model submitted in the original NDA submission, which was developed to the assessment of elagolix drug-drug interaction (DDI). As stated by the Applicant in Figure 3, there was no change to the base PBPK model submitted in the original NDA submission, except the formulation in Absorption was changed from "solution" to "solid formulation" in able to incorporate the in vitro dissolution data. Because of this change in model, the Applicant evaluated the model with clinical study M13-995 after incorporation of dissolution data, and further verified it with observed food effect study M15-817, before predicting the impact of slower dissolution on exposure of elagolix.

Figure 3 summarized the modeling strategy for this PBPK model.

**Figure 3. Overview of the PBPK Modeling Strategy**



*Reviewer's comments: The parameters in base PBPK model were obtained from literature and in vitro experiments, and were further optimized by fitting elagolix clinical PK and DDI studies. After communicated with Office of Clinical Pharmacology, the proposed PBPK model is acceptable for the evaluation of DDIs. There was no change in base model except the change in formulation (from solution to solid formulation) to incorporate dissolution into the model. Two different PK datasets (M13-995 and M15-817, respectively) were used for the model development and verification before model prediction. Overall the model development strategy seems reasonable.*

**2.3. Parameters and study design**

The input parameters for the models were shown in Table 1 in Appendix.

Elagolix is rapidly absorbed in the gastrointestinal tract with time to observed maximum plasma concentration (Tmax) of approximately 1 hour. Elagolix is eliminated with an apparent terminal half-life (t1/2) of approximately 4 to 6 hours and shows minimal accumulation following 150 mg QD or 200 mg BID dosing at steady state. Additionally, there is no significant food effect on exposures of elagolix with elagolix AUC decreased by 24% in the presence of a high-fat meal. In vitro, elagolix is primarily metabolized by the cytochrome P450 CYP3A enzyme and to a lesser extent by CYP2D6 and CYP2C8 enzymes. Elagolix is also a substrate of the efflux transporter, P-gp, and the influx hepatic transporter OATP1B1. In a human mass balance study (Study NBI-56418-0601), following a single oral dose, the main route of elimination of elagolix was predominantly via the feces (~90% of the administered dose), with 38% being eliminated as parent drug. Renal excretion accounted for approximately 3% of the total elimination of elagolix.

The input parameters for enzymes and transporters in the disposition of elagolix was initially based on in vitro transporters and metabolism data, optimized based on mass balance data from an ADME study in humans (Study NBI-56418-0601) and the rifampin DDI study (Study M12-659).

*Reviewer comments: In order to predict elagolix PK, the permeability value obtained from P Caco-2 was optimized to 10 (passive) and regional permeability in Jejunum I and Jejunum II were optimized to 4 and 2, respectively (increased from 1.65 from default). Reviewer analysis showed that without these optimizations, the model would significantly underestimate AUC and Cmax. Elagolix is a substrate of OATP1B1, and the Jmax and Km obtained from in vitro transporter assay were 41.05 pmol/min/million cells and 0.66, respectively. The Applicant optimized this in vitro value by optimizing Jmax to 215 pmol/min/million fitting against clinical DDI study with single dose of 600 mg rifampin (M12-659), in which exposure change of elagolix was majorly a result of OATP1B1 inhibition. After the optimization of OATP1B1, the contribution of CYP3A4 were optimized based on clinical DDI study with multiple dose of rifampin (M12-659), in which the exposure change of elagolix was a combined effect of inhibition of OATP1B1 and induction of CYP3A4 and P-gp. The Jmax and Km of P-gp were estimated by fitting the clinical studies M12-790 (a multiple ascending dose study) and M12-659.*

*After optimization of these parameters, the PBPK model was verified by simulating clinical DDI study with ketoconazole (CYP3A4/P-gb inhibitor) (Study M12-660) to verify the component of CYP3A4/P-gp in the model, and clinical DDI study with digoxin (inhibition of P-gp substrate*

*digoxin, Study M12-652), midazolam (inhibition of CYP3A, study NBI-56418-0502 and study M12-659) to evaluate inhibition of CYP3A, and DDI with rosuvastatin (Study M13-756) to evaluate inhibition of OATP1B1/3 and BCRP, respectively. As such, different clinical PK data were used for model development/optimization and model verification, and elagolix PBPK model was considered to be verified. Furthermore, the optimized parameters for enzyme / transporter intrinsic clearance or inhibitor kinetics are most important for evaluation of drug-drug interaction. The evaluation of dissolution acceptance criterion will be less sensitive to the change in these parameters.*

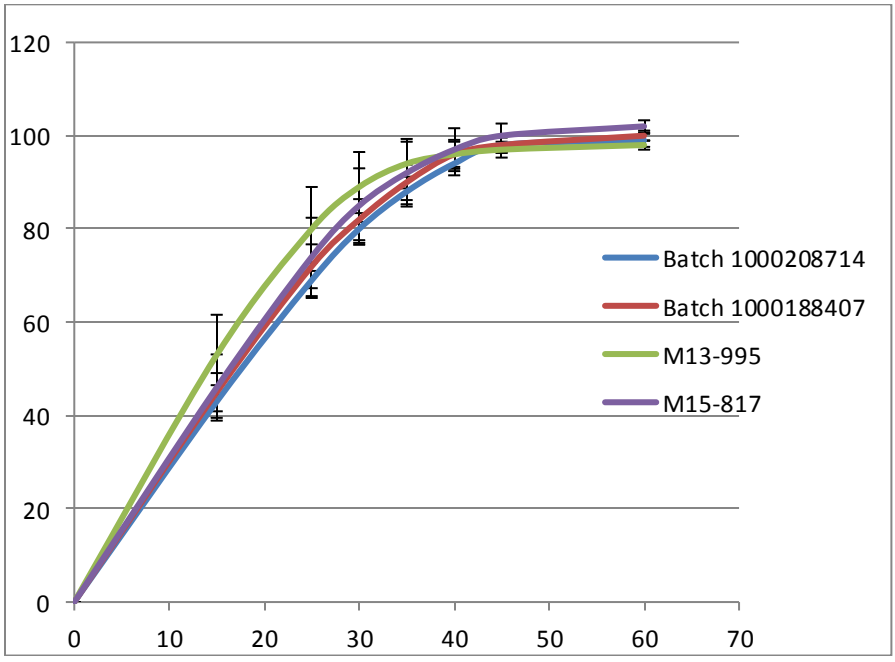
Compared to the PBPK model submitted to assess DDIs, the submitted PBPK model in this NDA amendment was the same, except the formulation in Absorption was changed from "solution" to "immediate release formulation with direct input of in vitro dissolution profiles". Because of this change, the revised PBPK model was further verified by simulating clinical study M13-995 (single dose study with Phase 3 formulation (b) (4)), and food effect study (M15-817 with to-be-marketed (b) (4) light orange formulation) (Table 2) by direct input of dissolution profiles of respective batches. The mean dissolution profiles of two batches and two additional commercial batches were shown in Figure 4. The dissolution profiles for batches used in clinical study M13-995 and M15-817 were (b) (4) for #1000208714 and #1000188407, respectively).

**Table 2. Summary of Study and Simulation Design**

| Study | Drug | Formulation | Route | Dose | Time of Administration | Fasting/Fed | Simulation Population | Reference |
|---|---|---|---|---|---|---|---|---|
| M13-995 (N = 23) | Elagolix | (b) (4) | PO | 200 mg | SD | Fasting | Population Representative | [3] |
| M15-817 (N = 54) | Elagolix | (b) (4) light orange | PO | 200 mg | SD | Fasting and Non-Fasting | Population Representative | [4] |

PO = orally; SD = single dose

**Figure 4. Mean dissolution profiles of M13-995 and M15-817 (used in PBPK modeling) and two commercial batches**



The predicted AUC and Cmax for study M13-995 and M15-817 by this PBPK model were compared to clinical observations and the ratios were within 0.80-1.25.

**2.4 Model evaluation criterion for model acceptance, the PBPK model predictions were deemed to be acceptable if the ratio of the predicted and the observed pharmacokinetic parameters (Cmax and AUC∞) were within 0.8 – 1.25.**

*Reviewer comments: There is no widely agreed model acceptance criterion for PBPK modeling. Here, the criterion for model acceptance is the ratio of PK parameters is within 0.8-1.25, which is a criterion used in BE study. Since the simulation was conducted by Population Representation in SimCYP (a single subject simulation not a population simulation), no confidence interval of ratio could be calculated. Overall, the criterion measuring the model performance is reasonable. Furthermore, the Applicant provided the simulated concentration-time profiles overlapped with individual observation, and overall, the simulations overlapped reasonably with clinical observations (Figure 1 and Figure 2 in Appendix).*

**2.5. Model simulation results**

**Q1. *Can PBPK model reasonably describe the PK of elagolix after input of dissolution data?***
Yes. With the incorporation of in vitro dissolution profiles, the ratio of predicted Cmax and AUC by PBPK model to respective clinical observations were within 0.80-1.25 (Table 3).

**Table 3. Predicted vs. Observed Exposures of Elagolix Following a Single 200 mg Dose Under Fasting and Non-Fasting Conditions**

| Pharmacokinetic Parameter (units) | | Predicted | Observed Mean | Ratio (Predicted:Observed) |
|---|---|---|---|---|
| **Study M13-995 (Fasting)** | | | | |
| $C_{max}$ | (ng/mL) | 808 | 845 | 0.956 |
| $AUC_{\infty}$ | (ng•hr/mL) | 1800 | 2220 | 0.811 |
| **Study M15-817 (Fasting)** | | | | |
| $C_{max}$ | (ng/mL) | 840 | 738 | 1.14 |
| $AUC_{\infty}$ | (ng•hr/mL) | 1840 | 1920 | 0.958 |
| **Study M15-817 (Non-Fasting)** | | | | |
| $C_{max}$ | (ng/mL) | 603 | 498 | 1.21 |
| $AUC_{\infty}$ | (ng•hr/mL) | 1440 | 1410 | 1.02 |

***Reviewer comments:***
*The submitted PBPK model was developed by SimCYP V15. However, the reviewer identified some variability in predicted AUC under fed state between different versions of SimCYP (i.e. V15 and V16). Table 4 summarized the predicted AUC and Cmax based on reviewer's own analysis with Applicant's submitted model between V15 and V16. As shown in Table 4, there is slight difference in predicted Cmax under fasting state between V15 and V16; however, the ratio between predicted and observed was still within 0.80-1.25. In V15, the Applicant's model well predicted the Cmax and AUC of elagolix under fed state. But in V16, the Applicant's model failed to predict the observed food effect on the exposure of elagolix, and the AUC ratio of predicted to observed is 1.30, which is slightly outside of 0.85-1.25. A side-by-side comparison of simulation outputs from V15 and V16, found that the difference in predicted AUC under fed*

*state was on fa (fraction of absorption) (fa is 0.78 in V15 and 0.98, respectively). Per SimCYP, this difference in fa (i.e. apparent fa) between V15 and V16 is a result of different enterohepatic recirculation model (EHR) (a bug was corrected in ADAM model in V16). This version difference would unlikely affecting the conclusion with the following rationales:*

*1. The parameters in PBPK model developed in SimCYP V15 have been verified by internal and external dataset (e.g. various PK datasets and DDI studies), and PBPK model has been used to predict DDI studies. Overall, the predicted exposure change of elagolix in the presence of digoxin and midazolam were satisfactory. Therefore, the model developed by V15 was robust and validated, and based on clinical pharmacology reviewer, Dr. Peng Zou, PBPK model was acceptable from the perspective of clinical pharmacology.*

*Due to the version difference, it is expected that there is software refinement or bug correction in the new version of the software (e.g. like EHR here). As fact of that, the model developed by V15 should go through the whole model development and refinement process again in V16, and additional parameter optimization might be necessary because of this model development and verification process. Therefore, it is not appropriate to conclude that there is a deficiency in the model because of failure to predict clinical observation, if we directly apply the model developed in V15 to do simulation in V16 without any model refinement and verification.*

*2. The difference in EHR between V15 and V16 was only observed at fed state. Under fast state, there is no difference in gall bladder drug mass (or EHR) between V15 and V16. Considering the significant difference in AUC between different versions is only found for fed state simulation, and to support the proposed dissolution acceptance criterion, all the simulations were conducted at fast state, where no version difference was found. The food effect study was applied as an external validation for the model, and the model could well predict the Cmax and AUC as well as concentration-time profiles in V15, and PK at fast state in both V15 and V16. Therefore, the submitted PBPK model was verified with external validation dataset.*

**Table 4. Reviewer's own analysis on the comparison of predicted PK parameters between SimCYP V15 and SimCYP V16**

| Predicted PK Parameters | SimCYP V15 | SimCYP V16 | Observed |
|---|---|---|---|
| **Study M13-995 (Fasting) 200 mg QD** | | | |
| **Cmax (ng/mL)** | **808** | **747.7** | **845** |
| **AUC (ng.hr/mL)** | **1800** | **1793** | **2220** |
| **Study M15-817 (Fasting)** | | | |
| **Cmax (ng/mL)** | **840** | **768.2** | **738** |
| **AUC (ng.hr/mL)** | **1840** | **1830** | **1920** |
| **Study M15-817 (Fed)** | | | |
| **Cmax (ng/mL)** | **602.6** | **595** | **498** |
| **AUC (ng.hr/mL)** | **1443.2** | **1840** | **1410** |

***Q3. Can PBPK models provide a reasonable prediction of the impact of slow dissolution on in vivo exposure of elagolix?***

To support the proposed dissolution acceptance criterion of NLT (b)(4)% (Q) in 45 min for 200 mg strength, the Applicant predicted PK parameters of a batch with slower dissolution by input of a theoretical dissolution profiles with slower release as shown in Figure 5. Drug release at 45 min in this theoretical dissolution profile was (b)(4)%, which would fail the proposed dissolution acceptance criterion of NLT (b)(4)% (Q) in 45 min. The predicted Cmax and AUC at fasted state for this slower dissolution profile were 741 ng/mL and 1830 ng.hr/mL, respectively, which were similar as batches with faster dissolution profiles (batches used in M13-995 and M15-817) and within 0.80-1.25 of observed data (Table 5).

**Figure 5. Dissolution profiles of theoretical dissolution profiles and other batches**

***Reviewer's comments:***

*The theoretical dissolution profile the Applicant tested was not a complete dissolution profile but with the consideration of only three time points. The reviewer further test the predicted Cmax and AUC by input of dissolution profile shown in Figure 6 and conducted simulation at fast state (All the simulations were conducted in V16, since as shown in Table 4, the difference between V15 and V16 at fast state was not significant). The dissolution profile shown in Figure 6 was adapted from the tested units from commercial batch 1000208714 with the slowest release rate shown in Figure 1B, which represented a real case scenario of slower dissolution. The dissolution at (b)(4)min was (b)(4)%, which failed to meet the dissolution acceptance criterion of NLT (b)(4)% (Q) in (b) (4)min, but would meet the proposed revised dissolution acceptance criterion of NLT (b)(4)% (Q) in 45 min. The predicted AUC was1780 ng.hr/mL. Compared to the clinical observation for AUC, which ranges from 1920-2220 ng.hr/mL or predicted AUC ranged of 1793-1830 ng.hr/mL with faster dissolution as used in M13-995 and M15-817 (target), the AUC ratio of predicted to observed or ratio of predicted to targeted was all within 0.80-1.25. Similarly, the predicted Cmax with this dissolution profile as an input was 741.7 ng/mL, and the Cmax ratio of predicted to observed (ranges from 738-845 ng/mL) or ratio of predicted to target (ranges from 747-768 ng/mL) was also within 0.80-1.25. Therefore, although that batch failed to*

*release more than (b)(4)% at (b)(4)min, the slower dissolution would not significantly affect the in vivo exposure of elagolix.*

**Table 5. Predicted Cmax and AUC for batches with different dissolution rates conducted by reviewer**

| Predicted PK Parameters | Predicted targeted (dissolution in M13-995 or M15-817) | Theoretical dissolution profiles from the Applicant | Slowest release units in batch 1000208714 | Observed |
|---|---|---|---|---|
| Cmax (ng/mL) | 808-840 | 741 | 741.7 | 738-845 |
| AUC (ng.hr/mL) | 1800-1840 | 1830 | 1780 | 1920-2220 |

**Figure 6. Dissolution profiles of batches used for model simulation (slow units represented dissolution profile of units in commercial batch 1000208714 with the slowest dissolution)**

***Q4. Can PBPK modeling support a clinically relevant dissolution acceptance criterion?***

Yes, the PBPK model supported a clinically relevant dissolution acceptance criterion of NLT (b) (4)% (Q) in 45 min. The Applicant conducted a simulation with an input of theoretical dissolution profile with release of (b)(4)% elagolix at 45 min. The prediction indicated a similar AUC and Cmax compared to clinical batches. To further evaluate the impact of slower dissolution on drug exposure with a real case dissolution data, the reviewer predicted Cmax and AUC with a slower dissolution found in dissolution data of commercial batch 1000208714, in which the dissolution of elagolix was (b)(4)% at (b)(4)min but more than (b)(4)% at 45 min. As dissolution profiles shown in Figure 6 and Table 5, whether for batch failed to release more than (b) (4)% at (b) (4)min (slowest units in batch 1000208714) or for batch failed to release more than (b)(4)% at 45 min (theoretical profiles), the predicted Cmax and AUC was all within 0.80-1.25-fold of

clinical observations or targeted batch. Therefore, the model simulation demonstrates that given a wider dissolution acceptance criterion of NLT (b)(4)% (Q) in 45 min rather than NLT (b)(4)% (Q) in (b)(4)min would still result in a similar in vivo drug exposure as the clinical batch.

### *2.6 Conclusion*

Based on the submitted dissolution data for release of two commercial batches and additional long-term stability batches, a significant number of tested units from 200 mg strength tablets failed to meet the originally proposed dissolution acceptance criterion of NLT (b)(4)% (Q) in (b)(4) min at Stage 1, while all of them passed dissolution acceptance criterion of NLT (b)(4)% (Q) in 45 min at Stage 1. To demonstrate that those units failed to release more than (b)(4)% at (b)(4)min would still have equivalent drug exposure as clinical batches, the Applicant modified the originally submitted PBPK model supporting DDI and verified it with additional PK data from dose ascending study and food effect study. Overall, the submitted PBPK model is acceptable from Biopharmaceutics perspective. This PBPK model predicted a similar elagolix exposure for batches with slower dissolution rate compared to the clinical batches. Therefore, a wider dissolution acceptance criterion of NLT (b)(4)% (Q) in 45 min would still ensure a consistent quality and clinical performance of drug product.

As a conclusion, the proposed dissolution acceptance criterion of NLT (b)(4)% (Q) in 45 min for 200 mg strength is acceptable. From Biopharmaceutics perspective, NDA 210450 amendment is adequate for approval.

# Appendix

## Table 1. Input Parameters of Elagolix PBPK Model Using SimCYP (V15.0.86.0)

| Parameter | Experimental/ Initial Parameter Value | Final Parameter Value used in SimCYP Model | Source |
|---|---|---|---|
| **Physiochemical and Blood Binding** | | | |
| Molecular Weight (g/mol) | 631.600 | 631.600 | [20] |
| log P | 1.340 | 1.340 | [20] |
| Compound Type | Ampholyte | Ampholyte | [20] |
| $pK_a$ 1 | 4.000 | 4.000 | [20] |
| $pK_a$ 2 | 7.900 | 7.900 | [20] |
| Blood Plasma | 0.62 | 0.62 | [5] |
| $f_u$ | 0.210 | 0.210 | [21] |
| **Absorption** | | | |
| **Absorption Model** | | ADAM | |
| Peff,man Type | | Regional | |
| P Caco-2 ($10^{-6}$ cm/s) | 2.00 | 10.000 | Optimized to predict elagolix PK Profile |
| Reference Compound | | Propranolol | [22] (Table 3) |
| Reference Value ($10E^{-6}$ cm/s) | | 19.600 | |
| Scalar | | 1.079 | SimCYP Default |
| Peff,man ($10^{-4}$ cm/s) | | 1.650 | SimCYP Predicted |
| Peff,man Duodenum ($10^{-4}$ cm/s) | | 1.650 | SimCYP Predicted |
| Peff,man Jejunum I ($10^{-4}$ cm/s) | NA | 4.000 | Optimized to predict elagolix PK profile |
| Peff,man Jejunum II ($10^{-4}$ cm/s) | | 2.000 | |
| Peff,man Ileum I ($10^{-4}$ cm/s) | | 1.650 | SimCYP Predicted |
| Peff,man Ileum II ($10^{-4}$ cm/s) | | 1.650 | SimCYP Predicted |
| Peff,man Ileum III ($10^{-4}$cm/s) | | 1.650 | SimCYP Predicted |
| Peff,man Ileum IV ($10^{-4}$ cm/s) | | 1.650 | SimCYP Predicted |
| Peff,man Colon ($10^{-4}$ cm/s) | | 1.650 | SimCYP Predicted |
| Input Form | High solubility compound | Solution | [20] |

*Appendix continued on following page.*

| Parameter | Experimental/ Initial Parameter Value | Final Parameter Value used in SimCYP Model | Source |
|---|---|---|---|
| **Distribution** | | | |
| **Distribution Model** | | Full PBPK Model | |
| $V_{ss}$ input type | NA | Predicted using Method 2 | SimCYP Predicted |
| log Po:w | 1.340 | 1.340 | [20] |
| $K_a$, AP input type | NA | Predicted | NA |
| logP vo:w input type | NA | Predicted | NA |
| **Elimination** | | | |
| **Clearance Type** | | | |
| **In vitro metabolic system** | | | |
| **Enzyme** | | CYP3A4 | |
| $CL_{int}$ (µL/min/pmol of isoform) | 0.072 | 0.300 | [23] optimized based on rifampin DDI Study (Study M12-659 [7]) |
| $f_u$ mic | 0.581 | 0.581 | [23] |
| System | NA | BD SUP | NA |
| ISEF | 0.240 | 0.240 | SimCYP Default |
| **Enzyme** | | CYP2C8 | |
| $CL_{int}$ (µL/min/pmol of isoform) | 0.029 | 0.029 | [23] |
| $f_{u\ mic}$ | 0.633 | 0.633 | [23] |
| System | NA | BD SUP | NA |
| ISEF | 0.430 | 0.430 | SimCYP Default |
| **Enzyme** | | CYP2D6 | |
| $CL_{int}$ (µL/min/pmol of isoform) | 0.49 | 0.700 | [23] |
| $f_{u\ mic}$ | 0.596 | 0.596 | [23] |
| System | NA | BD SUP | NA |
| ISEF | 0.750 | 0.750 | SimCYP Default |
| $CL_{renal}$ (L/h) | NA | 1.600 | To account for non-CYP clearance pathways and optimized to predict elagolix PK Profile (Study M12-790) [1] |
| Additional Systemic CL/F (L/h) | NA | 9.000 | |

*Appendix continued on following page.*

**Figure 1. Observed and Predicted Mean Concentration – Time Profile of Elagolix Following a Single 200 mg Dose Under Fasting Conditions (Study M13-995)**

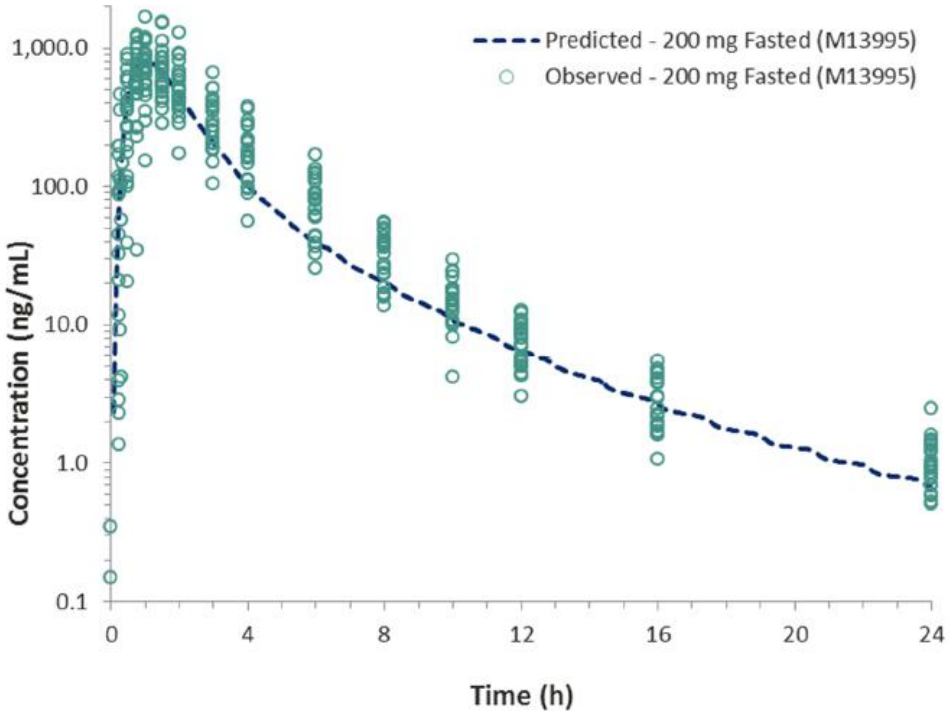
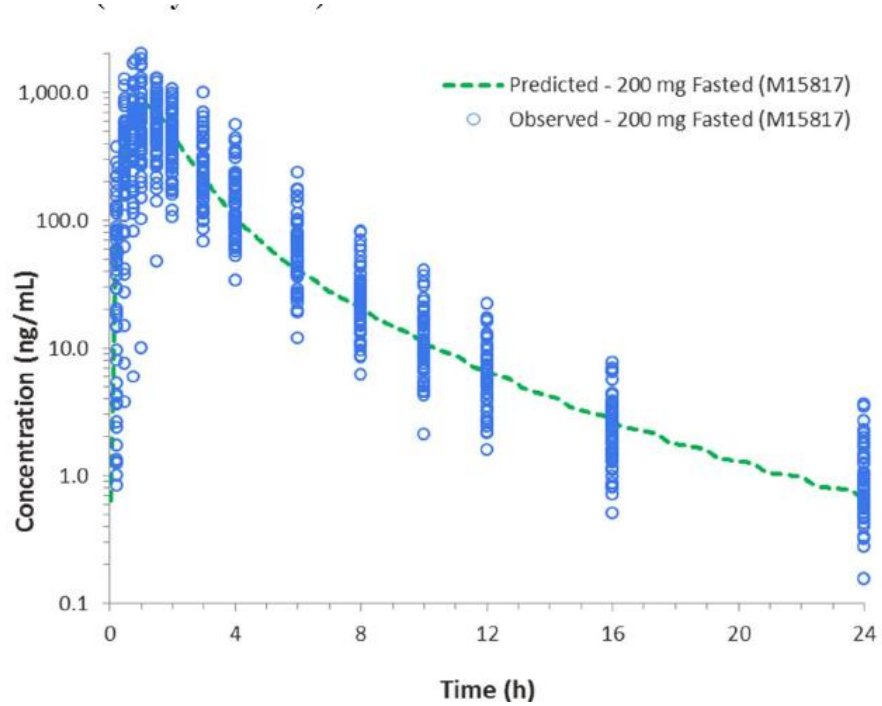



**Figure 2. Observed and Predicted Mean Concentration – Time Profile of Elagolix Following a Single 200 mg Dose Under Fasting Conditions (Study M15-817)**



Peng Duan

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Vidula Kolhatkar

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# BIOPHARMACEUTICS

IQA Review Guide Reference

**Product Background:**

**NDA: 210450**

**Drug Product Name / Strength: Elagolix 200 mg and 150 mg**

**Route of Administration: Oral**

**Formulation: Immediate release tablets**

**Applicant Name: Abbvie**

**Indication(s): Management of endometriosis with associated pain**

***Review Recommendation: Pending***
***The dissolution method and dissolution acceptance criterion for 150 mg strength are acceptable. Biowaiver request for the lower strength 150 mg tablets is granted. Although the review for NDA amendment submitted to support the change in dissolution acceptance criterion for 200 mg strength is currently pending, from the Biopharmaceutics perspective; no approvability issues are expected for NDA 210450.***

***Review Summary:*** The proposed drug product, elagolix 200 mg and 150 mg are immediate release tablets, indicated for the management of endometriosis with associated pain. According to the applicant Elagolix is a BCS 3 compound, with high solubility. The Applicant submitted the dissolution method development report to support the proposed dissolution method. The dissolution method is acceptable. The applicant's proposed dissolution acceptance criterion for 150 mg product, NLT (b) (4)% (Q) in 30 min is acceptable. Dissolution acceptance criterion for 200 mg product, NLT (b) (4)% (Q) in 45 minutes, as submitted in the NDA amendment is currently under review.

During the formulation development, the Applicant developed several formulations. These formulations were appropriated bridged to the to-be-marketed (TBM) by Bioequivalence (BE) studies. The BE studies would be reviewed by the reviewer from the Office of Clinical Pharmacology. From Biopharmaceutics perspective, the formulation bridging is acceptable.

The sponsor submitted a biowaiver request for 150 mg commercial formulation ( (b) (4) commercial 150 mg) based on BE study conducted on 200 mg commercial formulation

(b) (4) 200 mg coated commercial) and 100 mg Phase 3 formulation ((b) (4)). The formulation of 150 mg and 200 mg (b) (4) TBM tablets is compositionally proportional, with the difference in formulation in the color of film coating, which contributes to (b) (4) the total formulation. The dissolution profiles of 150 mg and 200 mg (b) (4) TBM tablets are similar in all three dissolution media tested. Therefore, the biowaiver request for the lower strength 150 mg tablets is acceptable.

**Concise Description Outstanding Issues Remaining:**
**The applicant submitted an amendment with PBPK modeling and additional dissolution data to support revised dissolution acceptance criteria, NLT (b) (4)%(Q) in 45 minutes, for the 200 mg product. This amendment is currently under review and is not expected to be an approvability issue. Other than dissolution acceptance criterion for the 200 mg product NDA 210450 is adequate from Biopharmaceutics perspective.**

***BCS Designation***

**Reviewer's Assessment:**
**Elagolix is likely a BCS 3 compound. But the Applicant didn't intend to apply BCS designation, and no data were submitted.**

**Solubility:** The lowest solubility at pH 5.65 is 0.890 mg/mL. Therefore, the solubility is relative high (200 mg/ 0.890 mg/mL= 220 mL < 240 mL).

**Permeability:** Based on in vitro Caco-2 study, the in vitro permeability of elagolix is low to moderate.

**Dissolution: See below**

***Dissolution Method and Acceptance Criteria***

**Reviewer's Assessment:** ***{Adequate/Inadequate} Pending on the review of NDA amendment***

***{Assess method development, method robustness, and criteria; modeling approach}***

The pKa of Elagolix is 4.0 and 7.9, and the solid form of the drug substance is amorphous and there is no crystalline form identified. The proposed dissolution method is shown in Table 1.

(b) (4)



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(b) (4)

The proposed dissolution acceptance criterion of NLT (b) (4)% (Q) in 30 min for 150 mg strength is acceptable.

On Dec 08, 2017, the Applicant submitted an amendment to the dissolution acceptance criterion of 200 mg elagolix tablet and proposed a new dissolution acceptance criterion of NLT (b) (4)% (Q) in 45 min (b) (4) To support the proposed change, the Applicant submitted the following information and analysis:

1. Dissolution results from two additional commercial scale batches and stability test
2. A PBPK model to support the conclusion that a slower dissolution would not affect in vivo exposure of elagolix

The acceptance of the proposed change in dissolution acceptance criterion for 200 mg strength is pending on the review of new data submitted in NDA amendment. The review for NDA amendment will be submitted into Panorama separately.

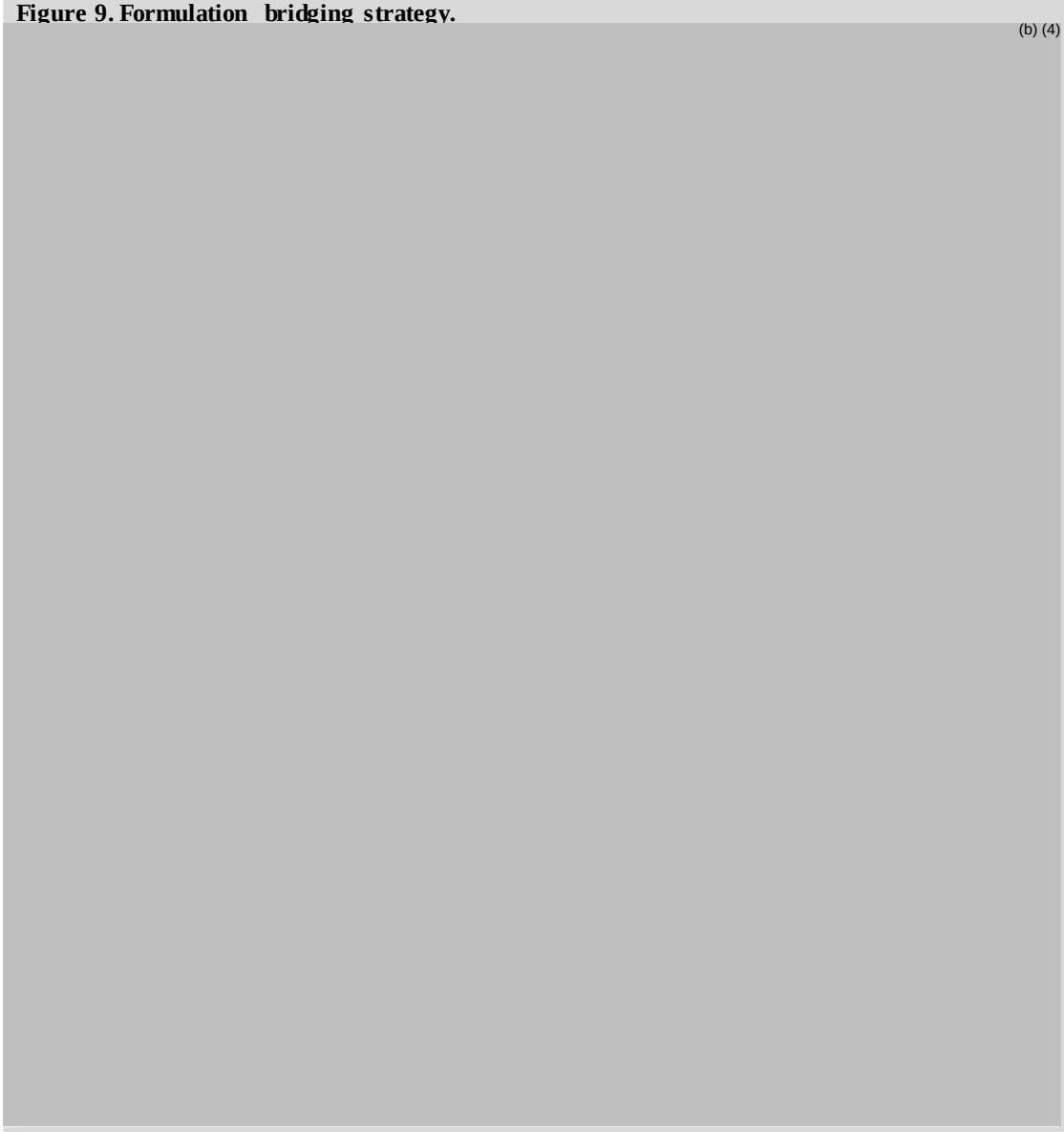
***Bridging of Formulations***

**Reviewer's Assessment:** ***{Adequate/Inadequate} Adequate***

Figure 9 summarized the history of the formulation development of the proposed drug product. Several formulations of elagolix, also referred to as NBI-54618 by NBI, were initially evaluated by NBI in the NBI Phase 1 and Phase 2 studies including oral

(b) (4) various immediate release (IR) (b) (4) (b) (4) and (b) (4) tablet formulations. After license of elagolix transferred to AbbVie (the current Applicant) from NBI on June 15, 2010, the Applicant determined (b) (4) as the formulation for future clinical development (Based on study NB-56418-701 between (b) (4) and (b) (4)). Later on, the Applicant developed prototype Phase 3 formulations using two alternate processes: (b) (4)

**Figure 9. Formulation bridging strategy.**




(b) (4) 100 mg and 150 mg tablets were used in the Phase 3 clinical studies, as well as in additional Phase 1 clinical studies conducted by AbbVie. (b) (4) 150 mg and 200 mg tablets were used in Phase 3 clinical studies. (b) (4) 300 mg tablets were used in Phase 1

DDI studies (Figure 10). Formulation (b) (4) was demonstrated to be bioequivalent to the Phase 1 and 2 formulation (b) (4) in Study M12-653; clinical formulation (b) (4) was determined to be bioequivalent to (b) (4) in Study M13-995; (b) (4) 200 mg light orange commercial formulation was determined to be bioequivalent to two 100 mg tablets of (b) (4) in Study M15-817; (b) (4) formulation (later discontinued and not intend for commercialization) was demonstrated to be bioequivalent to (b) (4) in Study M14-731. Since all the formulations were properly bridged by in vivo BE studies, the bridging of formulations is adequate, pending on the review of above BE studies by OCP reviewer.

**Figure 10. Reviewer's plot of formulations development and strategy for formulation bridging**

***Biowaiver Request***

**Reviewer's Assessment:** ***{Adequate/Inadequate} Adequate***

The sponsor request biowaiver request for 150 mg commercial formulation ((b) (4) commercial 150 mg) based on BE study conducted on 200 mg commercial formulation ((b) (4) 200 mg coated commercial) and two 100 mg tablets of phase 3 formulation ((b) (4) (M15-817).

The composition of the two strengths of the TBM of ((b) (4) is shown in Table 2. As the formulation shown in Table 2, the formulation of 150 mg and 200 mg ((b) (4) TBM tablets is compositionally proportional, with the only difference in formulation in the color of film coating, which contributes to ((b) (4) the total formulation.

**Table 2. Composition of Elagolix Tablets**

| | | Dosage Strength | 150 mg | 200 mg |
|---|---|---|---|---|
| Component | Quality Standard | Function | Amount (mg)/Tablet | |
| (b) (4) | | | | |
| Elagolix Sodium | In-house standard | Drug Substance | 155.2 | 207.0 |
| Mannitol | USP/Ph. Eur. | (b) (4) | | |
| Pregelatinized Starch | NF | | | |
| Povidone (b) (4) (b) (4) | USP/Ph. Eur. | | | |
| Sodium Carbonate Monohydrate | NF/Ph. Eur. | | | |
| Magnesium Stearate | NF/Ph. Eur. | | | |
| (b) (4) | | | | |
| Film-Coating (b) (4) (b) (4) | In house standard | Film Coat | (b) (4) | - |
| Film-Coating (b) (4) (b) (4) | In house standard | Film Coat | - | (b) (4) |
| (b) (4) | | | | |
| **Coated Tablet Weight** | | | 468.0 | 624.0 |
| (b) (4) | | | | |

To support the biowaiver request for the lower strength of 150 mg TBM tablets based on BE study conducted on 200 TBM mg tablets, the Applicant conducted comparative dissolution study on 150 mg TBM tablets (Lot 15-006121) and 200 TBM tablets (Lot 15-006116) in three different dissolution media, including the QC medium pH 6.8 buffer (Figure 11).

**Figure 11A. Dissolution profiles of Elagolix Tabs, 150 mg vs. 200 mg in 0.1 N HCl**

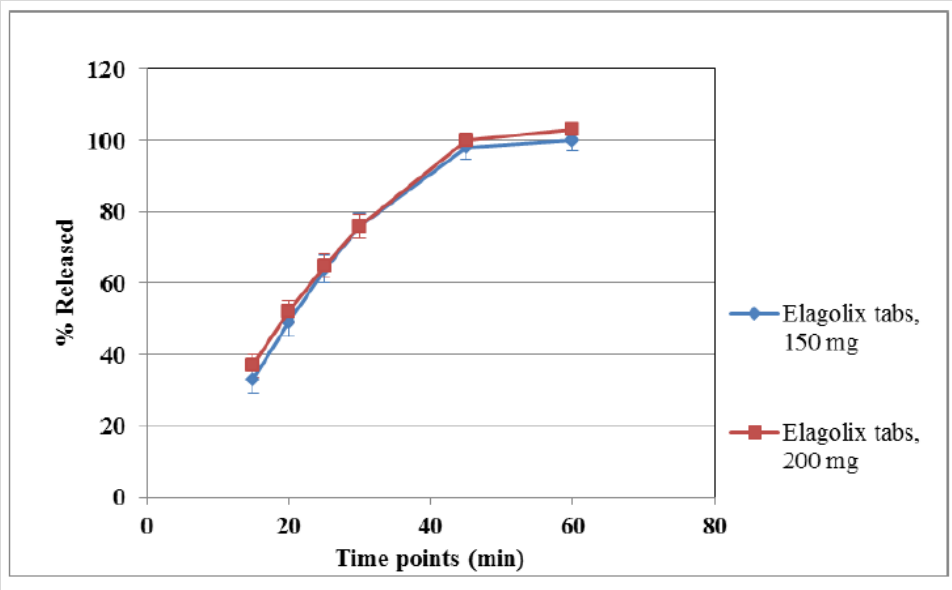



**Figure 11B. Dissolution profiles of Elagolix Tabs, 150 mg vs. 200 mg in pH 4.5 buffer**

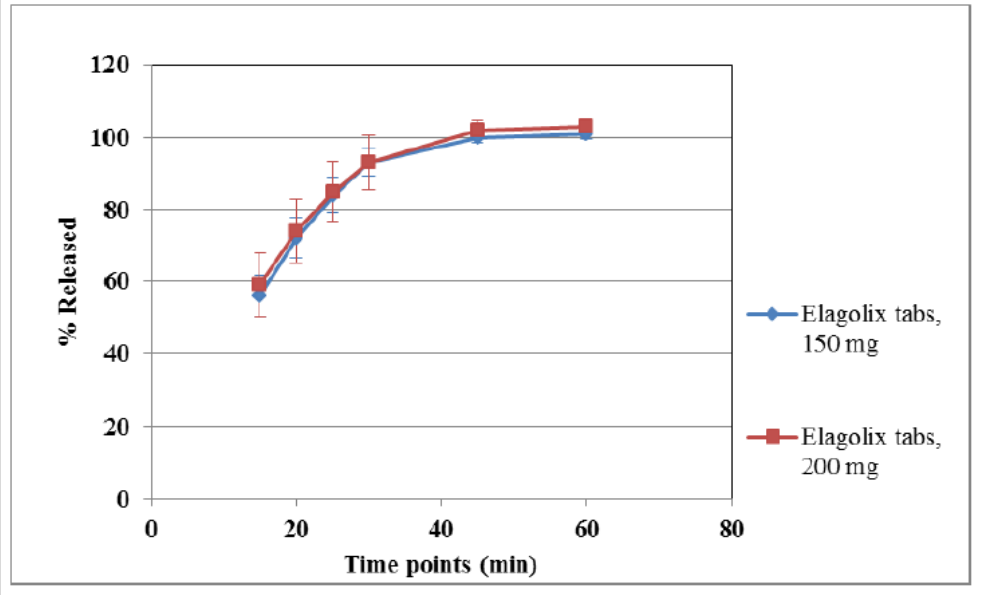
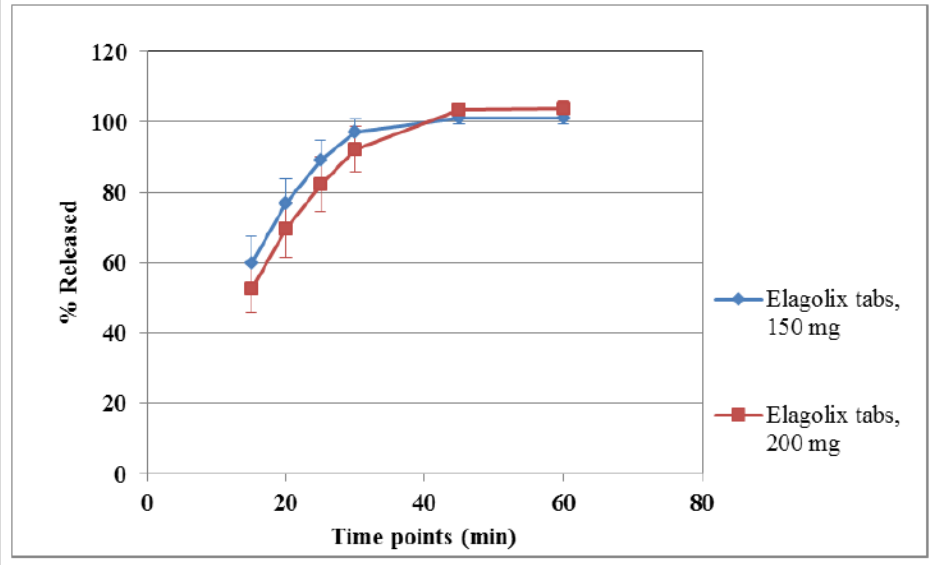


**Figure 11C. Dissolution profiles of Elagolix Tabs, 150 mg vs. 200 mg in pH 6.8 buffer**




The f2 calculations from the Applicant were shown in Table 3.

**Table 3. f2 calculation from the Applicant on two strengths of the proposed drug product**

| Similarity Factor (1) ($f_2$ NLT 50) | SK ($p$-value NMT 0.05) | Media | Number of Dissolution Time Points |
|---|---|---|---|
| 78 | 1.9E-02 | 0.1 N HCl | 6 |
| 84 | 7.4E-08 | pH 4.5 | 5 |
| 61 | 7.8E-12 | pH 6.8 | 5 |

The reviewer's f2 calculations are overall consistent with the Applicant's calculations, and the dissolution profiles of 150 mg and 200 mg (b) (4) TBM tablets are similar in all three-media tested.

Therefore, the biowaiver for the lower strength 150 mg tablets is granted.

***List of Deficiencies:***

***Pending on the review of NDA amendment submitted on Dec 8, 2017.***

***Recommendation:***

***The dissolution method and dissolution acceptance criterion for 150 mg strength are acceptable. Biowaiver request for the lower strength 150 mg tablets is granted. Although the review for NDA amendment submitted to support the change in***

***dissolution acceptance criterion for 200 mg strength is currently pending, from the Biopharmaceutics perspective, no approvability issues are expected for NDA 210450.***

***Primary Biopharmaceutics Reviewer Name and Date: Vincent (Peng) Duan, Ph.D. 01/09/2018***

***Secondary Reviewer Name and Date (and Secondary Summary, as needed):***

Vidula Kolhatkar

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GUID: 54579633000330547a76e69866efb4b3

# ENVIRONMENTAL

IQA Review Guide Reference

## R Regional Information

Summary: The applicant submitted an environmental assessment (EA) for elagolix. FDA concludes that the EA contains sufficient information to enable FDA to determine whether the proposed action may significantly affect the quality of the human environment, per 21CFR25.15(a). FDA concludes that the proposed action does not significantly affect the environment. FDA also recommends a prudent use of label language that provides guidance regarding environmentally protective disposal practices. A finding of no significant impact (FONSI) is recommended for elagolix.

***Environmental***

Under IND 064802, the applicant asked in a Type C meeting request, dated June 10, 2016, whether elagolix would be granted a categorical exclusion from an environmental assessment (EA) because its expected introduction concentration (EIC) would be < 1 ppb (µg/L), per 21CFR25.31(b), and the following factors:

1. Elagolix is an oral acting, nonpeptide, gonadotropin-releasing hormone (GnRH) antagonist that competitively binds to GnRH receptors in the pituitary gland and rapidly inhibits the production of luteinizing hormone (LH) and follicle-stimulating hormone (FSH), which in females results in a dose-dependent decrease in ovarian steroid (estradiol and progesterone) concentrations with no hormonal flare as is observed with peptide GnRH agonists. The fish receptor might be expected to have less affinity for elagolix than mammalian receptors based on its earlier evolutionary status and the evolutionary time to the last common ancestor. Consequently, fish receptors would, in turn, have lower receptor affinity to elagolix than the human GnRH receptor; this would contribute an additional safety factor relative to the factor noted below.

2. The estimated concentration of elagolix at the point of entry into the aquatic environment, or EIC, is predicted to be approximately (b) (4) µg/L, and that this is assuming no degradation, dilution, and other removal mechanisms. Furthermore, GnRH receptors are present in fish, which, based on several factors, are considered the sentinel aquatic species for ecological risk. The applicant thus used the "fish plasma model" (FPM) to estimate a steady state blood concentration of elagolix in fish exposed to (b) (4) µg/L concentration of elagolix in the aquatic environment, finding that such a concentration would be approximately (b) (4) the non-adverse concentrations of elagolix non-pregnant rats, or in embryo-fetal developmental toxicity studies in pregnant rats or rabbits, and is approximately (b) (4) that of the lowest biologically relevant (GnRH receptor mediated) levels of elagolix in women ($C_{max}$ = 112 ng/mL). Also, because of the highly conservative nature of FPM, and

factors such as the binding affinity of elagolix to the GnRH receptor of fish likely being equivalent to or less than that of rats or rabbits, the safety margin is realistically closer to the [redacted] using the lower biologically relevant $C_{max}$. Consequently, the applicant notes, it is anticipated that elagolix will not have any endocrine/reproductive effects on fish at predicted aquatic environmental concentrations.

The applicant concluded that risks to aquatic organisms are low and testing for endocrine disruption is not necessary. They stated that if FDA did not agree, the applicant proposes the following studies:

- Solubility (OECD 105)
- Microbial Inhibition (OECD 209)
- [redacted]
- Alga Growth Inhibition (OECD 201), Tier 2
- [redacted]
- [redacted]

The applicant also noted that if an environmental assessment is required, they would diligently work to complete the studies prior to the NDA submission (projected August 2017). In the situation where the majority of the studies are included in the initial application, the applicant asked if it would be acceptable to submit the report from the [redacted] during the review period, with a submission no later than the 120-day safety update, without it being considered an application deficiency resulting in a refusal-to-file (RTF) issue or a major amendment (and subsequently cause for an extension period).

In response to these questions, FDA noted that while the applicant appeared to have conducted a thorough and comprehensive assessment of the available data, the available data were insufficient to make the determination that risks to aquatic organisms were low and testing for endocrine disruption was not necessary, per new FDA guidance at the time, Questions and Answers Regarding Drugs With Estrogenic, Androgenic, or Thyroid Activity (FDA, 2016). The human therapeutic plasma level, rather than the nonclinical levels noted in the question above, should be used for comparing to estimated concentrations in fish, as recommended by Huggett et al. (2003). This would result in an estimated safety margin of [redacted] This lower margin is substantially lower than the minimum margin of 1,000 recommended in the literature (Huggett et al., 2003), especially given the endocrine-related nature of this drug. In addition, the $\log K_{ow}$ that was used, [redacted] from chemicalize.org. These higher values would result in safety margins of only around [redacted] There also is uncertainty regarding the robustness of the FPM for regulatory review in the absence of other data, such as other examples of GnRH antagonists that could be used for "read across" purposes, and any data on metabolism, fate, and transport. Finally, elagolix has a high expected introduction concentration relative to other endocrine-active substances in the environment. Thus, based on the weight of evidence, it appeared an EA would be needed.

FDA examined the proposed approach to an EA, and agreed to it with the following exceptions:

1. Given the potential endocrine-related effects from elagolix, use either of two options. One option was the combined and extended versions of two assays, [redacted] (b) (4) . Medaka can be used due to its relatively short lifecycle. A second option is using the newly released OECD 240 (Medaka Extended One Generation Reproduction Test), although a limited number of labs have used this assay compared to the first option. If either of these options is used, [redacted] (b) (4) (b) (4)

2. Given the need to focus on potential chronic effects, replace [redacted] (b) (4) with OECD 211 (daphnia reproduction test).

3. To address at least three trophic levels, add OECD 201 (freshwater alga and cyanobacteria, growth inhibition test).

4. To better predict fate and transport, add the following or equivalents: OECD 106 (absorption/desorption); OECD 107 (partition coefficient), plus OECD 305 (bioaccumulation in fish) if the results of OECD 107 show the potential to bioaccumulate; OECD 308 (aerobic and anaerobic transformation in aquatic sediment systems); and OECD 314B (activated sludge die-away, if needed for making allowances for the biodegradation of the compound in treatment plants).

FDA also directed the applicant to submit available study results or protocols within the environmental assessment in the initial application. Addenda could be submitted as additional results are obtained, and an updated environmental assessment could be submitted upon completion of all studies, including post-approval.

As part of the NDA submission, the applicant submitted an initial EA, dated July 28, 2017, which presented the planned assays, and the results of assays that had been completed to date. All but three assays had been completed, i.e., Adsorption/Desorption on Soils & Sewage Sludge (OECD 106), Transformation in Aerobic and Anaerobic Aquatic Sediment Systems (OECD 308), and Medaka Extended One Generation Reproduction Test (MEOGRT). A brief examination of the EA indicated that it was being adequately developed, and no changes were needed.

The applicant then submitted an updated EA, dated March 9, 2018, though this EA was still draft, pending completion of assays. Updated results of the FPM (Huggett et al., 2003) were presented. The effects ratio (ER) was determined to be approximately 1200. The model of Huggett et al. assumes that an ER < 1000 as an initial evaluation might

warrant an additional assessment in fish. Because of uncertainty regarding the robustness of the FPM for regulatory review and the absence of other data, the EIC and additional assays still would need to be examined.

A final EA was submitted and made available for review on June 29, 2018. This EA contained the results of the remaining assays and is considered complete.

The elagolix EIC calculated for the final EA is 0.6 µg/L. This EIC was conservatively utilized as the relevant exposure concentration for aquatic organisms, without consideration of applicable removal and dissipation mechanisms such as metabolism, degradation, and dilution. In addition, a more conservative value of 1 µg/L was treated as the relevant exposure concentration for aquatic organisms. Water solubility and partitioning assays indicated that elagolix was considered highly soluble, had a low potential to bioaccumulate, and low affinity to bind to sludge and be transported to the terrestrial compartment. Elagolix partitioned steadily from the water phase to the sediment phase in both the aerobic and anaerobic sediment systems, and transformed to multiple metabolites. The removal of 14[C]elagolix was slower under anaerobic conditions, with production of fewer metabolites. An activated sludge respiration inhibition study was conducted in accordance with OECD 209, which resulted in a No Observed Effect Concentration (NOEC) of 1000 mg/L, the highest concentration tested.

The potential for elagolix to impact aquatic species representing three trophic levels was investigated by the applicant. The three tests were (1) Freshwater Alga, Growth Inhibition Test (OECD 201), (2) *Daphnia magna* Reproduction Test (OECD 211), and (3) Medaka Extended One Generation Reproduction Test (MEOGRT) (OECD 240). For algae, the NOEC was determined to be 50 mg/L for all measured parameters, and the lowest effect concentration (LOEC) was 100 mg/L. For *D. magna*, the NOEC for all measured parameters was determined to be 10 mg/L, the highest concentration tested.

The Medaka study results showed no survival, growth, or behavior effects at any concentration up to 1000-fold EIC (the highest concentration tested). Hatching success effects were seen in the middle (0.105 mg/L) and highest test concentration (1.074 mg/L) for the F1 generation. These changes in hatching success were noted as not either dose-dependent or severe, with the lower concentration being approximately 100 times the EIC. Similarly, early survival to four weeks post fertilization was statistically significantly lower than controls at concentrations of elagolix ≥ 0.033 mg/L, but the statistical changes were not considered dose-dependent or meaningful, in part due to high rate of fungal infections that variably affected different replicates across treatment groups was considered the most likely cause for decreased hatching and early survival. This fungal infection resulted, for example, in high mortality (up to 100%) in some control groups of the failed spawns of both the F1 and F2 generations. The applicant also noted that at the higher concentrations there were some slight differences in histological findings in gonads and vitellogenin levels, but these occurred at concentrations that were well above expected environmental concentrations, that did not follow a dose-response relationship, and that had no effect on population relevant endpoints. The applicant concluded that there was no effect of elagolix at any concentration (up to 1000-fold EIC)

on apical or mechanistic endpoints, and there were no adverse effects on population relevant endpoints or endocrine biomarkers at any test concentration during the F0, F1, and F2 generation exposures. Thus the NOEC for this assay was 1.074 mg/L.

The applicant concluded that based on the available data, elagolix is not believed to represent a risk to the aquatic environment.

**Reviewer's Assessment:** Adequate

The main goals of this review of the elagolix EA, per 21 CFR 25.15(a) and (b), are to determine (1) whether the EA contains sufficient information to enable the Agency to determine whether the proposed action may significantly affect the quality of the human environment and (2) if so, whether the proposed action will significantly affect the environment.

The EA for elagolix contains sufficient information to enable a determination of whether the proposed action may significantly affect the quality of the human environment. The available data appear to be accurate and objective.

During FDA review of the March 2018 draft of the EA, the LOEC among the assays and all endpoints, including nonapical, appeared to be (b) (4) µg/L, which when adjusted using an assessment factor (AF) of (b) (4) resulted in a predicted no-effects concentration (PNEC) of (b) (4) µg/L. This value resulted in a margin of exposure (MOE) of (b) (4) when compared to the EIC of 1 µg/L. This EIC was considered worst-case, however, because the calculation of the EIC did not take into consideration (1) metabolism, (2) degradation during wastewater treatment, or (3) dilution, degradation, or removal in surface water. FDA expected that an expected exposure concentration (EEC) would be more than an order of magnitude below the EIC, thus adding an order of magnitude to the margins of safety noted in the assessment.

In the final EA of June 2018, the expanded results and discussion compared to the March 2018 draft EA describes the rationale for a NOEC of 1.074 mg/L. FDA agrees that the fungal infections, lack of monotonic dose responses, and lack of clear apical effects at lower doses indicate that this value is the appropriate NOEC to use. Given these results, FDA agrees that elagolix likely poses no significant environmental impact via this application. Nevertheless, some uncertainty exists regarding this conclusion due to the various other effects concentrations, including the (b) (4) µg/L, and issues such as nonmonotonic dose responses and cumulative effects from other substances and stressors with similar mechanisms of action and endpoints. Also, the lowest FPM ER of (b) (4) is lower than the recommended minimum of 1000, although this carries little weight given the detailed EA that has since been developed. Therefore, as a mitigation measure, FDA recommends a prudent use of label language that is similar to that used in the EU and is consistent with the FDA label review tool (FDA, 2017). Specifically:

1. In Sections 16 and 17 of the prescribing information, include a statement such as "Dispose of unused medicine via a take-back option if available. Otherwise, follow FDA instructions for disposing of medicine in the household trash, www.fda.gov/drugdisposal. Do NOT flush down the toilet."

2. In Medication Guide, in the last section, "General information…", after the last sentence, "Dispose of unused medicines…", add "See www.fda.gov/drugdisposal for more information. Do NOT flush down the toilet."

3. On relevant carton/container labels, add "Do NOT flush unused medicine."

Decision:

The EA is adequate. It contains sufficient information to enable FDA to tentatively determine whether the proposed action may significantly affect the quality of the human environment. Based on an evaluation of the information provided in the EA and additional reports, and on the scientific validity of the conclusions of the EA, no significant adverse environmental impacts are expected from the approval of this NDA. FDA recommends a prudent use of label language that provides guidance regarding environmentally protective disposal practices. Based on the information available to date, a FONSI is recommended for this portion of the application.

References:

EMA. 2016. Questions and answers on 'Guideline on the environmental risk assessment of medicinal products for human use'.

FDA. 2016. Environmental Assessment: Questions and Answers Regarding Drugs With Estrogenic, Androgenic, or Thyroid Activity. Center for Drug Evaluation and Research. US Food and Drug Administration, Silver Spring, MD. Available at https://www.fda.gov/downloads/Drugs/Guidances/UCM444658.pdf

FDA. 2017. Labeling Review Tool (Internal Use Only). Center for Drug Evaluation and Research, US Food and Drug Administration, Silver Spring, MD.

Huggett, D. B., J. C. Cook, J. F. Ericson and R. T. Williams. 2003. "A Theoretical Model for Utilizing Mammalian Pharmacology and Safety Data to Prioritize Potential Impacts of Human Pharmaceuticals to Fish." Human and Ecological Risk Assessment: An International Journal 9(7): 1789-1799.

***Primary Environmental Reviewer Name and Date:*** James P. Laurenson, July 10, 2018

***Secondary Reviewer Name and Date (and Secondary Summary, as needed):*** M. Scott Furness, July 10, 2018

James Laurenson

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GUID: 51dc6bdb0000c62de59b85452e59746f

Michael Furness

Digitally signed by Michael Furness
Date: 7/11/2018 10:36:14AM
GUID: 502e8c7600003dd8331cf6eebf43697a

# Finding of No Significant Impact

## NDA 210450, Elagolix, tablets in two strengths, 150 mg (once daily) and 200 mg (twice daily)

### Food and Drug Administration
### Center for Drug Evaluation and Research

The National Environmental Policy Act of 1969 (NEPA) requires Federal agencies to assess the environmental impact of their actions. The Food and Drug Administration (FDA) is required under NEPA to consider the environmental impact of approving certain drug product applications as an integral part of its regulatory process.

AbbVie Inc. requests approval of NDA 210450, elagolix, which is a small molecule, orally active gonadotropin-releasing hormone (GnRH) receptor antagonist for the treatment of endometriosis with associated pain. In support of its application, AbbVie prepared an EA for elagolix (attached). This EA evaluates the potential environmental impact from the use and disposal of this product. The FDA Center for Drug Evaluation and Research (CDER) has reviewed the EA and additional information, and has carefully considered the potential environmental impact due to approval of this application. Based on the CDER review of the entirety of this information, FDA has determined that approval of the present application is not expected to have a significant impact on the human environment. Therefore, FDA is issuing a finding of no significant impact (FONSI), and thus an environmental impact statement will not be prepared.

Attachments: June 29, 2018, Environmental Assessment

## 1.0 Title Page

# Environmental Assessment

# Elagolix (ABT-620)

# 150 or 200 mg film-coated tablets

# R&D/17/0698

# Updated

# June 29, 2018

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# 3.0 Abbreviations

| | |
|---|---|
| **Regulatory** | |
| CAS | Chemical Abstracts Service |
| EAT | Estrogenic, Androgenic, or Thyroid |
| FDA | Food and Drug Administration |
| NDA | New Drug Application |
| **Environmental Tests** | |
| ADME | Absorption, Distribution, Metabolism, and Excretion |
| AR | Applied Radioactivity |
| BCF | Bioconcentration Factors |
| CAKE | Computer Assisted Kinetic Evaluation |
| $C_{max}$ | Maximum (or Peak) Serum Concentration |
| $DT_{50}$ | Degradation Time for 50% Removal |
| $DT_{90}$ | Degradation Time for 90% Removal |
| $EC_{10}$ | Effective/Effect Concentration, 10% of test population |
| $EC_{20}$ | Effective/Effect Concentration, 20% of test population |
| $EC_{50}$ | Effective/Effect Concentration, 50% of test population |
| FSH | Follicle Stimulating Hormone |
| FssPC | Fish Steady-State Plasma Concentration |
| GnRH | Gonadotropin-Releasing Hormone |
| $IC_{50}$ | Inhibitory Concentration whereby Response is Reduced by 50% |
| HPLC | High-Performance Liquid Chromatography |
| HτPC | Human Therapeutic Plasma Concentration |
| $K_f^{ads}$ | Freundlich Adsorption Distribution Coefficient |
| $K_{foc}^{ads}$ | Coefficient of Adsorption per Unit Organic Carbon |
| $K_f^{des}$ | Freundlich Desorption Distribution Coefficient |
| $K_{foc}^{des}$ | Coefficient of Desorption per Unit Organic Carbon |
| LH | Luteinizing Hormone |
| l/n | Exponent of the Freundlich Adsorption Isotherm |
| LOEC | Lowest Observed Effect Concentration |
| MEOGRT | Medaka Extended One Generation Reproduction Test |
| NOEC | No Observed Effect Concentration |
| log $P_{ow}$/Log $K_{ow}$ | Log Value of the Octanol/Water Partition Coefficient |
| OECD | Organization for Economic Co-operation and Development |
| $P_{blood:water}$ | Partitioning Between Aqueous Phase and Arterial Blood |
| pKa | Dissociation Constant |
| RNA | Ribonucleic Acid |
| SD | Standard Deviation |
| vtg1 | Vitellogenin 1 Gene |

| Environmental Terms | |
|---|---|
| EA | Environmental Assessment |
| EIC | Expected Introduction Concentration |
| ER | Effect Ratio |
| POTW | Publically Owned Treatment Works |
| **Units** | |
| g | Grams |
| g/L | Grams per Liter |
| g/mole | Grams per Mole |
| kg | Kilograms |
| kg/yr | Kilograms per year |
| mg | Milligrams |
| mg/L | Milligrams per Liter |
| mm | Millimeters |
| nM | Nanomolar |
| ng/mL | Nanograms per Milliliter |
| ppb | Parts per Billion |
| µg/kg | Micrograms per Kilogram |
| µg/L | Micrograms per Liter |
| *vtg*1/ng total RNA | Vitellogenin 1 Gene (*vtg*1)/ng of total RNA |

# 4.0 Applicant Information

## 4.1 Name of Applicant

AbbVie Inc.

## 4.2 Address of Applicant

All correspondence should be directed to:

Glen W. Spears, Ph.D.
Director, Regulatory Affairs
1 N. Waukegan Road
Dept. PA72, Bldg. AP30-4
North Chicago, IL 60064

# 5.0 Description of Proposed Action

## 5.1 Requested Approval

Application Number NDA 210450. AbbVie Inc. has filed an NDA pursuant to Section 505(b) of the Federal Food, Drug, and Cosmetic Act for elagolix (ABT-620) tablets. Elagolix tablets are available in two strengths, 150 mg (once daily) and 200 mg (twice daily). Each strength has its own presentation:

- A 28-count monthly pack for the 150 mg elagolix strength. Each monthly pack contains four weekly blister packs for a total of 28 tablets (NDC 0074-0038-28). Each weekly blister pack contains seven tablets of 150 mg elagolix for one week of treatment.
- A 56-count monthly pack for the 200 mg elagolix strength. Each monthly pack contains four weekly blister packs for a total of 56 tablets (NDC 0074-0039-56). Each weekly blister pack contains 14 tablets of 200 mg elagolix for one week of treatment.

An EA has been submitted pursuant to 21 CFR Part 25.

## 5.2 Need for Action

Elagolix sodium (ABT-620) is a small molecule, orally active gonadotropin-releasing hormone (GnRH) receptor antagonist. It has the ability to suppress estradiol (E2) concentrations in a dose-dependent manner. AbbVie is applying to use elagolix for the treatment of endometriosis with associated pain. Elagolix is the first orally available GnRH antagonist, and as such may provide patients with relief from the painful symptoms of endometriosis while offering advantages over currently available injectable peptide-based treatments. The estimated patient population is over 170 million women worldwide. [1]

## 5.3 Locations of Use

Elagolix will be self-administered by patients in their homes.

### 5.4 Disposal Sites

In the home, empty or partially empty containers will often be disposed of by a community's solid waste management system, which may include landfills, incineration, and recycling, although minimal quantities of the unused drug could be disposed of in the sewer system. Many patients will choose to dispose of unused medications in a secure take-back process that prevents abuse and ensures the prevention of environmental release.

## 6.0 Identification of Substance that is the Subject of the Proposed Action

### 6.1 Nomenclature

#### 6.1.1 USAN Name

Elagolix sodium

#### 6.1.2 Generic Name/Proposed Brand Name

Elagolix (generic); Orilissa™ (proposed brandname)

#### 6.1.3 Chemical Name

Sodium 4-({(1*R*)-2-[5-(2-fluoro-3-methoxyphenyl) -3-{[2-fluoro-6-(trifluoromethyl)phenyl]methyl}-4-methyl-2,6-dioxo-3,6-dihydropyrimidin-1(2*H*)-yl]-1-phenylethyl}amino) butanoate

### 6.2 Chemical Abstracts Service (CAS) Registration Number

832720-36-2

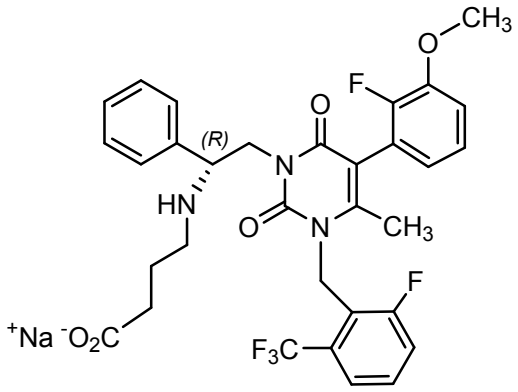
### 6.3 Molecular Formula

$C_{32}H_{29}F_5N_3O_5 \bullet Na$

### 6.4 Molecular Weight

653.58 g/mole (sodium salt), 631.60 g/mol (free form)

### 6.5 Structure and Identity




## 7.0 Environmental Issues

### 7.1 Assessing Toxicity to Environmental Organisms

Based upon marketing expectations, the concentration of elagolix at the point of entry into the aquatic environment is expected to be below 1 ppb (Appendix D). However, FDA has determined that extraordinary circumstances apply given the hormonal activity of elagolix, triggering FDA's Questions and Answers Regarding Drugs with Estrogenic, Androgenic, or Thyroid Activity (EAT Guidance).[2] FDA has required the development of an environmental assessment for elagolix, and the assessment has been prepared following FDA's Guidance for Industry on the Environmental Assessment of Human Drug and Biologics Applications.[3] At therapeutic dosages in humans, elagolix blocks GnRH receptors, leading to a decrease in the release of luteinizing (LH) and follicle stimulating hormone (FSH) with a subsequent dose-related suppression of estradiol secretion.[4] GnRH receptor antagonists are also known to decrease testosterone secretion in men.[5] This mechanism of action in humans raises concerns that elagolix has the potential to interact with estrogenic or androgenic hormone pathways in other species.

Elagolix is a potent antagonist of the human GnRH receptor (concentration producing 50% inhibition of inositol phosphate production [$IC_{50}$] = 1.5 nM).[6] Binding to the GnRH receptor of higher-order species such as the monkey and rabbit is comparable though slightly less than observed in humans, while binding affinity to the rat receptor is much less.[6-8] While the binding affinity of elagolix to fish GnRH receptor is not known, it might be expected to be lower than that of non-human mammalian species based on greater evolutionary distance.

The objective of this EA is to evaluate the possibility that elagolix might have an effect on aquatic species. Such a potential effect is possible in light of the fact that a few highly-conserved molecular forms of GnRH, as well as GnRH receptor subtypes, have been identified in several orders of fish.[9-12] It has also been shown that a mammalian peptide GnRH antagonist is capable of modulating GnRH-mediated activity in fish.[12,13] However, the hormonal pathways regulating gonadotropin secretion in fish are not completely analogous to those of mammals, and it has been suggested that LH synthesis in fish might be primarily regulated by steroid hormones in addition to contributions from GnRH.[13]

Using the model of Huggett et al.,[14] the fish steady-state plasma concentration of elagolix was estimated and an effect ratio (ER) was derived as a predictive tool to help inform the design of the EA program for elagolix. The model uses the expected introduction concentration (EIC) and the experimentally derived octanol/ water partition coefficient (from OECD 107) for elagolix. Calculations of the EIC, the estimated fish steady-state plasma concentration, and the ER for elagolix are presented in Appendix D. The ER was determined to be approximately 1200 based upon AbbVie's current production estimates over a five-year period from 2018 to 2022. The model of Huggett et al.[14] assumes that an ER < 1000 as an initial evaluation might warrant an additional assessment in fish.

The model of Huggett et al.,[14] relies upon hydrophobicity (log $K_{ow}$) of a compound as a predictor of uptake into the bloodstream of fish, but does not take into account potency or any other compound-specific factors that might affect fish physiology. As a result, there is uncertainty regarding the robustness of this model to predict the effects of a

hormone-active compound upon fish in the environment. In light of the recent concerns raised by researchers and the newly released FDA guidance, extraordinary circumstances have been applied to elagolix based upon hormonal activity. For this reason, a partial lifecycle study of elagolix in fish was initiated as requested by FDA based upon a Type C briefing package submitted by AbbVie in July 2016 (details provided in Section 7.2). The potential for elagolix to impact aquatic species representing three trophic levels was investigated. The environmental assessment program conducted by AbbVie is described below.

## 7.2 General Principles for the Risk Evaluation

The EA for elagolix was developed in a scientifically directed manner based on the mechanism of action of the compound and in consultation with the FDA. A briefing package was submitted to the FDA on July 18, 2016 (Type C), with responses from the agency on August 24, 2016. Follow-up questions submitted by AbbVie on September 7, 2016 received a response from FDA on September 13, 2016. The testing strategy was developed with reference to the FDA's Guidance for Industry on the Environmental Assessment of Human Drug and Biologics Applications [3] and the clarifications provided in FDA's EAT Guidance. [2] In their responses to the Type C briefing package, the FDA indicated that the available data were insufficient to make a determination that risks to aquatic organisms were low and that testing for endocrine disruption was not necessary. The FDA also expressed uncertainty regarding the robustness of the fish plasma model for regulatory review and action in the absence of other data, such as other examples of GnRH antagonists that could be used for "read across" purposes, and any data on metabolism, fate, and transport. In addition, the high expected introduction concentration of elagolix relative to other endocrine-active substances in the environment was of concern to the FDA. The agency indicated that "... notwithstanding the 1 ppb categorical exclusion, extraordinary circumstances still apply given the hormonal activity relevant to FDA's recent guidance regarding drugs with estrogenic, androgenic, or thyroid pathway activity (USFDA 2016)." The following table lists the tests requested by FDA in addition to, or as a replacement for, environmental

tests proposed by AbbVie; a summary of the results is provided in Appendix A. Summary tables from the test for transformation in aerobic and anaerobic aquatic sediment are presented in Appendix B. Relevant tables and results from the Medaka extended one generation reproduction test are provided in Appendix C.

**Environmental Fate and Effects Studies Completed**

| Study Title | Guideline | Status in EA | AbbVie Report Number | Reference Number |
|---|---|---|---|---|
| Physicochemical properties of elagolix (ABT-620; A-1278823.5) | AbbVie Inc., Internal | Final Report | PTR-16-0001 | 15 |
| ABT-620: Partition Coefficient | OECD 107 | Final report | R&D/17/0384 | 16 |
| ABT-620: Water Solubility | OECD 105 | Final report | R&D/16/0556 | 17 |
| Analytical Method Verification for the Determination of ABT-620/Elagolix in Fresh Water | SANCO/3029/99 rev. 4 | Final report | R&D/17/0249 | 18 |
| ABT-620: Activated Sludge Respiration Inhibition Test | OECD 209 | Final report | R&D/16/0435 | 19 |
| ABT-620: *Daphnia magna* Reproduction Test | OECD 211 | Final report | R&D/17/0482 | 20 |
| ABT-620: Algal Growth Inhibition Test | OECD 201 | Final report | R&D/17/0481 | 21 |
| ABT-620/Elagolix: A Non-GLP Range Finding Trial for a Medaka Extended One Generation Reproduction Test (MEOGRT) | OECD 240 | Final report | R&D/17/0159 | 22 |
| ABT-620: Adsorption/Desorption on Soils & Sewage Sludge | OECD 106 | Final report | R&D/17/0757 | 38 |
| ABT-620: Transformation in Aerobic and Anaerobic Aquatic Sediment Systems | OECD 308 | Final report | R&D/17/0756 | 39 |
| ABT-620/Elagolix: Medaka Extended One Generation Reproduction Test (MEOGRT) | OECD 240 | Final report | R&D/17/0537 | 35 |

# 8.0 Environmental Assessment

## 8.1 Environmental Fate of Released Substances

This environmental assessment is based upon projected peak commercial manufacture of elagolix within the first five years of anticipated market entry. The resulting estimation of elagolix concentration at the point of entry into the aquatic environment is conservatively utilized as the relevant exposure concentration for aquatic organisms, without consideration of applicable removal and dissipation mechanisms such as metabolism, degradation, and dilution. Elagolix is expected to enter predominately into the aquatic

environment, and as a result the effect studies focus on aquatic organisms. Tests of water solubility, dissociation constants, octanol/water partition coefficient, binding to soils and sludges, and transformation in aerobic and anaerobic aquatic sediment systems were conducted. Vapor pressure was not measured based on known characteristics of elagolix.

## 8.2 Environmental Concentrations

### 8.2.1 Expected Introduction Concentration (EIC)

Based on projected commercial manufacture of elagolix over the five-year period following the NDA approval, the EIC of elagolix into the aquatic environment is predicted to be approximately 0.6 ppb. A conservative value of 1 ppb is treated as the relevant exposure concentration for aquatic organisms, without consideration of metabolism, degradation, dilution, or other removal or dissipation mechanisms. Calculation of the EIC is provided in Appendix D.

### 8.2.2 Human Metabolism and Excretion

Metabolism of elagolix was not considered when calculating the EIC. Rather, any expected metabolites were conservatively considered to have the same pharmacologic activity as elagolix, and all the manufactured volumes of the parent drug were taken into account during calculation of the EIC. Studies of the metabolism of elagolix demonstrate substantial removal. Radiolabeled absorption, distribution, metabolism, and excretion (ADME) studies were conducted to determine the metabolic profiles of elagolix in plasma and excreta from healthy male human volunteers after administration of a single oral dose of [$^{14}$C]elagolix. The percentage of elagolix excreted as metabolites was 52%. In humans, the primary pathways involved in the clearance of elagolix are the following (in order of their significance based on the percentage of dose eliminated): *O*-demethylation > excretion of unchanged elagolix and its glucuronide > monooxidation > lactam formation > N-dealkylation. The *O*-demethylation pathway for [$^{14}$C]elagolix resulted in one major metabolite (> 38% of the dose was excreted as *O*-demethyl [$^{14}$C]elagolix) and related metabolites in human excreta.[23]

## 8.3 Physical-Chemical Properties and Fate

### 8.3.1 Dissociation Constant (pKa)

The acid dissociation constants of elagolix were determined by potentiometric titration with the following results:

| Ionizable Groups | Measured pKa | AbbVie Report Number | Reference Number |
|---|---|---|---|
| Carboxylic acid | 4.0 | PTR-16-0001 | 15 |
| Secondary amine | 7.9 | | |

Elagolix exists primarily as a zwitterion between pH 4.0 and 7.9.

### 8.3.2 Water Solubility (OECD 105)

A solubility study [17] was conducted using HPLC analysis in accordance with OECD 105. [24] The aqueous solubility of elagolix was determined in purified water and in buffer solutions (pH 5, pH 7, or pH 9). Results are summarized in the following table:

| Media | Solubility, g/L | AbbVie Report Number | Reference Number |
|---|---|---|---|
| Purified water | > 250 | R&D/16/0556 | 17 |
| pH 5 buffer solution | > 250 | | |
| pH 7 buffer solution | > 250 | | |
| pH 9 buffer solution | > 250 | | |

Elagolix is classified as highly water soluble according to the Biopharmaceutics Classification System. [25,26]

### 8.3.3 Partition Coefficient (OECD 107)

The n-octanol/water partition coefficient was determined using the shake flask method in accordance with OECD 107. [27,16] Elagolix was dissolved in n-octanol (saturated with water), and measured volumes were mixed with measured volumes of buffer solutions (pH 5, pH 7, or pH 9). After mixing at 20°C, the mixtures were centrifuged, allowed to

stand for one hour, the phases separated, and the concentrations of elagolix in both phases determined by HPLC. Results are summarized in the following table:

| pH | Log $P_{ow}$ | AbbVie Report Number | Reference Number |
|---|---|---|---|
| 4 | 1.8 | R&D/17/0384 | 16 |
| 7 | 1.8 | | |
| 9 | 0.7 | | |

Based on accepted environmental guidance documents, compounds with a log $K_{ow} < 3.5$ do not present a concern regarding the potential to bioaccumulate. Since the log $P_{ow}$ of 1.8 at pH 7 is below the accepted trigger value of 3.5, further evaluation for bioaccumulation in fish (OECD 305) [28] was not required.

### 8.3.4 Adsorption/ Desorption on Soils and Sewage Sludge (OECD 106)

The adsorption and desorption behavior of [$^{14}$C]elagolix on three soils and two activated sludges was investigated in accordance with OECD 106. [29]

The Freundlich adsorption coefficients corrected for organic carbon content ($K_{foc}^{ads}$) values ranged from 327 to 916 for soils and were 189 and 261 for sludges, as shown in the following table. Using the McCall binding classification system described in test guideline OECD 106, the data demonstrate a low potential for binding to sludges and a low to medium potential for binding to soils. Consequently, elagolix would not be expected to bind to sludge in a wastewater treatment plant and then be transported to the terrestrial compartment by way of land application. This section of the environmental assessment has been updated with final, audited data from the finalized study report.

| Matrix | %Organic Carbon Content | $K_f^{ads}$ | $K_{foc}^{ads}$ | l/n | $K_f^{des}$ | $K_{foc}^{des}$ | l/n |
|---|---|---|---|---|---|---|---|
| **Soils** | | | | | | | |
| Bromsgrove | 1.2 | 7.11 | 593 | 0.91 | 19.0 | 1580 | 0.90 |
| Drayton | 2.5 | 22.9 | 916 | 0.93 | 59.9 | 2400 | 0.96 |
| Elmton | 4.4 | 14.4 | 327 | 0.88 | 27.0 | 614 | 0.84 |
| **Sludges** | | | | | | | |
| Loughborough | 45.6 | 86.3 | 189 | 0.91 | 84.1 | 184 | 0.82 |
| Worlingworth | 44.8 | 117 | 261 | 0.92 | 165 | 369 | 0.89 |

$K_f^{ads}$: Freundlich adsorption distribution coefficient

$K_{foc}^{ads}$: Coefficient of adsorption per unit organic carbon

$K_f^{des}$: Freundlich desorption distribution coefficient

$K_{foc}^{des}$: Coefficient of desorption per unit organic carbon

l/n: Exponent of the Freundlich adsorption isotherm

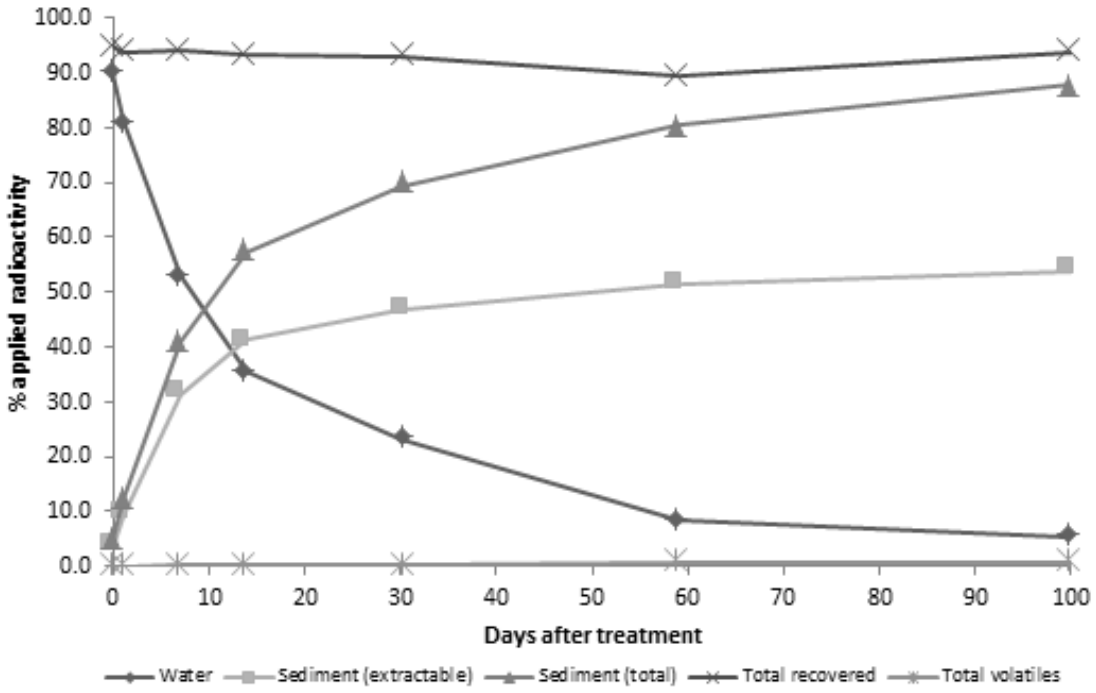
### 8.3.5 Transformation in Aerobic and Anaerobic Aquatic Sediment Systems (OECD 308)

The degradation (transformation) and distribution of [$^{14}$C]elagolix were investigated according to OECD Guideline 308 [30] in two different water/sediment systems under aerobic (100 days) and anaerobic (99 days) conditions. The amount of radioactivity in the sediment layer generally increased over the course of the study as elagolix partitioned from the water to the sediment. This increase in sediment elagolix content is summarized in the following table. Detailed data from the study are presented in Appendix B, Table 1 and Table 2. This section of the environmental assessment has been updated with final, audited data from the finalized study report.

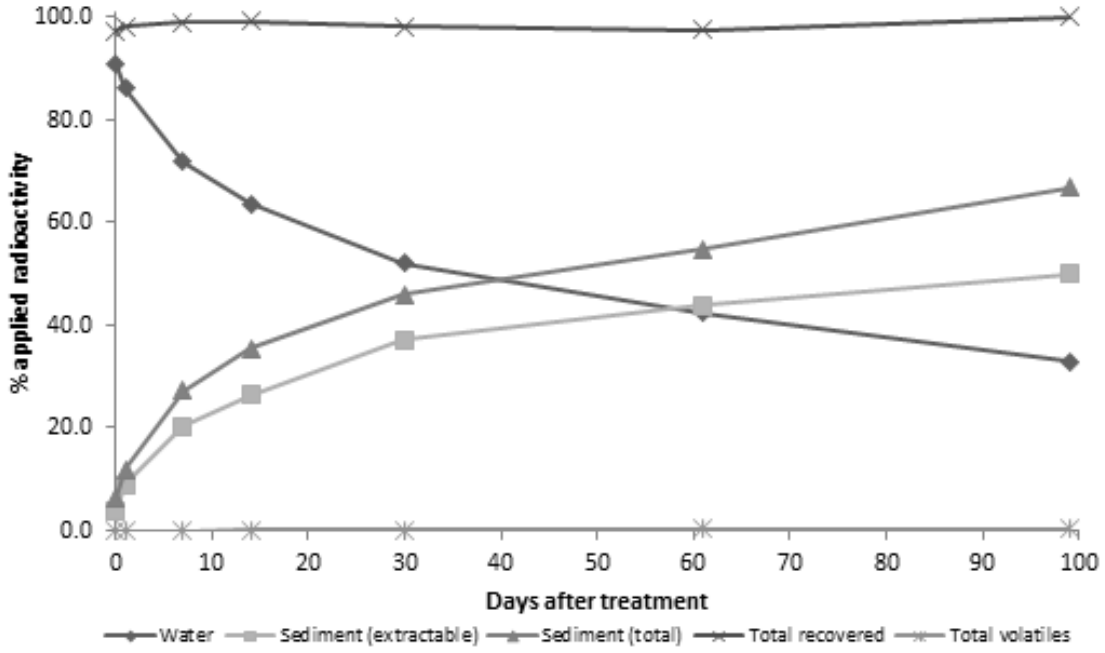
| Sediment System | Day 0: Aerobic Conditions | Day 100: Aerobic Conditions | Day 0: Anaerobic Conditions | Day 99: Anaerobic Conditions |
|---|---|---|---|---|
| Calwich Abbey Lake | 5.0% | 88.0% | 6.5% | 66.9% |
| Emperor Lake | 4.4% | 87.9% | 3.9% | 63.0% |

The aerobic and anaerobic partitioning trends for Calwich Abbey Lake and Emperor Lake are similar. Distribution of radioactivity over 100/99 days under aerobic and anaerobic conditions for Calwich Abbey Lake is presented in the following figures as representative of the pattern observed in both test systems. The data are presented in Appendix B, Table 1 and Table 2.

**Distribution of Total Radioactivity in Calwich Abbey Lake Aquatic Sediment System (Aerobic Conditions)**



**Distribution of Total Radioactivity in Calwich Abbey Lake Aquatic Sediment System (Anaerobic Conditions)**




Transformation products (metabolites) in the sediments were analyzed in the Day 100 aerobic samples and in the Day 99 anaerobic samples. The data are presented in Appendix B, Table 1 and Table 2. Metabolite samples from Day 100/99 were analyzed, and all metabolites present in the sediment at levels of 10% or greater were identified. The results are summarized below.

Eleven transformation products were identified under aerobic conditions in sediments from both Calwich Abbey Lake and from Emperor Lake, whereas seven and six transformation products were identified under anaerobic conditions in the Calwich Abbey and Emperor systems, respectively. Metabolite E reached the highest percentage of any metabolite in Calwich Abbey Lake, with 34.3% applied radioactivity (AR) in aerobic sediments and 44.9% AR in the anaerobic sediments. Metabolites D and F were present at 9.8% and 12.8% AR, respectively, in the aerobic sediments of Emperor Lake, and Metabolite E was present at 18.6% in the anaerobic sediments of Emperor Lake.

The $DT_{50}$ and $DT_{90}$ values for [$^{14}$C]elagolix estimated through Day 100 (aerobic) and Day 99 (anaerobic) were calculated using Computer Assisted Kinetic Evaluation (CAKE). All calculations by CAKE were single first order. The $DT_{50}$ and $DT_{90}$ values and statistical parameters for elagolix in each sediment system at 20°C are summarized in the following table.

| Sediment System | Layer | $DT_{50}$, 20°C (days) | $DT_{90}$, 20°C (days) |
|---|---|---|---|
| | | **Aerobic** | |
| Calwich Abbey (Silt Loam) | Water | 7.87 | 26.2 |
| | Sediment | 50.6 | 168 |
| | Total System | 13.7 | 45.3 |
| | | **Anaerobic** | |
| | Water | 11.6 | 38.5 |
| | Sediment | 18.5 | 61.3 |
| | Total System | 13.1 | 43.7 |
| | | **Aerobic** | |
| Emperor (Sandy Loam) | Water | 7.91 | 26.3 |
| | Sediment | 36.4 | 121 |
| | Total System | 18.2 | 60.4 |
| | | **Anaerobic** | |
| | Water | 27.3 | 90.8 |
| | Sediment | 43.3 | 144 |
| | Total System | 41.3 | 137 |

In conclusion, elagolix partitioned steadily from the water phase to the sediment phase in both the aerobic and anaerobic sediment systems, and transformed to multiple metabolites. The metabolic pathways in samples from both lakes were found to be similar. The removal of $^{14}$[C]elagolix was slower under anaerobic conditions, with production of fewer metabolites.

## 8.4 Microbial Inhibition

### 8.4.1 Activated Sludge, Respiration Inhibition Test (OECD 209)

An activated sludge respiration inhibition study[19] was conducted in accordance with OECD 209[31] at concentrations of 10, 30, 100, 300, and 1000 mg/L elagolix over a three-hour period. No significant inhibition was observed and the effective concentration for 50% of the test population ($EC_{50}$) was determined to be > 1000 mg/L. The No Observed Effect Concentration (NOEC) was determined to be 1000 mg/L, the highest concentration tested.

## 8.5 Aquatic Effect Studies

### 8.5.1 Freshwater Alga, Growth Inhibition Test (OECD 201)

An alga growth inhibition study[21] was conducted at nominal concentrations of 6.25, 12.5, 25, 50, and 100 mg/L elagolix using the freshwater green alga, *Pseudokirchneriella subcapitata*, in accordance with OECD 201.[32] Results are summarized in the following table.

| Biological Parameter Inhibition | Endpoint | | | | | AbbVie Report Number | Reference Number |
|---|---|---|---|---|---|---|---|
| | $EC_{10}$ | $EC_{20}$ | $EC_{50}$[a] | NOEC | LOEC | | |
| 72-Hour Growth Rate | > 100 | > 100 | > 100 | 50 | 100 | R&D/17/0481 | 21 |
| 72-Hour Yield | 62 | 78 | > 100 | 50 | 100 | | |
| 72 Hour Biomass Integral | 59 | 76 | > 100 | 50 | 100 | | |

a. It was not possible to calculate 95% confidence limits for the $EC_{50}$ values as the data generated did not fit the models available for the calculation.

The NOEC was determined to be 50 mg/L for all measured parameters. The lowest effect concentration (LOEC) was 100 mg/L.

### 8.5.2 *Daphnia magna* Reproduction Test (OECD 211)

A daphnia reproduction study[20] was conducted at nominal concentrations of 0.625, 1.25, 2.5, 5.0, and 10 mg/L elagolix using the freshwater invertebrate, *Daphnia magna* in accordance with OECD 211.[33] The potential for chronic effects of elagolix on survival, reproduction, and growth (length, top of head to base of spine) were measured. Results are summarized in the following table.

| | Endpoint (mg/L) | | | AbbVie Report Number | Reference Number |
|---|---|---|---|---|---|
| Parameter[a] | Survival | Reproduction | Length | | |
| $EC_{10}$ | > 10 | > 10 | > 10 | R&D/17/0482 | 20 |
| $EC_{50}$ | > 10 | > 10 | > 10 | | |
| NOEC | 10 | 10 | 10 | | |

a. 95% confidence intervals could not be determined.

$EC_{10}$ and $EC_{50}$ values for survival, reproduction, and length were estimated to be greater than 10 mg/L, the highest concentration tested. The NOEC for all measured parameters was determined to be 10 mg/L, the highest concentration tested.

### 8.5.3 Fish Range-Finding Toxicity Test (Supporting OECD 240)

A fish range-finding toxicity study[22] was conducted on Japanese medaka (*Oryzias latipes*) in support of a subsequent OECD 240[34] definitive study. Adult breeding groups (F0) of Japanese medaka were exposed to elagolix at nominal concentrations of 0, 0.01, 0.1, 1 and 10 mg/L (measured concentrations provided below) under flow-through conditions for 21 days. Eggs collected from the breeding groups were exposed under the same conditions for the duration of incubation, and then hatched embryos (F1) were exposed under these same conditions for approximately 48 hours after completion of hatch. Survival and reproductive parameters (fecundity and fertility) in the F0 generation, and hatching success and survival in the F1 generation, were unaffected by exposure to elagolix at measured concentrations up to 12 mg/L (the highest measured concentration tested) in the surrounding water as shown in the following tables.

**Day 21 F0 Generation Results (Mean ± SD)**

| Mean Measured Concentration (mg/L) | Percent Survival to Day 23 of Exposure | Cumulative Number of Eggs Produced | Eggs Per Female Per Day | Percent Fertility | AbbVie Report Number | Reference Number |
|---|---|---|---|---|---|---|
| Negative Control | 100 ± 0.0 | 1091 ± 137 | 47.5 ± 5.97 | 92.3 ± 6.3 | R&D/17/0159 | 22 |
| 0.01 | 100 ± 0.0 | 1069 ± 230 | 46.5 ± 9.99 | 94.6 ± 3.8 | | |
| 0.10 | 100 ± 0.0 | 988 ± 136 | 42.9 ± 5.92 | 89.0 ± 12.5 | | |
| 1.1 | 100 ± 0.0 | 1038 ± 131 | 45.1 ± 5.71 | 92.3 ± 5.0 | | |
| 12 | 100 ± 0.0 | 1055 ± 66 | 45.9 ± 2.85 | 94.8 ± 2.4 | | |

**F1 Generation Survival (Mean ± SD)**

| Mean Measured Concentration (mg/L) | Percent Embryo Hatching Success | Percent Larval Survival 48 Hours Post-Hatch | AbbVie Report Number | Reference Number |
|---|---|---|---|---|
| Negative Control | 74.6 | 86.9 | R&D/17/0159 | 22 |
| 0.01 | 98.3 | 96.7 | | |
| 0.10 | 92.5 | 92.6 | | |
| 1.1 | 86.7 | 96.1 | | |
| 12 | 96.6 | 97.5 | | |

The NOEC for reproductive parameters and survival of adult fish, embryos, and larva was determined to be 12 mg/L (the highest concentration tested) within the parameters of this range-finding test.

Results of the range-finding test were used to determine test concentrations for the definitive Medaka Extended One Generation Test (MEOGRT) study. Five test concentrations plus a negative control concentration were chosen for the MEOGRT, with a spacing factor between adjacent treatment levels of approximately 3.2, as recommended in the OECD 240 guideline.[34] The lowest test concentration was approximately 100 times lower than the highest concentration in accordance with the guideline. Based upon an assumption that the EIC of elagolix approximates 1 ppb (actual value 0.6 ppb), the lowest test concentration chosen was 0.01 mg/L, which is about 10-fold greater than

the estimated concentration of elagolix at the point of entry into the aquatic environment. Using a spacing factor of approximately 3.2, the remaining test concentrations were chosen, resulting in concentrations of 0.01, 0.033, 0.105, 0.336, and 1.074 mg/L of elagolix for the definitive study. These concentrations represent approximately 10-, 33-, 105-, 336-, and 1074-fold the concentration of elagolix at the point of entry into the aquatic environment. This range of test concentrations between approximately 10- and 1000-fold the EIC provided a sufficiently wide range of concentrations well above the anticipated exposure concentrations to fish in the natural aquatic environment, while allowing a reasonable range in which to establish an effect concentration, if any.

### 8.5.4 Medaka Extended One Generation Reproduction Test (MEOGRT) (OECD 240)

An extended one generation reproduction test [35] was conducted on Japanese medaka (*Oryzias latipes*) in accordance with OECD 240. [34] Results were evaluated using endpoints grouped within three categories: overt toxicity (survival, growth, behavior, hatching success/early survival), apical endpoints (fecundity, fertility, gonadal phenotype), and endocrine-mediated mechanistic endpoints (anal fin papillae, vitellogenin, genetic sex, sex reversal, and gonadal pathology). Nominal concentrations evaluated were control, 0.10, 0.033, 0.105, 0.336, and 1.074 mg ABT-620/L.

Reproductively active breeding pairs of Japanese medaka were exposed to test concentrations for 33 days. Eggs were collected from the F0 generation to start a new generation (F1) and exposure continued through reproductive development and reproduction of the F1 generation. Eggs from the F1 generation were then used to start a third generation (F2), which was only monitored for hatching success. Genetic sex was determined from fin clips for the F0 and F1 generations in order to verify XX-XY reproductive pairs. Concentrations of elagolix were measured within the aquaria at periodic intervals throughout the study, and were maintained within ±20% of nominal concentrations with rare exceptions.

There were no effects at any concentration up to 1000-fold the EIC (the highest concentration tested) on survival, growth, behavior, or hatching success, with the exception of hatching success in the middle (0.105 mg/L) and highest test concentration (1.074 mg/L) for the F1 generation. These observed changes in F1 hatching success were not dose-dependent and were not severe, and occurred at exposures that were 100-fold greater than the point of entry into the aquatic environment. There was no effect of elagolix at any concentration up to 1000-fold EIC on either apical or mechanistic endpoints, including no effect on reproduction and no endocrine-disrupting activity. Overall, there were no effects on survival, growth, or reproduction in this study that would lead to population level effects at exposures up to 1000-fold EIC concentrations. Results from the final audited study report are presented in Appendix C and summarized in this section. Endpoints are reported in the context of genetic sex unless otherwise noted, and the results are reported using nominal concentrations. The outcomes across three generations are summarized in the following table:

**Effects of Elagolix at Concentrations up to 1.074 mg/L (1000-fold EIC) in the MEOGRT Study**

| Endpoint | Generation | | |
|---|---|---|---|
| | F0 | F1 | F2 |
| **Overt Toxicity** | | | |
| Survival | No effect | No effect | NA |
| Growth | No effect | No effect | NA |
| Behavior | No effect | No effect | No effect |
| Hatching success/ early survival | NA | No effect | No effect |
| **Apical Endpoints** | | | |
| Fecundity | No effect | No effect | NA |
| Fertility | No effect | No effect | NA |
| Gonadal phenotype | NA | No effect | NA |
| **Mechanistic Endpoints** | | | |
| Anal fin papillae | NA | No effect | NA |
| Vitellogenin | NA | No effect | NA |
| Genetic sex | NA | No effect | NA |
| Sex Reversal | NA | No effect | NA |
| Gonadal pathology | NA | No effect | NA |

NA: not applicable

Hatching success of both the F1 and F2 generations was impacted by fungal infections and variable mortality across replicates and resulted in multiple re-initiations of the hatch for both the F1 and F2 generations in order to achieve a valid study. In response to this situation, the incubation system was switched from flow-through to a static renewal system for the final F2 hatch, resulting in increased hatching success in the F2 generation (Appendix C, Table 3). This successful resolution of fungal infections resulted in no effect of elagolix on hatching success in the F2 generation. For the spawning event that was used for the F1 generation, the hatching success of control and treatment groups exceeded the minimum performance requirement of 80% for control cultures established by the OECD 240 test guideline, with two exceptions (Appendix C, Table 2). Hatching success in the F1 generation for the controls was 97%, which was statistically significantly higher than the hatching success of 54, 86, and 41% for the three highest test

concentrations of elagolix (0.105, 0.336, 1.074 mg/L, respectively). Early survival to four weeks post fertilization was also statistically significantly lower at concentrations of elagolix ≥ 0.33 mg/L. However, early survival was > 86% in all but the mid concentration (0.105 mg/L) and the statistical changes were not considered meaningful.

As addressed in the study report, it was considered unlikely that decreased F1 hatching success and early survival were related to exposure to elagolix for the following reasons. The trend for hatching success and early survival was not dose-responsive and was not consistent with hatching success in the range-finding study at higher concentrations of elagolix (> 10-fold; 12 mg/L), nor was it affected by elagolix within the F2 generation. The high rate of fungal infections that variably affected different replicates across treatment groups was considered the most likely cause for decreased hatching and early survival among the F1 embryos.

In the version of the environmental assessment submitted in March, 2018, AbbVie included an initial analysis of preliminary data that used a very conservative interpretation of the results. That interpretation assumed the possibility of an overt toxic effect on hatching success at the 0.105 mg elagolix/L test concentration, which resulted in a reported lowest observed effect (LOEC) of 0.105 mg/L and a no observed effect concentration (NOEC) of 0.033 mg/L. At present, however, a revised interpretation of the findings is supported in light of contextual information about the study. For example, there was high mortality (up to 100%) in some control groups of the failed spawns of both the F1 and F2 generations. Following discussions with individuals experienced in fish culture, and with consideration of factors that were previously discussed, such as lack of a dose response and no elagolix-related effect on hatching success in the rangefinding study or F2 generation, it was concluded that there was no effect of elagolix on hatching success in the F1 generation. Consequently, AbbVie has revised its previous interpretation of the hatching data to the conclusion that appears in this final version of the environmental assessment.

There was a statistically significant increase in mean male vitellogenin at 0.105 mg elagolix/L. In addition, a statistically significant decrease in mean female vitellogenin at 0.336 mg elagolix/L was found, as well as a decrease (not significant) at 1.074 mg/L

(Appendix C, Table 9 and Table 10). These changes were not considered related to exposure to elagolix, as there was not a consistent dose response in male vitellogenin measurements, and these apparent minor changes in vitellogenin among males or females were not associated with impacts on any other endpoint, such as growth, fertility, or anal fin papillae. All male and female vitellogenin levels measured within all treatment groups were within the range of historical control values within the conducting laboratory, and were also aligned with published control values for MEOGRT studies.[36] Exposure to elagolix was not considered to have an effect on vitellogenin levels at any concentration of elagolix.

In the testes of F1 generation males, there were no microscopic findings in the negative control group or in any treatment groups. The main microscopic findings in the ovaries of F1 generation females included differences in developmental stage, oocyte atresia, and numbers of post-ovulatory follicles. However, these findings were not considered to be compound-related since the differences did not follow a monotonic dose-response pattern, and the changes seen histologically were incongruent with fecundity data.

The overall conclusion of this study was that there were no adverse effects on population relevant endpoints or endocrine biomarkers at any test concentration during the F0, F1 and F2 generation exposures. The data did not demonstrate any adverse effects consistent with a pattern of response along the hypothalamic-pituitary-gonadal axis characteristic of endocrine disruptors. Elagolix exerted no adverse effects on growth or reproduction performance at the individual fish level or that could be extrapolated to the population level. Moreover, neither gonad histology nor VTG levels were observed to have clearly adverse effects from elagolix treatment, further confirming a lack of disruption of the endocrine mediated mechanisms for these biomarkers. At the higher concentrations there were some slight differences in histological findings in gonads and VTG levels that occurred at concentrations well above expected environmental concentrations but these findings did not follow a dose-response relationship and had no effect on population relevant endpoints. These slight differences were not determined to be adverse based on lack of effect on the apical endpoints (i.e., growth and reproduction), however they may

reflect a manifestation of a subtle pharmacologic effect of elagolix. The overall NOEC in this study was 1.074 mg elagolix/L, the highest concentration tested, which is over 1000 times the EIC value of 1 ppb. The results of this study strongly indicate that predicted environmental exposures of elagolix in aquatic ecosystems from patient use will not cause endocrine disruption or population level effects in fish.

## 8.6 Summary, Outcome of Studies

Elagolix is highly soluble at > 250 g/L in water (> 250,000 mg/L), with pKa of 4.0 and 7.9. The n-octanol/water partition coefficient, log $P_{ow}$ 1.8 at pH 7, was substantially below 3.5, the log value above which the potential for bioaccumulation is of concern. As a result, further evaluation for bioaccumulation in fish (OECD 305) was not warranted or required (as per OECD 105). Elagolix has a low potential for binding to sludges and a low to medium potential for binding to soils. Elagolix partitioned steadily from the water phase to the sediment phase of both the aerobic and anaerobic aquatic sediment systems, and transformed to multiple metabolites.

A test of microbial respiration inhibition revealed no effect of elagolix at concentrations up to 1000 mg/L, the highest concentration tested. The aquatic effect studies included a growth inhibition test in alga, a chronic reproduction toxicity test in daphnia, and range-finding and definitive reproduction studies in medaka. In these studies, there was no observable effect of elagolix at test concentrations up to 50, 10, or 12 mg/L in the alga, daphnia, and range-finding study in fish, respectively. The NOECs in the studies conducted are approximately 10,000 to 50,000 times greater than the expected concentration of elagolix at the point of entry into the aquatic environment (roughly 0.001 mg/L). The LOEC of 100 mg/L in the alga test was approximately 100,000-fold greater than the EIC of elagolix. In the MEOGRT study, there were no ABT-620 related effects at any concentration (up to 1000-fold EIC) on survival, growth, behavior, or hatching success. There was no effect of elagolix at any concentration (up to 1000-fold EIC) on apical or mechanistic endpoints.

Based on the available data, elagolix does not represent a risk to the aquatic environment.

## 9.0 Mitigation Measures

The studies supporting the environmental assessment for elagolix have not identified an environmental risk for the use of elagolix.

## 10.0 Alternatives to the Proposed Action

No potential adverse environmental effects have been identified for the proposed action. The only identified alternative is the No Action alternative, which would be to refrain from requesting or receiving approval for elagolix. However, this alternative was not considered because it would deny the medical benefit of elagolix to patients with an unmet medical need.

## 11.0 List of Preparers

**Preparation of the environmental assessment**:

Donna R Davila, Ph.D.
Principal Research Scientist, AbbVie Inc.

**Expert review of the environmental assessment**:

Richard T Williams, Ph.D.
President, Environmental Science & Green Chemistry Consulting, LLC

Appendix E contains additional information relevant to the environmental expert.

## 12.0 References and Study Reports

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**NONCONFIDENTIAL**

## Appendix A. Data Summary Table

| Elagolix Data Summary | |
|---|---|
| **Physical/Chemical Characterization** | |
| Water Solubility | > 250 g/L (purified water)<br>> 250 g/L (pH 5, 7, 9 buffer solutions) |
| Dissociation Constants | 4.0 (carboxylic acid)<br>7.9 (secondary amine) |
| Log Octanol/Water Partition Coefficient (log $P_{ow}$) | 1.8 (pH 4)<br>1.8 (pH 7)<br>0.7 (pH 9) |
| **Depletion Mechanisms** | |
| Transformation in Aerobic and Anaerobic Aquatic Sediment Systems | Essentially complete removal from water with partitioning to sediment; transformation to multiple metabolites. Day 100/99 in sediment: > 87% aerobic; ≥ 63% anaerobic |
| Adsorption/Desorption on Soils and Sewage Sludge | Low binding to sludges; low to medium binding to soils |
| **Environmental Effects** | |
| Microbial Respiration Inhibition | $EC_{50}$ > 1000 mg/L<br>NOEC: 1000 mg/L (highest concentration tested) |
| Freshwater Alga Growth Inhibition (72-hour growth rate, yield, biomass integral) | $EC_{50}$ > 100 mg/L<br>NOEC: 50 mg/L<br>LOEC: 100 mg/L |
| *Daphnia magna* Reproduction (survival, reproduction, length) | $EC_{50}$ > 10 mg/L<br>NOEC: 10 mg/L (highest concentration tested) |
| Fish 21-Day Range Finding study (survival, reproduction, hatchability/ 48-hr larvae survival) | NOEC: 12 mg/L (highest concentration tested) |
| Medaka Extended One Generation Reproduction Test | No effects on overt toxicity, apical or mechanistic endpoints up to 1000-fold EIC concentrations; not considered endocrine disrupting |

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James Laurenson

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Michael Furness

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Date: 7/11/2018 10:39:16AM
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# LABELING

## R. Regional Information

## 1.14 Labeling

## I. Package Insert

### 1. HIGHLIGHTS OF PRESCRIBING INFORMATION

#### 1) Title

TRADENAME (elagolix) tablets for oral use
Initial U.S. Approval: 201X

#### 2) DOSAGE FORMS AND STRENGTHS

Oral tablets: 150 mg and 200 mg. (3)

| Item | Information Provided in NDA | Reviewer's Comment and Recommendations |
|---|---|---|
| **Drug name (201.57(a)(2))** | | |
| Proprietary name and established name | TRADENAME (elagolix) tablets | Provided.<br><br>**Satisfactory** |
| Dosage form, route of administration | tablets for oral use | Provided.<br><br>**Satisfactory** |
| Controlled drug substance symbol (if applicable) | | N/A |
| **Dosage Forms and Strengths (201.57(a)(8))** | Oral tablets: 150 mg and 200 mg | Provided.<br><br>**Satisfactory** |
| Whether the drug product is scored | Not applicable | Not applicable |

### 2. "FULL PRESCRIBING INFORMATION

#### 1) #3: DOSAGE FORM AND STRENGTHS

150 mg, light pink, oblong, film-coated tablets with "EL 150" debossed on one side.

200 mg, light orange, oblong, film-coated tablets with "EL 200" debossed on one side.

| Item | Information Provided in NDA | Reviewer's Comment and Recommendations |
|---|---|---|
| Available dosage forms | 150 mg, light pink, oblong, film-coated tablets with "EL 150" debossed on one side.<br>200 mg, light orange, oblong, film-coated tablets with "EL 200" debossed on one side. | Oblong film-coated tablets.<br>**Satisfactory** |
| Strengths: in metric system | 150mg and 200mg | Provided.<br>**Satisfactory** |
| Active moiety expression of strength with equivalence statement (if applicable) | Not provided. | Should be revised to include active moiety expression:<br>150mg tablets are light pink, oblong, film-coated tablets with "EL 150" debossed on one side. Each tablet contains 155.2 mg of elagolix sodium equivalent to 150 mg of elagolix.<br>200mg tablets are light orange, oblong, film-coated tablets with "EL 200" debossed on one side. Each tablet contains 207 mg of elagolix sodium equivalent to 200 mg of elagolix.<br>**Unsatisfactory** |
| A description of the identifying characteristics of the dosage forms, including shape, color, coating, scoring, and imprinting, when applicable. | Not provided | 150 mg, light pink, oblong, film-coated tablets with "EL 150" debossed on one side.<br>200 mg, light orange, oblong, film-coated tablets with "EL 200" debossed on one side.<br>**Satisfactory** |

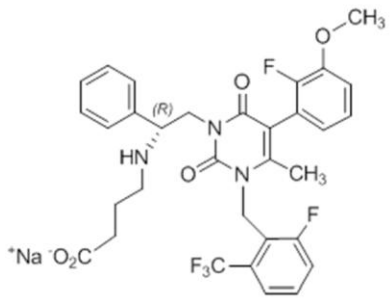
The dosage form and strength must be revised to include active moiety expression of strength with equivalence statement. The following revisions are recommended:

1) 150mg tablets are light pink, oblong, film-coated tablets with "EL 150" debossed on one side. Each tablet contains 155.2 mg of elagolix sodium equivalent to 150 mg of elagolix.
2) 200 mg tablets are light orange, oblong, film-coated tablets with "EL 200" debossed on one side. Each tablet contains 207 mg of elagolix sodium equivalent to 200 mg of elagolix.

## 2) #11: DESCRIPTION

TRADENAME (elagolix) is chemically described as sodium 4-({(1R)-2-[5-(2-fluoro-3-methoxyphenyl)-3-{[2-fluoro-6-(trifluoromethyl)phenyl]methyl}-4-methyl-2,6-dioxo-3,6-dihydropyrimidin-1(2H)-yl]-1-phenylethyl}amino)butanoate. Its molecular formula is $C_{32}H_{29}F_5N_3O_5Na$, (b) (4) a molecular weight of 653.58 (b) (4)

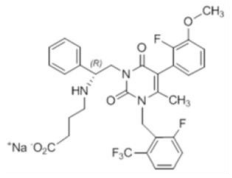
(b) (4) has the following structural formula:




(b) (4) is a white to off white to light yellow powder and is freely soluble in water.

TRADENAME 150 mg tablets contain the following inactive ingredients: mannitol, sodium carbonate monohydrate, pregelatinized starch, povidone, magnesium stearate, polyvinyl alcohol, titanium dioxide, polyethylene glycol, talc, and carmine high tint. The 150 mg tablets are light pink.

TRADENAME 200 mg tablets contain the following inactive ingredients: mannitol, sodium carbonate monohydrate, pregelatinized starch, povidone, magnesium stearate, polyvinyl alcohol, titanium dioxide, polyethylene glycol, talc, and iron oxide red. The 200 mg tablets are light orange.

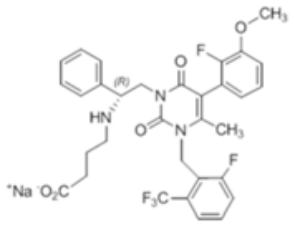
| Item | Information Provided in NDA | Reviewer's Comment and Recommendations |
|---|---|---|
| Proprietary name and established name | TRADENAME (elagolix) | Provided.<br><br>**Satisfactory** |
| Dosage form and route of administration | TRADENAME 150 mg tablets<br>TRADENAME 200 mg tablets | Rout of administration is not provided.<br><br>**Unsatisfactory** |
| Active moiety expression of strength with equivalence statement (if applicable) | Not provided | Not provided.<br><br>**Unsatisfactory** |
| Inactive ingredient information (quantitative, if injectables 21CFR201.100(b)(5)(iii)), listed by USP/NF names (if any) in alphabetical order (USP <1091>) | TRADENAME 150 mg tablets contain the following inactive ingredients: mannitol, sodium carbonate monohydrate, pregelatinized starch, povidone, magnesium stearate, polyvinyl alcohol, titanium dioxide, polyethylene glycol, talc, and carmine high tint. The 150 mg tablets are light pink.<br><br>TRADENAME 200 mg tablets contain the following inactive ingredients: mannitol, sodium carbonate monohydrate, pregelatinized starch, povidone, magnesium stearate, polyvinyl alcohol, titanium dioxide, polyethylene glycol, talc, and iron oxide red. The 200 mg tablets are light orange. | Provided.<br><br>**Satisfactory** |
| Statement of being sterile (if applicable) | Not applicable | Not applicable |
| Pharmacological/ therapeutic class | Not provided | Not provided.<br><br>**Unsatisfactory** |
| Chemical name, structural formula, molecular weight | sodium 4-({(1R)-2-[5-(2-fluoro-3-methoxyphenyl)-3-{[2-fluoro-6-(trifluoromethyl)phenyl]methyl}-4-methyl-2,6-dioxo-3,6-dihydropyrimidin-1(2H)-yl]-1-phenylethyl}amino)butanoate.<br><br>Its molecular formula is $C_{32}H_{29}F_5N_3O_5Na$, which corresponds to a molecular weight of 653.58 (b) (4)<br><br>(b) (4) has the following structural formula:<br><br>  | The structural formula provided is for elagolix sodium (b) (4)<br><br>**Unsatisfactory** |
| If radioactive, statement of important nuclear characteristics. | Not applicable | Not applicable |

| | | |
|---|---|---|
| Other important chemical or physical properties (such as pKa or pH) | (b) (4) is a white to off white to light yellow powder and is freely soluble in water. | The API, elagolix sodium is a white to off white to light yellow powder and is freely soluble in water (b) (4)<br><br>**Unsatisfactory** |

This section must be revised to include, route of administration, active moiety expression of strength with equivalence statement, and pharmacological/ therapeutic class. Also (b) (4) must be replaced with "elagolix sodium" in the references to the structural formula and chemical or physical properties. The following revisions is suggested:

1) TRADENAME (elagolix) Tablets for oral administration contain elagolix sodium, the sodium salt of the active moiety elagolix. Elagolix sodium is a short-acting, nonpeptide small molecule, gonadotropin-releasing hormone (GnRH) receptor antagonist. Elagolix sodium is chemically described as sodium 4-({(1R)-2-[5-(2-fluoro-3-methoxyphenyl)-3-{[2-fluoro-6-(trifluoromethyl)phenyl]methyl}-4-methyl-2,6-dioxo-3,6-dihydropyrimidin-1(2H)-yl]-1-phenylethyl}amino)butanoate. Elagolix sodium has the molecular formula of $C_{32}H_{29}F_5N_3O_5Na$ and the molecular weight of 653.58. Elagolix free form has the molecular weight of 631.60.

2) Elagolix sodium has the following molecular structure:



3) TRADENAME 150 mg tablets are light pink, oblong, film-coated tablets with "EL 150" debossed on one side. Each tablet contains 155.2 mg of elagolix sodium (equivalent to 150 mg of elagolix) as the active ingredient and the following inactive ingredients: mannitol, sodium carbonate monohydrate, pregelatinized starch, povidone, magnesium stearate, polyvinyl alcohol, titanium dioxide, polyethylene glycol, talc, and carmine high tint. The 150 mg tablets are light pink.

4) TRADENAME 200 mg tablets are light orange, oblong, film-coated tablets with "EL 200" debossed on one side. Each tablet contains 207 mg of elagolix sodium (equivalent to 200 mg of elagolix) as the active ingredient and the following inactive ingredients: mannitol, sodium carbonate monohydrate, pregelatinized starch, povidone, magnesium stearate, polyvinyl alcohol, titanium dioxide, polyethylene glycol, talc, and iron oxide red. The 200 mg tablets are light orange.

## 3) #16: HOW SUPPLIED/STORAGE AND HANDLING

TRADENAME tablets are available in two strengths: 150 mg and 200 mg.

TRADENAME 150 mg tablets:

Each weekly blister pack contains 7 tablets of 150 mg (b) (4) .

Each carton contains 4 weekly blister packs for a total of 28 tablets (NDC 0074-0038-28).

TRADENAME 200 mg tablets:

Each weekly blister pack contains 14 tablets of 200 mg (b) (4)

Each carton contains 4 weekly blister packs for a total of 56 tablets (NDC 0074-0039-56).

Store at 2°C to 30°C (36°F to 86°F).

| Item | Information Provided in NDA | Reviewer's Comment and Recommendations |
|---|---|---|
| Strength of dosage form | Each weekly blister pack contains 7 tablets of 150 mg<br>Each weekly blister pack contains 14 tablets of 200 mg | Active moiety expression of strength with equivalence statement not provided.<br><br>**Unsatisfactory** |
| Available units (e.g., bottles of 100 tablets) | TRADENAME 150 mg tablets:<br>Each weekly blister pack contains 7 tablets of 150 mg (b) (4)<br>Each carton contains 4 weekly blister packs for a total of 28 tablets (NDC 0074-0038-28).<br><br>TRADENAME 200 mg tablets:<br>Each weekly blister pack contains 14 tablets of 200 mg (b) (4)<br>Each carton contains 4 weekly blister packs for a total of 56 tablets (NDC 0074-0039-56). | Provided.<br><br>**Satisfactory** |
| Identification of dosage forms, e.g., shape, color, coating, scoring, imprinting, NDC number | Not provided | Not provided.<br><br>**Unsatisfactory** |
| Special handling (e.g., protect from light) | Not applicable | Not applicable |
| Storage conditions | Store at 2°C to 30°C (36°F to 86°F) | Storage conditions should be revised to "store at 25ºC to 30ºC (77ºF to 86ºF), with excursion permitted 5ºC to 40ºC (41ºF to 104ºF)"<br><br>**Unsatisfactory** |
| Manufacturer/distributor name (21 CFR 201.1(h)(5)) | Manufactured by<br>AbbVie Inc.<br>North Chicago, IL 60064 | Provided at the end of the PI.<br><br>**Satisfactory** |

This section must be revised to include the identification of dosage form with an appropriate storage condition. The following revision is recommended:

TRADENAME tablets are available in two strengths: 150 mg and 200 mg (which are equivalent to 155.2mg and 207mg of elagolix sodium, respectively).

1) 150 mg tablets are light pink, oblong, film-coated tablets with "EL 150" debossed on one side. 150 mg tablets are packaged in weekly blister packs. Each blister pack contains 7 tablets supplying the drug product for one week (b) (4). 4 blister packs (total of 28 tablets) are packaged into a carton that provides the drug product for 4 weeks (NDC 0074-0038-28).
2) 200 mg tablets are light orange, oblong, film-coated tablets with "EL 200" debossed on one side. 200 mg tablets are packaged in weekly blister packs. Each

blister pack contains 14 tablets supplying the drug product for one week (b) (4) . 4 blister packs (total of 56 tablets) are packaged in a carton that provide the drug product for 4 weeks (NDC 0074-0039-56).

3) Store at 25ºC to 30ºC (77ºF to 86ºF), with excursion permitted 5ºC to 40ºC (41ºF to 104ºF)

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| Item | Information Provided in NDA | Reviewer's Comment and Recommendations |
|---|---|---|
| Proprietary name, established name (font size and prominence (21 CFR 201.10(g)(2)) | The trade name and established name are displayed. | The size and prominence of the establish name are inadequate.<br><br>**Unsatisfactory** |
| Dosage strength | 150mg and 200mg | Similar to established name the prominence is inadequate. The strength needs to include statement of equivalence.<br><br>**Unsatisfactory** |
| Net contents | 150mg: 7 tablets<br>200mg: 14 tablets | **Satisfactory** |
| "Rx only" displayed prominently on the main panel | Displayed. | **Satisfactory** |
| NDC number (21 CFR 207.35(b)(3)(i)) | Displayed. | **Satisfactory** |
| Lot number and expiration date (21 CFR 201.17) | The location on the blister pack wallet where the lot number and expiration will be placed has been designated. | The expiration date should be added to each individual blister.<br><br>**Unsatisfactory** |
| Storage conditions | Store at 2°C to 30°C (36°F to 86°F) is displayed. | Storage condition should be revised to "store at 25ºC to 30ºC (77ºF to 86ºF), with excursion permitted 5ºC to 40ºC (41ºF to 104ºF)"<br><br>**Unsatisfactory** |
| Bar code (21CFR 201.25) | Displayed. | **Satisfactory** |
| Name of manufacturer/distributor | Displayed. | **Satisfactory** |
| And others, if space is available | Additional dosing information is provided. | **Satisfactory.** |

Revise the immediate container, blister labels to address the following:

1) Correct the size and prominence for the established name and dosage strength
2) Include the equivalence statement: "Trade name (elagolix) Tablets, 150mg" equivalent to 155.2mg elagolix sodium. And "Trade name (elagolix) Tablets, 200mg" equivalent to 207mg elagolix sodium.
3) Add the expiration period to each individual blister.
4) Revise the proposed storage conditions with "Store at 25ºC to 30ºC (77ºF to 86ºF), with excursion permitted 5ºC to 40ºC (41ºF to 104ºF)"

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

| Item | Information Provided in NDA | Reviewer's Comment and Recommendations |
|---|---|---|
| Proprietary name, established name (font size and prominence (21 CFR 201.10(g)(2)) | Provided. | The size and prominence of the establish name are inadequate.<br><br>**Unsatisfactory** |
| Dosage strength | Tablets 150mg<br>Tablets 200mg | Provided. However, the strength needs to include statement of equivalence.<br><br>**Unsatisfactory** |
| Net contents | 28 Tablets for 28 days<br>56 Tablets for 28 days | Provided.<br><br>**Satisfactory** |
| "Rx only" displayed prominently on the main panel | Displayed | Displayed.<br><br>**Satisfactory** |
| NDC number (21 CFR 207.35(b)(3)(i)) | Displayed | Displayed.<br><br>**Satisfactory** |
| Lot number and expiration date (21 CFR 201.17) | The location on the carton where the lot number and expiration will be placed has been designated. | Provided.<br><br>**Satisfactory** |
| Storage conditions | Store at 2°C to 30°C (36°F to 86°F) | Storage condition should be revised to "store at 25ºC to 30ºC (77ºF to 86ºF), with excursion permitted 5ºC to 40ºC (41ºF to 104ºF)"<br><br>**Unsatisfactory** |
| Bar code (21CFR 201.25) | Displayed | Displayed.<br><br>**Satisfactory** |
| Name of manufacturer/distributor | AbbVie Inc.<br>North Chicago, IL 60064<br><br>Product of Singapore | Displayed.<br><br>**Satisfactory** |
| And others, if space is available | (b) (4) | Provided<br><br>**Satisfactory** |

Revise the carton labels to address the following:

1) Correct the size and prominence for the established name and dosage strength
2) Include the equivalence statement: "Trade name (elagolix) Tablets, 150mg" equivalent to 155.2mg elagolix sodium. And "Trade name (elagolix) Tablets, 200mg" equivalent to 207mg elagolix sodium.
3) Revise the proposed storage conditions with the standard storage conditions of "Store at 25ºC to 30ºC (77ºF to 86ºF), with excursion permitted 5ºC to40ºC (41ºF to 104ºF)"

# III. LIST OF DEFICIENCIES:

## A. Regarding PI

**Full Prescribing Information**

**#3: Dosage Forms and Strengths**

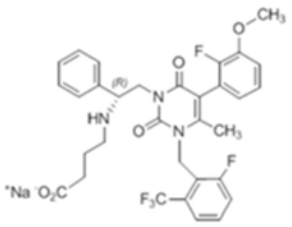
The dosage form and strength must be revised to include active moiety expression of strength with equivalence statement. The following revisions are recommended:

1) 150mg tablets are light pink, oblong, film-coated tablets with "EL 150" debossed on one side. Each tablet contains 155.2 mg of elagolix sodium equivalent to 150 mg of elagolix.
2) 200 mg tablets are light orange, oblong, film-coated tablets with "EL 200" debossed on one side. Each tablet contains 207 mg of elagolix sodium equivalent to 200 mg of elagolix.

**#11: Description**

This section must be revised to include, route of administration, active moiety expression of strength with equivalence statement, and pharmacological/ therapeutic class. Also (b) (4) must be replaced with "elagolix sodium" in the references to the structural formula and chemical or physical properties. The following revisions is suggested:

1) TRADENAME (elagolix) Tablets for oral administration contain elagolix sodium, the sodium salt of the active moiety elagolix. Elagolix sodium is a short-acting, nonpeptide small molecule, gonadotropin-releasing hormone (GnRH) receptor antagonist. Elagolix sodium is chemically described as sodium 4-({(1R)-2-[5-(2-fluoro-3-methoxyphenyl)-3-{[2-fluoro-6-(trifluoromethyl)phenyl]methyl}-4-methyl-2,6-dioxo-3,6-dihydropyrimidin-1(2H)-yl]-1-phenylethyl}amino)butanoate. Elagolix sodium has the molecular formula of $C_{32}H_{29}F_5N_3O_5Na$ and the molecular weight of 653.58. Elagolix free form has the molecular weight of 631.60.
2) Elagolix sodium has the following molecular structure:



3) TRADENAME 150 mg tablets are light pink, oblong, film-coated tablets with "EL 150" debossed on one side. Each tablet contains 155.2 mg of elagolix sodium (equivalent to 150 mg of elagolix) as the active ingredient and the following inactive ingredients: mannitol, sodium carbonate monohydrate, pregelatinized starch, povidone, magnesium stearate, polyvinyl alcohol, titanium dioxide, polyethylene glycol, talc, and carmine high tint. The 150 mg tablets are light pink.
4) TRADENAME 200 mg tablets are light orange, oblong, film-coated tablets with "EL 200" debossed on one side. Each tablet contains 207 mg of elagolix sodium (equivalent to 200 mg of elagolix) as the active ingredient and the following inactive ingredients: mannitol, sodium carbonate monohydrate, pregelatinized starch, povidone, magnesium stearate, polyvinyl alcohol, titanium dioxide, polyethylene glycol, talc, and iron oxide red. The 200 mg tablets are light orange.

**#16: How Supplied/Storage and Handling**

This section must be revised to include the identification of dosage form with an appropriate storage condition. The following revision is recommended:

TRADENAME tablets are available in two strengths: 150 mg and 200 mg (which are equivalent to 155.2mg and 207mg of elagolix sodium, respectively).
.

1) 150 mg tablets are light pink, oblong, film-coated tablets with "EL 150" debossed on one side. 150 mg tablets are packaged in weekly blister packs. Each blister pack contains 7 tablets (b) (4) . 4 blister packs (total of 28 tablets) are packaged into a carton that provides the drug product for 4 weeks (NDC 0074-0038-28).
2) 200 mg tablets are light orange, oblong, film-coated tablets with "EL 200" debossed on one side. 200 mg tablets are packaged in weekly blister packs. Each blister pack contains 14 tablets (b) (4) 4 blister packs (total of 56 tablets) are packaged in a carton that provide the drug product for 4 weeks (NDC 0074-0039-56).

3) Store at 25ºC to 30ºC (77ºF to 86ºF), with excursion permitted 5ºC to 40ºC (41ºF to 104ºF)

## B. Regarding of the Container/Carton Labels:

**a) Immediate container labels: Blister Wallets/Blisters:**

The following revisions should be made to the blister wallets and individual blisters:

1) Correct the size and prominence for the established name and dosage strength on the blister wallets
2) Include the equivalence statement on the blister wallets: "Trade name (elagolix) Tablets, 150mg" equivalent to 155.2mg elagolix sodium. And "Trade name (elagolix) Tablets, 200mg" equivalent to 207mg elagolix sodium.
3) Add the expiration date to each individual blister.
4) Replace the proposed storage conditions with the standard storage conditions of "Store at 25ºC to 30ºC (77ºF to 86ºF), with excursion permitted 5ºC to 40ºC (41ºF to 104ºF)" on the blister wallets.

**b) Carton labels:**

The following revisions should be made to the overpack cartons:

1) Correct the size and prominence for the established name and dosage strength
2) Include the equivalence statement: "Trade name (elagolix) Tablets, 150mg" equivalent to 155.2mg elagolix sodium. And "Trade name (elagolix) Tablets, 200mg" equivalent to 207mg elagolix sodium.
3) Replace the proposed storage conditions with the standard storage conditions of "Store at 25ºC to 30ºC (77ºF to 86ºF), with excursion permitted 5ºC to 40ºC (41ºF to 104ºF)"

## IV. OVERALL ASSESSMENT AND RECOMMENDATION:

- Multiple PI labeling deficiencies have been noted.
- Blister wallets labels as provided do not display the required immediate container information.
- The carton labels require revisions.

## Recommendation:

From the ONDP perspective, this application is ***not*** recommended for approval per 21 CFR 314.125(b)(6) until the deficiencies delineated above are satisfactorily resolved.

### *Primary Labeling Reviewer Name:*

Hamid Shafiei, Ph.D.
Reviewer, Branch V
DNDP II/ONDP/OPQ

### *Secondary Reviewer Name:*

I concur with Dr. Shafiei's assessment and his recommendation that the labels and labeling are ***not*** ready for approval in its present form per 21 CFR 314.125 (b)(6) from the ONDP perspective.

Moo-Jhong Rhee, Ph.D.
Chief, Branch V
DNDP II/ONDP/OPQ

Hamid Shafiei

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Moo Jhong Rhee

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