CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

209405Orig1s000

PRODUCT QUALITY REVIEW(S)

U.S. FOOD & DRUG ADMINISTRATION

RECOMMENDATION

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

NDA 209405
Levonorgestrel and Ethinyl Estradiol Tablets
Assessment #1

Drug Product Name	Levonorgestrel and Ethinyl Estradiol Tablets *Note: Proprietary name to be determined*
Dosage Form	Tablet
Strength	0.1 mg / 0.02 mg
Route of Administration	Oral
Rx/OTC Dispensed	Rx
Applicant	Exeltis USA Inc.
US agent, if applicable	A. Sosa, RPI, Regulatory Professionals / Premier Research, Newark/Castro Valley, Calif. (as of 01/24/2020). Previously no designated US agent.

Submission(s) Assessed	Document Date	Discipline(s) Affected
Resubmission after RTF (0006)	05/30/2019	All
SN0007	07/16/2019	Manufacturing
SN0008	07/22/2019	Drug Product; Biopharmaceutics
SN0009	08/21/2019	Labeling
SN0011	10/07/2019	Drug Product
SN0012	10/08/2019	Drug Product
SN0013	10/15/2019	Biopharmaceutics
SN0014	10/24/2019	Labeling
SN0017	11/15/2019	Manufacturing
SN0019	11/22/2019	Drug Product
SN0023	12/19/2019	Drug Product; Manufacturing
SN0024	01/03/2020	Manufacturing
SN0025	01/10/2020	Manufacturing
SN0027	02/07/2020	Labeling
SN0028	02/14/2020	Drug Product
SN0029	02/14/2020	Biopharmaceutics; Manufacturing
SN0030	02/20/2020	Drug Product; Manufacturing; Biopharmaceutics

SN0031	02/21/2020	Labeling
SN0032	02/24/2020	Labeling
SN0034	03/04/2020	Labeling
SN0035	03/10/2020	Labeling
SN0036	03/18/2020	Labeling
SN0037	03/23/2020	Labeling
SN0038	03/24/2020	Labeling
SN0039	03/25/2020	Labeling
SN0040	03/27/2020	Labeling
SN0041	03/27/2020	Labeling

Submissions prior to SN 0006 were not reviewed. The 0006 resubmission was complete from the CMC perspective.

QUALITY ASSESSMENT TEAM

Discipline	Primary Assessment	Secondary Assessment
Drug Substance	Soumya Mitra	Donna Christner
Drug Product	Hong Cai	Moo-Jhong Rhee
Manufacturing	Zhao Wang	Jean Tang
Microbiology	Zhao Wang	Jean Tang
Biopharmaceutics	Rajesh Savkur	Hansong Chen
Regulatory Business Process Manager	Marquita Burnett	
Application Technical Lead	Mark Seggel	
Laboratory (OTR)	not applicable	not applicable
Environmental	Hong Cai	Moo-Jhong Rhee

U.S. FOOD & DRUG ADMINISTRATION

EXECUTIVE SUMMARY

IQA NDA Assessment Guide Reference

I. RECOMMENDATIONS AND CONCLUSION ON APPROVABILITY

Exeltis USA Inc.'s resubmission of 505(b)(2) New Drug Application #209405 for Levonorgestrel and Ethinyl Estradiol Tablets is recommended for approval.

Sufficient information and supporting data have been provided in accordance with 21CFR 314.50 to ensure the identity, strength, quality, purity, potency and bioavailability of the drug product. An expiration dating period (shelf-life) of 18 months for product stored at 20ºC to 25ºC has been established.

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

As revised, the product labeling and labels conform to the requirements in 21 CFR 201.

The claim for a categorical exclusion from an EA under 21 CFR 25.31(a) is acceptable.

II. SUMMARY OF QUALITY ASSESSMENTS

A. Product Overview

While there are several approved combined oral contraceptive (COC) tablets containing norethindrone (or norethindrone acetate) and ethinyl estradiol that are (b) (4) there are currently no approved levonorgestrel (LNG) and ethinyl estradiol (EE) COCs that are considered (b) (4)

In 2013, Everett Laboratories, Chatham, NJ, submitted a pre-IND meeting request to discuss the development of a levonorgestrel and ethinyl estradiol (b) (4) tablet (EV402). While a U.S. IND was never opened, the sponsor (eventually operating as Exeltis USA Inc.) did engage the Agency on several occasions for advice. On January 7, 2019, Exeltis submitted NDA 209405 for Levonorgestrel and Ethinyl Estradiol (b) (4) Tablets, 0.10 mg/0.02 mg. A Refuse to File letter was issued on March 8, 2019 because of incomplete clinical datasets. The application was resubmitted on May 30, 2019 and was found acceptable for filing.

There are many approved COCs, including innovator products and numerous generic equivalents. The proposed drug product was

'developed' as an alternative for women who prefer an LNG + EE COC, but who have difficulty swallowing a COC tablet.

(b) (4)

(b) (4) In this case, the established name for the drug product is 'levonorgestrel and ethinyl estradiol tablets.' That the product may be chewed or swallowed whole can be described in the labeling.

(b) (4)

As such, the proposed new 505(b)(2) drug product is not expected to introduce any new risks to patients beyond those (b) (4) many other LNG + EE COCs. Oral tolerability was confirmed during the pivotal BE study. Perhaps the only 'risk' is the potential that some women may not find the chewed tablet to be palatable (b) (4)

The finished product consists of a blister card with 21 active tablets and 7 placebo tablets. The latter are intended to facilitate adherence to the recommended dosing regimen.

Proposed Indication(s) including Intended Patient Population	The drug product is a fixed-dose combination of levonorgestrel, a progestin, and ethinyl estradiol, an estrogen, indicated for use by females of reproductive potential to prevent pregnancy.

Duration of Treatment	Use to be continued for as long as contraception is desired.
Maximum Daily Dose	One active tablet (0.1 mg levonorgestrel and 0.02 mg ethinyl estradiol) for 21 consecutive days, followed by one inert, placebo tablet for 7 days.
Alternative Methods of Administration	Not applicable

B. Quality Assessment Overview

Drug Substance: Adequate

Levonorgestrel and ethinyl estradiol are widely used active ingredients in contraceptive drug products. The chemistry, manufacturing and controls (CMC) of these drug substances is documented in Type II Drug Master File (DMF) (b) (4) and DMF (b) (4) respectively. Both DMFs have been found adequate to support use of the drug substances in the drug product. Adequate supporting information is also provided within NDA 209405. This NDA is recommended for APPROVAL from the drug substance perspective. See Chapter I, Drug Substance, for details.

Drug Product: Adequate

The finished drug product consists of a small aluminum push-through foil and (b) (4) film blister pack with three rows of 7 white active tablets and a single row of 7 peach colored placebo tablets. The tablets, which are (b) (4) are ca. 6.4 mm in diameter and 2.6 mm in thickness. (b) (4) Rather, the tablets may be swallowed whole or chewed and swallowed. (b) (4)

The excipients in the active tablets are commonly used in tablet formulations. Lactose monohydrate, (b) (4) inactive ingredient in the active tablets. Other inactive ingredients include corn starch, pregelatinized starch, povidone, crospovidone, and magnesium stearate. In addition to these excipients, the placebo tablets also contain FD&C Red #40 Lake and D&C Yellow #10 Lake. All inactive ingredients meet USP/NF quality standards and are suitable for use in the product.

(b) (4)

The drug product specification includes the typical battery of tests for ensuring identity, strength, purity, quality and bioavailability of the active tablets. Tests of specific relevance to the proposed product are (b) (4) hardness ((b) (4) N), (b) (4), (b) (4), disintegration (b) (4) minutes), and dissolution [see discussion under Biopharmaceutics]. The proposed limits for degradation products / related substances are acceptable to the Pharm/Tox review team. Overall, the tests, associated analytical procedures, and acceptance criteria, as revised, are suitable for ensuring that the product has the quality requisite for safe and efficacious use. The placebo tablet specification includes tests for hardness ((b) (4) N) and disintegration ((b) (4) minutes).

Product stability was characterized under long term (25ºC/60% RH) for 18 to 24 months, intermediate conditions (30ºC/65% RH) for 12 months, and accelerated conditions (40ºC/75% RH) for 6 months. (b) (4) The current lack of dissolution data at the 30-minute sampling timepoint for product stored longer than 18 months, (b) (4) precludes extrapolation of an expiration dating period shelf-life beyond 18-months at this time. An expiration dating period of 18-month is granted for product stored at 20ºC-25ºC (68ºF-77ºF). Temperature excursions are not permitted.

Environmental Assessment:
The applicant has requested a Categorical Exclusion from the EA requirements in accordance with 21 CFR 25.31(a) since approval of the application is not expected to increase use of the active ingredients. The applicant also confirms that to the best of its knowledge no extraordinary circumstances exist per 21 CFR 25.15(d). The categorical exclusion is therefore granted.

Overall, the application is recommended for APPROVAL from the drug product perspective.

See IQA Chapter II for details of the Drug Product assessment.

Labeling: Adequate

The relevant sections of the prescribing information (PI) and the container carton labels were evaluated for conformance with the requirements of 21 CFR 201. Deficiencies were identified and recommendations for revision

were conveyed to the Applicant. The applicant revised the labels and labeling accordingly. For example, product nomenclature was revised (b) (4) along with inclusion of the option for swallowing the tablets whole in addition to chewing, and revision of the format of the drug product established name). Changes to the storage statements were made to conform to current best practices. Revisions to the structures of the active ingredients provided under Section 11, Description, of the PI, were made to improve consistency. Other improvements to the labels and labeling are discussed in IQA Chapter IV: Labeling, and associated Addendum.

The proposed proprietary name (b) (4) has been denied by DMEPA. The product will be labeled only with the drug product established name, "levonorgestrel and ethinyl estradiol tablets" until an acceptable tradename is identified.

The revised container / carton labels and the revised prescribing information as submitted on March 26, 2020 (sn0040) and on March 27, 2020 (sn0041), respectively, are factually correct and meet the requirements of 21 CFR 201. This application is now recommended for APPROVAL from the CMC labeling perspective.

Manufacturing: Adequate

The Manufacturing Integrated Assessment documents the evaluation of the active and placebo tablet manufacturing and packaging processes, the drug substance and drug product manufacturing, packaging and testing facilities, and the controls for ensuring that the finished product meets quality microbiology standards. For comments on the latter see the section on Microbiology below.

Process: (b) (4) (b) (4)

(b) (4)

Facilities: The drug product manufacturing and packaging facility, Laboratorios León Farma S.A., was found acceptable for the manufacture of tablets based on a District File Review (DFR). All other drug stance manufacturing and testing facilities, as well as the finished product testing facilities, and An Overall manufacturing Inspection recommendation of APPROVE was issued on December 4, 2019. No changes in compliance status have been reported since the December recommendation was made.

From the manufacturing process and facilities perspective this application is found ADEQUATE. See attached 'Manufacturing Integrated Assessment' for details.

Biopharmaceutics: Adequate

The Biopharmaceutics assessment of NDA 209405 focused on development of the dissolution test method, dissolution data, the dissolution test acceptance criterion, and the tablet disintegration test acceptance criterion.

Because of the very low doses of LNG and EE in the proposed product, both are considered highly soluble compounds per the BCS guidance.

(b) (4)

[redacted] However, the dissolution profiles of Levonorgestrel and Ethinyl Estradiol in four media across the physiological pH range indicate that [redacted]% of both Levonorgestrel and Ethinyl Estradiol is dissolved at the 15-minute time point, indicative of an immediate release formulation. Exeltis concluded that testing in a medium of polysorbate 80 (5 µg/g) in water could discriminate dissolution profiles between whole and ground tablets, a conclusion not shared by the Biopharmaceutics review team. Both ground and whole tablets are dissolved in under 15 minutes. Further evidence of the discriminatory ability of the method was not sought. However, the Agency requested that the acceptance criteria be [redacted] NLT [redacted]%(Q) for LNG and EE. Exeltis balked, but after further communication with the Agency, they agreed to rerevise the acceptance criteria. The regulatory dissolution test is based on USP Apparatus II (paddles) at 75 rpm and 500 mL of polysorbate 80 (5 µg/g) in water at 37°C. The acceptance criterion for both LNG and EE is Q= [redacted]% dissolved in 30 minutes.

Exeltis also agreed to a disintegration test that requires both active and placebo tablets disintegrate in not more than [redacted] minutes.

From the Biopharmaceutics perspective this application, with the revised acceptance criteria for dissolution and disintegration, is adequate for APPROVAL.

Microbiology (if applicable): Adequate

Product Quality Microbiology was evaluated by the Manufacturing review team. Microbial tests are performed at release and on stability according to USP <61>/<62>, and the acceptance criteria conform to USP <1111>. Reduced test frequency (one in ten batches) is acceptable. Overall, the manufacturing and controls are adequate to ensure the microbiological quality of a solid oral dosage form. See attached 'Manufacturing Integrated Assessment' for details.

C. Risk Assessment

From Initial Risk Identification			Assessment		
Attribute/ CQA	Factors that can impact the CQA	Initial Risk Ranking	Risk Mitigation Approach	Final Risk Evaluation	Lifecycle Considerations/ Comments
Appearance	• Formulation • Raw materials • Process parameters • Scale/equipment • Site	LOW	(b) (4)	Acceptable	
Assay	• Formulation • Raw materials • Process parameters • Scale/equipment • Container/closure System (CCS) • Site	MEDIUM		Acceptable	(b) (4)
Related Substances Impurities / Degradants	• Formulation • Process parameters • Container/closure system	LOW		Acceptable	(b) (4)
Physical Stability (solid state)	• Formulation • Raw materials • Process parameters • Scale/equipment • Site	MEDIUM		Acceptable	(b) (4)
(b) (4)	• API • Process parameters • Container/closure system (CCS)	LOW		Acceptable	
Uniformity of Dosage Units	• Formulation • Raw materials • Process parameters • Scale/equipment • Site	HIGH		Acceptable	(b) (4)
Palatability	• Formulation • Raw materials • Process parameters • Scale/equipment • Site	MEDIUM		Acceptable	(b) (4)
Tablet Hardness	• Formulation • Raw materials • Process parameters • Scale/equipment • Site	LOW		Acceptable	(b) (4)
Dissolution	• Formulation • Raw materials • Process parameters • Scale/equipment • Site	MEDIUM		Acceptable	Data at 30-minute timepoint from stability testing is currently limited to 18 mo. (b) (4)
Disintegration	-	-		Acceptable	
Microbial Limits	• Raw materials • Process parameters •Equipment and handling • Moisture content • Site	LOW		Acceptable	Reduced testing (one in ten batches) acceptable

Note: (b) (4)

D. List of Deficiencies for Complete Response

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

Not applicable.

2. Drug Substance Deficiencies

Not applicable.

3. Drug Product Deficiencies

Not applicable.

4. Labeling Deficiencies

Not applicable.

5. Manufacturing Deficiencies

Not applicable.

6. Biopharmaceutics Deficiencies

Not applicable.

7. Microbiology Deficiencies

Not applicable.

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

Not applicable.

Application Technical Lead Name and Date:

Mark R. Seggel
CMC Lead for DUOG
ONDP/DNDPII/Br4

March 29, 2020

U.S. FOOD & DRUG ADMINISTRATION

QUALITY ASSESSMENT DATA SHEET

IQA NDA Assessment Guide Reference

1. RELATED/SUPPORTING DOCUMENTS

A. DMFs:

DMF #	Type	Holder	Item Referenced	Status	Date Assessment Completed	Comments
(b) (4)	II		(b) (4)	Adequate	01/27/2020 and 03/11/2020 S. Mitra	
	II			Adequate	05/17/2017 D. Skanchy	
	III			Adequate	-	Sufficient info in NDA
	III			Adequate	-	Sufficient info in NDA

^ foremerly N.V. Organon

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

Document(s)	Application	Description
Pre-IND meeting packages and supporting information, and Agency responses	IND 119353 Pre-submission	Everett Laboratories^ 08/07/2013 pre-IND submission for EV402 (LNG+EE (b) (4) tablets). ^Subsequently operating as Exeltis USA Inc.*
NDA	Cadence Health NDA 20683 for Alesse LNG+EE) 0.1 mg/0.02 mg tablets AP 03/27/1997	Per OB, Alesse is DISCN but remains the RLD
ANDA	Mayne Pharma ANDA 76625 for Lutera (LNG+EE) 0.1 mg/0.02 mg tablets AP 11/18/2004	The current Reference Standard for LNG+EE COC 0.1 mg/0.02 mg tablets
(b) (4)		

(b) (4)

2. CONSULTS

Discipline	Status	Recommendation	Date	Assessor
Biostatistics	na			
Pharmacology/ Toxicology	Complete	Limits for related substances are acceptable	10/23/19	M.M. Tsai-Turton
CDRH-ODE	na			
CDRH-OC	na			
Clinical	na			
Other	na			

56 Page(s) have been Withheld in Full as b4 (CCI/TS) immediately following this page

U.S. FOOD & DRUG ADMINISTRATION

CHAPTER IV: LABELING

IQA NDA Assessment Guide Reference

1.0 PRESCRIBING INFORMATION

Assessment of Product Quality Related Aspects of the Prescribing Information:

Review of the Prescribing Information is based on the submission on 03/10/2020 (SN0035). Only the sections related to quality, product title and dosage forms and strengths in the highlight section and section #3, #11 and #16 of PI are assessed in this review.

1.1 HIGHLIGHTS OF PRESCRIBING INFORMATION

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use TRADENAME safely and effectively. See full prescribing information for TRADENAME.

TRADENAME (levonorgestrel and ethinyl estradiol) tablets
Initial U.S. Approval: 1968 (norgestrel and ethinyl estradiol)

----------**DOSAGE FORMS AND STRENGTHS**----------

Tradename consists of 28 tablets:

- 21 white tablets (active), each containing levonorgestrel 0.1 mg and ethinyl estradiol 0.02 mg.
- 7 peach-colored tablets (inactive placebo).

Item	Information Provided in the NDA	Assessor's Comments
Product Title in Highlights		
Proprietary name	**TRADENAME tablets**	**Satisfactory**
Established name(s)	**(levonorgestrel and ethinyl estradiol) tablets**	**Satisfactory**
Route(s) of administration	Not provided	**Not Satisfactory** Add the route of administration "for oral use"
Dosage Forms and Strengths Heading in Highlights		
• Summary of the dosage form(s) and strength(s) • in metric system.	Tradename consists of 28 tablets: • 21 white tablets (active), each	**Not Satisfactory** To specify the order of the 28 tablet arrangement, revise "Tradename

	containing levonorgestrel 0.1 mg and ethinyl estradiol 0.02 mg. • 7 peach-colored tablets (inactive placebo).	consists of 28 tablets" to "Tradename consists of 28 tablets **in the following order**:"
Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state "functionally scored"	Not applicable	**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 applicable	**Not applicable** This drug is for oral administration.

1.2 FULL PRESCRIBING INFORMATION

1.2.1 Section 2 (DOSAGE AND ADMINISTRATION)

2 DOSAGE AND ADMINISTRATION

2.1 [redacted]

Tradename [redacted] swallowed whole or chewed [redacted] and then immediately swallowed with a full glass of 240 mL water on an empty stomach. *[see Dosage and Administration (2.2)]*.

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)	• Tradename [redacted] swallowed whole, [redacted] or chewed [redacted] and then immediately swallowed with a full glass of 240 mL water on an empty stomach (2.1) [redacted] Tradename [redacted] swallowed whole or chewed [redacted] and then immediately swallowed with a full glass of 240 mL water on an empty stomach. *[see Dosage and Administration (2.2)]*.	**Not Satisfactory** The description for administration is not consistent between "Dosage and Administration" in Highlights of Prescribing Information and Section 2.1 [redacted] of Full Prescribing Information. [redacted] Revise to either swallowed whole or chewed and then swallowed with water. Final recommendation is deferred to OND team.

1.2.2 Section 3 (DOSAGE FORMS AND STRENGTHS)

3 DOSAGE FORMS AND STRENGTHS

Tradename consists of 28 tablets:

- 21 active tablets are white, round, and debossed with 30 on one side and L2 on the other side. Each active tablet contains levonorgestrel 0.1 mg and ethinyl estradiol 0.02 mg.
- 7 inactive tablets (placebo) are peach-colored, round, and debossed with [redacted] on one side and L2 on the other side.

Item	Information Provided in the NDA	Assessor's Comments
DOSAGE FORMS AND STRENGTHS section		
Available dosage form(s)	Tradename consists of 28 tablets:	**Satisfactory**
Strength(s) in metric system	• 21 active tablets are white, round, and debossed with 30 on one side and L2 on the other side. Each active tablet contains levonorgestrel 0.1 mg and ethinyl estradiol 0.02 mg. • 7 inactive tablets (placebo) are peach-colored, round, and debossed with (b) (4) on one side and L2 on the other side.	**Satisfactory**
If the active ingredient is a salt, apply the USP Salt Policy per FDA Guidance	Not Applicable	**Not Applicable**

A description of the identifying characteristics of the dosage forms, including shape, color, coating, scoring, and imprinting	• 21 active tablets are white, round, and debossed with 30 on one side and L2 on the other side. Each active tablet contains levonorgestrel 0.1 mg and ethinyl estradiol 0.02 mg. • 7 inactive tablets (placebo) are peach-colored, round, and debossed with (b) (4) on one side and L2 on the other side.	**Not Satisfactory** 1. For clarity, revise "Tradename consists of 28 tablets" to "Tradename consists of 28 tablets in the following order:" 2. Per updated drug product specification dated February 20, 2020 (SN0030), revise "7 inactive tablets (placebo) are peach-colored, round, and debossed with (b) (4) on one side and L2 on the other side." to "7 inactive tablets (placebo) are peach-colored, round, and debossed with (b) (4) on one side and 1 on the other side."
Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state "functionally scored"	Not Applicable	**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 Applicable	**Not Applicable**

1.2.3 Section 11 (DESCRIPTION)

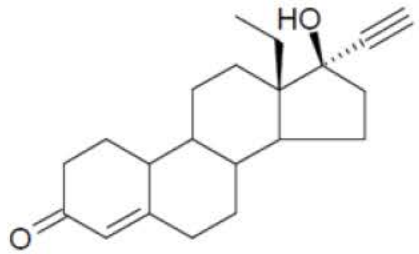
10 DESCRIPTION

Tradename (levonorgestrel and ethinyl estradiol) tablets [redacted] an oral contraceptive [redacted] consists of 21 white active tablets and 7 peach- colored inactive tablets.

Twenty one white active tablets, each contains 0.1 mg of levonorgestrel, a progestin, and 0.02 mg of ethinyl estradiol, an estrogen. Each tablet also contains the following inactive ingredients: corn starch, crospovidone, lactose monohydrate, magnesium stearate, povidone, and pregelatinized starch.

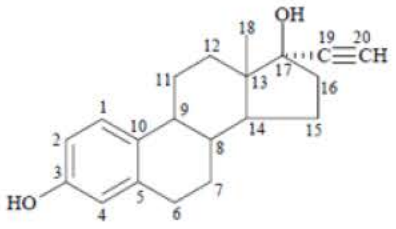
Seven peach-colored inactive tablets, each contains anhydrous lactose, corn starch, crospovidone, D&C yellow No. 10 aluminum lake, FD&C Red No. 40 aluminum lake, magnesium stearate, and povidone.

The chemical name for levonorgestrel is 18,19-Dinorpregn-4-en-20-yn-3-one, 13-ethyl-17-hydroxy-, (17α)-(-)-. It has the molecular formula of $C_{21}H_{28}O_2$, the molecular weight of 312.5, and the [redacted] below:



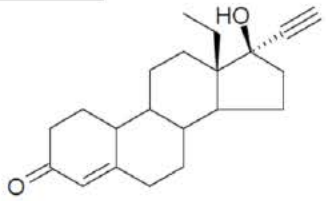
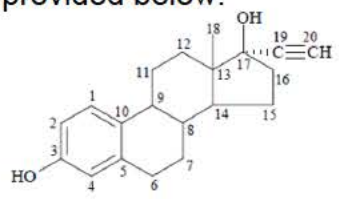
[redacted]

The chemical name for ethinyl estradiol is 19-norpregna-1,3,5(10)-trien-20-yne-3,17-diol, (17α)-. It has the molecular formula of $C_{20}H_{24}O_2$, the molecular weight of 296.4, and the [redacted] provided below:



[redacted]

Item	Information Provided in the NDA	Assessor's Comments
DESCRIPTION section		
Proprietary and established name(s)	Tradename (levonorgestrel and ethinyl estradiol) tablets	**Satisfactory**
Dosage form(s) and route(s) of administration	tablets	**Satisfactory**
If the active ingredient is a salt, apply the USP Salt Policy and include the equivalency statement per FDA Guidance.	Not applicable.	**Not Applicable** The active ingredients levonorgestrel and ethinyl estradiol are not salts.
List names of all inactive ingredients. Use USP/NF names. Avoid Brand names.	[Active] Each tablet also contains the following inactive ingredients: corn starch, crospovidone, lactose monohydrate, magnesium stearate, povidone, and pregelatinized starch. Seven peach-colored inactive tablets, each contains anhydrous lactose, corn starch, crospovidone, D&C yellow No. 10 aluminum lake, FD&C Red No. 40 aluminum lake, magnesium stearate, and povidone.	**Satisfactory**
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 Applicable	**Not Applicable**
If alcohol is present, must provide the amount of alcohol in terms of percent volume of absolute alcohol	Not Applicable	**Not Applicable**

Statement of being sterile (if applicable)	Not Applicable	**Not Applicable**
Pharmacological/ therapeutic class	Twenty one white active tablets, each contains 0.1 mg of levonorgestrel, a progestin, and 0.02 mg of ethinyl estradiol, an estrogen.	**Satisfactory**
Chemical name, structural formula, molecular weight	The chemical name for levonorgestrel is 18,19-Dinorpregn-4-en-20-yn-3-one, 13-ethyl-17-hydroxy-, (17α)-(-)-. It has the molecular formula of $C_{21}H_{28}O_2$, the molecular weight of 312.5, and the (b) (4) below:  (b) (4) The chemical name for ethinyl estradiol is 19-norpregna-1,3,5(10)-trien-20-yne-3,17-diol, (17α)-. It has the molecular formula of $C_{20}H_{24}O_2$, the molecular weight of 296.4, and the (b) (4) provided below:  (b) (4)	**Not Satisfactory** 1. Revise "10 DESCRIPTION" to "11 DESCRIPTION". 2. Indicate all of the chiral centers in the structures of levonorgestrel and ethinyl estradiol. 3. The presentation format of the chemical structure should be consistent for levonorgestrel and ethinyl estradiol. Refer to USP dictionary of USAN and International Drug Names for their chemical structures. 4. Remove (b) (4)
If radioactive, statement of important nuclear characteristics.	Not Applicable	**Not Applicable**

Other important chemical or physical properties (such as pKa or pH)	Not Provided	**Satisfactory** Both levonorgestrel and ethinyl estradiol are well known as contraceptive drugs on the US markets. The information provided in this section is consistent with many approved NDAs using levonorgestrel and ethinyl estradiol.

Section 11 (DESCRIPTION) Continued

Item	Information Provided in the NDA	Assessor's Comments
For oral prescription drug products, include gluten statement if applicable	Not Applicable	**Not Applicable**
Remove statements that may be misleading or promotional (e.g., "synthesized and developed by Drug Company X," "structurally unique molecular entity"	Not Applicable	**Not Applicable**

1.2.4 Section 16 (HOW SUPPLIED/STORAGE AND HANDLING)

14 HOW SUPPLIED/STORAGE AND HANDLING

14.1 How Supplied

Tradename (levonorgestrel and ethinyl estradiol) tablets are available as follows:

Each blister card contains 28 tablets: 21 active tablets and 7 inactive tablets. The 21 active tablets are white, round, and debossed with 30 on one side and L2 on the other side; each contains levonorgestrel 0.1 mg and ethinyl estradiol 0.02 mg. The 7 inactive tablets (placebo) are peach colored, round, and debossed with (b) (4) on one side and L2 on the other side.

NDC 0642-7471-01, one carton containing 1 individual blister card
NDC 0642-7471-03, one carton containing 3 individual blister cards
NDC 0642-7471-06, one carton containing 6 individual blister cards

14.2 Storage and Handling

Store at controlled room temperature 20°C to 25°C (68°F to 77°F). Excursions are NOT permitted. Protect from light and excessive heat.

Item	Information Provided in the NDA	Assessor's Comments
HOW SUPPLIED/STORAGE AND HANDLING section		
Available dosage form(s)	tablets	**Satisfactory**
Strength(s) in metric system	each contains levonorgestrel 0.1 mg and ethinyl estradiol 0.02 mg.	**Satisfactory**
Available units (e.g., bottles of 100 tablets)	Tradename (levonorgestrel and ethinyl estradiol) tablets are available as follows: Each blister card contains 28 tablets: 21 active tablets and 7 inactive tablets. NDC 0642-7471-01, one carton containing 1 individual blister card NDC 0642-7471-03, one carton containing 3 individual blister cards NDC 0642-7471-06, one carton containing 6 individual blister cards	**Not Satisfactory** 1. Revise the section number from "14" to "16". Also correct 2. For clarity, revise "Each blister card contains 28 tablets:" to "Each blister card contains 28 tablets in the following order:" 3. Correct (b) (4) to "1" for the description of the deboss patter of the 7 inactive tablets.
Identification of dosage forms, e.g., shape, color, coating, scoring, imprinting, NDC number	Provided. See the content in the section of available units	**Satisfactory**
Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state "functionally scored"	Not applicable	**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 applicable	**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.)	Store at controlled room temperature 20°C to 25°C (68°F to 77°F). Excursions are NOT permitted. Protect from light and excessive heat.	**Satisfactory**
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."	Not applicable	**Not applicable**
Storage conditions. Where applicable, use USP storage range rather than storage at a single temperature.	Store at controlled room temperature 20°C to 25°C (68°F to 77°F). Excursions are NOT permitted. Protect from light and excessive heat.	**Satisfactory**
Latex: If product does not contain latex and manufacturing of product and container did not include use of natural rubber latex or synthetic	Not applicable	**Not applicable**

derivatives of natural rubber latex, state: "Not made with natural rubber latex. Avoid statements such as "latex-free."		
Include information about child-resistant packaging	Not applicable	**Not applicable**

1.2.5 Manufacturing Information After Section 17 (for drug products)

Manufactured for: Exeltis USA, Inc., Florham Park, NJ 07932

Manufactured by: Laboratorios León Farma, S.A., León, Poligono Industrial Navatejera
C/ La Vallina, s/n
24008 Navatejera
Leon, Spain 24008

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 for: Exeltis USA, Inc., Florham Park, NJ 07932 Manufactured by: Laboratorios León Farma, S.A., León, Poligono Industrial Navatejera C/ La Vallina, s/n 24008 Navatejera Leon, Spain 24008	**Not Satisfactory** Add the street address of the business per 21 CFR201.1.

2.0 PATIENT LABELING

The Product Quality Related Aspects of Patient Labeling (e.g., Medication Guide, Patient Information, Instructions for Use) should be consistent with the approved information in PI. The storage condition is not provided in the Patient Information and Instructions for Use. This deficiency should convey to the applicant. See the list of the deficiencies.

8 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	(b) (4)	**Not Satisfactory** The established name of the drug product should be kept on the same line as following: "Levonorgestrel and ethinyl estradiol tablets"
Dosage strength	0.1 mg/0.02 mg	**Satisfactory**
Route of administration	Oral use	**Satisfactory** The dosage form is tablets and "Oral use" is presented on the carton label.
If the active ingredient is a salt, include the equivalency statement per FDA Guidance	Not applicable	**Not applicable**

Net contents (e.g. tablet count)	Blister card: **"Contains:** 1 blister card of 28 tablets (b) (4)" Carton using the one for 6 blister cards as an example: "Contains: 6 blister cards of 28 tablets (b) (4)Each blister card contains 21 white tablets each containing 0.1 mg levonorgestrel and 0.02 mg ethinyl estradiol and 7 peach inert tablets."	**Not Satisfactory** 1. Revise the statement "**Contains:** 1 blister card of 28 tablets (b) (4) to "**Contains:** 1 blister card of 28 tablets.". 2. For clarity and consistency, revise the following statement from "21 white tablets each containing 0.1 mg levonorgestrel with 0.02 mg ethinyl estradiol and 7 peach inert tablets." to "**Each blister card contains** 21 white tablets each containing 0.1 mg levonorgestrel with 0.02 mg ethinyl estradiol and 7 peach inert tablets."
"Rx only" displayed on the principal display	Rx only	**Satisfactory**

NDC number	Carton for one blister card: NDC 0642-7471-01 Carton for three blister cards: NDC 0642-7471-03 Carton for six blister cards: NDC 0642-7471-06	**Satisfactory**
Lot number and expiration date	provided	**Satisfactory**
Storage conditions. If applicable, include a space on the carton labeling for the user to write the new BUD.	Store at 20°C-25°C (68°F-77°F); Excursions are NOT permitted. Protect from light and excessive heat.	**Satisfactory**
For injectable drug products for parental administration, use appropriate package type term (e.g., single-dose, multiple-dose, single-patient-use)	Not applicable	**Not applicable**
Other package terms include pharmacy bulk package and imaging bulk package which require “Not for direct infusion” statement.	Not applicable	**Not applicable**
If alcohol is present, must provide the amount of alcohol in terms of percent volume of absolute alcohol	Not applicable	**Not applicable**
Bar code	Provided	**Satisfactory**

Item	Information Provided in the NDA	Assessor's Comments about Carton Labeling
Name of manufacturer/distributor	Distributed by: Exeltis USA, Inc., Florham Park, NJ 07932 1-877-324-9349 www.exeltisUSA.com Manufactured by: Laboratorios Leon Farma S.A. C/ La Vallina s/n. Pol. In. Navatejeta 24008 Navatejera, León, Spain.	**Satisfactory**
Medication Guide (if applicable)	Provided	**Defer to OND labeling review team**
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 applicable	**Not applicable**
And others, if space is available	Carton: "Tablets may be chewed and swallowed or swallowed whole."	**Satisfactory** Defer to DMEPA for final comments.

Assessment of Carton and Container Labeling: *Inadequate.*
This review is based on the carton and container labels submitted on March 10, 2020 (SN0035). In summary, there are three configurations proposed for the commercial packing: one carton containing either 1, 3 or 6 blister card (s). Additionally, there is the carton with one blister card for physician sample package information. The identified deficiencies are delineated below.

LIST OF DEFICIECIES:

A. Prescribing information

The Highlights Section:

1. Add the route of administration "for oral use" to the product title in the highlight section as following:

   TRADENAME (levonorgestrel and ethinyl estradiol) tablets, for oral use

2. Dosage Forms and Strengths in Highlights: For clarity, revise "Tradename consists of 28 tablets" to "Tradename consists of 28 tablets in the following order:".

Full Prescribing Information Section:

1. **Dosage Forms and Strengths** (Section 3):
   i. For clarity, revise "Tradename consists of 28 tablets" to "Tradename consists of 28 tablets in the following order:"
   ii. Revise the description of the deboss patter of (b) (4) on one side of the inactive tablets to "1".

2. **Description (Section #11):**
   i. Revise "10 DESCRIPTION" to "11 DESCRIPTION".
   ii. Indicate all of the chiral centers in the structures of levonorgestrel and ethinyl estradiol.
   iii. The presentation format of the chemical structure should be consistent for levonorgestrel and ethinyl estradiol. Refer to USP dictionary of USAN and International Drug Names for their chemical structures.
   iv. Remove (b) (4) (b) (4)

3. **How Supplied/Storage And Handling (Section 16):**
   i. Revise "14 HOW SUPPLIED/STORAGE AND HANDLING" to "16 HOW SUPPLIED/STORAGE AND HANDLING",
   ii. Provide the street address of the business in the manufacturing information after Section 17.

Patient Labeling:

- Provide the storage condition in the Patient Information and Instructions for Use.

Container Labels and Carton Labeling*:*

1. Keep the presentation of the established name of the drug product "levonorgestrel and ethinyl estradiol tablets" on the same line as follows, since now the space permits it.
   Tradename
   (levonorgestrel and ethinyl estradiol) tablets
   Note: if there is no proprietary name for the drug product, the parentheses around "levonorgestrel and ethinyl estradiol" should be omitted entirely.

2. For clarity and consistency, revise the following statement from "21 white tablets each containing 0.1 mg levonorgestrel with 0.02 mg ethinyl estradiol and 7 peach inert tablets." to "**Each blister card contains** 21 white tablets each containing 0.1 mg levonorgestrel with 0.02 mg ethinyl estradiol and 7 peach inert tablets."
   We have made similar comment in our previous communication dated February 27, 2020. However, we have noticed this statement has not been revised in some of the carton and container labels from the recent submission dated March 10, 2020, SN0035. For example, the carton label for 3 blister packs.
3. Revise the statement "**Contains:** 1 blister card of 28 tablets (b) (4) to "**Contains:** 1 blister card of 28 tablets.".

Overall Assessment and Recommendation:

Initial CMC review of labeling and label in January 2020 was based on the information in the following submissions: The Prescribing Information (PI) submitted on August 21, 2019 (SN0009) and the proposed labels for the carton and container on December 17, 2019 (SN0022). The following deficiencies per 21 CFR Part 201 as well as the FDA Labeling Review Tool (October 2018 version):were initially identified.

A. Prescribing information

<u>The Highlights Section:</u>

1. *Revise the product title in the highlight section to the following:*

   TRADENAME (levonorgestrel and ethinyl estradiol) (b) (4) tablets

2. *Revise Dosage Forms and Strengths in Highlights to the following:*

   Tradename consists of 28 (b) (4) tablets:
   - *21 white (b) (4) tablets (active), each containing levonorgestrel 0.1 mg and ethinyl estradiol 0.02 mg.*
   - *7 peach colored (b) (4) tablets (inactive placebo).*

<u>Full Prescribing Information Section:</u>

1. *Revise* ***Dosage Forms and Strengths*** *(Section 3) to the following:*

Tradename consists of 28 [redacted] tablets:

- *21 active [redacted] tablets are white, round, and debossed with 30 on one side and L2 on the other side. Each active tablet contains levonorgestrel 0.1 mg and ethinyl estradiol 0.02 mg. 7 inactive [redacted] tablets (placebo) are peach colored, round, and debossed with [redacted] on one side and L2 on the other side.*

2. *Revise **Description (Section #11)** as follows:*

- *Add proprietary and established name as following: "Tradename (levonorgestrel and ethinyl estradiol) [redacted] tablets"*
- *Provide pharmacological classes for both APIs: Levonorgestrel is a progestin and ethinyl estradiol is an estrogen.*
- *Provide the chemical name and structural formula of the active ingredients and their molecular weights.*
- *Remove [redacted]*
- *For the color additives, revise to the following to include "Aluminum Lake": D&C yellow No. 10 Aluminum Lake; FD&C Red No. 40 Aluminum Lake.*

*In **How Supplied/Storage and Handling Section** (#16):*

Revise the established name, strength and the drug product characteristics expression to the following:

- *Tradename (levonorgestrel and ethinyl estradiol) [redacted] tablets are available as follows:*
  Each blister card contains 28 [redacted] tablets: 21 active [redacted] tablets and 7 inactive [redacted] tablets. The 21 active [redacted] tablets are white, round, and debossed with 30 on one side and L2 on the other side; each contains levonorgestrel 0.1 mg and ethinyl estradiol 0.02 mg. The 7 inactive [redacted] tablets (placebo) are peach colored, round, and debossed with [redacted] on one side and L2 on the other side.
- *Provide the street address and zip code (León Farma) of the business in the manufacturing information after Section 17.*

Container Labels and Carton Labeling:

1. *The difference and its intended usage between the following file names: "Blister Carton [redacted] Tradename 0.1-0.02 mg 1x21+7" and "Blister Carton [redacted] Tradename 0.1-0.02 mg 1x21+7 Serialized"*
2. *Describe the intended use for the following file. "Blister Envelope [redacted] Tradename 0.1-0.02 mg x21+7"*
3. *Submit the physician sample packaging configuration information in the Container and Closure Section (3.2.P.7) of your NDA.*
4. ***For both carton and blister labels:***

a) *Revise "[levonorgestrel and ethinyl estradiol], (b) (4) tablets 0.1 mg/0.02mg" to "(levonorgestrel and ethinyl estradiol) (b) (4) tablets 0.1mg/0.02mg". Remove "," between [levonorgestrel and ethinyl estradiol] and (b) (4) tablets.*

b) *The storage condition should be consistent with the statement in section #16 of PI: "Store at 20°C-25°C (68°F-77°F); Excursions are NOT permitted. Protect from light and excessive heat".*

c) (b) (4)

5. ***For the carton labels:***

a) *For clarification, revise the statement (b) (4) to "Each blister card contains 21 white tablets each containing 0.1 mg levonorgestrel and 0.02 mg ethinyl estradiol and 7 peach inert tablets."*

b) *Include the statement of the inactive ingredients for both active and placebo (b) (4) tablets.*

Those deficiencies were conveyed to the applicant either separately or combined with OND on February 5, 2020, February 14, 2020, and February 27, 2020. Subsequently, the applicant submitted the amendments on February 7, 2020 (SN0027) to clarify questions 1-3 for the carton and container labels, and further amendments were submitted on February 21 (SN0031), February 24 (SN0032), March 04, 2020 (SN0034) to address additional deficiencies from CMC as well as other labeling issues from other disciplines from OND.

(b) (4)

(b) (4)

In response to this communication, the applicant submitted the revised PI, Carton and Container labeling and labels in the amendment on March 10, 2020 (SN0035), and in this submission, the applicant has accepted the agency's advice that the established name for the drug product should be revised to "levonorgestrel and ethinyl estradiol tablets". The dosage form for this drug product is "tablets" (b) (4)

However, there are still deficiencies not fully resolved in the submitted PI and Carton and Container labeling and labels, which are delineated in the above "**List of Deficiencies**".

Since, as of this review, the proposed proprietary name (b) (4) has been denied by DMEPA on March 16, 2020 (Refer to DARRTS with document reference ID4575123), "**Tradename**" is used when needed for illustration purpose in this review.

Therefore, from the ONDP perspective, this application is ***not*** **deemed ready for approval** in its present form per 314.125(b)(6) until the deficiencies delineated above are satisfactorily resolved.

Primary Labeling Assessor Name and Date:

Hong Cai, Ph.D.

Drug product Reviewer

Branch IV/DNDP II/ONDP/OPQ

Date of Review: March 16, 2020

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

I agree with Dr. Cai's assessment on the labels and labeling and concur with her recommendation that this application is not ready for approval in its present form until the deficiencies delineated in the **List of Deficiencies** are satisfactorily resolved.

Moo-Jhong Rhee, Ph.D.
Chief, Branch IV
DNDPII/ONDP/OPQ
March 16, 2020

1 Page(s) has been Withheld in Full as b4 (CCI/TS) immediately following this page

Hong Cai

Digitally signed by Hong Cai
Date: 3/24/2020 08:17:05PM
GUID: 55919d6500e16bdaad5825645e4f22ff

Moo Jhong Rhee

Digitally signed by Moo Jhong Rhee
Date: 3/25/2020 06:40:55AM
GUID: 502d0913000029f9798ca689a802fa55

Memorandum

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

Date: **March 28, 2020**

From: **Hong Cai, Ph.D.**
Drug Product Reviewer
Office of New Drug Products
Branch IV/DNDP II

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

To: **CMC Labeling Review #1 of NDA 209405**
for Levonorgestrel and Ethinyl Estradiol tablets, 0.1 mg / 0.02 mg

Subject: **An Addendum for Final Recommendation - APPROVAL**

The Labeling Review #1 has recommended that NDA 209405 is not ready for approval in its present form on March 16, 2020 from the CMC perspective. Consequently, the applicant, Exeltis USA inc., has submitted the revised carton labeling and container labels on March 26, 2020 (SN0040) and the prescribing information (PI) on (March 27, 2020, SN0041) and incorporated FDA comments. In these submissions, the applicant has resolved all the CMC related deficiencies (Highlight of Prescribing Information, Section #3, #11 and #16 of PI, and Carton Labeling and Container Labels). Therefore, CMC related information is now deemed satisfactorily resolved from the CMC labeling perspective. (See the Appendix-I for CMC relevant sections in Prescribing Information (PI) and Appendix-II for the mockup of the container/carton labeling/labels).

It is noted that the proposed proprietary name of (b) (4) was "Unacceptable" to DMEPA. Refer to DMEPA review by John Morris in DARRTS with Reference ID 4574830 dated March 13, 2020. Although the applicant has submitted a new proprietary name "Tyblume" on March 25, 2020, SN0039, but it was decided that DMEPA will review it post approval (Refer to RPM Nikia Morris email dated March 26, 2020). The applicant then withdrew the Proprietary Name Request (PNR) and has acknowledged that should the NDA be approved, a PNR will be submitted as a Post Approval Supplement (SN0042 on March 27, 2020). Therefore, this application will be approved without tradename, but only the drug product established name, "levonorgestrel and ethinyl estradiol tablets" until an acceptable tradename is identified.

Recommendation:
This application is recommended for **approval** from the CMC labeling perspective.

Hong Cai, Ph.D.
Drug Product Reviewer
Branch IV, Division II, ONDP

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

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

Hong Cai

Digitally signed by Hong Cai
Date: 3/29/2020 10:46:28AM
GUID: 55919d6500e16bdaad5825645e4f22ff

Moo Jhong Rhee

Digitally signed by Moo Jhong Rhee
Date: 3/29/2020 11:14:48AM
GUID: 502d0913000029f9798ca689a802fa55

28 Page(s) have been Withheld in Full as b4 (CCI/TS) immediately following this page

BIOPHARMACEUTICS

Product Background:
NDA/ANDA: NDA-209405-ORIG-1

Drug Product Name / Strength: EV402 (Levonorgestrel/Ethinyl Estradiol) (b) (4) tablets, 0.1 mg/0.02 mg

Route of Administration: Oral

Applicant Name: Exeltis USA, Inc.

Review Summary:
The Listed Drug (LD) Alesse® (Levonorgestrel/Ethinyl Estradiol tablets, 0.1 mg/0.02 mg), developed by Cadence Health was approved by the FDA under NDA 020683 on 3/27/1993. The Listed Drug has been discontinued in the USA for reasons other than safety and efficacy. Mayne Pharma developed a generic version of Levonorgestrel/Ethinyl Estradiol tablets, 0.1 mg/0.02 mg (Lutera®) that was approved by the FDA under ANDA 076625 on 11/18/2004, and now serves as the Reference Standard (RS).

Using Alesse®/Lutera® as the LD/RS, the Applicant is developing a new formulation Levonorgestrel/Ethinyl Estradiol tablets (b) (4) of the same strength of 0.1 mg/0.02 mg. The Applicant offers an alternative dosage form to users who may have difficulty or a dislike for swallowing whole tablets. The Applicant originally submitted this NDA (NDA-209405) for review on 1/7/2019 and re-submitted this NDA under section 505 (b)(2) to the Division of Bone, Reproductive, and Urology Products for review on 5/30/2019.

The Biopharmaceutics review focuses on the dissolution method development, dissolution data, the dissolution acceptance criterion, and the disintegration acceptance criterion.

The final dissolution method and acceptance criterion as agreed upon by the Agency and the Applicant are stated below:

Method:	USP monograph
Apparatus:	Apparatus II (paddle)
Medium:	Polysorbate 80 (5 µg/g) in water
Volume:	500 mL
Temperature:	37.0 ± 0.5 °C
Speed:	75 rpm

Dissolution Acceptance Criterion:
Q = (b) (4) ***% of the labeled amount of Levonorgestrel is dissolved in 30 minutes***

Q = (b) (4) ***% of the labeled amount of Ethinyl Estradiol is dissolved in 30 minutes***

The final disintegration acceptance criterion (for both the active and placebo tablets) as agreed upon by the Agency and the Applicant are stated below:

Disintegration Acceptance Criterion:
Disintegration Time: (b) (4) **minutes**

From the Biopharmaceutics perspective, this Reviewer concludes that NDA-209405-ORIG-1 for Levonorgestrel/Ethinyl Estradiol, 0.1 mg/0.02 mg, is **Adequate** for approval.

List Submissions being reviewed:

5/30/2019	Re-submission/Sequence 0006
7/22/2019	Information Request – Quality/Sequence 0008
10/15/2019	Information Request – Quality/Sequence 0013
12/2/2019	Information Request – Quality/Sequence 0020
2/14/2020	Information Request – Quality/Sequence 0029
2/20/2020	Information Request – Quality/Sequence 0030

Concise Description Outstanding Issues Remaining:
None

Solubility:
The solubility of the Levonorgestrel API in various aqueous media is presented in Table 1A. As seen in Table 1A, Levonorgestrel exhibits uniform solubility across the physiological pH range of 1.2 – 7.5. At the highest proposed dose of 0.1 mg i.e. 100 µg and at the lowest solubility of 0.93 µg/mL (at pH 1.2), (b) (4) , Levonorgestrel can be classified as a highly soluble compound as per the BCS guidance. The Applicant has classified Levonorgestrel as a BCS class I compound.

Table 1A: Aqueous solubility data of Levonorgestrel

Medium	Levonorgestrel (µg/mL)
Water	1.46
Buffer **pH 1,2**	0.93
Buffer **pH 4,5**	1.08
Medium	**Levonorgestrel (µg/mL)**
Buffer **pH 6,8**	0.95
Buffer **pH 7,5**	0.99

The solubility of the Ethinyl Estradiol API in various aqueous media is presented in Table 1B. As seen in Table 1B, Ethinyl Estradiol exhibits uniform solubility across the physiological pH range of 1.2 – 7.5. At the highest proposed dose of 0.02 mg i.e. 20 µg and at the lowest solubility of 8.04 µg/mL (at pH 6.8), (b) (4) Ethinyl Estradiol can be classified as a highly soluble compound as per the BCS guidance. The Applicant has classified Ethinyl Estradiol as a BCS class I/III compound.

Table 1B: Aqueous solubility data of Ethinyl Estradiol

Medium	Ethynil Estradiol (µg/mL)
Water	10.47
Buffer pH 1,2	9.89
Buffer pH 4,5	9.04
Buffer pH 6,8	8.04
Buffer pH 7,5	8.13

Reviewer's Assessment:

This Reviewer has noted that the Applicant has submitted the solubility data of Levonorgestrel and Ethinyl Estradiol in aqueous media as a function of pH. Based on the solubility data, this Reviewer concludes that Levonorgestrel and Ethinyl Estradiol are highly soluble compounds as per the BCS guidance.

Permeability:

The Applicant has classified Levonorgestrel as a BCS Class I compound. The log P of Levonorgestrel has been reported as 3.48. Ethinyl Estradiol has been classified by the Applicant a BCS class I/III compound. The log P of Ethinyl Estradiol has been reported as 3.87. The Applicant has stated that Ethinyl Estradiol has a high first-pass metabolism which results in a 40% - 50% bioavailability, thus reducing its permeability.

Reviewer's Assessment:

Apart from the log P values, the Applicant has not reported any permeability data in this submission to justify their claim that Levonorgestrel is a highly permeable compound. There is no BCS claim for Levonorgestrel and Ethinyl Estradiol in this submission.

Dissolution: See the review below

Dissolution Method and Acceptance Criterion

1. **Dissolution Method:**

The FDA database directs the Applicant to refer to the USP monograph for a dissolution method for Levonorgestrel and Ethinyl Estradiol tablets. The USP monograph for Levonorgestrel and Ethinyl Estradiol tablets states a dissolution method for routine dissolution testing of the LD and the RS. (b) (4) . The dissolution method for routine dissolution testing of the proposed product is stated below:

Method:	USP monograph
Apparatus:	Apparatus II (paddle)
Medium:	Polysorbate 80 (5 µg/g) in water
Volume:	500 mL
Temperature:	37.0 ± 0.5 °C
Speed:	75 rpm
Proposed Acceptance Criterion:	
For Levonorgestrel:	Q = (b) (4)
For Ethinyl Estradiol:	Q =

In the Re-submission (Sequence 0006), the Applicant submitted data wherein the dissolution of the proposed product was evaluated in the proposed media [Polysorbate 80 (5 µg/g) in water] and under physiological conditions of pH 1.2, 4.5 and 6.8. The

dissolution data and profiles of Levonorgestrel and Ethinyl Estradiol in the various media conditions are shown below:

Table 2A: Dissolution data for Levonorgestrel and Ethinyl Estradiol tablets in water + Polysorbate 80 (5 µg/g)

Levonorgestrel *n= 12 vessels*			
Time (minutes)	Mean % Dissolved	RSD (%)	Min-Max
0	0	0	--
5	62	13.2	(b) (4)
10	100	1.2	
15	103	0.7	
20	104	0.7	
30	104	0.7	
45	105	0.7	
60	105	0.6	

EthinylEstradiol *n= 12 vessels*			
Time (minutes)	Mean % Dissolved	RSD (%)	Min-Max
0	0	0	--
5	69	12.8	(b) (4)
10	100	1.4	
15	100	2.0	
20	101	2.6	
30	100	2.0	
45	101	2.4	
60	101	2.7	

Table 2B: Dissolution data for Levonorgestrel and Ethinyl Estradiol tablets in pH 1.2 media

703055/LFD0293 *Levonorgestrel* *n= 12 vessels*			
Time (minutes)	Mean % Dissolved	RSD (%)	Min-Max
0	0	0	--
5	60	19.7	(b) (4)
10	86	5.2	
15	92	4.2	
20	96	2.8	
30	97	2.8	
45	98	2.9	
60	98	2.4	

703055/LFD0293 EthinylEstradiol *n= 12 vessels*			
Time (minutes)	Mean % Dissolved	RSD (%)	Min-Max
0	0	0	--
5	84	15.3	(b) (4)
10	99	4.5	
15	99	4.6	
20	99	5.1	
30	99	5.6	
45	98	6.5	
60	96	7.6	

Table 2C: Dissolution data for Levonorgestrel and Ethinyl Estradiol tablets in pH 4.5 media

703055/LFD0293 *Levonorgestrel* *n= 12 vessels*			
Time (minutes)	Mean % Dissolved	RSD (%)	Min-Max
0	0	0	--
5	55	22.2	(b) (4)
10	90	5.5	
15	97	2.4	
20	101	1.8	
30	102	2.4	
45	102	2.0	
60	104	2.0	

703055/LFD0293 EthinylEstradiol *n= 12 vessels*			
Time (minutes)	Mean % Dissolved	RSD (%)	Min-Max
0	0	0	--
5	67	17.8	(b) (4)
10	94	2.1	
15	95	1.9	
20	94	2.2	
30	94	2.4	
45	93	2.4	
60	93	2.7	

Table 2D: Dissolution data for Levonorgestrel and Ethinyl Estradiol tablets in pH 6.8 media

703055/LFD0293 *Levonorgestrel* *n= 12 vessels*				703055/LFD0293 EthinylEstradiol *n= 12 vessels*			
Time (minutes)	Mean % Dissolved	RSD (%)	Min-Max	Time (minutes)	Mean % Dissolved	RSD (%)	Min-Max
0	0	0	--	0	0	0	--
5	43	20.5	(b) (4)	5	58	20.0	(b) (4)
10	77	6.5		10	87	3.5	
15	86	3.2		15	89	2.4	
20	89	2.6		20	89	2.3	
30	93	2.9		30	90	2.3	
45	93	1.9		45	91	2.6	
60	94	1.7		60	91	2.3	

Figure 1A: Multi-media in vitro dissolution profiles for Levonorgestrel

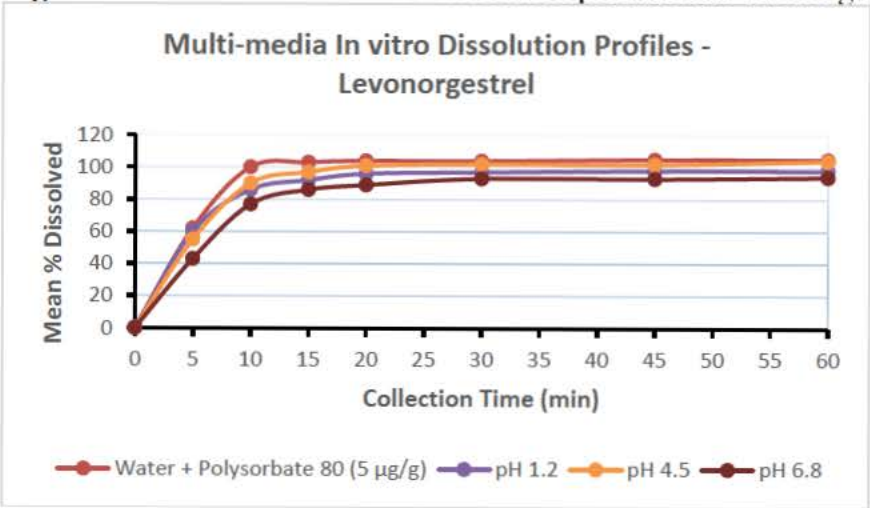
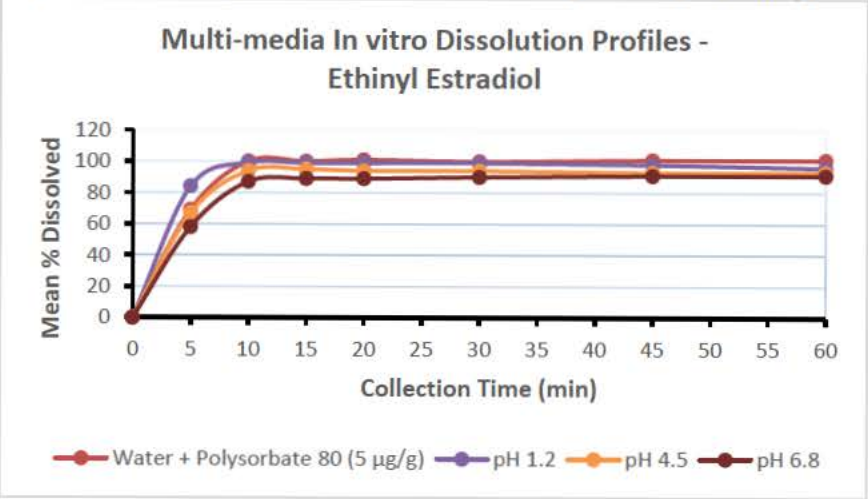


Figure 1B: Multi-media in vitro dissolution profiles for Ethinyl Estradiol



Reviewer's Assessment:

The dissolution profiles of Levonorgestrel and Ethinyl Estradiol in the four media indicate that (b) (4)% of the drug product (both Levonorgestrel and Ethinyl Estradiol) is dissolved at the 15-minute time point. The dissolution profiles in the four media can be considered to be similar (f2 calculations have not been performed because (b) (4)% of the drug product is dissolved in 15 minutes). Hence, Levonorgestrel and Ethinyl Estradiol can be classified as Immediate Release products with highly soluble APIs.

In the Re-submission (Sequence 0006), the Applicant submitted data wherein another dissolution method (b) (4) possessed discriminatory ability between the whole tablet and the grinded tablet. In the IR that was communicated to the Applicant on 7/17/2019 (IR1), the Applicant was requested to submit information whether the proposed dissolution method [USP Apparatus II; Polysorbate 80 (5 µg/g) in water; 75 rpm] could discriminate between the whole and grinded tablets. In the IR response that was received by the Agency on 7/22/2019 (Sequence 0008), the Applicant submitted data wherein they evaluated the ability of the proposed dissolution method [USP Apparatus II; Polysorbate 80 (5 µg/g) in water; 75 rpm] to discriminate between the whole and grinded tablets. The Agency's IR comments, the Applicant's IR response and the Reviewer's conclusions are presented in Appendix 2. The Applicant's IR response is summarized below. The Reviewer's assessment is presented below the summary:

Table 3A/Figure 2A: Comparative dissolution data and profile for Levonorgestrel for the whole tablet and grinded tablet in the proposed dissolution medium

LEVO 0,100/ EE 0,020 mg 704103/LFD0415 whole tablets			LEVO 0,100/ EE 0,020 mg 704103/LFD0415 gringed tablets		
Levonogestrel			Levonogestrel		
n=12 vessels			n=6 vessels		
Time (minutes)	Mean % Dissolved	RSD (%)	Time (minutes)	Mean % Dissolved	RSD (%)
0	0	0	0	0	0
5	50	15,9	5	96	1,1
10	90	3,5	10	98	1,3
15	97	2,0	15	99	1,3
20	98	1,8	20	99	1,5
30	99	2,1	30	99	1,5
45	100	2,0	45	99	1,8
60	100	2,0	60	99	1,8
Infinite point	100	2,4	Infinite point	100	3,3

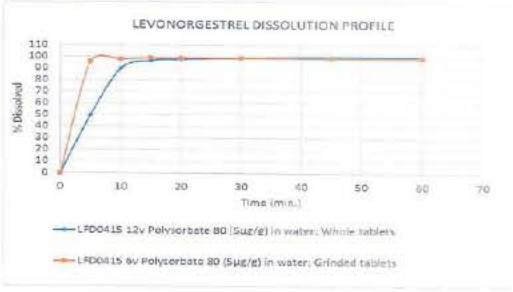
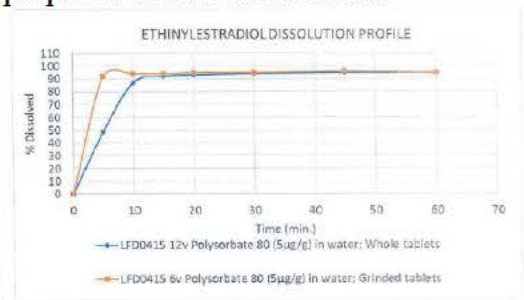


Table 3B/Figure 2B: Comparative dissolution data and profile for Ethinyl Estradiol for the whole tablet and grinded tablet in the proposed dissolution medium

LEVO 0,100/ EE 0,020 mg 704103/LFD0415 whole tablets			LEVO 0,100/ EE 0,020 mg 704103/LFD0415 gringed tablets		
Ethinylestradiol			Ethinylestradiol		
n=12 vessels			n=6 vessels		
Time (minutes)	Mean % Dissolved	RSD (%)	Time (minutes)	Mean % Dissolved	RSD (%)
0	0	0	0	0	0
5	49	16,9	5	92	3,5
10	87	4,4	10	94	2,4
15	92	2,4	15	94	2,4
20	93	2,4	20	95	2,9
30	94	1,2	30	95	1,2
45	95	1,4	45	96	2,0
60	95	2,0	60	95	1,9
Infinite point	95	1,9	Infinite point	96	2,8



The Applicant has stated that the comparative dissolution profiles in Polysorbate 80 µg/g in water (USP medium), show difference between grinded tablets and whole tablets. Whole tablets show lower drug release rate than grinded tablets at initial times of dissolution

profiles. LFD0415 whole tablets has less 51% of both APIs dissolved at 5 minutes, however, LFD0415 grinded tablets has more than 90% for both APIs at the same dissolution time. Based on the differential dissolution between the whole tablet and the grinded tablet at the 5-minute time point, the Applicant concluded that the dissolution method in Polysorbate 80 µg/g in water (USP medium) can discriminate dissolution profile between whole and grinded tablets.

Reviewer's Assessment:

Based on the submitted data, (b) (4) of the test products (both Levonorgestrel and Ethinyl Estradiol) of the whole and grinded tablets are dissolved in under 15 minutes. Hence the dissolution profiles for Levonorgestrel and Ethinyl Estradiol between the whole and grinded tablets are similar (f2 calculation is not needed). Hence, this Reviewer concludes that the proposed dissolution method [USP Apparatus II; Polysorbate 80 (5 µg/g) in water; 75 rpm] cannot discriminate between the whole and grinded tablets. The lack of discriminatory ability is probably due to the drug product being an Immediate Release product and Levonorgestrel and Ethinyl Estradiol being highly soluble APIs. Based on the submitted information, this Reviewer has not requested further evidence of the discriminatory ability of the proposed dissolution method.

2. Acceptance Criterion:

In the Re-submission (Sequence 0006), the Applicant submitted the complete 12-unit dissolution data on two of the batches used in the clinical studies (LFD09251 and LFD0556). In the IR that was communicated to the Applicant on 7/17/2019 (IR1), the Applicant was requested to submit the complete dissolution data on the third batch used in the clinical study (LFD0415). In the IR response dated 7/22/2019 (Sequence 0008), the Applicant submitted the complete dissolution data on the third batch used in the clinical study (LFD0415). The 12-unit dissolution data for Levonorgestrel and Ethinyl Estradiol for the three batches used in the clinical studies is presented in Appendix 1.

Reviewer's Assessment:

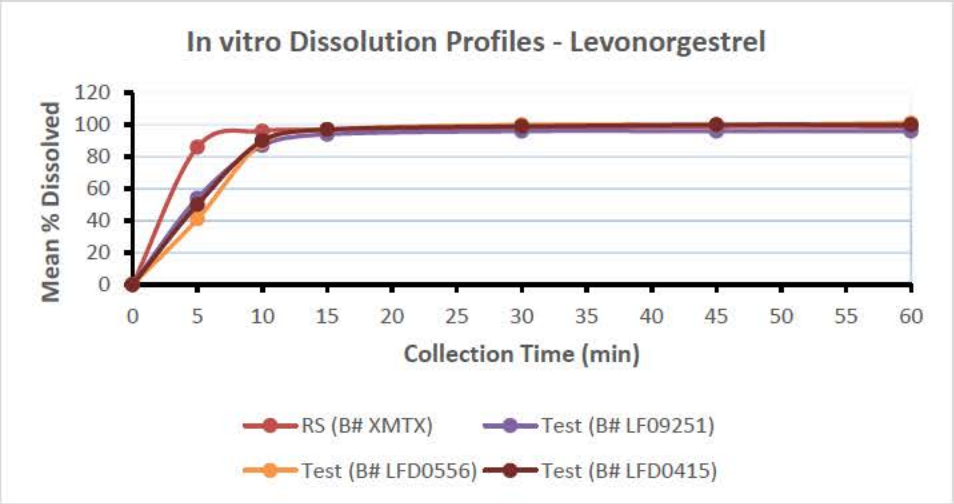
For Levonorgestrel:

This Reviewer has summarized the dissolution data for Levonorgestrel for the three batches used in the clinical studies in Table 4A and in Figure 3

Table 4A: *Summary of mean in vitro dissolution data for Levonorgestrel for the proposed product (three batches used in the clinical studies) and the RS (Lutera®)*

Batch/Time (minutes)	5	10	15	30	45	60
	% Dissolved					
RS (B# XMTX)	(b) (4)					
Test (B# LF09251)						
Test (B# LFD0556)						
Test (B# LFD0415)						

Figure 3: *In vitro dissolution profiles for Levonorgestrel for the proposed product (three batches used in the clinical studies) and the RS (Lutera®)*



In the Re-submission (Sequence 0006), the Applicant proposed an acceptance criterion of "Q = (b)(4)% of the labeled amount of Levonorgestrel is dissolved in (b)(4) minutes".

To establish the appropriate acceptance criterion for Levonorgestrel, this Reviewer decided to take into consideration the dissolution data of the three commercial exhibit batches (in addition to the three batches used in the clinical studies). The complete dissolution data for these commercial exhibit batches was not submitted in the Re-submission (Sequence 0006). In the IR response dated 7/22/2019 (Sequence 0008), the Applicant submitted the requested complete dissolution data at release on the three commercial exhibit batches – LF05712, LF05736 and LF05737. To establish the appropriate acceptance criterion for Levonorgestrel, this Reviewer has summarized the in vitro dissolution data for the three commercial exhibit batches (Table 4B).

***Table 4B:** Summary of mean in vitro dissolution data for Levonorgestrel for the proposed product (three commercial exhibit batches) at release*

Batch/Time (minutes)	5	10	15	30	45	60
	% Dissolved					
Test (B# LF05712)	(b) (4)					
Test (B# LF05736)						
Test (B# LF05737)						

Based on the submitted data for all the six batches (the three clinical batches and the three commercial exhibit batches), (b) (4)% of the labeled amount of Levonorgestrel is dissolved in under 30 minutes (also at the 15-minute time point). Hence, the Applicant's proposed acceptance criterion of Q = (b) (4) is liberal. In the IR that was communicated to the Applicant on 11/26/2019 (IR3), the following acceptance criterion was recommended by the Agency for Levonorgestrel:

"Q =(b) (4)% of the labeled amount of Levonorgestrel is dissolved in 30 minutes"

The Applicant responded to the IR on 12/2/2019 (Sequence 0020). The Agency's IR comments, the Applicant's response and the Reviewer's conclusion are stated in Appendix 2. The Reviewer's assessment is given below:

The Applicant stated that the stability data at the 30-minute time point was available only for clinical batch LF09251A and not for the exhibit batches. Furthermore, the Applicant stated that the Agency's proposed acceptance criterion is satisfied only for conditions of Long Term stability and not for accelerated conditions. The Applicant stated that the dissolution at 30 minutes was not analyzed in the exhibit batches during stability. This Reviewer informed the Applicant that the acceptance criterion is established based on the dissolution data of fresh clinical/exhibit batches at release and not from the stability data. For immediate release products, the selection of the acceptance criterion time point should be where Q = (b) (4) dissolution occurs or the plateau of drug dissolved is reached. Based on the submitted data, (b) (4) % of the test product is dissolved in under 30 minutes. Hence, the Applicant's justification and proposed acceptance criterion of "Q = (b) (4) % of the labeled amount of Levonorgestrel is dissolved i (b) (4) minutes" is unacceptable.

In the new IR that was communicated to the Applicant on 2/11/2020 (IR4), the following dissolution acceptance criterion was recommended:
*"**Q = (b) (4) % of the labeled amount of Levonorgestrel is dissolved in 30 minutes**"*

The Applicant responded to the IR on 2/15/2020 (Sequence 0029). The Agency's IR comments, the Applicant's response and the Reviewer's conclusion are stated in Appendix 2. The Reviewer's assessment is given below:

*The Applicant has accepted the Agency's recommendation and the acceptance criterion for Levonorgestrel has been amended to "**Q = (b) (4) in 30 min**".*

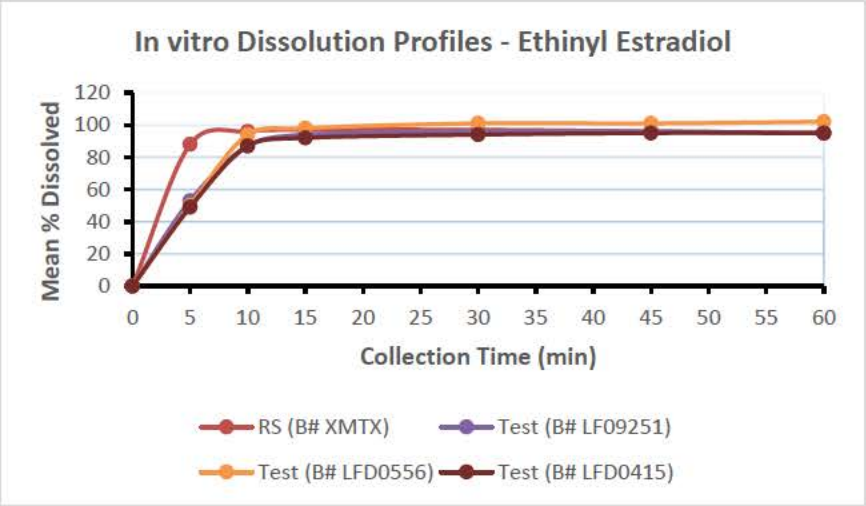
The Applicant's response to IR4 Item 1 is acceptable and adequate.

***For Ethinyl Estradiol**:*
This Reviewer has summarized the dissolution data for Ethinyl Estradiol for the three batches used in the clinical studies in Table 5A and in Figure 4.

***Table 5A:** Summary of mean in vitro dissolution data for Ethinyl Estradiol for the proposed product (three batches used in the clinical studies) and the RS (Lutera®)*

Batch/Time (minutes)	5	10	15	30	45	60
	% Dissolved					
RS (B# XMTX)	(b) (4)					
Test (B# LF09251)						
Test (B# LFD0556)						
Test (B# LFD0415)						

***Figure 4:** In vitro dissolution profiles for Ethinyl Estradiol for the proposed product (three batches used in the clinical studies) and the RS (Lutera®)*



In the Re-submission (Sequence 0006), the Applicant proposed an acceptance criterion of "Q = (b) (4) of the labeled amount of Ethinyl Estradiol is dissolved in (b) (4) minutes".

To establish the appropriate acceptance criterion for Ethinyl Estradiol, this Reviewer decided to take into consideration the dissolution data of the three commercial exhibit batches (in addition to the three batches used in the clinical studies). The complete dissolution data for these commercial exhibit batches was not submitted in the Resubmission (Sequence 0006). In the IR response dated 7/22/2019 (Sequence 0008), the Applicant submitted the requested complete dissolution data at release on the three commercial exhibit batches – LF05712, LF05736 and LF05737. To establish the appropriate acceptance criterion for Ethinyl Estradiol, this Reviewer has summarized the in vitro dissolution data for the three commercial exhibit batches (Table 5B).

***Table 5B:** Summary of mean in vitro dissolution data for Ethinyl Estradiol for the proposed product (three commercial exhibit batches) at release*

Batch/Time (minutes)	5	10	15	30	45	60
	% Dissolved					
Test (B# LF05712)	(b) (4)					
Test (B# LF05736)						
Test (B# LF05737)						

Based on the submitted data for all the six batches (the three clinical batches and the three commercial exhibit batches), (b) (4) % of the labeled amount of Ethinyl Estradiol is dissolved in under 30 minutes (also at the 15-minute time point). Hence, the Applicant's proposed acceptance criterion of Q = (b) (4) is liberal. In the IR that was communicated to the Applicant on 11/26/2019 (IR3), the following acceptance criterion was recommended by the Agency for Ethinyl Estradiol:

"Q = (b) (4) of the labeled amount of Ethinyl Estradiol is dissolved in 30 minutes"

The Applicant responded to the IR on 12/2/2019 (Sequence 0020). The Agency's IR comments, the Applicant's response and the Reviewer's conclusion are stated in Appendix 2. The Reviewer's assessment is given below:

The Applicant stated that the stability data at the 30-minute time point was available only for clinical batch LF09251A and not for the exhibit batches. Taking into consideration the acceptance criterion of Q = (b) (4) in 30 minutes satisfies both the Long Term and Accelerated stability conditions for this clinical batch. Hence, the Applicant's justification of considering dissolution data of stability under accelerated conditions are not appropriate and unacceptable. However, the Applicant has stated that the stability data at the 30-minute time point has not been determined for the exhibit batches. This Reviewer informed the Applicant that the acceptance criterion is established based on the dissolution data of fresh clinical/exhibit batches at release and not from the stability data. For immediate release products, the selection of the acceptance criterion time point should be where Q (b) (4) % dissolution occurs or the plateau of drug dissolved is reached. Based on the submitted data, (b) (4) of the test product is dissolved in under 30 minutes. Hence, the Applicant's justification and proposed acceptance criterion of "Q = (b) (4) % of the labeled amount of Ethinyl Estradiol is dissolved in (b) (4) minutes" is unacceptable.

In the new IR that was communicated to the Applicant on 2/11/2020 (IR4), the following dissolution acceptance criterion was recommended based on the dissolution data submitted:
"Q = (b) (4) of the labeled amount of Ethinyl Estradiol is dissolved in 30 minutes"

The Applicant responded to the IR on 2/15/2020 (Sequence 0029). The Agency's IR comments, the Applicant's response and the Reviewer's conclusion are stated in Appendix 2. The Reviewer's assessment is given below:

*The Applicant has accepted the Agency's recommendation, and the acceptance criterion for Ethinyl Estradiol has been amended to "**Q (b) (4) % in 30 min**".*

The Applicant's response to IR4 Item 1 is acceptable and adequate.

Clinical relevance of dissolution method & acceptance criterion (e.g., IVIVR, IVIVC, In Silico Modeling, small scale in vivo)

Reviewer's Assessment:
The Applicant has not performed an in vitro-in vivo correlation. The dissolution method proposed by Applicant is to ensure batch-to-batch consistency, and this is acceptable.

Disintegration: See the review below
Disintegration Method:

(b) (4)
In the Re-submission (Sequence 0006), the Applicant did not propose disintegration as one of the specifications. In the IR that was communicated to the Applicant on 10/9/2019 (IR2), the Applicant was requested to submit the complete disintegration data and proposed an acceptance criterion to the Agency for review. In the IR response that was received by the

Agency on 10/15/2019 (Sequence 0013), the Applicant submitted information on the disintegration methodology, and this is stated below:

Method: USP
Apparatus: USP disintegrating apparatus
Medium: Water
Temperature: 37.0 ± (b) (4) °C
Proposed Acceptance Criterion:
Disintegration time: (b) (4) minutes

Reviewer's Assessment:

The proposed disintegration method for Levonorgestrel/Ethinyl Estradiol (b) (4) tablets is based on the method stated in the USP <701> Disintegration. The Reviewer finds the disintegration method to be acceptable.

Disintegration Acceptance Criterion:

In the IR response dated 10/15/2019 (Sequence 0013), the Applicant submitted the disintegration data on a batch used in the bioequivalence study (batch# LF09251A).

Table 6: Disintegration time at release for batch# LF09251A

Batch LF9251A Disintegration		
Sample	Time (minutes y seconds)	Time (minutes)
1		(b) (4)
2		
3		
4		
5		
6		
7		
8		
9		
10		
11		
12		

Mean	3
sd	0
%RSD	0
min	(b) (4)
max	

The Applicant has proposed a disintegration time of (b) (4) minutes".

Reviewer's Assessment:

The Reviewer notes that for the clinical batch LF09251A, the test product is completely disintegrated in under (b) (4) minutes with minimal variability between the tablets. Hence, the Applicant's proposed disintegration acceptance criterion of "(b) (4) minutes" is liberal. In the IR that was communicated to the Applicant on 11/26/2019 (IR3), the following acceptance criterion was recommended:

"Disintegration time (b) (4) minutes"

The Applicant responded to the IR on 12/2/2019 (Sequence 0020). The Agency's IR comments, the Applicant's response and the Reviewer's conclusion are stated in Appendix 2. This Reviewer's assessment is given below:

This Reviewer noted that based on the Applicant's response of October 15, 2019 (Sequence 0013), the disintegration data submitted for clinical batch LF09251A (Table 1; page 2) indicates that the test product is completely disintegrated in under (b) (4) minutes with minimal variability between the tablets. This Reviewer requested further clarification as to how the disintegration data for batch LF09251 presented in Table 5; page 5 of the Applicant's December 02, 2019 (Sequence 0020) response differs from the data presented for the same batch in the response of October 15, 2019. This clarification has been requested for in the new IR that was communicated to the Applicant on 2/11/2020 (IR4).

In addition, in the new IR that was communicated to the Applicant on 2/11/2020 (IR4), this Reviewer requested the Applicant to submit the complete disintegration data at release (individual n=12/batch, mean, SD, %RSD) for the clinical batches - LFD0556, LFD0415, and the commercial exhibit batches - LF05712, LF05736 and LF05737 in the proposed disintegration medium to the Agency for review. Furthermore, in the Telecon between the Applicant and the Agency on 2/13/2020, the Applicant was informed that the acceptance criterion for disintegration was also based on the data from the clinical/exhibit batches at release (b) (4)

The Applicant responded to the IR on 2/14/2020 (Sequence 0029). The Agency's IR comments, the Applicant's response and the Reviewer's conclusion are stated in Appendix 2. The Reviewer's assessment is given below:

The other two batches used in the clinical studies – LFD0415A and LFD0556A have a mean disintegration time (at release) of <3 minutes.

Batch LFD0415A

	time (minutes seconds)	time (minutes)
1	(b) (4)	
2		
3		
4		
5		
6		
7		
8		
9		
10		
11		
12		

MEAN	1
SD	0
RSD (%)	36
MIN	(b) (4)
MAX	

Batch LFD0556A

	time (minutes seconds)	time (minutes)
1	(b) (4)	
2		
3		
4		
5		
6		
7		
8		
9		
10		
11		
12		

MEAN	1
SD	1
RSD (%)	36
MIN	(b) (4)
MAX	

For the three exhibit batches - LF05712, LF05736 and LF05737, since the disintegration time data at release was not available, the data presented for these batches were (b) (4)

extensive sampling that was performed every (b) (4) tablets. Based on the submitted data, the disintegration times for batches LF05712 and LF05737 is (b) (4) minutes. However, the disintegration times for batch LF05736 is (b) (4) minutes.

(b) (4)

*This Reviewer concluded that the disintegration (b) (4) should not be taken into consideration when establishing the acceptance criterion. Hence, the Applicant's proposed acceptance criterion of **"Disintegration time as (b) (4) minutes"** is unacceptable.*

In the new IR that was communicated to the Applicant on 2/18/2020 (IR5), based on the disintegration data at release for the three clinical batches - LF09251, LFD0415A and LFD0556A, the following disintegration acceptance criterion was recommended for both the active and the placebo tablets:
"Disintegration time (b) (4) minutes"

The Applicant responded to the IR on 2/20/2020 (Sequence 0030). The Agency's IR comments, the Applicant's response and the Reviewer's conclusion are stated in Appendix 2. The Reviewer's assessment is given below:

*The Applicant has accepted the Agency's recommendation, and the disintegration acceptance criterion for both the active (Levonorgestrel/Ethinyl Estradiol) and the placebo tablets has been amended to (b) (4) **minutes**".*

The Applicant's response to IR5 Item 1 is acceptable and adequate.

Bridging of Formulations

The Applicant has stated that two formulations were developed and used in clinical studies – formulation A and formulation B. The differences in the composition of the two formulations is shown in the table below:

Formulation A		Formulation B	
Excipient	% per Tablet	Excipient	% per Tablet
	(b) (4)	LNG EE Lactose Monohydrate, NF Corn starch, NF Pregelatinised Starch, NF Povidone, NF Crospovidone, NF Magnesium Stearate, NF	(b) (4)
Clinical Study: EHE-P4-469		Clinical Studies: EXS-P3-239 EXS-P3-821	

Formulation A was first developed and used in the first clinical study (study EHE-P4-469). Formulation A was followed by Formulation B – and is the to-be-marketed formulation. The Applicant has conducted clinical studies (studies EXS-P3-821 and EXS-P3-239) using the to-be-marketed formulation.

The Applicant has also stated that the batches for the to-be-marketed formulation were manufactured at a single site and using the same manufacturing process.

Based on this information, the Applicant has not submitted any data for the bridging of formulations.

Reviewer's Assessment:

Based on the submitted information, formulation A is not the final formulation in the exhibit batch. The clinical studies have been performed on the final to-be-marketed formulation (formulation B). Furthermore, formulation B has been manufactured at a single site and using the same manufacturing process. The proposed commercial formulation in the exhibit batches is identical to the formulation used in the clinical (bio) batch. Hence, bridging of formulations is not necessary.

Stability Data

Reviewer's Assessment:

The Applicant has stated that the stability testing was performed at a pilot scale on one exhibit batch – LFD0031 and on three commercial batches – LF05712, LF05736 and LF05737.

Use	Type Batch	Dose	Batch Size	Code Bulk Tablets	Batch Number Bulk Active Tablets	Embossed	Code final packed product	Pack size (tabs / blister)	Batch final product packed
Stability Study	Pilot-scale	Levonorgestrel / Ethinyl Estradiol 0.10 mg / 0.02 mg	(b) (4)	701087	LFD0031	Yes	206229	28 (active)	LFD0031A
Stability Study	Commercial batch			701486	LF05712	Yes	208147	21 (active) + 7 (placebo)	LF05712A
					LF05736				LF05736A
					LF05737				LF05737A
Bioequivalence (EXS-P3-239)	Commercial batch			701486	LF09251	Yes	208147	21 (active) + 7 (placebo)	LF09251A

The Applicant has submitted data on the Accelerated (6 months), Intermediate (12 months), and Controlled Room Temperature/Long Term (24 months) for the pilot-scale and the three commercial batches. In accordance with the recommended acceptance criterion of "Q = (b) (4)% of the labeled amount of Levonorgestrel/Ethinyl Estradiol is dissolved in 30 minutes", the Applicant has revised the acceptance criterion for the dissolution data at stability. Furthermore, in accordance with the newly proposed acceptance criterion of "Disintegration time (b) (4) minutes",

the Applicant has revised the acceptance criterion for the disintegration data at stability. The stability data is being further reviewed by the DS or DP reviewer.

Biowaiver Request

There is only one strength of the test product – 0.1 mg/0.02 mg. The Bioequivalence study was performed on the test product against the RS. The Applicant has stated that, under fasting and fed conditions, 90% CI for C_{max}, AUC_{0-t}, and $AUC_{0-\infty}$ was found between the BE criterion of 80% - 125%. The BE study is being evaluated by the Division of Clinical Pharmacology. The Applicant has not requested any waiver of in vivo bioavailability/bioequivalence studies.

Reviewer's Assessment:

There is only one strength of the proposed product. The BE study is being evaluated by the Division of Clinical Pharmacology. There is no request for any waiver of in vivo bioavailability/bioequivalence studies.

(b) (4)

9 Page(s) have been Withheld in Full as b4 (CCI/TS) immediately following this page

Rajesh Savkur

Digitally signed by Rajesh Savkur
Date: 2/21/2020 11:19:46AM
GUID: 5a4fe3d5001e3750f54a8daadb2faa06

Hansong Chen

Digitally signed by Hansong Chen
Date: 2/21/2020 11:58:06AM
GUID: 525d7d660003845a197a2e1682433d0d

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/

MARK R SEGGEL
03/29/2020 09:21:14 PM