CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

214846Orig1s000

PRODUCT QUALITY REVIEW(S)

U.S. FOOD & DRUG ADMINISTRATION

RECOMMENDATION

☐ Approval
☒ Approval with Post-Marketing Commitment
☐ Complete Response

NDA 214846
MYFEMBREE (relugolix, estradiol, and norethindrone acetate)
Assessment #1

Drug Product Name	MYFEMBREE (relugolix, estradiol, and norethindrone acetate) tablets
Dosage Form	tablets
Strength	relugolix 40 mg, estradiol 1 mg and norethindrone acetate 0.5 mg
Route of Administration	Oral
Rx/OTC Dispensed	Rx
Applicant	Myovant Sciences GmbH
US agent, if applicable	Myovant Sciences, Inc.

Submission(s) Assessed	Document Date	Discipline(s) Affected
Original Submission (0001)	06/01/2020	All
Amendment (0003)	07/07/2020	OPMA
Amendment (0005)	08/11/2020	OPMA
Amendment (0007)	09/09/2020	Drug Product, OPMA
Amendment (0011)	09/30/2020	Drug Product
Amendment (0015)	11/13/2020	ONDP, OPMA
Amendment (0019)	11/25/2020	OPMA, Drug Product, Biopharmaceutics
Amendment (0023)	12/04/2020	OPMA, Drug Product
Amendment (0028)	01/28/2021	OPMA
Amendment (0029)	01/29/2021	OPMA
Amendment (0030)	02/08/2021	EA
Amendment (0031)	02/19/2021	OPMA
Amendment (0032)	02/22/2021	Drug Product
Amendment (0033)	02/24/2021	Drug Product
Amendment (0035)	03/12/2021	All
Amendment (0036)	03/19/2021	Drug Substance
Amendment (0037)	03/25/2021	Drug Product

QUALITY ASSESSMENT TEAM

Discipline	Primary Assessment	Secondary Assessment
Drug Substance	Gaetan Ladouceur	Donna Christner
Drug Product	Venkateswara	Wendy Wilson-Lee
Manufacturing	Jingbo Xiao	Jean Tang
Microbiology	Jingbo Xiao	Jean Tang
Biopharmaceutics	Kalpana Paudel	Vidula Kolhatkar
Regulatory Business Process Manager	Marquita Burnett	
Application Technical Lead	Hong Cai, Ph.D.	
Laboratory (OTR)	-	-
Environmental	Venkateswara Pavuluri	Wendy Wilson-Lee
Labeling	Venkateswara Pavuluri	Wendy Wilson-Lee

EXECUTIVE SUMMARY

I. RECOMMENDATIONS AND CONCLUSION ON APPROVABILITY

The Office of Pharmaceutical Quality Review team has assessed NDA 214846 for MYFEMBREE (relugolix, estradiol, and norethindrone acetate) tablets, 40 mg, 1 mg and 0.5 mg, with respect to Chemistry, Manufacturing, and Controls (CMC) and has determined that it meets all applicable standards to support the identity, strength, quality, and purity that it purports. As such, OPQ recommends approval of this NDA from a quality perspective.

The labeling and labels as submitted on February 22, 2021 and March 25, 2021, respectively, 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 CGMP status. An overall manufacturing inspection recommendation of APPROVE was issued on January 29, 2021. The recommendation remains current as of this review.

The claimed categorical exclusion from the environmental assessment requirements under 21 CFR Part 25.31(b) is acceptable with the following Post-Marketing Commitment (PMC (b) (4): "Submit test report for the currently ongoing study titled "The Zebrafish Extended One-Generation Reproduction Test" to support the environmental risk assessment for relugolix." The PMC (b) (4) has been agreed upon by the applicant. The final report is due by August 31, 2021.

II. SUMMARY OF QUALITY ASSESSMENTS

A. Product Overview

The proposed drug product MYFEMBREE tablets is a fixed-dose combination (FDC) product containing three active pharmaceutical ingredients (APIs), relugolix (REL), a gonadotropin-releasing hormone (GnRH) receptor antagonist, estradiol (E2), an estrogen, and norethindrone acetate or NETA (also known as norethisterone acetate), a progestin. Relugolix is a new molecular entity (NME), and estradiol and norethindrone acetate are established drugs in the United States. Recently (within this NDA review cycle) a drug product containing relugolix as the active ingredient received marketing approval for the treatment of patients with advanced prostate cancer (ORGOVYX, NDA214621) from the same applicant. CMC information of the drug substance relugolix in this NDA has been cross referenced to NDA 214621.

MYFEMBREE tablets is also abbreviated as REL/E2/NETA FDC. Each tablet contains relugolix 40 mg, estradiol 1 mg, and norethindrone acetate 0.5 mg. MYFEMBREE tablets are round, light yellow to yellow, film-coated tablets debossed with “MVT” on one side and “415” on the other side. The commercial formulation was developed to provide a once a day single-tablet regimen administered orally to treat heavy menstrual bleeding associated with uterine fibroids. MYFEMBREE is an immediate-release tablets formulated with common tableting agents and (b) (4) film-coating. MYFEMBREE tablets are supplied in a white, opaque, high-density polyethylene bottle containing 28 tablets with desiccant and closed with an induction-sealed child resistant cap. MYFEMBREE tablets are stored at 15ºC to 30ºC with an expiration dating period of 24 months.

Proposed Indication(s) including Intended Patient Population	for the treatment of heavy menstrual bleeding associated with uterine fibroids.
Duration of Treatment	as needed
Maximum Daily Dose	40 mg of relugolix, 1 mg of estradiol, and 0.5 mg of norethindrone acetate.
Alternative Methods of Administration	na

B. Quality Assessment Overview

Drug Substance: Adequate

Relugolix: Relugolix is a free base white to off-white to slightly yellow solid, without chiral centers. While polymorphs are possible for relugolix, the most thermodynamically stable form, (b) (4) has been developed for commercial manufacture. (b) (4) . Relugolix drug substance information is cross-referenced to NDA 214621 application, which was approved on December 18, 2020. The specification in the referenced NDA and of this NDA are consistent between each other. The applicant also provided 3 DS batch analyses confirming the compliance to the specification.

The approved supplier is (b) (4) . A retest period of (b) (4) months has established for Relugolix stored at the recommended storage condition of (b) (4) °C.

Estradiol: The drug substance is estradiol hemihydrate. CMC information of estradiol hemihydrate is cross-referenced to DMF (b) (4), which was last reviewed by the Agency on 06/25/2020 (adequate). The retest period is (b) (4) months when stored at (b) (4) °C. The specification is included in the NDA. The applicant also provided the analysis results from 3

representative commercial batches confirming the compliance to the specification.

Estradiol (E2) is supplied by (b) (4) located at (b) (4)

Norethindrone acetate: CMC information of norethindrone acetate is cross-referenced to DMF (b) (4), which was last reviewed by the Agency on 08/14/2020 (adequate). The specification in the referenced DMF and of this NDA are consistent between each other. The applicant also provided 3 DS batch analyses confirming the compliance to the specification. The retest period is (b) (4) months when stored at (b) (4) C.

Norethindrone acetate is supplied by (b) (4) located at (b) (4)

The drug substance reviewer Dr. Gaetan Ladouceur finds the information on the drug substances relugolix, estradiol and norethindrone acetate is adequate to support the approval of the NDA. See IQA Chapter I, Drug Substance for details.

Drug Product: Adequate

MYFEMBREE is an immediate release fixed-dose combination (FDC) tablet containing 40 mg relugolix, 1 mg estradiol, and 0.5 mg norethindrone acetate for oral administration. MYFEMBREE tablets are round, light yellow to yellow, film-coated tablets debossed with “MVT” on one side and “415” on the other side.

In addition to the three APIs, each tablet contains the following inactive ingredients: mannitol (b) (4), sodium starch glycolate (b) (4), hydroxypropyl cellulose (b) (4), lactose monohydrate (b) (4) magnesium stearate (b) (4) and (b) (4) for film coating. All excipients except (b) (4) are of compendial grade. However, all components used in manufacture of (b) (4) coating are of compendial grade. No novel excipients were used in the manufacture of the FDC tablets. Lactose monohydrate (b) (4) (b) (4) (b) (4) Thus, the quality of all the excipients in MYFEMBREE tablets are acceptable.

The proposed specification for the drug product includes tests for appearance, identification (UV and HPLC retention times), assay, related substances, dissolution, content uniformity, (b) (4) (b) (4) It is noted that (b) (4)

(b) (4)

All the related substance acceptance criteria are either within the level of the approved drug or acceptable to the PharmTox review team. Although the acceptance criteria of three relugolix related substances (b) (4) exceed the ICHQ3B qualification thresholds (b) (4)%), but they are acceptable based on the recommendation from the PharmTox review team. Refer to the email communications from Dr. Laurie McLeod-Flynn dated February 16 and February 19, 2021. The proposed acceptance criteria for all the attributes are acceptable from the quality perspective.

The batch data for the registration batches and the supportive clinical batches conform to the specification. The applicant's proposal of not including the test for elemental impurities in drug product release specification is acceptable per ICH Q3D. The analytical methods used in analysis of the drug product batches, at release and in stability studies, were suitably validated and deemed adequate for the intended purpose.

The drug product is packaged in 28-count 60cc high-density polyethylene (HDPE) bottles with desiccant and induction seal lined polypropylene (PP), child-resistant screw-on closures. The materials used for manufacture of the container closure conform to relevant regulations on indirect food additives and relevant USP chapters. The suitability of the container closure system (CCS) selected has been demonstrated through stability studies conducted in the intended commercial packaging configuration. The proposed CCS is deemed adequate for its intended use with this solid oral dosage form.

Stability data provided to date support a 24-month shelf-life, when stored between 15°C to 30°C in the proposed container closure system.

The FDA EA Team reviewed the submitted EA data and concluded that approval of this application likely would appear to have no significant environmental impact, and therefore the claim for an exclusion from an EA is acceptable. However, the pending results of a chronic fish study for relugolix (an NME) will provide confirmation to support the exclusion claim. The applicant has agreed to a post marketing commitment (PMC# (b) (4)) and will submit a final report by August 31, 2021.

In summary, Dr. Pavuluri has recommended approval of this application from the drug product perspective. See IQA Chapter II, Drug Product including two addendums for details.

Labeling: Adequate

During the initial assessment of the labeling (prescribing information (PI),

and container/carton labels), several deficiencies were identified. The deficiencies were conveyed to the Applicant. Subsequently, the labeling and labels as submitted by Myovant on February 22, 2021 and March 25, 2021 respectively, meet the applicable statutory and regulatory requirements, and are acceptable from the CMC perspective. Refer to IQA Labeling Chapter for details.

Manufacturing Integrated Assessment: Adequate

Process: adequate

The manufacturing process for the finished drug product MYFEMBREE includes [redacted] The proposed commercial batches will be manufactured with the same formulation and at the same scale as the registration batches.

MYFEMBREE is a non-sterile solid oral dosage form drug product. The applicant has provided the microbial limits testing of TAMC and TYMC per USP<61>, E. coli per USP<62> and with the acceptance criteria per USP <1111> in the drug product release and stability specification. Test results for registration batches demonstrated that REL/E2/NETA FDC tablets consistently meet microbiological requirements. The microbiology information submitted in this application has been reviewed by the OPMA reviewer Dr. Jingbo Xiao who has found the information adequate to support the approval of this application from the microbiology perspective.

[redacted] is responsible for manufacturing and release testing for the drug product, REL/E2/NETA FDC tablets.

The OPMA reviewer Dr. Jingbo Xiao concluded that the batch formula, manufacturing processes, in-process controls, [redacted] for the drug product are adequate to demonstrate the robustness of the manufacturing process.

Facilities: adequate

The DS and DP manufacturers and external testing facilities are recommended for approval based on compliance history, acceptable profile codes and experience in the proposed responsibilities.

Note that one of the API manufacturing facilities, [redacted] for relugolix, was found not incompliant with CGMP during review. The applicant decided to withdraw the [redacted] facility from the commercial manufacturing. The [redacted] facility was only served as the relugolix API manufacturing, release and stability testing for clinical supplies only. Therefore, [redacted]

requires no further evaluation. The proposed commercial API manufacturing site for API relugolix, [redacted] is acceptable.

See IQA OPMA Chapter for manufacturing process, the facilities and the microbiology for detailed assessment.

Biopharmaceutics: Adequate

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

The Dissolution Method: The dissolution method for the drug substance relugolix is USP 2 at 50 rpm, in 900 mL of 50 mM citrate buffer, pH 5.5 and 37ºC±0.5ºC with the dissolution acceptance criterion "Q = [redacted]% at 30 min"; The method for E2 and NETA is USP 2 at 50 rpm, in 500 mL of 0.3% Sodium dodecyl sulfate, and 37ºC±0.5ºC with the dissolution acceptance criterion "Q = [redacted]% at 30 min". The biopharmaceutics reviewer, Dr. Kalpana Paudel, has concluded the dissolution methods are deemed acceptable.

The applicant conducted a bioequivalence (BE) study (MVT-601-042) to bridge Pivotal Phase 3 (40 mg relugolix tablet co-administered with Activella® tablets (1 mg estradiol and 0.5 mg norethindrone acetate)) and to-be-marketed formulations (FDC tablets of 40 mg relugolix/1 mg estradiol/0.5 mg norethindrone acetate). This study will be reviewed by OCP review team (Refer to clinical pharmacology review for additional details).

However, the in vitro dissolution profiles of relugolix, E2 and NETA are similar for the product used in BE study and the to-be-marketed formulation, thus, there is no effect of relugolix on the release of E2 and NETA components, and E2/NETA do not impact the release profile of relugolix in FDC tablets under the tested condition.

Overall, the Applicant has adequately established the suitable dissolution test methods and acceptance criteria for the drug substances, relugolix, E2 and NETA to ensure the quality and bioavailability of MYFEMBREE (relugolix, estradiol and norethindrone acetate) tablets, 40mg, 1mg and 0.5mg. The biopharmaceutics reviewer, Dr. Kalpana Paudel has recommended the approval of this application from biopharmaceutics perspective. See IQA Biopharmaceutics Chapter for details.

Microbiology (if applicable): Adequate

See the detailed review from Dr. Jingbo Xiao in the manufacturing process and the facilities Chapter of the IQA.

Analytical Methods Verification: Choose an item.

Analytical methods verification by FDA's St. Louis laboratories (OPQ/OTR/DPA) was not requested.

FACILITY STATUS REPORT AND OVERALL RECOMMENDATION

(b) (4)

C. Risk Assessment

Risk Assessment for NDA 214846 MYFEMBREE™ Tablets, 40 mg, 1 mg and 0.5 mg (a fixed-dose combination film-coated, immediate release tablets)

CQAs*	Initial Risk Ranking**	Risk Mitigation Approach	Final Risk Evaluation	Lifecycle Considerations/Comments***
Description (Appearance)		(b) (4)	L	
Assay	M		L	
Related Substances	M		L	
Content Uniformity	M		L	
Dissolution	M		L	
(b) (4)	L		L	
	M		L	
(b) (4)	L		L	

*CQAs: Critical Quality Attributes

**Risk ranking applies to the product CQAs

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

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

Application Technical Lead Name and Date:

Hong Cai, Ph.D.
CMC Lead (acting)

QUALITY ASSESSMENT DATA SHEET

1. RELATED/SUPPORTING DOCUMENTS

A. DMFs:

DMF #	Type	Holder	Item Referenced	Status	Date Assessment Completed	Comments
(b) (4)	II	(b) (4)		Adequate	Last reviewed 06/25/2020	See IQA Chapter 1, Drug Substance for additional information
	II			Adequate	Last reviewed 06/25/2020	See IQA Chapter II, Drug Substance for additional information
	III			NA		
	III			NA		
	III			NA		

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*

Document	Application Number	Description
IND submissions, associated reviews, and communications	IND 118736	Investigational use of relugolix tablets for the

		treatment of prostate cancer (IND 118736).
IND submissions, associated reviews, and communications	(b) (4)	
IND submissions, associated reviews, and communications	IND 131161	Investigational use of relugolix, estradiol and norethindrone acetate tablets for the treatment of heavy menstrual bleeding associated with uterine fibroids
NDA submissions, associated reviews, and communications	NDA 214621 Orgovyx (relugolix) tablets	CMC information of the drug substance relugolix is referenced
NDA application(s) as the Listed Drugs	NDA 020907	Activella (estradiol/norethindrone acetate) tablets

2. CONSULTS

Discipline	Status	Recommendation	Date	Assessor
Biostatistics	na			
Pharmacology/Toxicology	na			
CDRH-ODE	na			
CDRH-OC	na			
Clinical	na			
Other	na			

CHAPTERS: Primary Quality Assessment

CHAPTER I: Drug Substance

CHAPTER II: Drug Product

CHAPTER III: Environmental Assessment (see Chapter II)

CHAPTER IV: Labeling

CHAPTER V: Manufacturing Integrated Assessment

CHAPTER VI: Biopharmaceutics

CHAPTER VII: Microbiology (see Chapter V)

CHAPTER VIII: Additional Quality Disciplines *Not applicable*

Hong Cai

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

Date: **Feb 18, 2021**

From: **Venkateswara R. Pavuluri, Ph.D., R. Ph.**
Drug Product Reviewer
Branch 4/DNDP II
Office of New Drug Products

Through: **Wendy Wilson-Lee, Ph.D.**
Division Director / DNDP II
Office of New Drug Products

To: **Drug Product Review for NDA 214846**
for MYFEMBREE®
Subject: PMC on Environmental Assessment for Relugolix.

Though Applicant's claim of categorical exclusion from preparation of an Environmental Assessment for Relugolix (MVT-601), in accordance with 21 CFR 25.31(b), is acceptable, Dr. James Laurenson, EA Team, ONDP opinioned that the results of a chronic fish study requested earlier by FDA would provide confirmation. Since the final results of the chronic fish study are not expected to be available before the PDUFA Goal date for this NDA, Agency sent a request for information on 05-FEB-2021, for the applicant to agree for a post marketing commitment (PMC) on the final report. Applicant agreed to provide the final report for Zebrafish Extended One-Generation Reproduction Test (ZEOGRT), by end of Aug 2021.

This addendum is to document the comments from Dr, James Laurenson, EA Team, ONDP (**Attachment-1**); and Applicant's agreement, to submit the final report for Zebrafish Extended One-Generation Reproduction Test (ZEOGRT) (Attachment-2).

The NDA 214846 was otherwise complete and adequate from the drug product perspective, per the review dated 25-JAN-2021.

Recommendation:

The outstanding issues related to EA assessment have been satisfactorily resolved. This application is now recommended for **approval** from the Drug product CMC perspective.

Venkateswara R. Pavuluri, Ph. D., R. Ph.
Drug Product Reviewer
Branch 4, DNDP II, ONDP

Wendy Wilson-Lee, Ph. D,
Div. Director, DNDP II, ONDP

Attachment-1: Comments from Dr, James Laurenson, EA Team, ONDP on NDA 214846 MYFEMBREE®

For relugolix, the applicant submitted a claim for a categorical exclusion from an environmental assessment (EA) in accordance with 21 CFR 25.31(b), which is for substances that increase in use but result in an expected introduction concentration (EIC) of < 1 ppb. The estimated use amounts were consistent with the claim. The applicant (b) (4) to support the exclusion claim, per FDA guidance (USFDA, 2016, Environmental Assessment: Questions and Answers Regarding Drugs with Estrogenic, Androgenic, or Thyroid Activity). **The results of a chronic fish study, which are expected later in 2021 and have been requested by FDA, will provide confirmation.**

For both estradiol and norethindrone acetate, the applicant submitted a claim for the same categorical exclusion as for relugolix, 21 CFR 25.31(b), but also 21 CFR 25.31(c), which is for substances that occur naturally in the environment when the action does not alter significantly the concentration or distribution of the substance, its metabolites, or degradation products in the environment. (b) (4) were also included that provided support for these claims for both substances.

The FDA EA Team reviewed the submitted EA data and concluded that approval of this application would appear to have no significant environmental impact, and therefore the claim for an exclusion from an EA is acceptable. The required statement of no extraordinary circumstances was provided for all three substances, in accordance with 21 CFR 25.15. Due to uncertainties such as cumulative risk from other substances with a similar mechanism of action in the environment, however, the use of label/insert language or other messaging addressing environmentally protective disposal practices, similar to language used for relugolix (NDA 214621), is recommended.

Attachment-2: Applicant's Response to IR, submitted in SN 0030 on 08-FEB-2021:

FDA REQUEST 1

Please refer to your New Drug Application (NDA) 214846 dated and received June 1, 2020, submitted under section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for relugolix, estradiol and norethindrone acetate, fixed-dose combination tablet. Please also refer to your claim in CTD 1.12.14 for a categorical exclusion from an environmental assessment (EA), in accordance with 21 CFR 25.31, and to the supporting EA data, including the in-progress Zebrafish Extended One-Generation Reproduction Test (ZEOGRT). As noted in post-marketing commitment (PMC) 3962-2 for the referenced application NDA214621, the ZEOGRT report is needed to support the relugolix categorical exclusion from an environmental assessment. [redacted (b) (4)] ***.***

The proposed date for final submission is August 31, 2021. Please provide a commitment by February 8, 2021 to submit the aforementioned ZEOGRT report to NDA 214846 by August 31, 2021. Refer to your response submitted to "FDA PMC 1" in NDA 214621 dated November 20, 2020 (SN0045) (See NDA 214621 PMC 3962-2).

Myovant Response:

Reference is made to Myovant's claim for categorical exclusion from an environmental assessment for relugolix in accordance with CFR 25.31(b) as stated in NDA 214846 Module 1.12.14. Reference is also made to the post-marketing commitment 3962-2 for NDA 214621. Myovant hereby provides the same commitment for NDA 214846 to submit the final ZEOGRT report by 31Aug2021.

APPEARS THIS WAY ON ORIGINAL

Venkateswara Pavuluri

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Wendy Wilson- Lee

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CHAPTER IV: LABELING

IQA NDA Assessment Guide Reference

1.0 PRESCRIBING INFORMATION

Assessment of Product Quality Related Aspects of the Prescribing Information: submitted as of 09/29/2020

(b) (4)

Revised: 09/2020

Item	Information Provided in the NDA	Assessor's Comments
Product Title in Highlights		
Proprietary name	MYFEMBREE®	Acceptable per DMEPA review.
Established name(s)	(relugolix/estradiol/norethindrone acetate) tablets,	**Not Acceptable.** Revise the text separating established names of drugs by punctuation mark comma (,) in place of backslash (/) to read as "(relugolix, estradiol,

		and norethindrone acetate) tablets”
Route(s) of administration	for oral use	Acceptable.
Dosage Forms and Strengths Heading in Highlights		
Summary of the dosage form(s) and strength(s) in metric system.	Tablets: 40 mg of relugolix, 1 mg of estradiol and 0.5 mg of norethindrone acetate	Acceptable/
Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state “functionally scored”	Not Scored.	Not Applicable.
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.	Not an injectable.	Not Applicable.

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)	None.	Not Applicable.

1.2.2 Section 3 (DOSAGE FORMS AND STRENGTHS)

3. DOSAGE FORMS AND STRENGTHS

(b) (4)

Item	Information Provided in the NDA	Assessor's Comments
DOSAGE FORMS AND STRENGTHS section		
Available dosage form(s)	Tablet	Acceptable.
Strength(s) in metric system	(b) (4)	Acceptable. However, the sentence may be simplified as "relugolix 40 mg, estradiol 1 mg, and norethindrone acetate 0.5 mg".
If the active ingredient is a salt, apply the USP Salt Policy per FDA Guidance	No salt form used.	Not applicable.
A description of the identifying characteristics of the dosage forms, including shape, color, coating, scoring, and imprinting	light yellow to yellow, round, film-coated tablets with "MVT" on one side and "415" on the other side.	Acceptable.
Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state "functionally scored"	Not scored.	Not Applicable.
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.	Not an injection.	Not Applicable.

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Item	Information Provided in the NDA	Assessor's Comments
DESCRIPTION section		
Proprietary and established name(s)	MYFEMBREE (relugolix, estradiol, norethindrone acetate)	Acceptable.
Dosage form(s) and route(s) of administration	tablets for oral administration.	Acceptable.
If the active ingredient is a salt, apply the USP Salt Policy and include the equivalency statement per FDA Guidance.	No salt form used.	Not Applicable.
List names of all inactive ingredients. Use USP/NF names. Avoid Brand names.	lactose monohydrate, mannitol, sodium starch glycolate, hydroxypropyl cellulose, magnesium stearate, hypromellose, titanium dioxide, triacetin, and iron oxide yellow.	Acceptable.
For parenteral injectable dosage forms, include the name and quantities of all inactive ingredients. For ingredients added to adjust the pH or make isotonic, include the name and statement of effect.	Not an Injectable.	Not Applicable.
If alcohol is present, must provide the amount of alcohol in terms of percent volume of absolute alcohol	No Alcohol was used.	Not Applicable.
Statement of being sterile (if applicable)	Not a sterile product.	Not Applicable.
Pharmacological/ therapeutic class	Relugolix - GnRH receptor antagonist; Estradiol - an estrogen; Norethindrone acetate - a progestin.	Acceptable.
Chemical name, structural formula, molecular weight	Structures include as reproduced above in this section of review.	Acceptable.
If radioactive, statement of important nuclear characteristics.	Not Radioactive.	Not Applicable.

Other important chemical or physical properties (such as pKa or pH)	No information included.	Not Applicable.

Section 11 (DESCRIPTION) Continued

Item	Information Provided in the NDA	Assessor's Comments
For oral prescription drug products, include gluten statement if applicable	Not Included.	Acceptable.
Remove statements that may be misleading or promotional (e.g., "synthesized and developed by Drug Company X," "structurally unique molecular entity"	No misleading statements included.	Acceptable.

1.2.4 Section 16 (HOW SUPPLIED/STORAGE AND HANDLING)

16. HOW SUPPLIED/STORAGE AND HANDLING

16.1. How Supplied

MYFEMBREE film-coated tablets contain [redacted] (b) (4) [redacted] (b) (4) The tablets are light yellow to yellow, round film-coated tablet with "MVT" on one side and "415" on the other side.

MYFEMBREE tablets are supplied in a white, opaque, high-density polyethylene bottle containing 28 tablets with desiccant and closed with an induction-sealed child-resistant cap (NDC Code xxxxx-xxx-xx).

16.2. Storage and Handling

Store at 15ºC to 30ºC (59ºF to 86ºF).

Dispose unused medication via a take-back option if available. Otherwise, follow FDA instructions for disposing medication in the household trash, www.fda.gov/drugdisposal. Do NOT flush down the toilet.

Item	Information Provided in the NDA	Assessor's Comments
HOW SUPPLIED/STORAGE AND HANDLING section		
Available dosage form(s)	Film-coated tablets.	Acceptable.
Strength(s) in metric system	(b) (4)	Acceptable. However, the sentence may be simplified as "relugolix 40 mg, estradiol 1 mg, and norethindrone acetate 0.5 mg".
Available units (e.g., bottles of 100 tablets)	bottle containing 28 tablets	Acceptable.
Identification of dosage forms, e.g., shape, color, coating, scoring, imprinting, NDC number	light yellow to yellow, round film-coated tablet with "MVT" on one side and "415" on the other side.	Acceptable.
Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state "functionally scored"	Not Scored.	Not Applicable.
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.	Not an Injectable.	Not Applicable.

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.)	Not Applicable.	Not Applicable.
If the product contains a desiccant, ensure the size and shape differ from the	Contains Desiccant (b) (4)	Acceptable.

dosage form and desiccant has a warning such as “Do not eat.”	(b) (4)	
Storage conditions. Where applicable, use USP storage range rather than storage at a single temperature.	Store at 15ºC to 30ºC (59ºF to 86ºF).	Acceptable.
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.”	Not Applicable.	Not Applicable.
Include information about child-resistant packaging	CRC present.	Acceptable.

1.2.5 Other Sections of Labeling

Statement on disposal of unused and/or expired drug product as included in the PI, at the end of section 16. Storage and Handling is acceptable per current Agency guidance.

“Dispose unused medication via a take-back option if available . Otherwise, follow FDA instructions for disposing medication in the household trash, www.fda.gov/drugdisposal. Do NOT flush down the toilet.”

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	Manufactured by Patheon Inc., Mississauga, Ontario L5N 7K9, Canada Distributed by: Myovant Sciences, Inc., Brisbane, CA 94005	Acceptable. Omission of street address is acceptable based on listing of the company name and address in current city directory or telephone directory.

2.0 PATIENT LABELING

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

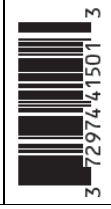
3.0 CARTON AND CONTAINER LABELING (SN 0026 as of 21-JAN-2021)

3.1 Container Label

(b) (4)

3.2 **Carton Labeling:** Not applicable

Item	Information Provided in the NDA	Assessor's Comments about Container Labeling
Proprietary name, established name, and dosage form (font size and prominence	Myfembree (relugolix, estradiol, and norethindrone acetate) tablets	Acceptable.
Dosage strength	40 mg/1 mg/0.5 mg	**Not Acceptable**. The dosage strengths shall be separated by "," as "40 mg, 1 mg, and 0.5 mg"
Route of administration	No specific text included to indicate the route of administration on the wallet or outer carton.	Acceptable.
If the active ingredient is a salt, include the equivalency statement per FDA Guidance	No salt present in the drug product.	Not Applicable.
Net contents (e.g. tablet count)	28 tablets	Acceptable.
"Rx only" displayed on the principal display	Rx only	Acceptable.
NDC number	NDC 72974-415-01	Acceptable.
Lot number and expiration date		
Storage conditions. If applicable, include a space on the carton labeling for the user to write the new BUD.	Store at 15°C to 30°C (59°F - 86°F)	Acceptable.
For injectable drug products for parental administration, use appropriate package type term (e.g., single-dose, multiple-dose, single-patient-use)	Not an injection.	Not Applicable.
Other package terms include pharmacy bulk package and imaging bulk package which require "Not for direct infusion" statement.	None.	Not Applicable.

If alcohol is present, must provide the amount of alcohol in terms of percent volume of absolute alcohol	No Alcohol present	Not Applicable.
Bar code		Acceptable.

Item	Information Provided in the NDA	Assessor's Comments about Carton Labeling
Name of manufacturer/distributor	Distributed by: Myovant Sciences, Inc. Brisbane, CA Made in Canada	Acceptable.
Medication Guide (if applicable)	Not Applicable.	Not Applicable.
No text on Ferrule and Cap overseal	Not Applicable.	Not Applicable.
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.	Not a compendial drug product	Not Applicable.
And others, if space is available	Keep this and all medications out of reach of children. Do not flush unused medicine.	Acceptable.

Assessment of Carton and Container Labeling: Inadequate

ITEMS FOR ADDITIONAL ASSESSMENT

Prescribing Information

HIGHLIGHTS

1. Revise the text separating established names of drugs by punctuation mark comma (,) in place of backslash (/) to read as: “(relugolix, estradiol, and norethindrone acetate) tablets”

3 DOSAGE FORMS AND STRENGTHS

2. Revise the statement [redacted] (b) (4) to read as “Each tablet of MYFEMBREE contains relugolix 40 mg, estradiol 1 mg, and norethindrone acetate 0.5 mg.”

16 HOW SUPPLIED/STORAGE AND HANDLING

3. Revise the statement [redacted] (b) (4) to read as “MYFEMBREE film-coated tablet contains relugolix 40 mg, estradiol 1 mg, and norethindrone acetate 0.5 mg.”

Container Label:

4. Revise the dosage strength statement “40 mg/1 mg/0.5 mg” to be separated by punctuation mark comma (,) in place of backslash (/) and to read as: 40 mg, 1 mg, and 0.5 mg”.

Overall Assessment and Recommendation:

As of this review, this application is not deemed ready for approval in its present form per 21 CFR 314.125(b)(8) from the CMC labeling/labels perspective until the deficiencies delineated above are satisfactorily resolved.

Primary Labeling Assessor Name and Date:

Venkateswara. R. Pavuluri; 25-JAN-2021

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

Wendy Wilson-Lee; 25-JAN-2021

Venkateswara Pavuluri

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Wendy Wilson- Lee

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Date: 1/26/2021 09:26:33AM
GUID: 50816dbc000085595ca3284bbca465a8

Memorandum

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

Date: **Feb 23, 2021**

From: **Venkateswara R. Pavuluri, Ph.D., R. Ph.**
Drug Product Reviewer
Branch 4/DNDP II
Office of New Drug Products

Through: **Wendy Wilson-Lee, Ph.D.**
Div. Director /DNDP II
Office of New Drug Products

To: **CMC Labeling Review of NDA 214846**
for MYFEMBREE®
Subject: Final Recommendation - APPROVAL

At the time when Labeling Review of NDA 214846 was completed, on 25-JAN-2021, this NDA was not recommended for approval per 21 CFR 314.125(b)(8) for deficiencies listed below. The NDA for this drug product was otherwise complete and adequate from the drug product perspective, per the review dated 25-JAN-2021.

Labeling/Label Deficiencies identified in Labeling review on 25-JAN-2021:

Prescribing Information

HIGHLIGHTS

1. Revise the text separating established names of drugs by punctuation mark comma (,) in place of backslash (/) to read as: "(relugolix, estradiol, and norethindrone acetate) tablets"

DOSAGE FORMS AND STRENGTHS

2. Revise the statement [redacted] (b) (4) to read as "Each tablet of MYFEMBREE contains relugolix 40 mg, estradiol 1 mg, and norethindrone acetate 0.5 mg."

HOW SUPPLIED/STORAGE AND HANDLING

3. Revise the statement [redacted] (b) (4) to read as "MYFEMBREE film-coated tablet contains relugolix 40 mg, estradiol 1 mg, and norethindrone acetate 0.5 mg."

Container Label:

4. Revise the dosage strength statement "40 mg/1 mg/0.5 mg" to be separated by

punctuation mark comma (,) in place of backslash (/) and to read as: 40 mg, 1 mg, and 0.5 mg".

This labeling addendum is to document the most updated information in packaging insert (**Attachment-1**), and container label (**Attachment-2**) as submitted on Feb 22, 2021. The labeling and labels are now acceptable from the CMC labeling perspective.

Recommendation: The CMC label/labeling issues identified in the labeling review have been satisfactorily resolved, as reproduced in attachments 1 & 2 below. This application is now recommended for APPROVAL from the CMC labeling/label perspective.

Venkateswara R. Pavuluri, Ph. D., R. Ph.,
Drug Product Reviewer
Branch 4, DNDP II, ONDP

Wendy Wilson-Lee, Ph. D.,
Div. Director, DNDP II, ONDP

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

Wendy Wilson- Lee

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Venkateswara Pavuluri

Digitally signed by Venkateswara Pavuluri
Date: 2/23/2021 12:49:26PM
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BIOPHARMACEUTICS

Product Background:

NDA: NDA-214846-ORIG-1

Drug Product Name / Strength: Relugolix (REL), estradiol (E2) and norethindrone acetate (NETA) fixed-dose combination tablet (40 mg, 1 mg and 0.5 mg)

Route of Administration: Oral

Applicant Name: Myovant Sciences GmbH

Submission:
The Applicant has submitted NDA 214846, a fixed dose combination (FDC) of the active ingredients relugolix, estradiol and norethindrone acetate tablets (40 mg, 1 mg and 0.5 mg) for the treatment of heavy menstrual bleeding associated with uterine fibroids. Relugolix is a new molecular entity, and estradiol and norethindrone acetate are established products in the United States.

Review Recommendation: **ADEQUATE**

Review Summary:
The Biopharmaceutics review is focused on the evaluation of dissolution method and acceptance criteria for Relugolix, E2 and NETA in the FDC tablet, bridging between the to-be-marketed and pivotal clinical formulations.

Dissolution Method and Acceptance Criterion: ADEQUATE
The following dissolution method and acceptance criteria for the release of relugolix, E2 and NETA from the FDC tablets are deemed acceptable:

Component	USP Apparatus	Speed (RPMs)	Medium/Temperature	Volume (mL)	Acceptance criterion
Relugolix	II (Paddle)	50	50 mM citrate buffer, pH 5.5 /37°C ± 0.5°C	900	Q = (b) (4)% in 30 minutes
E2 and NETA	II (Paddle)	50	0.3% Sodium dodecyl sulfate/37°C ± 0.5°C	500	Q = (b) (4)% in 30 minutes

Bridging of clinical formulations: ADEQUATE from Biopharm perspective
The applicant conducted a bioequivalence (BE) study (MVT-601-042) to bridge Pivotal Phase 3 and to-be-marketed formulations. This study will be reviewed by OCP review team (please refer to clinical pharmacology review for additional details).

Bridging of manufacturing sites: ADEQUATE

(b) (4) is the commercial manufacturing site and has manufactured the three registration/primary stability batches, one of which was used in the BE study. Therefore, bridging of manufacturing sites is not required.

Biowaiver Request: Not requested
Only one strength is developed.

List of Submissions reviewed:
Application 214846 - Sequence 0001 06/01/2020 Original
Application 214846 - Sequence 0019 11/25/2020 Response to IR

Highlight Key Outstanding Issues from Last Cycle: The Applicant was requested to provide dissolution data obtained using (b) (4) for E2 and NETA component of the FDC.

Concise Description of Outstanding Issues Remaining: None.

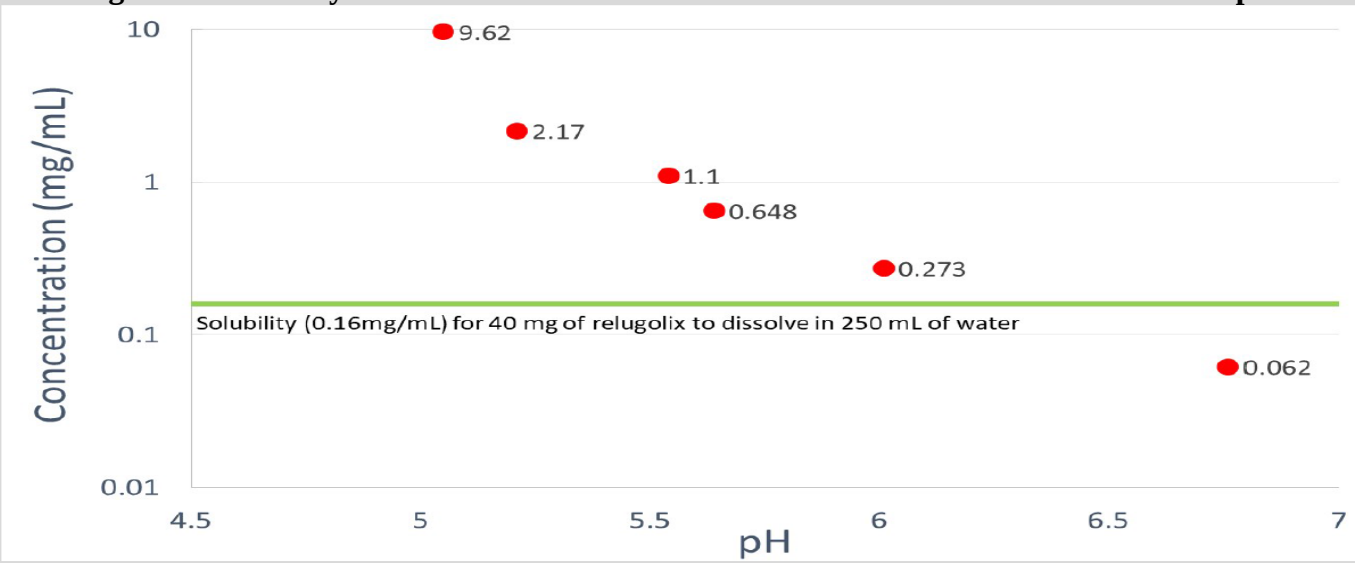
From Biopharmaceutics perspective, NDA 214846 for Relugolix, Estradiol, and Norethindrone acetate FDC tablets (40 mg, 1 mg and 0.5 mg) is recommended for APPROVAL.

BCS Designation

Reviewer's Assessment:
The Applicant has not claimed or requested any BCS classification for their drug product. The solubility and permeability information of the drug product components is provided in the document below:
\\cdsesub1\evsprod\nda214846\0001\m3\32-body-data\32p-drug-prod\relugolix-e2-neta\32p2-pharm-dev\phara-develop-drug-product.pdf

Solubility
Relugolix:
Relugolix is an organic amine with a pKa of 8.63 and has increasing solubility as pH is lowered below the pKa. Per the Applicant, Relugolix is a BCS Class IV compound. Based on the pH-solubility profile shown in Figure 1, a 40 mg dose would fully dissolve in 250 mL of an aqueous medium at pH ≤ 6. Therefore, REL meets the BCS threshold for the high solubility classification over the majority of the physiologically relevant pH range. The Applicant noted that a sample was prepared at an initial pH of 1.2. The concentration of this sample reached approximately 50 mg/mL after 30 minutes and decreased to 1.1 mg/mL at 24 hours (shown in Figure 1). This decrease in REL solution concentration was accompanied by precipitate formation and a shift in pH to 5.5. The Applicant noted that despite the decrease in solubility and increase in pH, relugolix solubility at pH ≤ 6 would meet the high solubility classification.
Overall, Relugolix appears to have low solubility over physiological pH range.

Figure 1: Solubility of REL After 24 Hours at 37°C as a Function of Final Measured pH



E2 and NETA:

Based on the pH profile data (Figure 2 and 3), a 1 mg dose of E2 and a 0.5 mg dose of NETA would fully dissolve in 250 mL of an aqueous medium between pH 1.1 and pH 6.8. Therefore, E2 and NETA meet the BCS threshold for the high solubility classification over the physiologically relevant pH range.

Figure 2: Solubility of Estradiol Hemihydrate After 16 Hours at Room Temperature as a Function of pH

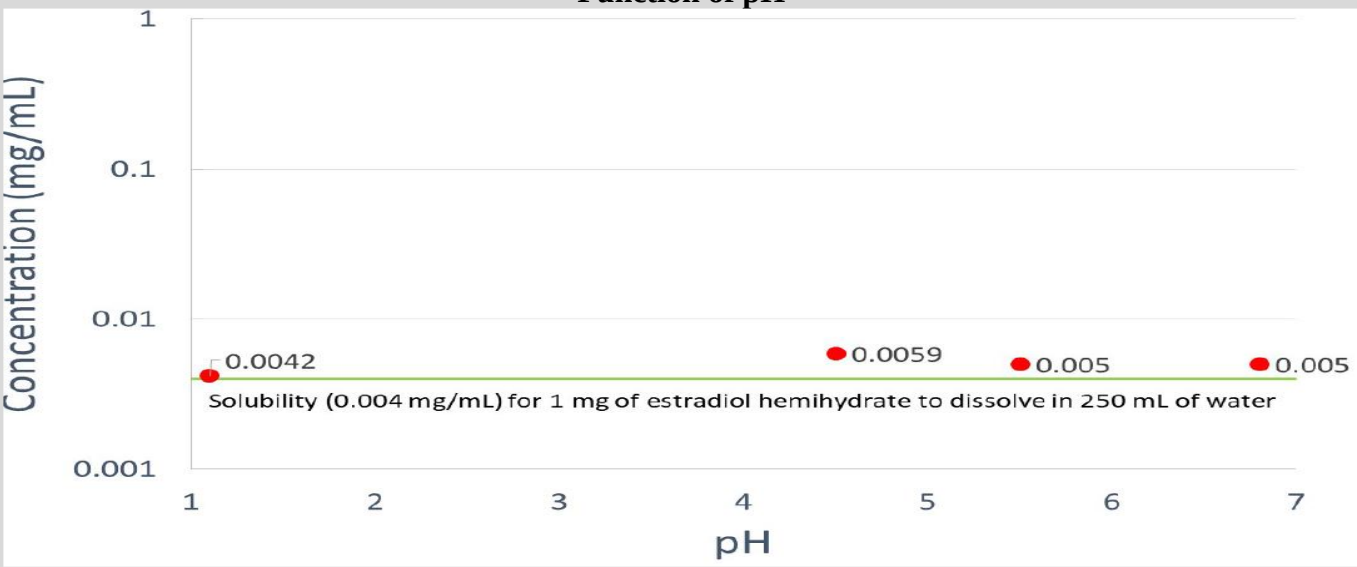
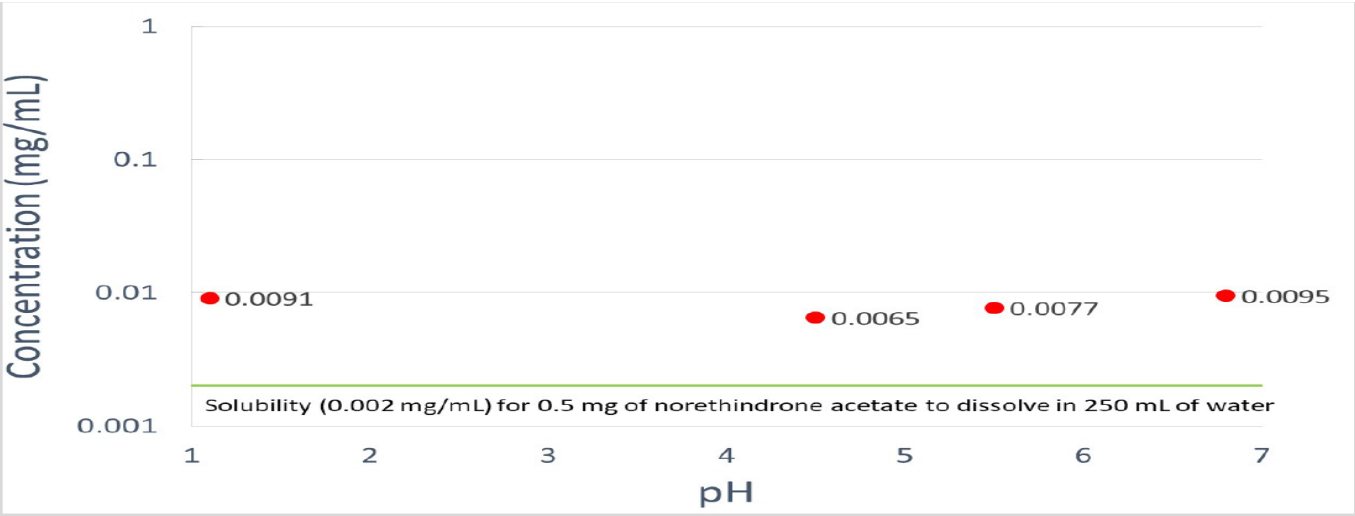


Figure 3: Solubility of Norethindrone Acetate After 16 Hours at Room Temperature as a Function of pH



Permeability

Relugolix:

The Applicant stated that the apparent permeability values of relugolix across Caco-2 cell monolayers is 0.513×10^{-6} cm/s and 8.43×10^{-6} cm/s from apical to basal and basal to apical, respectively.

E2 and NETA:

The Applicant mentions that both drug substances meet the BCS threshold for high solubility and high permeability for a 1mg dose of E2 and a 0.5 mg dose of NETA (Summary of Biopharmaceutic studies).

Dissolution: Please see below.

Drug Product

The FDC tablet is an immediate-release formulation manufactured (b) (4)

The composition of the FDC drug product is provided below.

Table 1: Composition of Relugolix/Estradiol/Norethindrone Acetate tablets, 40/1/0.5 mg

Component	Quality Standard	Function	Composition	
			(% w/w)	(mg/Tablet)
Core Tablet				
Relugolix	In-house	Active ingredient	(b) (4)	40.0
Estradiol	In-house[a]	Active ingredient		1.0[b]
Norethindrone acetate	In-house[a]	Active ingredient		0.5
Mannitol	USP-NF/Ph. Eur.	(b) (4)		(b) (4)
Sodium starch glycolate	USP-NF/Ph. Eur.			
Hydroxypropyl cellulose	USP-NF/Ph. Eur.			
Lactose monohydrate	USP-NF/Ph. Eur.			
Magnesium stearate	USP-NF/Ph. Eur.			
(b) (4)				(b) (4)
Film-Coated Tablet				
(b) (4)				

Abbreviations: Ph. Eur = European Pharmacopoeia; qs = quantum sufficit; USP-NF = United States Pharmacopoeia–National Formulary.

[a] In-house standard is based on USP-NF/Ph. Eur. and includes the manufacturer-specific testing outlined in Sections S.4.1 (estradiol) and S.4.1 (norethindrone acetate).

(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 relugolix, E2, and NETA in the FDC tablets.

Relugolix

Proposed dissolution method and acceptance criterion

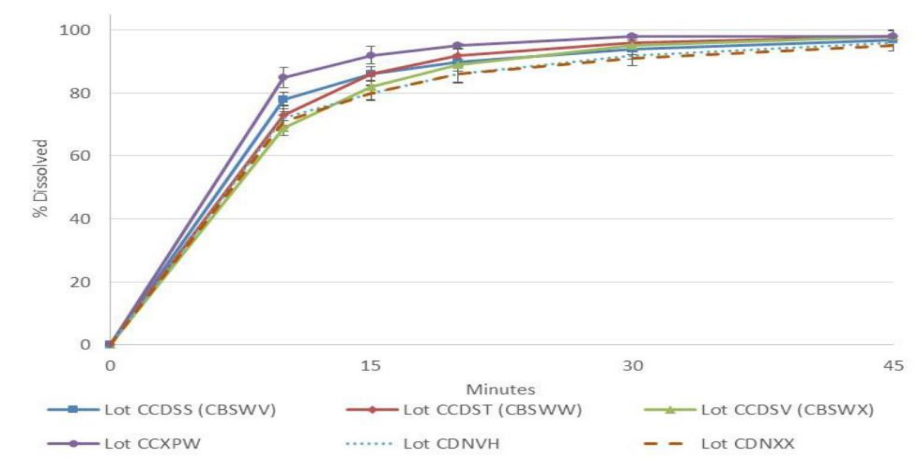
The following dissolution method and acceptance criterion were proposed for dissolution testing of relugolix in REL/E2/NETA FDC Tablet.

Table 2: Dissolution method for relugolix

Component	USP Apparatus	Speed (RPMs)	Medium/Temperature	Volume (mL)	Acceptance criterion
Relugolix	II (Paddle)	50	50 mM citrate buffer, pH 5.5 /37°C ± 0.5°C	900	Q = (b) (4) % in 30 minutes

The dissolution profiles of relugolix at release and stability obtained from clinical batches, and primary stability batches of the FDC tablet are summarized in the link (starting page 19) below: \\cdsesub1\evsprod\nda214846\0001\m3\32-body-data\32p-drug-prod\relugolix-e2-neta\32p5-contr-drug-prod\32p56-justif-spec\justification-of-specifications.pdf. These dissolution profile data were used to establish the dissolution acceptance criterion for the relugolix component. The dissolution lot release results including, the individual data, are provided in \\cdsesub1\evsprod\nda214846\0001\m3\32-body-data\32p-drug-prod\relugolix-e2-neta\32p5-contr-drug-prod\32p54-batch-analys\rel-stab-diss-data.xlsx. The dissolution profiles of relugolix at release is presented below.

Figure 4: Relugolix Dissolution of FDC Tablets



Dissolution method development

(b) (4)

[redacted]

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(b) (4)

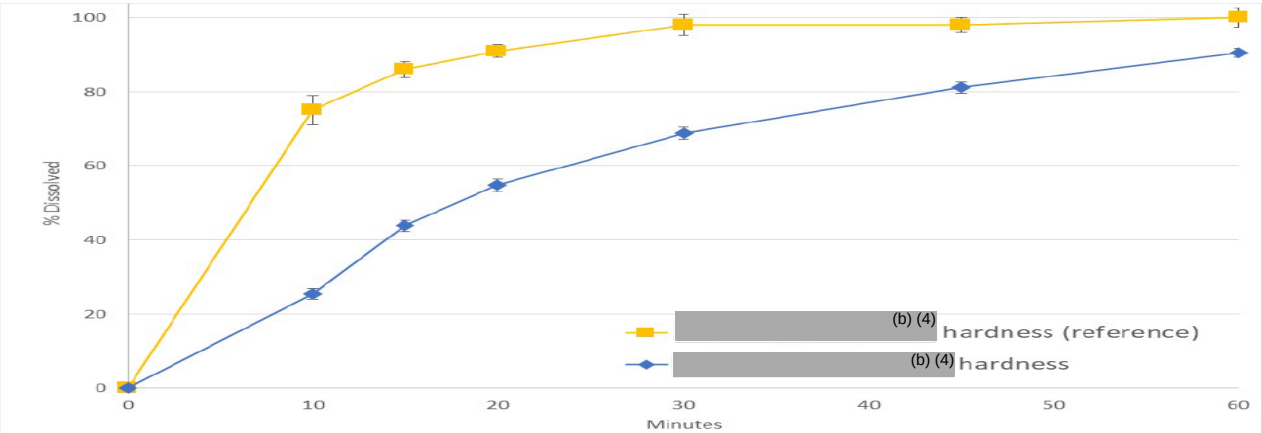
Discriminating ability of the dissolution method

The Applicant provided data for the discriminating ability of the dissolution method for relugolix component of the FDC tablets. The details are provided in the dissolution method development report (Page 117, link above). To evaluate the discriminatory capability, tablets were intentionally manufactured with variations to the composition, process, or material attributes. Aberrant tablets were evaluated with large particle size relugolix drug substance, increased disintegration time (b) (4) In addition, each aberrant formulation was made by compressing tablets to different hardness. The Applicant noted that given the robust formulation, significant changes were necessary to generate tablets with poor dissolution.

Per the Applicant, the relugolix (b) (4) (b) (4). This is similar to drug substance particle size (b) (4) for drug product (batch#CBSWW) used in in vivo studies. (b) (4) (b) (4) As shown in Figure 7 below, only in the extreme case where the REL drug substance (b) (4) was (b) (4), a slowdown in dissolution was observed. (b) (4)

(b) (4)

Figure 7: Effect of Relugolix Dissolution of FDC Tablets Manufactured with (b) (4) (Apparatus 2, 50 rpm, 50 mM Citrate Buffer pH 5.5)

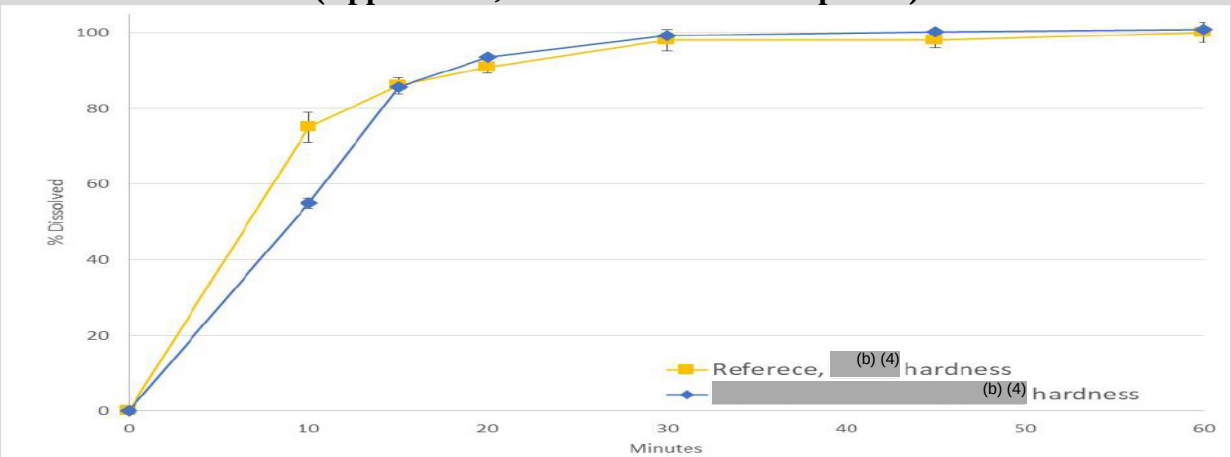


50 mM citrate buffer pH 5.5, 900 mL, 50 rpm (n = 6 for aberrant and n = 12 for reference)
Lot CBSWW for reference and CCMGC (b) (4) hardness) for aberrant tablet

Figure 8: Effect of (b) (4) and Tablet Hardness on Relugolix Dissolution of FDC Tablets (Apparatus 2, 50 rpm, 50 mM Citrate Buffer pH 5.5)

(b) (4)

Figure 9: Effect of (b) (4) on Relugolix Dissolution of FDC Tablets (Apparatus 2, 50 mM Citrate Buffer pH 5.5)



50 mM citrate buffer pH 5.5, 900 mL, 50 rpm (n = 6 each)

E2 and NETA

Proposed dissolution method and acceptance criterion

The proposed dissolution method for E2 and NETA component in the FDC tablet is the same as approved by FDA for Activella (E2/NETA) tablets and are specified in USP Monograph for Estradiol and Norethindrone Acetate Tablets. The following dissolution method and acceptance criterion were proposed.

Table 3: Dissolution Method for E2 and NETA in FDC tablets

Component	USP Apparatus	Speed (RPMs)	Medium/Temperature	Volume (mL)	Acceptance criterion
E2 and NETA	II (Paddle)	50	0.3% Sodium dodecyl sulfate/37°C ± 0.5°C	500	Q = (b) (4)% in 30 minutes

The dissolution profiles of E2 and NETA at release and stability obtained from clinical batches, and primary stability batches of the FDC tablet are summarized in the link (starting page 20) below: \\cdsesub1\evsprod\nda214846\0001\m3\32-body-data\32p-drug-prod\relugolix-e2-neta\32p5-contr-drug-prod\32p56-justif-spec\justification-of-specifications.pdf. The dissolution lot release results including, the individual vessel dissolution data, are provided in \\cdsesub1\evsprod\nda214846\0001\m3\32-body-data\32p-drug-prod\relugolix-e2-neta\32p5-contr-drug-prod\32p54-batch-analys\rel-stab-diss-data.xlsx. The dissolution profiles of E2 and NETA at release are presented below.

Figure 10: Dissolution Profiles of E2 from FDC tablets

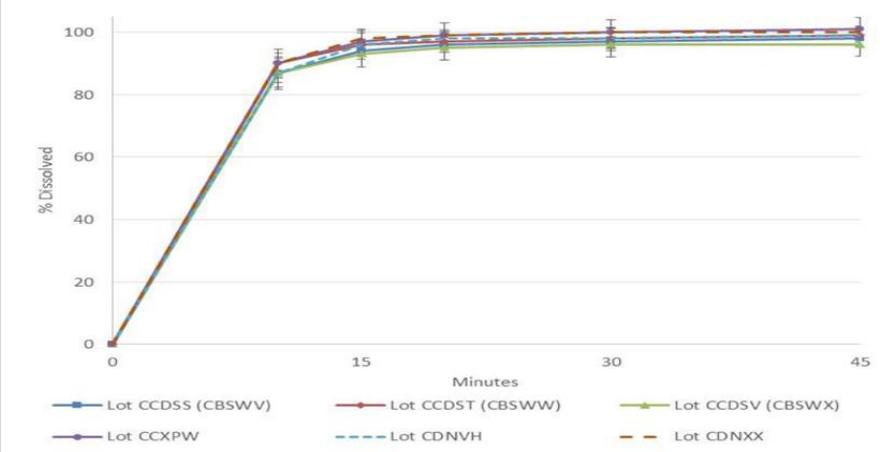
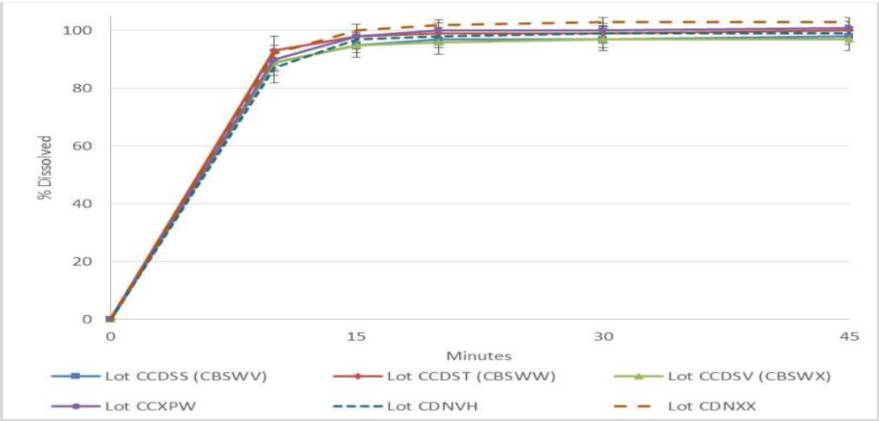


Figure 11: Dissolution Profiles of NETA from FDC tablets



Dissolution method development

(b) (4)

[redacted]

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(b) (4)

Discriminating ability of the dissolution method

The same aberrant tablets as described above for relugolix were used to evaluate the discriminatory capability of dissolution method for E2 and NETA component of the FDC tablets. Similar to relugolix, (b) (4) in all three hardness. The (b) (4) did not impact hormone dissolution.

Figure 15: Effect of (b) (4) and Tablet Hardness on Estradiol Dissolution of FDC Tablets (Apparatus 2, 50 rpm, 0.3% SDS)

(b) (4)

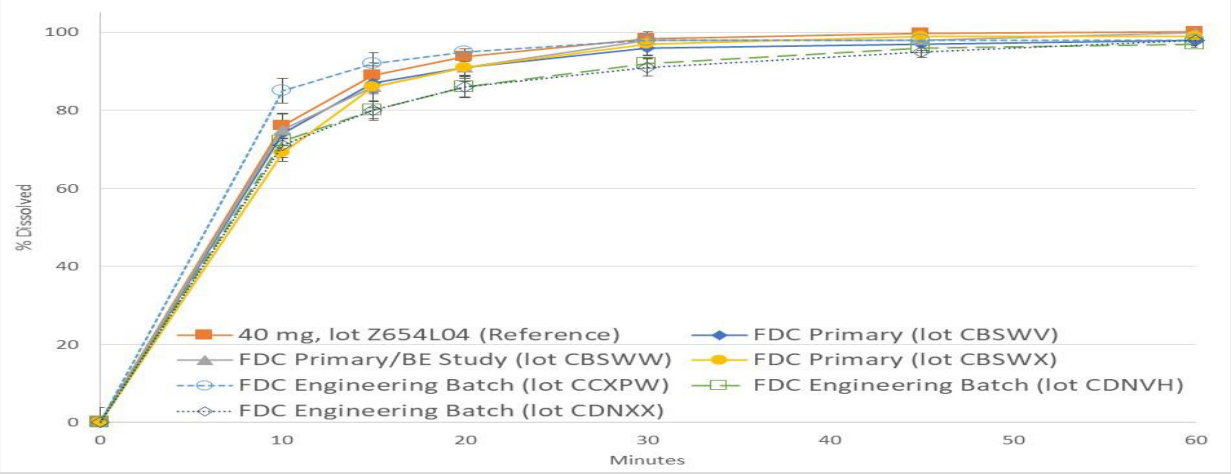
Figure 16: Effect of (b) (4) and Tablet Hardness on Norethindrone Acetate Dissolution of FDC Tablets (Apparatus 2, 50 rpm, 0.3% SDS)

(b) (4)

In Vitro Interaction Between the Activella® Component and Relugolix Component

A bioequivalence clinical study was performed to demonstrate BE of the to-be-marketed FDC tablets (40 mg relugolix/1 mg estradiol/0.5 mg norethindrone) to product administered in the Phase 3 study: the 40 mg relugolix tablet co-administered with Activella® tablets (1 mg estradiol and 0.5 mg norethindrone acetate). The dissolution of relugolix was evaluated for the primary stability and engineering batches of FDC tablets compared to the 40 mg single agent batch used in the BE study by the proposed FDC dissolution method, pH 5.5 citrate buffer. The dissolution profiles show that the products have similar dissolution for relugolix and hence insignificant interactions between E2/NETA and relugolix components under *in vitro* conditions (>85% release within 15 minutes was observed in all tested formulations) as shown in the figures below.

Figure 17: Dissolution profiles of Relugolix from 40 mg single tablet and FDC tablets



Similarly, dissolution of E2 and NETA was also evaluated for the primary stability and engineering batches of FDC tablets compared to Activella® tablets used in the BE study. As shown in the figures below, both E2 and NETA achieved > 85% dissolved within 15 minutes from all batches.

Figure 18: Dissolution Profiles of E2 from E2/NETA, 1/0.5 mg Tablets and Co-study with Relugolix FDC Tablets

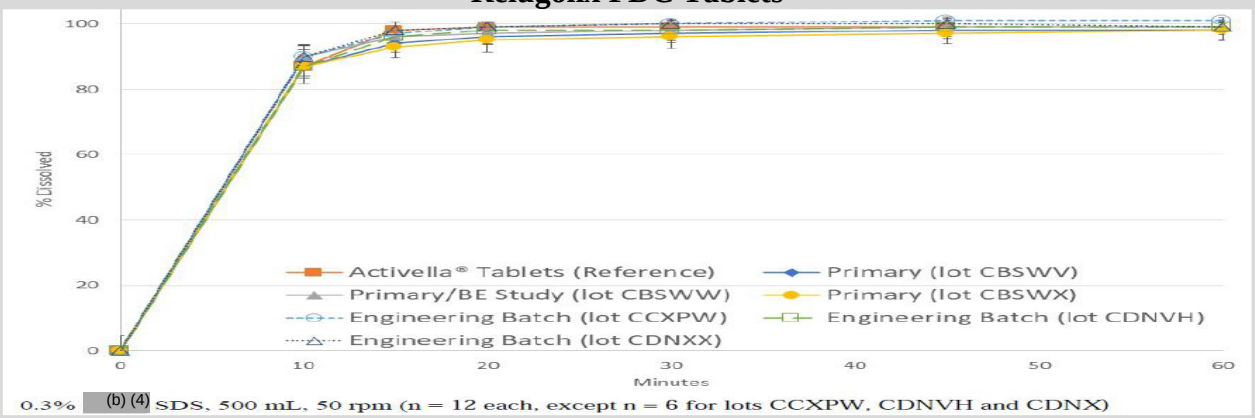
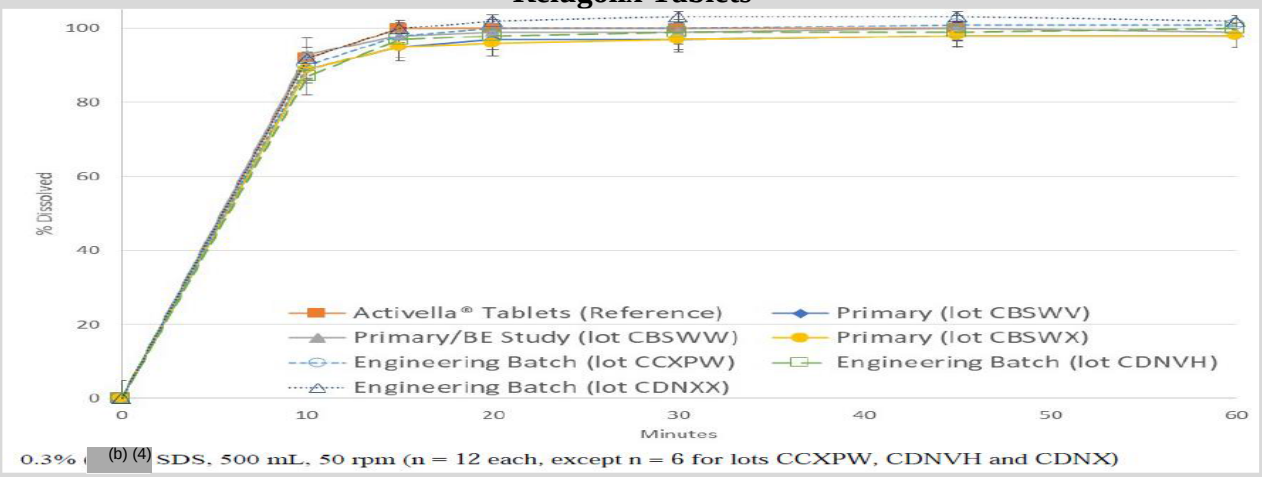


Figure 19: Dissolution Profiles of NETA from E2/NETA, 1/0.5 mg Tablets and Co-study with Relugolix Tablets



Reviewer's assessment:

Relugolix component

- The Applicant has developed and validated a dissolution method using USP apparatus II at 50 RPM for relugolix in FDC tablet. The proposed dissolution method showed some discriminating ability towards relugolix drug substance particle size and (b) (4). The proposed dissolution method is acceptable.
- Data show that release of relugolix is not affected by E2/NETA components in FDC tablet.
- The Applicant's proposed dissolution acceptance criterion *Q*= (b) (4) *% in 30 minutes* for relugolix is acceptable based on all the data provided.

E2 and NETA component

- The proposed dissolution method for E2 and NETA components in FDC tablet is the same as approved for Activella (E2/NETA) tablets and as specified in USP Monograph for Estradiol and

Norethindrone Acetate Tablets. A 0.3% concentration of SDS (b) (4) as the dissolution medium is acceptable since no added advantage in dissolution was observed with (b) (4). The proposed dissolution method showed some discriminating ability towards (b) (4) The proposed dissolution method is deemed acceptable for the FDC tablet given that there is no effect of relugolix on the release of E2 and NETA components, and a consistent performance in testing of primary stability batches.

- The Applicant proposed dissolution acceptance criterion *Q*= (b) (4) *% in 30 minutes* for both E2 and NETA component, which is acceptable based on the data.

Bridging of Clinical Formulations

Bridging of clinical formulations: ADEQUATE

Relugolix was first formulated as a single-agent tablet containing 40 mg of relugolix. For Phase 3 studies, relugolix 40 mg tablet (T4B formulation) was co-administered with commercially available E2/NETA tablets (1/0.5 mg), namely Activelle® (EU brand), Kliovance® (EU brand), or Activella® (US brand) that were over-encapsulated for blinding purposes. Subsequently, REL/E2/NETA FDC tablets were developed and a bioequivalence (BE) study (MVT-601-042) was conducted to bridge the product used in pivotal Phase 3 studies to the REL/E2/NETA FDC tablets. This BE study will be reviewed by the Clinical Pharmacology team.

The dissolution profiles of relugolix from relugolix/E2/NETA FDC tablets (to-be-marketed formulation) and the 40-mg T4B single-agent tablets (formulation used in the pivotal phase 3 studies) are similar and shown in Figure 17.

Comparability between the European and US brands of E2/NETA

The Applicant has provided data and documents to show comparability between the European and US brands of E2/NETA (1/0.5 mg) tablets used in phase 3 studies. Novo Nordisk, the commercial manufacturer of the Activelle, Kliovance, and Activella used in phase 3, has provided a signed declaration of comparability with supporting data and certificates of analysis which will be reviewed by the Drug Product reviewer. Additionally, the Applicant has provided dissolution testing on Activelle, Kliovance, and Activella (as shown in the figures below) that shows similar release profiles between the three brands. The details are provided in the link below (starting page 57):

\\cdsesub1\evsprod\nda214846\0001\m3\32-body-data\32p-drug-prod\relugolix-e2-neta\32p2-pharm-dev\phara-develop-drug-product.pdf

Figure 20: Estradiol Dissolution Profiles of Hormone Tablets

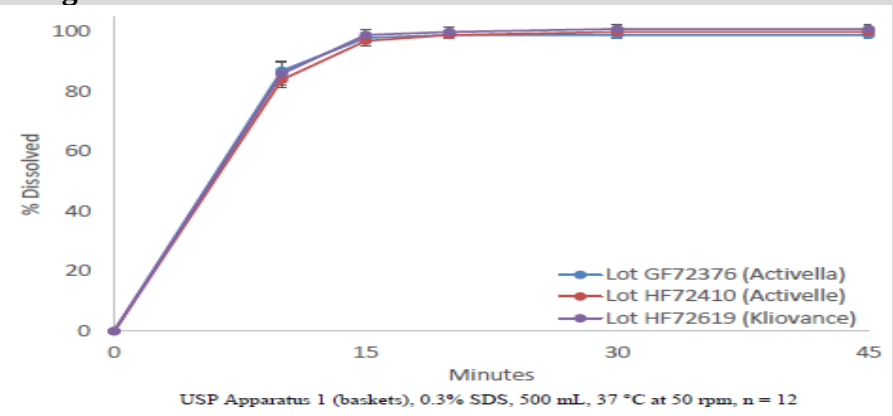
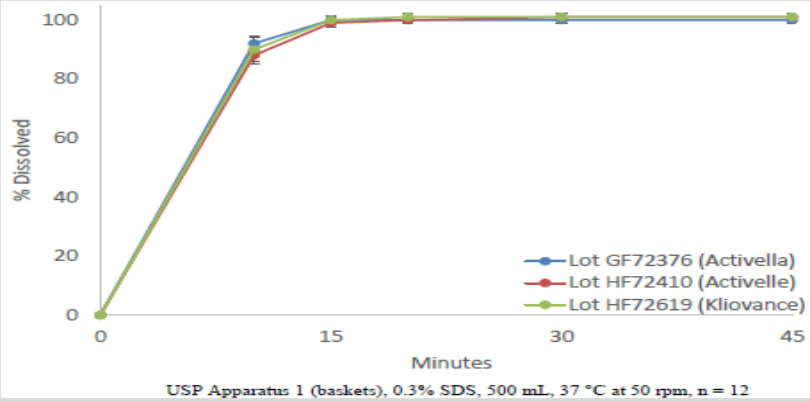


Figure 21: Norethindrone Acetate Dissolution Profiles of E2/NETA Tablets

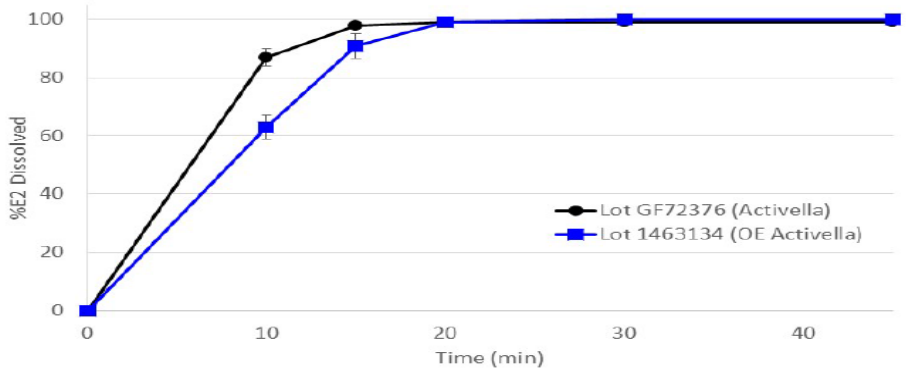


USP Apparatus 1 (baskets), 0.3% SDS, 500 mL, 37 °C at 50 rpm, n = 12

Effect of encapsulation of E2/NETA tablets

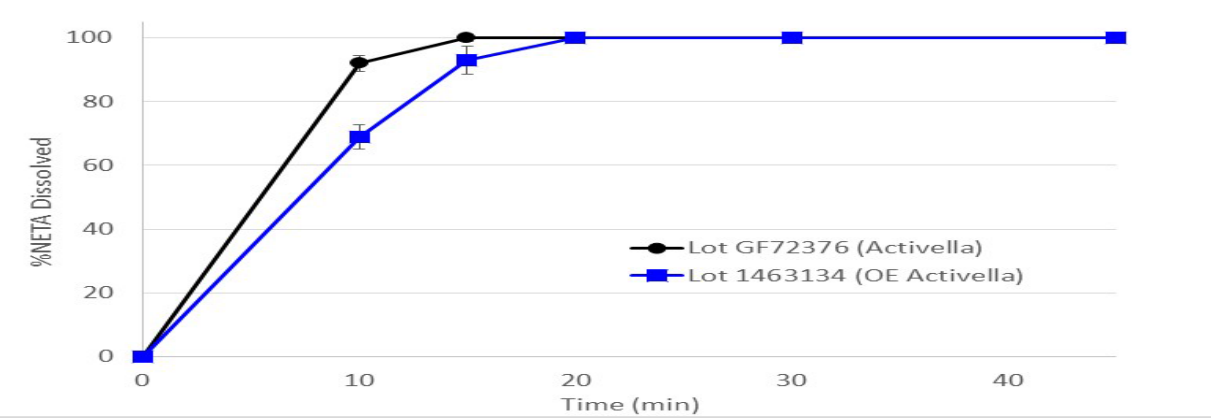
The Applicant used over-encapsulated (OE) Activella®, Activelle®, or Kliovance® tablets for the phase 3 studies for blinding purposes. (b) (4) The dissolution profiles of E2 and NETA from Activella tablet and encapsulated Activella tablet in proposed QC dissolution medium (0.3% SDS (b) (4)) is similar after 20 minutes as shown in the figures below. The difference in percent dissolved for both components was less than 10% by the 15-minute time point demonstrating the presence of the (b) (4) shell had no meaningful impact on the dissolution process. The details are provided in the link (Page 16) \\cdsesub1\evsprod\nda214846\0001\m3\32-body-data\32p-drug-prod\relugolix-e2-neta\32p2-pharm-dev\phara-develop-drug-product.pdf.

Figure 22. Dissolution of E2 from Activella® and Over-Encapsulated Activella®



Method: USP dissolution apparatus 1 (basket), 50 rpm speed, 37°C, 500 mL of 0.3% SDS. All data represent average of n=12 tablets (Lot GF72376) or n=6 tablets (Lot 1463134) with error bars representing 1 standard deviation.

Figure 23. Dissolution of NETA from Activella® and Over-Encapsulated Activella®



The Applicant also compared the dissolution profiles of Kliovance® and over-encapsulated Kliovance® for both E2 and NETA in three required media (b) (4) per the Guidance. Since all European and US products are similar in QC dissolution medium, Activella® and the Activella® encapsulated tablets can be expected to have similar profiles in these 3 pH mediums, further supporting the lack of any meaningful impact of over-encapsulation on drug availability.

Bridging of manufacturing sites

Bridging of manufacturing sites: ADEQUATE

Patheon Inc., located in Ontario, Canada, is the commercial manufacturing site and has manufactured the three registration/primary stability batches, one of which was used in the BE study (Section P.3.1, Manufacturers). Therefore, bridging of manufacturing sites is not required.

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 214846 is recommended for APPROVAL.

Appendix 1

The Information Request conveyed to the Applicant during the review process

Information Request 1 (IR 1)

1. You have proposed to use 0.3% SDS (b) (4) as the medium for dissolution method of E2 and NETA in your proposed drug product. Provide dissolution data obtained using (b) (4) for both E2 and NETA.

Primary Biopharmaceutics Reviewer Name: Kalpana Paudel, Ph.D.
Secondary Reviewer Name: Vidula Kolhatkar, Ph.D.

Kalpana Paudel

Digitally signed by Kalpana Paudel
Date: 1/25/2021 02:24:13PM
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Vidula Kolhatkar

Digitally signed by Vidula Kolhatkar
Date: 1/25/2021 02:27:24PM
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This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

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