

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

213388Orig1s000

PRODUCT QUALITY REVIEW(S)

RECOMMENDATION

<input checked="" type="checkbox"/> Approval
<input type="checkbox"/> Approval with Post-Marketing Commitment
<input type="checkbox"/> Complete Response

NDA 213388

Assessment #1

Drug Product Name	ORIAHNN (elagolix, estradiol, and norethindrone acetate capsules; elagolix capsules)
Dosage Form	Capsules
Strength	<ul style="list-style-type: none"> • elagolix, estradiol and norethindrone acetate capsules 300 mg/1 mg/0.5 mg (AM dose) • elagolix capsules 300 mg (PM dose) [elagolix sodium, 310.5 mg, is equivalent to 300 mg elagolix free acid]
Route of Administration	Oral
Rx/OTC Dispensed	Rx
Applicant	AbbVie Inc.
US agent, if applicable	-
Application Type	505(b)(2)
NDA Classification Code*	Type 4, New combination (physical)
Combination Product	na

* Previously referred to as the "Chemistry Classification Code."

Submission(s) Assessed	Document Date	Discipline(s) Affected
Original NDA Submission (0001)	07/31/2019	All
Product Packaging Samples (0004)	09/26/2019	ONDP Labeling
Response (0006)	10/21/2019	Manufacturing
Amendment with Labeling (0007)	10/24/2019	ONDP Labeling
Response (0011)	12/13/2019	ONDP Labeling
Response (0015)	02/14/2020	Biopharmaceutics
Response (0016)	02/12/2020	Manufacturing
Response (0018)	03/09/2020	Manufacturing
Container Carton Labels (0020)	04/24/2020	ONDP Labeling
Amendment with Labeling (0021)	05/07/2020	ONDP Labeling
Container Carton Labels (0022)	05/14/2020	ONDP Labeling
Container Carton Labels (0023)	05/26/2020	ONDP Labeling

QUALITY ASSESSMENT TEAM

Discipline	Primary Assessment	Secondary Assessment
Drug Substance	Joseph Leginus	Donna Christner
Drug Product / Labeling	Mike Theodorakis	Moo-Jhong Rhee
Manufacturing	Zhao Wang	Yubing Tang
Microbiology	Zhao Wang	Yubing Tang
Biopharmaceutics	Kalpana Paudel	Vidula Kolhatkar
RBPM	Marquita Burnett	
ATL	Mark Seggel	
Laboratory (OTR)	na	na
Environmental	James Laurenson	Scott Furness

EXECUTIVE SUMMARY

I. RECOMMENDATIONS AND CONCLUSION ON APPROVABILITY

AbbVie's 505(b)(2) New Drug Application 213388 for ORIAHNN (elagolix, estradiol, and norethindrone acetates capsules; elagolix capsules) is recommended for APPROVAL from the OPQ perspective.

Sufficient chemistry, manufacturing and controls information and supporting data have been provided in accordance with 21 CFR 314.50 to ensure the identity, strength, quality, purity, and bioavailability of the drug product.

From the CMC perspective, the revised drug product labels as submitted on May 26, 2020 and the labeling as submitted May 7, 2020 are accurate, complete and comply with the requirements under 21 CFR 201.

All drug substance and product-related manufacturing, packaging and testing facilities have acceptable drug CGMP status. An overall manufacturing inspection recommendation of APPROVE was issued on March 15, 2020. The recommendation remains current as of this review.

An expiration dating period of 24 months for product stored in (b) (4)/aluminum foil blisters at 20°C to 25°C is granted.

The claimed categorical exclusion from the environmental assessment requirements under 21 CFR Part 25.31(b) is acceptable.

II. SUMMARY OF QUALITY ASSESSMENTS

A. Product Overview

Product Description:

ORIAHNN (elagolix, estradiol and norethindrone acetate capsules; elagolix capsules) is a fixed-dose combination indicated for the management of heavy menstrual bleeding (HMB) associated with uterine fibroids. Elagolix is a gonadotropin-releasing hormone (GnRH) receptor antagonist. Estradiol (E2) and norethindrone acetate (NETA) are included in the product to supplement endogenous estrogen and progesterone, respectively. This "add-back therapy" is intended to minimize bone mineral density loss and hot flashes seen during treatment with elagolix.

The product (kit) consists of 300 mg elagolix capsules and capsules containing 300 mg elagolix, 1 mg estradiol and 0.5 mg norethindrone acetate. One capsule containing elagolix alone (referred to as the 'PM' capsule) is administered in the evening, while one elagolix, E2 and

NETA capsule (the 'AM' capsule) is taken in the morning. The capsules are supplied in a carton (monthly overpack) of 4 weekly blister cards (booklet), each with 7 'AM' capsules and 7 'PM' capsules.

The capsules are manufactured by the encapsulation of 300 mg elagolix tablets and (b) (4) estradiol and norethindrone acetate (b) (4) tablets, 1 mg/0.5 mg.

Background:

AbbVie's 505(b)(1) NDA 210450 for ORILISSA (elagolix) tablets, 150 mg and 200 mg, was approved July 23, 2018. ORILISSA is indicated for the management of moderate to severe pain associated with endometriosis.

ACTIVEVELLA (estradiol and norethindrone acetate) Tablets 1 mg/ 0.5 mg was approved November 18, 1998 under NDA 20907. This estrogen and progestin combination is indicated for the treatment of vasomotor symptoms (VMS) and symptoms of vulvar-vaginal atrophy (VVA). It is also indicated for the prevention of postmenopausal osteoporosis.

While elagolix tablets and estradiol and norethindrone acetate tablets are commercially available, AbbVie's new fixed-dose combination product, ORIAHNN, the higher strength elagolix formulation provides the desired treatment effect and addresses the hypoestrogenic effects of elagolix in a single product.

(b) (4)

The manufacture of the 300 mg elagolix capsules and the FDC capsules begins with the manufacture of the 300 mg film-coated tablets. Unlike the manufacture of ORILISSA 150 mg and 200 mg tablets, (b) (4)

(b) (4)

the 300 mg tablets.

It should be noted that several different formulations and presentations (tablet or capsule (i.e., encapsulated tablets); individually or combined), were used in the clinical studies conducted in support of the HMB indication. Different manufacturers were involved at different stages of development. (b) (4)

(b) (4)

(b) (4)

The phase 3 to commercial manufacturing site change was supported by comparison of in vitro dissolution profiles.

Proposed Indication(s) including Intended Patient Population	ORIAHNN is (b) (4) indicated for the management of heavy menstrual bleeding associated with uterine leiomyomas (fibroids).
Duration of Treatment	Duration may be limited to up to 2 years.
Maximum Daily Dose	<ul style="list-style-type: none"> • Elagolix: 600 mg (300 mg twice daily) • Estradiol: 1 mg (1 mg once daily) • Norethindrone Acetate: 0.5 mg (0.5 mg once daily)
Alternative Methods of Administration	Not applicable.

B. Quality Assessment Overview

Drug Substance: Adequate

The chemistry, manufacturing and controls (CMC) for elagolix, as elagolix sodium, is by cross-reference to AbbVie’s NDA 210450, approved July 23, 2018. Elagolix CMC is current as of this review.

Estradiol drug substance CMC and norethindrone acetate drug substance CMC is by cross-reference to Amneal’s NDA 20907, approved November 18, 1998. Amneal cross-references DMFs (b) (4) for estradiol and norethindrone acetate CMC (b) (4).

All drug substances used in the manufacture of ORIAHNN are adequate from the drug substance review perspective. See the attached assessment (IQA Chapter I) for details.

Drug Product: Adequate

ORIAHNN consists of elagolix capsules co-packaged with elagolix, estradiol and norethindrone acetate capsules. Each capsule contains a 300 mg elagolix tablet. In addition to an elagolix tablet, the elagolix, estradiol and norethindrone acetate capsules also contain an (b) (4) estradiol and norethindrone acetate 1 mg / 0.5 mg tablet.

The chemistry, manufacturing and controls of (b) (4) (b) (4). The product is used without modification. Amneal has provide a Letter of Authorization allowing cross-reference to the CMC information in their NDA. Information can also be found in the current prescribing information for ACTIVELLA tablets. Estradiol and Norethindrone Acetates Tablets are the subject of a USP monograph. [Note: Ownership of ACTIVELLA was transferred from Novo Nordisk to Amneal in June 2014. In November 2014, Amneal launched the first authorized generic of ACTIVELLA as LOPREEZA. Novo Nordisk continued to manufacturer the drug product. Supplement S-023 to NDA 20907, providing for the manufacture of ACTIVELLA tablets, 1 mg / 0.5 mg at (b) (4), was approved on July 29, 2019.]

Elagolix capsules, 300 mg, and elagolix, estradiol and norethindrone capsules, 300 mg / 1 mg / 0.5 mg, are differentiated by capsule shell color (white / yellow [morning] printed with "EL 300 AM" and white / blue [evening] printed with "EL 300 PM").

Inactive ingredients in the elagolix tablet are anhydrous sodium carbonate, polyethylene glycol 3350, crospovidone, colloidal silicon dioxide, and magnesium stearate, (b) (4) (b) (4) polyvinyl alcohol, titanium dioxide, polyethylene glycol, and talc). The size no. 0 capsule shell consists of gelatin, titanium dioxide, and either yellow iron oxide and FD&C Blue #2 (blue capsule cap) or FD&C Red #40, FD&C Yellow #5, and FD&C Yellow #6 (yellow capsule cap). Capsules are printed with an edible, black iron oxide-based printing ink. All inactive ingredients meet CFR or compendial requirements and are suitable for use for this orally administered product. [Note that the film-coated elagolix tablets do not have any identifying imprint.]

Capsules are packaged in (b) (4) (b) (4) film blisters with aluminum foil lidding.

The regulatory specifications for the capsules include tests for description, identification of each active ingredient, assay of each active, uniformity of dosage units (elagolix, by weight variation), impurities (degradation products) related to each active, dissolution of each active, water content (elagolix tablet), and microbiological quality. Overall, the tests, analytical procedures and acceptance criteria are suitable for ensuring the identity, strength, purity, quality and bioavailability of the product. The proposed acceptance criteria for elagolix degradation products are supported by nonclinical qualification data (see Leslie McKinney's March 24, 2020 Nonclinical Review). Note that verification of the analytical procedures by FDA's St. Louis laboratory was deemed unnecessary due to the relatively straightforward nature of the tests and the adequacy of the methods validation reported by the Applicant.

Based on 12-months long term and 6 months accelerated stability data from three registration batches manufactured by (b) (4) using elagolix granules manufactured by AbbVie Deutschland GmbH, and three-months of commercial site-specific data from three batches of product manufactured at AbbVie Ltd., Puerto Rico, a 24-month expiration dating period for product stored at 20°C to 25°C in blister packaging is granted.

See IQA Chapter II for the detailed ONDP Drug Product assessment.

Environmental Assessment: Adequate

The OPQ/ONDP EA Team determined that AbbVie's claim for a categorical exclusion from the environmental assessment requirements in accordance 21 CFR 25.31(b), was adequately supported by the submitted EA data. However, as in NDA 210450 inclusion of environmentally protective disposal practices in the labeling, is recommended. See IQA Chapter II Drug Product for the assessment provided by the EA Team.

Labeling: Adequate

Deficiencies in the prescribing information (PI) and container/carton labels were identified. For example, the proposed formats of the product title and established names were inconsistent with FDA's January 2018 draft guidance "Product Title... in the Highlights of Prescribing Information...", USP established name and product monograph title standards, and other FDA labeling resources. The proposed use of slash marks and 'and,' for example, were problematic. Other deficiencies identified included inadequate presentation of the storage condition statements, inadequate product description, and inadequate declaration of FD&C Yellow #5 and FD&C Yellow #6 (per 21 CFR 201.20). In collaboration with DUOG and

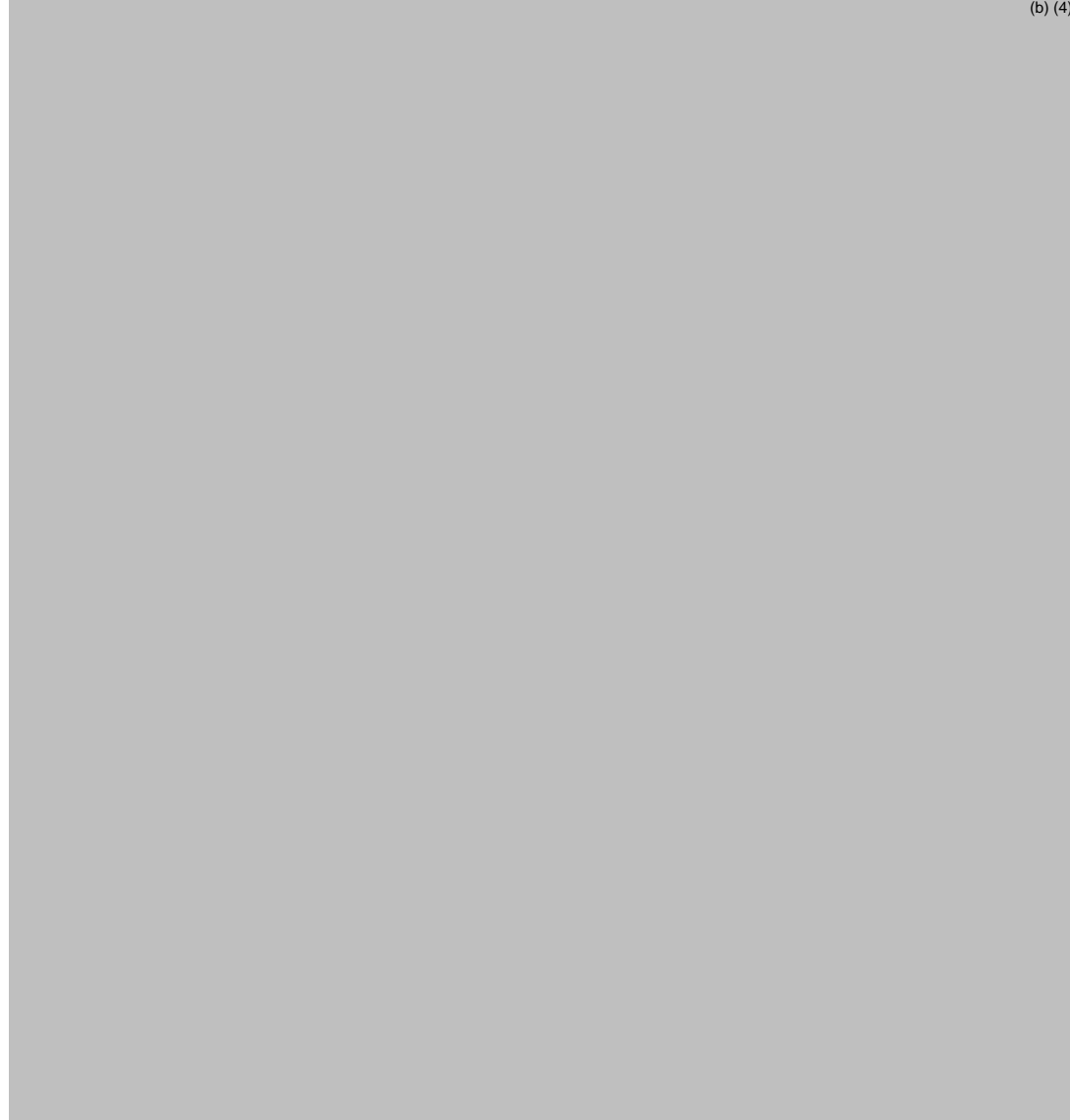
DMEPA, these and other deficiencies were conveyed to AbbVie along with recommended revisions.

The revised container and carton labels as submitted May 14, 2020 conform to the requirements under 21 CFR 201 and are deemed acceptable. Likewise, the revised prescribing information as submitted May 7, 2020 is deemed acceptable (see IQA Chapter IV, Labeling and the May 15, 2020 Addendum). Additional revisions to the container carton label were submitted on May 26, 2020. Further non-CMC revisions to the PI are anticipated. As of the data of this review, the labels and labeling are acceptable from the ONDP CMC perspective.

Manufacturing: Adequate

Process:

(b) (4)



**Biopharmaceutics: Adequate**

The Biopharmaceutics review focused on the evaluation of dissolution method and acceptance criteria for Elagolix, E2 and NETA in the FDC capsules, bridging between the commercial (to-be-marketed) and pivotal clinical formulations, and in vitro testing to support manufacturing site changes.

Drug release testing is performed in accordance with USP <711> Dissolution. The dissolution test and acceptance criteria for E2 and NETA in the FDC capsules are based on Test 1 of the USP monograph for Estradiol and Norethindrone Acetate Tablets (1 mg / 0.5 mg). The test for release of elagolix (from elagolix capsules and from the FDC capsules) is

performed with USP Apparatus I (basket) at 100 rpm and 900 mL of 0.05 M sodium phosphate pH 6.8 medium. The acceptance criterion is Q = (b) (4) % in 60 minutes. Tier-2 dissolution testing (enzymes added) is deemed acceptable with the same acceptance criteria as for Tier-1 testing.

In vitro release testing demonstrated that there is no interaction between the ACTIVELLA tablet and the elagolix tablet in the FDC.

Based on discussions during the IND stage, AbbVie conducted pivotal BE studies (Study M16-856 for the FDC elagolix/E2/NETA capsule (morning dose; formulation FDC4) and Study M19-648 for the elagolix capsule (evening dose; formulation EN03) to bridge the phase 3 investigational products and the commercial product. Refer to the Clinical Pharmacology Review.

The phase 3 to commercial manufacturing site change was supported by comparative in vitro dissolution profile data.

From Biopharmaceutics perspective, NDA 213388 is recommended for APPROVAL. See IQA Chapter VI Biopharmaceutics for details.

Microbiology (if applicable): Adequate

The product contains gelatin and the tablet manufacturing has an (b) (4) [redacted]
[redacted]
[redacted]
[redacted]
[redacted] See IQA Chapter V, Manufacturing Integrated Assessment for OPMA's assessment of the microbiological controls.

C. Risk Assessment

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**	
ELAGOLIX CAPSULES						
Purity	• Raw materials	L	• Drug substance purity controlled per the established drug substance control strategy	Adequate		
Description (Appearance)	• Raw materials, formulation, process	L	• Control of incoming bulk capsules • Encapsulation process and equipment	Adequate		
Identity	• CGMPs	L	(b) (4)	Adequate		
Assay (Potency)	• Raw materials, formulation, process	L		Adequate		
Uniformity of dosage units	• Raw materials, formulation, process	L		Adequate		
Degradation products	• Raw materials, formulation, process, CCS	L		Adequate	(b) (4)	
Solid state	-	-		Adequate		
Dissolution	• Raw materials, formulation, process, CCS	M		Adequate	(b) (4)	
Microbiological quality	• Raw materials, formulation, process, CCS	L		Adequate		
Water content	• Raw materials, formulation, process, CCS	L		Adequate	(b) (4)	
FDC CAPSULES						
Elagolix Tablets	See ELAGOLIX CAPSULES above				Adequate	
	(b) (4)			Adequate	(b) (4)	
CO-PACKAGED CAPSULES						
	• Packaging materials and process		Vision system to prevent packaging errors during commercial production. Capsule	Adequate		

*Risk ranking applies to product attribute/CQA

**For example, critical controls, underlying control strategies assumptions, post marketing commitment, knowledge management post approval, etc.

*** See NDA Filing Review 09/27/2019

CCS: container/closure system

D. List of Deficiencies for Complete Response

1. Overall Quality Deficiencies (Deficiencies that affect multiple sub-disciplines)

na

2. Drug Substance Deficiencies

na

3. Drug Product Deficiencies

na

4. Labeling Deficiencies

na

5. Manufacturing Deficiencies

na

6. Biopharmaceutics Deficiencies

na

7. Microbiology Deficiencies

na

8. Other Deficiencies (Specify discipline, such as Environmental)

na

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Application Technical Lead Name and Date:

Mark R. Seggel, Ph.D. May 8, 2020
CMC Lead (acting)

{see electronic signature page}

QUALITY ASSESSMENT DATA SHEET

1. RELATED/SUPPORTING DOCUMENTS

A. DMFs:

DMF #	Type	Holder	Item Referenced	Status	Date Assessment Completed	Comments
(b) (4)	III	(b) (4)	(b) (4)	Adequate	05/20/2018	NDA also includes sufficient info to support use
	III			Adequate	02/18/2010 09/26/2014	NDA also includes sufficient info to support use

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

B. OTHER DOCUMENTS: *IND, RLD, RS, Approved NDA*

Application Number	Document(s)	Description
IND 115528	Original IND, amendments, and associated reviews and meetings	Elagolix plus E2/NETA; treatment of uterine fibroids (AbbVie)
IND 64802	Original IND, amendments, and associated reviews and meetings (All investigational product CMC by cross-reference to IND 64802)	Elagolix; treatment of endometriosis (AbbVie)
IND (b) (4)	Original IND, amendments, and associated reviews and meetings	(b) (4)
NDA 210450	Original NDA	Elagolix tablets, AP 07/23/2018 (AbbVie)
NDA 20907	Original NDA	ACTIVEVILLA (E2/NETA tablets), AP 11/18/1998 (Amneal Pharm. Product formerly owned and manufactured by Novo Nordisk)

2. CONSULTS

Discipline	Status	Recommendation	Date	Assessor
Biostatistics	na			
Nonclinical	Complete	Impurity levels qualified	03/24/2020	L. McKinney
CDRH-OPEQ	na			
Clinical	na			
Other	na			

CHAPTERS: Primary Quality Assessment

CHAPTER I: Drug Substance

CHAPTER II: Drug Product

CHAPTER III: Environmental Assessment (see Ch. II)

CHAPTER IV: Labeling

CHAPTER V: Manufacturing Integrated Assessment

CHAPTER VI: Biopharmaceutics

CHAPTER VII: Microbiology (see Ch. V)

CHAPTER VIII: Additional Quality Disciplines (Not applicable)



Mark
Seggel

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CHAPTER IV: LABELING
[IQA NDA Assessment Guide Reference](#)

List of Submissions Reviewed and Discipline Reviews Cited:

Document Reviewed (eCTD #)	Dated Received	
eCTD-0001 (SDN-1) (ORIG-1)	07/31/2019	
eCTD-0004 (SDN-4) (GI-1)	09/26/2019	
eCTD-0005 (SDN-5) (GI-1)	10/08/2019	
eCTD-0007 (SDN-7) (ORG-1)	10/24/2019	

1.0 PRESCRIBING INFORMATION

The quality related aspects of the prescribing information are provided in eCTD-ORIG 1 dated 07/31/2019 and it is summarized below. On December 26, 2019 ORIAHNN was approved as tradename for this drug product by the Division of Medication Error Prevention and Analysis (DMEPA). The labeling for this drug product should be revised accordingly.

1.1 HIGHLIGHTS of PRESCRIBING INFORMATION

1. TITLE

TRADENAME (elagolix, estradiol and norethindrone acetate capsules, elagolix capsule), for oral use
Initial U.S. Approval: 20YY

2. DOSAGE FORMS and STRENGTHS

AM capsule: elagolix 300 mg/estradiol 1 mg/norethindrone acetate 0.5 mg.

PM Capsule: elagolix 300 mg.

Item	Information Provided in the NDA	Assessor's Comments
Product Title in Highlights: Drug product name §201.57(a)(2)		
Proprietary name	Tradename capsules	Acceptable. The tradename, ORIAHNN has been approved by FDA as proprietary name.

		<p>ORIAHNN co-packaged with two capsules:</p> <ol style="list-style-type: none"> 1. The morning (AM) capsule that contains elagolix, estradiol, norethindrone acetate. 2. The evening (PM) capsule that contains elagolix.
Established name(s)	(elagolix, estradiol, norethindrone acetate capsules; elagolix capsule) for oral use.	Not acceptable. It should be revised to: (elagolix, estradiol, and norethindrone acetate capsules; elagolix capsules), co-packaged for oral use.
Route of administration	Oral. AbbVie added to the name of the drug product “for oral use”.	Acceptable.
Controlled drug substance symbol	N/A	N/A
Initial U.S. Approval	20YY	Not Acceptable. It should indicate the year that this drug product is approved.
Dosage Forms and Strengths Heading in Highlights §201.57(a)(8)		
Summary of the dosage form(s) and strength(s) in metric system.	<p>AM capsule: elagolix 300 mg/estradiol 1 mg/norethindrone acetate 0.5 mg.</p> <p>PM Capsule: elagolix 300 mg.</p>	<p>Not Acceptable.</p> <p>It should be revised to: “The morning (AM) capsule is white and yellow, printed with “EL300 AM” on the bottom part of the capsule. It contains 300 mg elagolix, 1 mg estradiol and 0.5 mg norethindrone acetate.</p> <p>The evening (PM) capsule is white and light blue, printed with “EL300 PM” on the bottom part of the capsule. It contains 300 mg elagolix.”</p>

Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state “functionally scored”	N/A	N/A
For injectable drug products for parental administration, use appropriate package type term (e.g., single-dose, multiple-dose, single-patient-use). Other package terms include pharmacy bulk package and imaging bulk package.	N/A	N/A

1.2 FULL PRESCRIBING INFORMATION

1.2.1 Section 2 (DOSAGE and ADMINISTRATION)

Item	Information Provided in the NDA	Assessor’s Comments
DOSAGE and ADMINISTRATION section		
Special instructions for product preparation (e.g., reconstitution and resulting concentration, dilution, compatible diluents, storage conditions needed to maintain the stability of the reconstituted or diluted product)	N/A	N/A

1.2.2 Section 3 (DOSAGE FORMS and STRENGTHS)

AM Capsule: elagolix 300 mg/ estradiol 1 mg/ norethindrone acetate 0.5 mg.

PM Capsule: elagolix 300 mg.

Item	Information Provided in the NDA	Assessor's Comments
DOSAGE FORMS and STRENGTHS section		
Available dosage form(s)	Capsules	Acceptable
Strength(s) in metric system	AM Capsule: elagolix 300 mg/ estradiol 1 mg/ norethindrone acetate 0.5 mg. PM Capsule: elagolix 300 mg.	Acceptable. Strength for both capsules is expressed as per capsule. The slashes (/) should be replaced by commas (,).
If the active ingredient is a salt, apply the USP Salt Policy per FDA Guidance	The elagolix is active moiety of elagolix sodium	Acceptable. The strength is based on the active moiety per previously approved labeling for NDA 210450, ORILISSA (elagolix) Tablets (150 mg and 200 mg) and a proper equivalency statement should be expressed in the Description section.
A description of the identifying characteristics of the dosage forms, including shape, color, coating, scoring, and imprinting		Not Acceptable. ORIAHNN consists of two capsules: The morning (AM) capsule is white and yellow, printed on the bottom part of the capsule with "EL300 AM" It contains 300 mg elagolix, 1 mg estradiol and 0.5 mg norethindrone acetate. The evening (PM) capsule is white and light blue, printed on the bottom part of the capsule with "EL300 PM" It contains 300 mg elagolix.
Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state "functionally scored"	N/A	N/A

For injectable drug products for parental administration, use appropriate labeling term (e.g., single-dose, multiple-dose, single-patient-use). Other package type terms include pharmacy bulk package and imaging bulk package.	N/A	N/A
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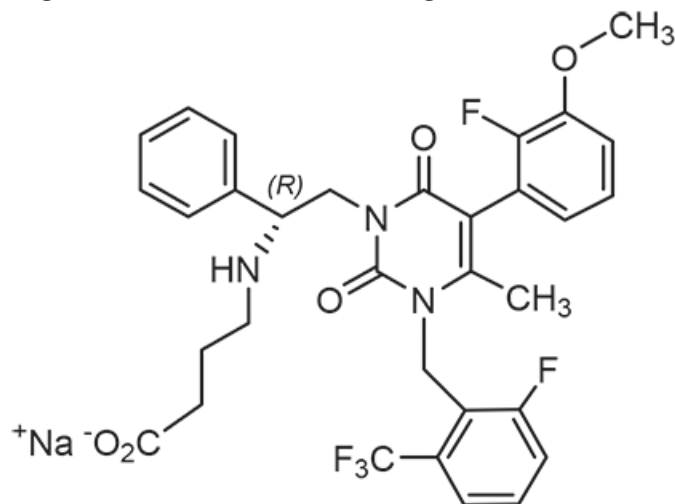
1.2.3 Section 11: DESCRIPTION

TRADENAME consists of two capsules: one to be taken in the morning (AM) and one to be taken evening (PM). The AM capsule is white and yellow and contains elagolix 300 mg and estradiol/norethindrone acetate 1 mg/0.5 mg. The PM capsule is white and blue and contains elagolix 300 mg.

Elagolix

TRADENAME (b) (4) sodium, (b) (4) salt of the active moiety elagolix. (b) (4) a nonpeptide small molecule, GnRH receptor antagonist. Elagolix sodium is chemically described as 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. Elagolix sodium has a molecular formula of C₃₂H₂₉F₅N₃O₅Na and a molecular weight of 653.58. Elagolix free acid has a molecular weight of 631.60.

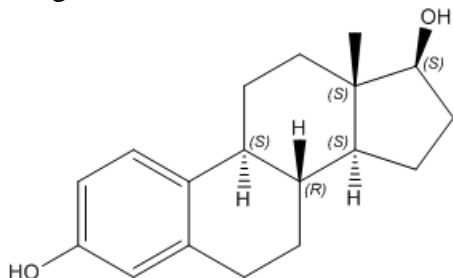
Elagolix sodium has the following structural formula:



Elagolix sodium is a white to off-white to light yellow powder and is freely soluble in water.

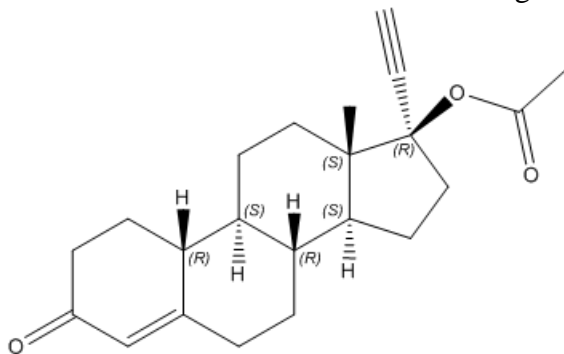
Estradiol

Estradiol (E2), an estrogen, is a white or almost white crystalline powder. Its chemical name is estra-1, 3, 5 (10)-triene-3, 17 β -diol with the empirical formula of C₁₈H₂₄O₂, and molecular weight of 272.38. The structural formula of E2 is as follows:



Norethindrone acetate

Norethindrone acetate (NETA), a progestin, is a white or yellowish white crystalline powder. Its chemical name is 17 β -acetoxymethyl-19-nor-17 α -pregn-4-en-20-yn-3-one with the empirical formula of C₂₂H₂₈O₃ and molecular weight of 340.46.



TRADENAME AM capsules contain the following inactive ingredients: anhydrous sodium carbonate, polyethylene glycol 3350, crospovidone, colloidal silicon dioxide, magnesium stearate, polyvinyl alcohol, titanium dioxide, polyethylene glycol, talc, purified water, lactose monohydrate, starch (corn), copovidone, talc, hypromellose, triacetin, and gelatin capsule shell. The capsule shell contains the following ingredients: FD&C Red #40, FD&C Yellow #5, FD&C Yellow #6, titanium dioxide, gelatin, and edible printing ink (shellac, dehydrated alcohol, isopropyl alcohol, butyl alcohol, propylene glycol, strong ammonia solution, black iron oxide, potassium hydroxide purified water).

TRADENAME PM capsules contain the following inactive ingredients: anhydrous sodium carbonate, polyethylene glycol 3350, crospovidone, colloidal silicon dioxide, magnesium stearate, polyvinyl alcohol, titanium dioxide, polyethylene glycol, and talc, purified water, and gelatin capsule shell. The capsule shell contains the following ingredients: FD&C Blue #2, FDA/E172 yellow iron oxide, titanium dioxide, gelatin, and edible printing ink (shellac, dehydrated alcohol, isopropyl alcohol, butyl alcohol, propylene glycol, strong ammonia solution, black iron oxide, potassium hydroxide purified water).

Item	Information Provided in the NDA	Assessor's Comments
DESCRIPTION section		
Proprietary and established names [21 CFR 201.57(c)(12)(i)(A)]	Tradename capsules	Acceptable Tradename and established name should be revised to, “ORIAHNN (elagolix, estradiol, and norethindrone acetate capsules; elagolix capsules), co-packaged for oral use”
Dosage form(s) and route(s) of administration [21 CFR 201.57(c)(12)(i)(B)]	Capsules, Oral	Acceptable
If the active ingredient is a salt, apply the USP Salt Policy and include the equivalency statement per FDA Guidance. [FD&C Act 502(e)(1)(A)(ii), 21 CFR 201.10(d)(1), 21 CFR 201.100(b)(4), USP <1121>]	Elagolix is present as the sodium salt. The statement “each TRADENAME capsule contains 300 mg elagolix equivalent to 310 mg elagolix sodium” has been included on the carton label <u>only</u> .	Not acceptable. The strength of the drug substance elagolix is correctly expressed in terms of the free acid and in terms of the sodium salt. The equivalency statement, “300 mg elagolix is equivalent to 310 mg elagolix sodium” should be included in the 11 DESCRIPTION section of the package insert.
List names of all inactive ingredients. Use USP/NF names. Avoid Brand names. [21 CFR 201.57(c)(12)(i)(C),]	Morning AM Capsule: anhydrous sodium carbonate, polyethylene glycol 3350, crospovidone, colloidal silicon dioxide, magnesium stearate, (b) (4) polyvinyl alcohol, titanium dioxide, polyethylene glycol, talc (b) (4) purified water, lactose monohydrate, starch (corn), copovidone, talc, hypromellose, triacetin, and gelatin capsule shell. The capsule shell contains the following ingredients: FD&C Red #40, FD&C	Not Acceptable. The proprietary name (b) (4) should be deleted from Section 11. DESCRIPTION. The (b) (4) Per 21 CFR §201.20(b) and (c) the presence of FD&C Yellow #5 , and FD&C Yellow #6 should be declared in the proper sections of labelling (labels and package insert).

	<p>Yellow #5, FD&C Yellow #6, titanium dioxide, gelatin, and printing ink (shellac, dehydrated alcohol, isopropyl alcohol, butyl alcohol, propylene glycol, strong ammonia solution, black iron oxide, potassium hydroxide purified water)</p> <p>Evening PM Capsule: anhydrous sodium carbonate, polyethylene glycol 3350, crospovidone, colloidal silicon dioxide, magnesium stearate, (b) (4)</p> <p>(b) (4) polyvinyl alcohol, titanium dioxide, polyethylene glycol, and talc (b) (4) purified water, and gelatin capsule shell. The capsule shell contains the following ingredients: FD&C Blue #2, FDA/E172 yellow iron oxide, titanium dioxide, gelatin, and printing ink (shellac, dehydrated alcohol, isopropyl alcohol, butyl alcohol, propylene glycol, strong ammonia solution, black iron oxide, potassium hydroxide purified water).</p>	
Statement of being sterile (if applicable)	N/A	N/A
Pharmacological/therapeutic class [21 CFR 201.57(c)(12)(i)(E),]	Elagolix, a gonadotropin releasing hormone (GnRH) receptor antagonist. Estradiol, estrogen Norethindrone acetate, a progestin	Acceptable
Chemical name, structural formula, molecular weight [21 CFR 201.57(c)(12)(i)(F),]	For each active pharmaceutical ingredient (API), elagolix sodium,	Acceptable

	estradiol and norethindrone acetate, the molecular and structural formula, and molecular weight are provided.	
If radioactive, statement of important nuclear characteristics.	N/A	N/A
Other important chemical or physical properties (such as pKa or pH)	N/A	N/A

Section 11 (DESCRIPTION) Continued

Item	Information Provided in the NDA	Assessor's Comments
For oral prescription drug products, include gluten statement if applicable	N/A	N/A
Remove statements that may be misleading or promotional (e.g., "synthesized and developed by Drug Company X," "structurally unique molecular entity")	N/A	N/A

1.2.4 Section 16 (HOW SUPPLIED/STORAGE and HANDLING)

TRADENAME consists of two capsules: one to be taken in the morning (AM) and one to be taken in the evening (PM).

TRADENAME AM capsules are white and yellow, printed with "EL 300 AM" and contain elagolix/estradiol/norethindrone acetate 300 mg/1 mg/0.5 mg.

TRADENAME PM capsules are white and light blue, printed with "EL 300 PM" and contain elagolix 300 mg.

TRADENAME is packaged in weekly blister packs. Each blister pack contains seven AM capsules and seven PM capsules. Four blisters are packaged into a carton (NDC 0074-1017-56).

Store at 20° - 25° C (68° - 77° F) [see USP Controlled Room Temperature]. Dispose unused medication via a take-back option if available. Otherwise, follow FDA instructions for disposing medication in the household trash,

Item	Information Provided in the NDA	Assessor's Comments
HOW SUPPLIED/STORAGE and HANDLING section		
Available dosage form(s)	Capsules,	Acceptable.
Strength(s) in metric system	<p>Morning (AM) capsule: elagolix 300 mg estradiol 1 mg, norethindrone acetate 0.5 mg.</p> <p>Evening (PM) capsule elagolix 300 mg.</p>	<p>Acceptable.</p> <p>Replace slashes (/) with commas (,).</p>
Available units (e.g., bottles of 100 tablets)	It is packaged in weekly blister packs. Each blister pack contains seven AM capsules and seven PM capsules. Four blisters are packaged into a carton	Acceptable.
Identification of dosage forms, e.g., shape, color, coating, scoring, imprinting, NDC number	<p>AM capsules are white and yellow, printed with "EL 300 AM" and contain elagolix/estradiol/norethindrone acetate 300 mg/1 mg/0.5 mg.</p> <p>PM capsules are white and light blue, printed with "EL 300 PM" and contain elagolix 300 mg.</p> <p>NDC 0074-1017-56</p>	<p>Acceptable.</p> <p>Replace slashes (/) with commas (,).</p>
Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state "functionally scored"	N/A	N/A
For injectable drug products for parental administration, use appropriate package type term (e.g., single-dose, multiple-dose, single-patient-use). Other package terms include pharmacy bulk package and imaging bulk package.	N/A	N/A

Section 16 (HOW SUPPLIED/STORAGE AND HANDLING) (Continued)

Item	Information Provided in the NDA	Assessor's Comments
Special handling about the supplied product (e.g., protect from light, refrigerate). If there is a statement to "Dispense in original container," provide reason why (e.g. to protect from light or moisture, to maintain stability, etc.)	N/A	N/A
If the product contains a desiccant, ensure the size and shape differ from the dosage form and desiccant has a warning such as "Do not eat."	N/A	N/A
Storage conditions. Where applicable, use USP storage range rather than storage at a single temperature.	Store at 20° - 25°C (68° - 77°F) [see USP Controlled Room Temperature].	Not Acceptable: Excursion statement should be included per USP. The storage conditions should be revised to read "Store at 20C° to 25°C (68F° to 77°F), excursions permitted to 15C° to 30°C (59° to 86°F). [See USP Controlled Room Temperature]"
Latex: If product does not contain latex and manufacturing of product and container did not include use of natural rubber latex or synthetic derivatives of natural rubber latex, state: "Not made with natural rubber latex. Avoid statements such as "latex-free."	N/A	N/A
Include information about child-resistant packaging	No information about child resistant packaging	Not Acceptable: The statement "Keep all medicines out of the reach of children." Should be included in the section.

1.2.5 Other Sections of Labeling

The Precaution section of the Prescribing Information should include a warning statement for the presence of FD&C Yellow #5.

1.2.6 Manufacturing Information After Section 17 (for drug products)

Item	Information Provided in the NDA	Assessor's Comments
Manufacturing Information After Section 17		
Name and location of business (street address, city, state and zip code) of the manufacturer, distributor, and/or packer	AbbVie Inc. North Chicago, IL 60064	Acceptable.

2.0 PATIENT LABELING

Assessment of Product Quality Related Aspects of Patient Labeling (e.g., Medication Guide, Patient Information, Instructions for Use):

Replace TRADENAME with ORIAHNN throughout the labeling.

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

Item	Information Provided in the NDA	Assessor's Comments about Carton Labeling
Proprietary name, established name, and dosage form (font size and prominence)	The font size for the proprietary name is double the size for the established name and dosage form. The prominence is adequate.	Acceptable.
Dosage strength	elagolix 300 mg, estradiol 1mg, norethindrone acetate 0.5 mg, and elagolix 300 mg.	Acceptable.
Route of administration	Oral	Acceptable.
If the active ingredient is a salt, include the equivalency statement per FDA Guidance	elagolix is present as elagolix sodium. The statement "elagolix 300 mg is equivalent to 310 mg elagolix sodium" is included in the labeling.	Acceptable.
Net contents (e.g. tablet count)	14 capsules per wallet/booklet. Supply for 7 days. Four (4) wallet/booklets per overpack carton has 56 capsules. Supply for 28 days.	Acceptable.
"Rx only" displayed on the principal display	It is displayed on both the Wallet/Booklet carton for the seven (7) days' supply and the overpack carton for the 28 days' supply.	Acceptable.
NDC number	NDC 0074-1074-56	Acceptable.
Lot number and expiration date	Both the wallet/Booklet carton (7 days) and the overpack carton (56 days) have a dedicated space for stamping the expiration date and the Lot Number.	Acceptable.
Storage conditions. If applicable, include a space on the carton labeling for the user to write the new BUD.	N/A	N/A
For injectable drug products for parental administration, use appropriate package type term (e.g., single-dose, multiple-dose, single-patient-use)	N/A	N/A

Other package terms include pharmacy bulk package and imaging bulk package which require “Not for direct infusion” statement.	N/A	N/A
If alcohol is present, must provide the amount of alcohol in terms of percent volume of absolute alcohol	N/A	N/A
Bar code	Bar Code is on the overpack carton	Acceptable.

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

tem	Information Provided in the NDA	Assessor's Comments about Carton Labeling
Proprietary name, established name, and dosage form (font size and prominence)	The font size for the proprietary name is double the size for the established name and dosage form. The prominence is adequate.	Acceptable.
Dosage strength	elagolix 300 mg, estradiol 1mg, norethindrone acetate 0.5 mg, and elagolix 300 mg.	Acceptable.
Route of administration	Oral	Acceptable.
If the active ingredient is a salt, include the equivalency statement per FDA Guidance	elagolix is present as elagolix sodium. The statement "elagolix 300 mg is equivalent to 310 mg elagolix sodium" is included in the labeling.	Acceptable.
Net contents (e.g. tablet count)	14 capsules per wallet/booklet. Supply for 7 days. Four (4) wallet/booklets per overpack carton has 56 capsules. Supply for 28 days.	Acceptable.
"Rx only" displayed on the principal display	It is displayed on both the Wallet/Booklet carton for the seven (7) days' supply and the overpack carton for the 28 days' supply.	Acceptable.
NDC number	NDC 0074-1074-56	Acceptable.
Lot number and expiration date	Both the wallet/Booklet carton (7 days) and the overpack carton (56 days) have a dedicated space for stamping the expiration date and the Lot Number.	Acceptable.
Storage conditions. If applicable, include a space on the carton labeling for the user to write the new BUD.	N/A	N/A
For injectable drug products for parental administration, use appropriate package type term (e.g., single-dose, multiple-dose, single-patient-use)	N/A	N/A

Other package terms include pharmacy bulk package and imaging bulk package which require “Not for direct infusion” statement.	N/A	N/A
If alcohol is present, must provide the amount of alcohol in terms of percent volume of absolute alcohol	N/A	N/A
Bar code	Bar Code is on the overpack carton	Acceptable.

Item	Information Provided in the NDA	Assessor’s Comments about Carton Labeling
Name of manufacturer/distributor	AbbVie Inc. North Chicago, IL 60064	Acceptable.
Medication Guide (if applicable)	The package insert has a Medication Guide part.	Acceptable.
No text on Ferrule and Cap Overseal	N/A	N/A
When a drug product differs from the relevant USP standard of strength, quality, or purity, as determined by the application of the tests, procedures, and acceptance criteria set forth in the relevant compendium, its difference shall be plainly stated on its label.	N/A	N/A
And others, if space is available	N/A	N/A

LIST OF DEFICIENCIES:**A. Regarding Highlight section of Prescribing Information:****1. TITLE**

- “TRADENAME (elagolix, estradiol and norethindrone acetate capsules, elagolix capsule), for oral use” should be revised to,

“ORIAHNN (elagolix, estradiol, and norethindrone acetate capsules; elagolix capsules), co-packaged for oral use.
- The initial approval date should indicate the date of approval of this application.

2. DOSAGE FORMS and STRENGTHS

- “AM capsule: elagolix 300 mg/estradiol 1 mg/norethindrone acetate 0.5 mg. PM Capsule: elagolix 300 mg.” should be revised to,

“The morning (AM) capsule is white and yellow, printed with "EL300 AM"00. It contains 300 mg elagolix, 1mg estradiol and 0.5 mg norethindrone acetate.

The evening (PM) capsule is white and light blue, printed with "EL300 PM". It contains 300 mg elagolix.”

B. Regarding Full Prescribing Information

- Replace throughout the labeling the TRADENAME with ORIAHNN.
- Throughout the Prescribing Information, the slashes(/) separating the active ingredient strengths in the established name should be replaced by commas (,).

1. Section 3 (DOSAGE and ADMINISTRATION)

- The statement, “AM Capsule: elagolix 300 mg/ estradiol 1 mg/ norethindrone acetate 0.5 mg. PM Capsule: elagolix 300 mg” should be revised to,

“ORIAHNN consists of two capsules:

The morning (AM) capsule is white and yellow, printed with “EL300 AM”. It contains 300 mg elagolix, 1 mg estradiol and 0.5 mg norethindrone acetate. The evening (PM) capsule is white and light blue, printed with “EL300 PM”. It contains 300 mg elagolix.”

- The statement, [REDACTED] (b) (4)
[REDACTED]
[REDACTED] (2.1)” should be revised to,

“One capsule (elagolix 300 mg, estradiol 1 mg, and norethindrone acetate 0.5 mg), in the morning and one capsule (elagolix 300 mg) in the evening for up to [REDACTED] (b) (4) months. (2.1).”

2. Section 11 (DESCRIPTION)

- An equivalency statement, “300 mg elagolix is equivalent to 310 mg elagolix sodium” should be included in the Description section
- A proper warning for the presence of FD&C Yellow #5 in the drug product should be stated in the **Warnings and Precautions** section in the Prescribing Information per 201.20 (b).

3. Section 16 (HOW SUPPLIED/STORAGE and HANDLING)

- Excursion statement should be included in the storage temperature as follows: Store at 20°C to 25°C (68°F to 77°F), excursions permitted to 15°C to 30°C (59°C to 86°F). [See USP Controlled Room Temperature]

C. Regarding Container and Carton labels

a. Container label

- The established name should be revised to read (elagolix, estradiol and norethindrone acetate capsules; elagolix capsules), co-packaged for oral use, 300 mg, 1 mg, and 0.5 mg; 300 mg.
- The proposed storage conditions should be revised to read “Store at [REDACTED] (b) (4), with excursion permitted 15°C to 30°C (59°F to 86°F), [See USP Controlled Room Temperature].”
- Per 21 CFR §201.20, the presence of FD&C Yellow #5, and FD&C Yellow #6, should be declared on the label.

b. Carton label:

- The established name should be revised to read (elagolix, estradiol and norethindrone acetate capsules; elagolix capsules), co-packaged for oral use. 300 mg, 1 mg, and 0.5 mg; 300 mg.
- The proposed storage conditions should be revised to read [REDACTED] (b) (4) [REDACTED], with excursion permitted 15°C to 30°C (59°F to 86°F), [See USP Controlled Room Temperature].”
- Per 21 CFR §201.20, the presence of FD&C Yellow #5, FD&C Yellow #6, should be declared on the label.

D. Regarding Patient Information

- Replace TRADENAME with ORIAHNN throughout the Patient Information.
- The established name, “(elagolix, estradiol and norethindrone acetate capsule co-formulated) and (elagolix capsule) for oral use” should be revised to,

“(elagolix, estradiol and norethindrone acetate capsules; elagolix capsules), co-packaged for oral use.”

Overall Assessment and Recommendation:**Primary Labeling Assessor Name and Date:**

As of this review, the application is not deemed ready for approval per 21 CFR 314.125 (b)(6) from the CMC labeling perspective until the delineated deficiencies listed in the **List of Deficiencies** are resolved satisfactorily.

Michael Theodorakis, Ph.D.
Senior Reviewer
Branch IV/DNDP II/ONDP

Secondary Assessor Name and Date (and Secondary Summary, as needed):

I agree with Dr. Theodorakis' assessment on the labels and labeling, and therefore, I concur with his recommendation that this application is not ready for approval from the CMC labeling perspective until the deficiencies are resolved satisfactorily.

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



Michael
Theodorakis

Digitally signed by Michael Theodorakis
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Moo Jhong
Rhee

Digitally signed by Moo Jhong Rhee
Date: 4/21/2020 07:59:21AM
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Memorandum

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

Date: May 15, 2020

From: Michael C. Theodorakis, Ph.D.
Drug Product Reviewer
Branch IV Division of New Drug Products II
Office of New Drug Products

Through: Moo-Jhong Rhee, Ph.D.
Chief, Branch IV
Division of New Drug Products II
Office of New Drug Products

To: Labeling Review #1 of NDA 213388

Subject: Finalized Label/Labeling of CMC Sections

Document Reviewed (eCTD #)	Dated Received
eCTD-0020 (SDN-20) (ORIG-1) Labeling	04/24/2020
eCTD-0022 (SDN-22) (TRIAGE-1) Labeling	05/14/2020

At the time when Labeling Review of this application was completed (04/21/2020), this NDA was not deemed ready for approval due to unresolved CMC label/labeling issues. On 04/24/2020, the Applicant submitted revised labels and labeling, however, the Applicant did not address satisfactorily the FDA comments for the labels of the primary and secondary container that were conveyed to the Applicant by FDA's General Advice Letter via email on April 13, 2020. On May 14, 2020, the Applicant addressed satisfactorily the remaining issues of the container labels per FDA recommendations (see the **Attachment**).

Recommendation:

The outstanding CMC container label issues have been satisfactorily resolved. Therefore, this application is deemed ready for approval from the CMC labeling/label perspective.

Michael C. Theodorakis, Ph.D.
Drug Product Reviewer
Branch V, Division II, ONDP

Moo-Jhong Rhee, Ph.D.
Branch Chief
Branch V, Division II, ONDP

Attachment; Final PI and Labels

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use ORIAHNN safely and effectively. See full prescribing information for ORIAHNN.

ORIAHNN (elagolix, estradiol, and norethindrone acetate capsules; elagolix capsules), co-packaged for oral use
Initial U.S. Approval: 2020

3 DOSAGE FORMS AND STRENGTHS

ORIAHNN consists of two capsules:

- The morning (AM) capsule is white and yellow, printed with “EL300 AM” containing 300 mg elagolix, 1 mg estradiol and 0.5 mg norethindrone acetate.
- The evening (PM) capsule is white and light blue, printed with “EL300 PM” containing 300 mg elagolix.

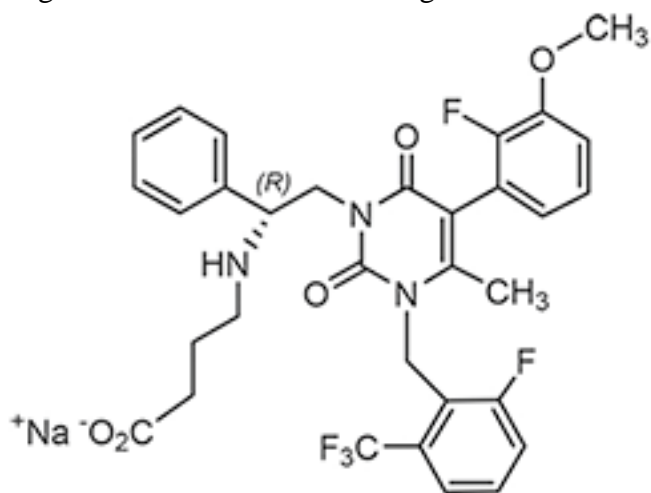
11 DESCRIPTION

ORIAHNN consists of two capsules: one to be taken orally in the morning (AM) and one to be taken orally in the evening (PM). The AM capsule is white and yellow and contains 300 mg elagolix (equivalent to 310 mg of elagolix sodium), 1 mg estradiol, and 0.5 mg norethindrone acetate. The PM capsule is white and light blue and contains 300 mg of elagolix (equivalent to 310 mg of elagolix sodium).

Elagolix

Elagolix sodium is the sodium salt of the active moiety elagolix, a nonpeptide small molecule, GnRH receptor antagonist. Elagolix sodium is chemically described as 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. Elagolix sodium has a molecular formula of $C_{32}H_{29}F_5N_3O_5Na$ and a molecular weight of 653.58. Elagolix free acid has a molecular formula of $C_{32}H_{30}F_5N_3O_5$ and a molecular weight of 631.60.

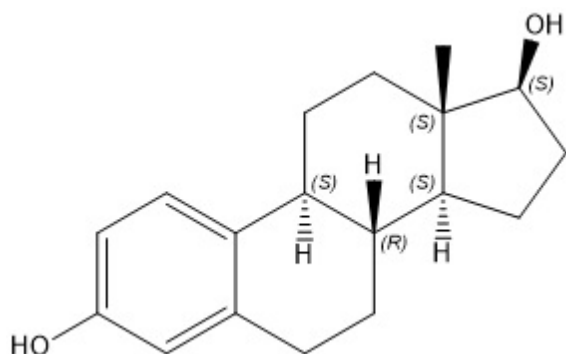
Elagolix sodium has the following structural formula:



Elagolix sodium is a white to off-white to light yellow powder and is freely soluble in water.

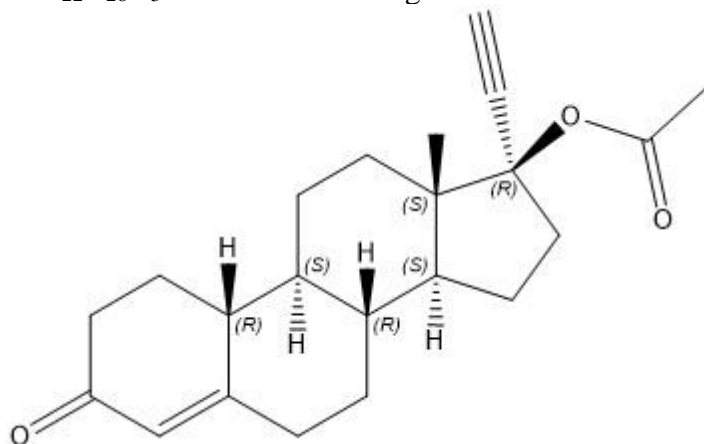
Estradiol

Estradiol (E2), an estrogen, is a white or almost white crystalline powder. Its chemical name is estra-1,3,5(10)-triene-3,17 β -diol with the molecular formula of $C_{18}H_{24}O_2$, and molecular weight of 272.38. The structural formula of E2 is as follows:



Norethindrone acetate

Norethindrone acetate (NETA), a progestin, is a white or yellowish white crystalline powder. Its chemical name is 17 β -acetoxy-19-nor-17 α -pregn-4-en-20-yn-3-one with the molecular formula of C₂₂H₂₈O₃ and molecular weight of 340.46.



ORIAHNN morning (AM) capsules contain the following inactive ingredients: anhydrous sodium carbonate, polyethylene glycol 3350, crospovidone, colloidal silicon dioxide, magnesium stearate, polyvinyl alcohol, titanium dioxide, polyethylene glycol, talc, purified water, lactose monohydrate, starch (corn), copovidone, talc, hypromellose, triacetin, and gelatin capsule shell. The capsule shell contains the following ingredients: FD&C Red #40, FD&C Yellow #5 [*see Warnings and Precautions (5.11)*], FD&C Yellow #6, titanium dioxide, gelatin, and printing ink (shellac, dehydrated alcohol, isopropyl alcohol, butyl alcohol, propylene glycol, strong ammonia solution, black iron oxide, potassium hydroxide, and purified water).

ORIAHNN evening (PM) capsules contain the following inactive ingredients: anhydrous sodium carbonate, polyethylene glycol 3350, crospovidone, colloidal silicon dioxide, magnesium stearate, polyvinyl alcohol, titanium dioxide, polyethylene glycol, talc, purified water, and gelatin capsule shell. The capsule shell contains the following ingredients: FD&C Blue #2, FDA/E172 yellow iron oxide, titanium dioxide, gelatin, and printing ink (shellac, dehydrated alcohol, isopropyl alcohol, butyl alcohol, propylene glycol, strong ammonia solution, black iron oxide, potassium hydroxide, and purified water).

16 HOW SUPPLIED/STORAGE AND HANDLING

ORIAHNN consists of two capsules: one to be taken in the morning (AM) and one to be taken in the evening (PM).

- morning (AM) capsules are white and yellow, printed with “EL300 AM” and contain elagolix 300 mg, estradiol 1 mg, and norethindrone acetate 0.5 mg.
- evening (PM) capsules are white and light blue, printed with “EL300 PM” and contain elagolix 300 mg.

ORIAHNN is packaged in weekly blister packs. Each blister pack contains seven AM capsules and seven PM capsules. Four blisters are packaged into a carton (NDC 0074-1017-56).

Store at 20°C to 25°C (68°F to 77°F), excursions permitted to 15°C to 30°C (59°F to 86°F). [See USP Controlled Room Temperature].

17 PATIENT COUNSELING INFORMATION

ORIAHNN Disposal Instructions

Instruct patients to dispose of unused medication via a take-back option if available or to otherwise follow FDA instructions for disposing of medication in the household trash, www.fda.gov/drugdisposal, and not to flush down the toilet.

Manufactured by AbbVie Inc. North Chicago, IL 60064

ORIAHNN is a trademark of AbbVie Inc.

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



Michael
Theodorakis

Digitally signed by Michael Theodorakis
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Moo Jhong
Rhee

Digitally signed by Moo Jhong Rhee
Date: 5/15/2020 02:37:15PM
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BIOPHARMACEUTICS

Product Background:

NDA: NDA-213388-ORIG-1

Drug Product Name / Strength: Elagolix, estradiol (E2) and norethindrone acetate (NETA) capsules (300 mg, 1 mg and 0.5 mg)

Route of Administration: Oral

Applicant Name: AbbVie Inc.

Submission:

The Applicant has submitted NDA 213388, a fixed dose combination (FDC) of the active ingredients Elagolix, estradiol and norethindrone acetate capsules (300 mg, 1 mg and 0.5 mg) for the management of heavy menstrual bleeding associate with Uterine Fibroids.

The current to-be-marketed drug product includes:

- Morning Dose: a FDC capsule containing a single intact 300 mg IR elagolix tablet (manufactured by (b) (4) and a single intact E2/NETA tablet (b) (4) 1 mg/0.5 mg).
- Evening Dose: a capsule containing a single intact 300 mg elagolix tablet (the same elagolix MG tablet as in the morning dose).

Review Recommendation: ADEQUATE

Review Summary:

The Biopharmaceutics review is focused on the evaluation of dissolution method and acceptance criteria for Elagolix, E2 and NETA in the FDC capsules, bridging between the to-be-marketed and pivotal clinical formulations, and manufacturing site changes.

Dissolution Method and Acceptance Criterion: ADEQUATE

The following dissolution method and acceptance criteria (Tier-1) for the release of elagolix (from elagolix 300 mg capsules and FDC capsules), and E2 and NETA from the FDC capsules are deemed acceptable:

Component	USP Apparatus	Speed (RPMs)	Medium/Temperature	Volume (mL)	Acceptance criterion
Elagolix	I (Basket)	100	0.05 M Sodium Phosphate pH 6.8 /37°C ± 0.5°C	900	Q = (b) (4)% in 60 minutes
E2 and NETA	II (Paddle)	50	0.3% Sodium lauryl sulfate/37°C ± 0.5°C	500	Q = (b) (4)% in 30 minutes

A Tier-2 dissolution method is also deemed acceptable for the release of elagolix and E2/NETA components from the FDC capsules with the same dissolution acceptance criteria as for Tier-1 testing.

Bridging of clinical formulations: ADEQUATE

Pivotal Phase 3 and to-be-marketed formulations were bridged with two pivotal Phase 1 bioequivalence (BE) and food effect studies: Study M16-856 for the FDC elagolix/E2/NETA capsule (morning dose; formulation FDC4) and Study M19-648 for the elagolix capsule (evening dose; formulation EN03). These studies will be reviewed by OCP review team (please refer to clinical pharmacology review for additional details).

Bridging of manufacturing sites: ADEQUATE

The dissolution profiles of commercial FDC capsules manufactured at AbbVie LTD (Barceloneta, PR, USA), the commercial site, are similar to the Primary Stability Batches (PSB) manufactured at (b) (4)

(b) (4)

Biowaiver Request: Not requested

Only one strength is developed.

List of Submissions reviewed:

Application 213388 - Sequence 0001 - 0001 (1) 07/31/2019 ORIG-1 /Multiple Categories/Subcategories
Application 213388 - Sequence 0015 - 0015 (16) 02/14/2020 ORIG-1 /Multiple Categories/Subcategories

Highlight Key Outstanding Issues from Last Cycle: The Applicant was requested to provide root cause analysis for the high variability in E2 and NETA release.

Concise Description of Outstanding Issues Remaining: None.

From Biopharmaceutics perspective, NDA 213388 for Elagolix, estradiol, and norethindrone acetate FDC capsules (300 mg, 1 mg and 0.5 mg) is recommended for APPROVAL.

BCS Designation

Reviewer's Assessment:

The Applicant has not claimed or requested any BCS classification for their drug product. However, elagolix data shows that between 77% – 90% of the 300 mg elagolix dose can be dissolved in 250 mL of medium over a pH range of 3.92-6.76. Elagolix's solubility in the two intestinal fluids FaSSIF and FeSSIF are greater than those in buffer solutions and all 300 mg of elagolix can be dissolved in 250 mL of both simulated fluids. Elagolix has low to moderate *in vitro* permeability per the Applicant. The solubility and permeability information on E2 and NETA components of the (b) (4) tablet is not provided here as it is already an approved product.

Solubility

The solubility information on elagolix is provided in the document <\\cdsesub1\evsprod\nda213388\0001\m3\32-body-data\32p-drug-prod\elagolix-e2-neta-capsule-all-abbvie\32p2-pharm-dev\pharmaceutical-development-devdrugproduct.pdf> (Page 61) and is also presented below.

Drug Product

Elagolix/estradiol/norethindrone acetate capsules, 300/1/0.5 mg are formulated as immediate release over-encapsulated tablets containing one 300 mg elagolix tablet and (b) (4) estradiol/norethindrone acetate, 1/0.5 mg (b) (4) tablet in a size No. 0 hard gelatin capsule with yellow opaque cap and white opaque body. This FDC capsule is intended for morning administration.

The elagolix capsule, 300 mg, contains one elagolix (300 mg) tablet in a size No. 0 hard gelatin capsule with light blue opaque cap and white opaque body, and intended for evening administration.

The elagolix 300 mg tablet used in the Elagolix 300 mg capsule and FDC capsule is manufactured (b) (4)
(b) (4)

The product and process development were conducted under a Quality by Design (QbD) paradigm to ensure desired product performance in terms of quality, safety, and efficacy. Dissolution was identified as one of the Critical Quality Attributes (CQAs) for the drug product.

The composition of the FDC drug product is provided below.

Table 3: Composition of Elagolix/Estradiol/Norethindrone Acetate Capsules, 300/1/0.5 mg

Component	Quality Standard	Function	Amount/Unit
Elagolix Tablet			
(b) (4)			
Elagolix Sodium	In-house Standard	Drug Substance	310.4 mg
Anhydrous Sodium Carbonate	NF/Ph. Eur.	(b) (4)	(b) (4)
Polyethylene Glycol 3350	USP/Ph. Eur.		
Crospovidone	NF/Ph. Eur.		
Colloidal Silicon Dioxide	NF/Ph. Eur.		
(b) (4)			
Colloidal Silicon Dioxide	NF/Ph. Eur.		
Magnesium Stearate	NF/Ph. Eur.	(b) (4)	
Estradiol/Norethindrone Acetate Tablet			
(b) (4)		(b) (4)	
(estradiol/norethindrone acetate, 1/0.5 mg)		Active	(b) (4)
Capsule			
Capule, Gelatin, No. 0, Yellow Cap and White Body ^d	In-house Standard	Capsule Shell	1 Capsule
Total Capsule Weight			720.9 mg ^e
(b) (4)			

Dissolution Method and Acceptance Criteria

Reviewer's Assessment: ADEQUATE

The biopharmaceutics review is focused on the evaluation of dissolution method and acceptance criteria for elagolix, E2, and NETA in the FDC capsules.

Elagolix

Proposed dissolution method and acceptance criterion

The following dissolution method and acceptance criterion were proposed for dissolution testing of elagolix in Elagolix/E2/NETA FDC Capsule (Morning Dose) and Elagolix Capsule 300 mg (Evening Dose).

Table 4: Dissolution Method for elagolix

Tier	USP Apparatus	Speed (RPMs)	Medium/Temperature	Volume (mL)	Acceptance criterion
Tier-1	I (Basket)	100	0.05 M Sodium Phosphate pH 6.8 /37°C ± 0.5°C	900	Q = ^(b) ₍₄₎ % in 60 minutes

(b) (4)

Because of the evidence of cross-linking (see 3.2.P.2.2.3 Physicochemical and Biological Properties), the Applicant has proposed a tier-2 test. Same acceptance criteria will be applied to tier-2 results.

Dissolution data obtained from the clinical batches, primary stability batches, and commercial sites-specific stability batches (SSB) of the FDC capsule and the elagolix capsule are summarized below. These dissolution profile data were used to establish the dissolution acceptance criterion for the elagolix component in both the FDC capsule and the elagolix capsule. The Applicant noted that since the development data shows that the release of elagolix component from the commercial FDC capsule and the elagolix capsule is comparable, the data sets from both drug products were combined for the purpose of setting their dissolution specifications. The individual and mean dissolution data are provided in <\\cdsesub1\evsprod\nda213388\0001\m3\32-body-data\32p-drug-prod\elagolix-e2-neta-capsule-all-abbvie\32p5-contr-drug-prod\32p56-justif-spec\justification-of-specifications-disso.pdf> and in <\\cdsesub1\evsprod\nda213388\0001\m3\32-body-data\32r-reg-info\sas-dissolutiondata-justificationofspec.pdf>.

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Biowaiver Request

The Applicant has not requested any biowaiver. There is only one strength of the FDC drug product proposed.

Conclusions and recommendation

From Biopharmaceutics perspective, NDA 213388 is recommended for **APPROVAL**.

Appendix 1

The Information Request conveyed to the Applicant during the review process

Information Request 1 (IR 1)

1. In the Pharmaceutical development section for FDC tablets data

(b) (4)

(b) (4)

Primary Biopharmaceutics Reviewer Name: Kalpana Paudel, Ph.D.

Secondary Reviewer Name: Vidula Kolhatkar, Ph.D.



Kalpana
Paudel

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