CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

216285Orig1s000

PRODUCT QUALITY REVIEW(S)

FDA U.S. FOOD & DRUG ADMINISTRATION

RECOMMENDATION

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

NDA 216285
Assessment 1

Drug Product Name	DROSPIRENONE CHEWABLE TABLETS
Dosage Form	Chewable Tablets
Strength	3.5 mg
Route of Administration	Oral
Rx/OTC Dispensed	Rx
Applicant	Exeltis USA, Inc.
US agent, if applicable	N/A

Submission(s) Assessed	Document Date	Discipline(s) Affected
Original Submission	08/30/2021	All
Proprietary Name Request	09/03/2021	All
Clinical Study Report	09/29/2021	Clinical
Patent Exclusivity Information	10/04/2021	All
Response to Quality Information Request - EA	11/08/2021	ONDP - EA
Draft Labeling	12/03/2021	All
Response to Quality Information Request	12/30/2021	ONDP
Response to Quality Information Request	02/07/2022	ONDP and OPMA
Proprietary Name Request	02/08/2022	All
Response to Clinical Information Request	03/18/2022	Clinical
Response to DMEPA Labeling Comments	04/11/2022	DMEPA and ONDP
Response to Quality Information Request	04/13/2022	ONDP and Biopharm

Response to Clinical Information Request	04/18/2022	Clinical
Draft Labeling – Container and Carton Labels	05/05/2022	All
Draft Labeling	06/13/2022	All

QUALITY ASSESSMENT TEAM

Discipline	Primary Assessor	Secondary Assessor
Drug Substance	Sukhamaya, Bain, Ph.D.	Donna Christner, Ph.D.
Drug Product	Hitesh Shroff, Ph.D.	Hong Cai, Ph.D.
Manufacturing	Loqman Mohamed, Ph.D.	Vaikunth Prabhu, Ph.D.
Microbiology	Loqman Mohamed, Ph.D.	Vaikunth Prabhu, Ph.D.
Biopharmaceutics		Tapash Ghosh, Ph.D.
Regulatory Business Process Manager	Dahlia Walters, M.S., PMP	
Application Technical Lead	Hamid Shafiei, Ph.D.	
Laboratory (OTR)	N/A	N/A
Environmental	Hitesh Shroff, Ph.D.	Hong Cai, Ph.D.

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EXECUTIVE SUMMARY

For more details about the items in this template, please see the Executive Summary chapter of the NDA IQA Guide

I. RECOMMENDATIONS AND CONCLUSION ON APPROVABILITY

- The applicant of this 505(b)(2) new drug application has provided sufficient CMC information to assure the identity, strength, purity, and quality of the drug substance, drospirenone and the drug product, Drospirenone Chewable Tablets, 3.5 mg.
- The Office Pharmaceutical Manufacturing Assessment has made the overall recommendation of adequate for the facilities involved in this application.
- The CMC issues on labels/labeling have been satisfactorily resolved.
- The applicant's request for the categorical exclusion from the preparation of the environmental assessment has been granted.

Therefore, from the OPQ perspective, this NDA is recommended for **approval** with the expiration dating period of **24 months.**

II. SUMMARY OF QUALITY ASSESSMENTS

A. Product Overview

Exeltis USA, Inc. has submitted this 505(b)(2) new drug application for Drospirenone Chewable Tablets, 3.5mg for oral use indicated as a contraceptive to prevent pregnancy. The drug product is packaged using aluminum push-through foil and PVC/PVDC film in blister cards. Each blister pack supplies 24 active film-coated white chewable tablets containing 3.5 mg drospirenone debossed with "C" on one side and "D" on the other side and 4 inert (placebo) film-coated green chewable tablets debossed with "C" on one side and "E" on the other side.

The active ingredient, drospirenone was first approved in 2001 in combination with ethinyl estradiol as the active ingredients of the brand name drug product Yasmin indicated for prevention of pregnancy. Since its first approval multiple brand name and generic products containing this active ingredient has been approved for marketing in the United States for the same indication. Yaz (drospirenone/ethinyl estradiol) Tablets, 3 mg/0.02 mg is used as the listed drug (LD) for this application.

For the prevention of pregnancy, female patients should start taking the first white active tablet on the first day of menses and continue with taking one active tablet per day until the last active tablet is consumed on day

24, followed by taking one green inert tablet per day for the next for 4 days. The tablets must be chewed completely before swallowing.

The drug product should be stored at 20°C to 25°C (68°F to 77°F); excursions permitted from 15°C to 30°C (59°F to 86°F). The currently assigned expiration dating period for this drug product is 24 months from the date of manufacture.

Proposed Indication(s) including Intended Patient Population	Prevention of pregnancy
Duration of Treatment	As prescribed by a physician
Maximum Daily Dose	3.5mg of drospirenone per day for 24 days followed by placebo product for 4 days
Alternative Methods of Administration	None

B. Quality Assessment Overview

Drug Substance: Adequate

The drug substance, drospirenone was first approved in 2001 in combination with ethinyl estradiol as the active ingredients of the brand name drug product Yasmin. Drospirenone is a compendial drug substance with a current USP monograph.

Drospirenone is a synthetic progestational compound and has been used as the active ingredient of oral contraceptive drug products. It is a white to almost white or slight yellow crystalline powder, slightly soluble in water, sparingly soluble in acetone and in DMF. Drospirenone is a neutral molecule with melting point at 198°C – 205°C and the specific optical rotation of -186° to -196° [αD20]. This drug substance does not exhibit polymorphic forms.

Drospirenone, USP for this application is manufactured b (b) (4) (b) (4) in accordance with current Good Manufacturing Practices (cGMP). The information regarding the manufacture of drospirenone supplied b (b) (4) is provided in DMF (b) (4) This DMF has been recently reviewed by Dr. E. Manivannan on March 16, 2021 and found to be adequate. It is tested and released against a specification that assures the identity, strength, purity, and quality of the drug substance at release and throughout its assigned retest date o (b) (4)

Relying on the previous review of DMF (b) (4) and the information provided in the drug substance module of this application, the Drug

Substance Reviewer, Dr. Sukhamaya, Bain, has found the totally of the drug substance information provided in this application adequate to support the approval of this application from the drug substance perspective. Dr. Bain's review is provided in the Drug Substance Chapter of the Integrated Quality Assessment (IQA).

Drug Product: Adequate

The drug product, Drospirenone Chewable Tablets, 3.5 mg is indicated as an oral contraceptive for prevention of pregnancy. The drug product is packaged using aluminum push-through foil and PVC/PVDC film in blister cards. Each blister pack supplies 24 active round unscored film-coated white chewable tablets containing 3.5 mg drospirenone debossed with "C" on one side and "D" on the other side and 4 inert (placebo) round unscored film-coated green chewable tablets debossed with "C" on one side and "E" on the other side.

Female patients should start taking the first white active tablet on the first day of menses and continue with taking one active tablet per day until the last active tablet is consumed on day 24, followed by taking one green inert tablet per day for the next for 4 days. The tablets must be chewed completely before swallowing.

Each active chewable tablet contains 3.5 mg of drospirenone as the active ingredient and microcrystalline cellulose, anhydrous lactose, colloidal silicon dioxide, magnesium stearate, polyvinyl alcohol partially hydrolyzed, talc, titanium dioxide, polyethylene glycol, an (b) (4) peppermint flavor as the inactive ingredients. Each inert chewable tablet consists of the following inactive ingredients: Lactose monohydrate, corn starch, povidon (b) (4) colloidal silicon dioxide, magnesium stearate, hypromellose 2910, titanium dioxide, polysorbate 80, triacetin, FD&C blue 2 aluminum lake, yellow ferric oxide, an (b) (4) peppermint flavor.

Drospirenone Chewable Tablets, 3.5 mg is manufactured by Laboratorios León Farma, S. A. for Exeltis USA, Inc. in accordance with the cGMP and is tested and released against a specification that assures the identity, strength, purity, and quality of the drug product at release and throughout its proposed expiration dating period of 24 months. Based on stability data provided in the application, the expiration dating period of 24 months is granted.

The drug product information provided in this application has been reviewed by the Drug Product Reviewer, Dr. Hitesh Shroff. Dr. Shroff has found the drug product information submitted adequate to support approval of this application from the drug product perspective. Dr. Shroff's review is provided in Drug Product Chapter of the IQA.

The applicant's request for categorial exclusion from preparation of the environmental assessment has also been reviewed by Dr. Shroff. Dr. Shroff has found the applicant's request valid and recommended granting the categorical exclusion to this application. Dr. Shroff's review of the categorical exclusion is provided in the Drug Product Chapter of the IQA.

Labeling: Adequate

The CMC sections of the prescribing information (PI) as well as the immediate container and carton labels have been reviewed by the Drug Product Reviewer, Dr, Hitesh Shroff. In his review dated May 11, 2022, Dr. Shroff had found labeling/labels deficiencies from the CMC perspective. The CMC deficiencies delineated in Dr. Shroff's review of labeling/label were communicated to the applicant. The applicant submitted a labeling amendment on June 13, 2022 that has adequately addressed the CMC labeling/label deficiencies. Therefore, in the labeling/label review addendum (memorandum) dated June 15, 2022, Dr. Shroff has recommended the approval of this application from the labeling/label perspective. Dr. Shroff's labeling/label review and the review addendum are provided in the Labeling Chapter of the IQA.

Manufacturing: Adequate

The manufacturing process for the drug product, Drospirenone Chewable Tablets includes the following major unit operations for both the active and the inert (placebo) tablets:

(b) (4)

The manufacturing process as well as the manufacturing facilities involved in this application have been reviewed by the Office of Pharmaceutical Manufacturing Assessment (OPMA), Dr. Loqman Mohamed. Dr. Mohamed has concluded that both the manufacturing process and the manufacturing facilities involved in this application are adequate to support the approval of this application from the OPMA perspective. Dr. Mohamed's review is provided in the Manufacturing Chapter of the IQA.

Biopharmaceutics: Adequate

The active ingredient, drospirenone is a poorly soluble and highly permeable drug substance and therefore, this API has been classified as a BCS class 2 compound.

The biopharmaceutics review of this application has been mainly focused on the determination of the in vitro method discriminating ability. Based on

the information submitted in this application, it has been concluded that the applicant has demonstrated discriminating ability of the method in relation to variations in particle size (b) (4). It has also been determined that no biowaiver is needed for this application.

The biopharmaceutics section of this application has been reviewed by the Biopharmaceutics Reviewer, Dr. Bryan Ericksen. Dr. Ericksen has found the biopharmaceutics information provided adequate to support the approval of this application from the biopharmaceutics perspective. Dr, Ericksen's review is provided in the Biopharmaceutics Chapter of the IQA

Microbiology (if applicable): Adequate

The drug product, Drospirenone Chewable Tablets, 3.5 mg for oral use is a solid dosage form product. Therefore, the review and evaluation of bioburden have been performed by the OPMA Reviewer, Dr. Loqman Mohamed. Dr. Mohamed has found the bioburden information provided in this application adequate and recommended the approval of this application from the microbiology perspective. Dr. Mohamed's review is captured in the Manufacturing Chapter of the IQA.

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**
Strength and Uniformity of Dosage Unit	(b) (4)	M	(b) (4)	Acceptable (Low)	None

D. List of Deficiencies for Complete Response

None

Application Technical Lead Name:

Hamid Shafiei, Ph.D.
Branch IV/DNDP 2/ONDP/OPQ

Hamid Shafiei

Digitally signed by Hamid Shafiei
Date: 6/15/2022 05:16:05PM
GUID: 507d824300005f344cf8b5e5989f0057

U.S. FOOD & DRUG ADMINISTRATION

QUALITY ASSESSMENT DATA SHEET

For more details about the items in this template, please see the Quality Assessment Data Sheet chapter of the NDA IQA Guide

1. RELATED/SUPPORTING DOCUMENTS

A. DMFs:

DMF #	Type	Holder	Item Referenced	Status	Date Assessment Completed	Comments
(b) (4)	II		(b) (4)	Adequate	Mach 16, 2021	Reviewed by E. Manivannan
	III			_____	_____	Adequate Information Provided in the NDA
	III			_____	_____	Adequate Information Provided in the NDA
	III			_____	_____	Adequate Information Provided in the NDA
	III			_____	_____	Adequate Information Provided in the NDA

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

Document	Application Number	Description
NDA	021676	LD

2. CONSULTS

Discipline	Status	Recommendation	Date	Assessor
Biostatistics	N/A			
Pharmacology/Toxicology	N/A			

CDRH	N/A			
Clinical	N/A			
Other	N/A			

CHAPTER IV: LABELING

1.0 PRESCRIBING INFORMATION

Assessment of Product Quality Related Aspects of the Prescribing Information:

(b) (4)

Item	Items in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments (If an item is Inadequate, provide more details on the issues, as appropriate)
Product Title in Highlights		
Established name(s)[1]	Adequate	Should be reformatted as: DROSPIRENONE chewable tablets
Route(s) of administration	Adequate	Oral

(b) (4)

Summary of the dosage form(s) and strength(s) in metric system	Adequate	Adequate information is provided. Revise this section as shown below.
Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state "functionally scored".	Adequate	Not scored

[1] Established name = [Drug] [Route of Administration] [Dosage Form]

For injectable drug products for parental administration, use appropriate package type term (e.g., single-dose, multiple-dose, single-patient-use). Other package terms include pharmacy bulk package and imaging bulk package.	N/A	N/A
If the drug product contains an active ingredient that is a salt, clearly state whether the strength is based on the active moiety (e.g., Tablets: 10 mg of drug-x) or active ingredient (e.g., Tablets: 10 mg of drug-x hydrochloride).	N/A	N/A

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

Drospirenone Chewable Tablets consists of 28 tablets in the following order (3):

- 24 white active chewable tablets each containing 3.5 mg of drospirenone
- 4 green inert chewable tablets

1.2 FULL PRESCRIBING INFORMATION

1.2.2 Section 3 (DOSAGE FORMS AND STRENGTHS)

(b) (4)

[redacted]

QUALITY ASSESSMENT

Item	Items in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments (If an item is Inadequate, provide more details on the issues, as appropriate)
DOSAGE FORMS AND STRENGTHS section		
Available dosage form(s)	Adequate	Chewable Tablet
Strength(s) in metric system	Adequate	24 Active Tablets: 3.5 mg of drospirenone, 4 Inert Tablets
If the active ingredient is a salt, apply the USP Salt Policy per FDA Guidance. Clearly state whether the strength is based on the active moiety (e.g., Tablets: 10 mg of drug-x) or active ingredient (Tablets: 10 mg of drug-x hydrochloride).	N/A	N/A
A description of the identifying characteristics of the dosage forms, including shape, color, coating, scoring, imprinting, and color and clarity of the solution, when applicable	Adequate	Round, film-coated and unscored chewable tablets. Debossing information provided. Reformat this section as shown below.
Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state "functionally scored"	Adequate	No scored
For injectable drug products for parental administration, use appropriate package type term (e.g., single-dose, multiple-dose, single-patient-use). Other package type terms include pharmacy bulk package and imaging bulk package.	N/A	N/A

3 DOSAGE FORMS AND STRENGTHS

Drospirenone Chewable Tablets is supplied in a blister card with 28 round, film-coated and unscored chewable tablets in the following order:

- 24 white active chewable tablets each containing 3.5 mg of drospirenone debossed with a "C" on one side and a "D" on the other side
- 4 green inert chewable tablets debossed with a "E" on one side and a "C" on the other side

Section 11 (DESCRIPTION)

(b) (4)

[redacted]

QUALITY ASSESSMENT

Item	Items in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments (If an item is Inadequate, provide more details on the issues, as appropriate)
DESCRIPTION section		
Proprietary and established name(s)	Adequate	Drospirenone chewable tablets
Dosage form(s) and route(s) of administration	Adequate	Tablet, Oral
If the active ingredient is a salt, apply the USP Salt Policy and include the equivalency statement per Salt Guidance and MAPP. For example: "TRADENAME contains 100 mg of drug-x (equivalent to 123.7 mg of drug-x hydrochloride)"	N/A	N/A
List names of all inactive ingredients. Use USP/NF names in alphabetical order. Avoid brand names.	Adequate	List inactive ingredients in alphabetical order as shown below.
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.	N/A	N/A
If alcohol is present, must provide the amount of alcohol in terms of percent volume of absolute alcohol	N/A	N/A
Sterility statement (if applicable)	N/A	N/A
Pharmacological/Therapeutic class	Adequate	Progestin
Chemical name, structural formula, molecular weight	Adequate	Information provided. Revise molecular formula and molecular weight as shown below.
If radioactive, statement of important nuclear characteristics.	N/A	N/A
Other important chemical or physical properties (such as pKa or pH)	Adequate	Information provided. Reformat this section as shown below.

Section 11 (DESCRIPTION) Continued

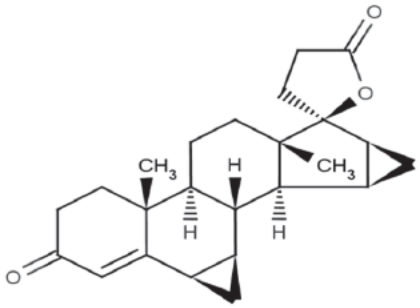
Item	Items in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments (If an item is Inadequate, provide more details on the issues, as appropriate)
For oral prescription drug products, include gluten statement (if applicable)	N/A	
Remove statements that may be misleading or promotional (e.g., "synthesized and developed by Drug Company X," "structurally unique molecular entity")	N/A	
If there is a USP monograph for the drug product and it contains a labeling requirement, ensure the labeling requirement is fulfilled. Note the labeling requirement may be applicable to another section of the PI (e.g., Section 2).	N/A	

11 DESCRIPTION

Drospirenone Chewable Tablets is an oral contraceptive. Drospirenone chewable tablets is supplied in a blister card with 28 round, film-coated and unscored chewable tables in the following order:

- 24 white active chewable tablets each containing 3.5 mg of drospirenone debossed with a "C" on one side and a "D" on the other side
- 4 green inert chewable tablets debossed with a "E" on one side and a "C" on the other side

Drospirenone is a white to almost white or slightly yellow crystalline powder. It is a progestin and neutral molecule with slight solubility in water. Drospirenone is chemically described as (6R,7R,8R,9S,10R,13S,14S,15S,16S,17S)-1,3',4',6,6a,7,8,9,10,11, 12,13,14,15,15a,16-hexadecahydro10,13-dimethylspiro-[17H-dicyclopropa- [6,7:15,16]cyclopenta[a]phenanthrene-17,2'(5'H)-furan]-3,5'(2H)-dione). It has a molecular weight of 366.49, a molecular formula of $C_{24}H_{30}O_3$, and the structural formula below:



The active chewable tablet is a 5 mm, round, unscored, film-coated, white chewable tablet that contains 3.5 mg of drospirenone as the active ingredient, and the following inactive ingredients: microcrystalline cellulose, anhydrous lactose, colloidal silicon dioxide and magnesium stearate. The white film coating is comprised of polyvinyl alcohol-partially hydrolyzed, polyethylene glycol (Macrogol) 3350, talc and titanium dioxide. The peppermint flavor contains peppermint oil, maltodextrin and modified starch (E 1450).

The inert chewable tablet is a 5 mm, round, unscored, film-coated, green chewable tablet that does not contain drospirenone. Each inert green chewable tablet contains the following inactive ingredients: lactose monohydrate, colloidal silicon dioxide, corn starch and magnesium stearate and povidone K 30. The peppermint flavor contains peppermint oil, maltodextrin and modified starch (E 1450). The green film coating consists of FD&C blue 2 aluminum lake, ferric oxide yellow, hypromellose 2910, polysorbate 80, titanium dioxide and triacetin.

1.2.4 Section 16 (HOW SUPPLIED/STORAGE AND HANDLING)

(b) (4)

[redacted]

Item	Items in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments (If an item is Inadequate, provide more details on the issues, as appropriate)
HOW SUPPLIED/STORAGE AND HANDLING section		
Available dosage form(s)	Adequate	Tablet
Strength(s) in metric system	Adequate	24 Active Tablets: 3.5 mg of drospirenone, 4 Inert Tablets
Available units (e.g., bottles of 100 tablets)	Adequate	28 Tablets per blister
Identification of dosage forms (e.g., shape, color, coating, scoring, imprinting, and color and clarity of the solution, when applicable); Include NDC(s)	Adequate	This information is provided. Reformat this section as shown below.
Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state "functionally scored"	Adequate	Not scored

For injectable drug products for parental administration, use appropriate package type term (e.g., single-dose, multiple- dose, single-patient-use). Other package terms include pharmacy bulk package and imaging bulk package.	N/A	
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.). For hazardous drugs, state "DRUG X is a hazardous drug. Follow applicable special handling and disposal procedures.[x]" with x numerical citation to "OSHA Hazardous Drugs."	N/A	
Storage conditions. Where applicable, use USP storage range rather than storage at a single temperature.	Adequate	Adequate
Latex: If product does not contain latex and manufacturing of product and container did not include use of natural rubber latex or synthetic derivatives of natural rubber latex, state: *"Not made with natural rubber latex. Avoid statements such as "latex-free."*	N/A	
Include information about child-resistant packaging	Adequate	Provided in Patient Information

16 HOW SUPPLIED/STORAGE AND HANDLING

16.1 How Supplied

Drospirenone chewable tablets is packaged in clear to a slightly opaque PVC-PVDC/Aluminum blister cards. Each blister card holds 28 5-mm round, film-coated and unscored chewable tables in the following order:

- 24 white active chewable tablets each containing 3.5 mg of drospirenone debossed with a "C" on one side and a "D" on the other side
- 4 green inert chewable tablets debossed with a "E" on one side and a "C" on the other side

DROSPIRENONE CHEWABLE TABLETS is supplied in cardboard carton containing a blister card of 28 chewable tablets: NDC 0642-7478-01

16.2 Storage and Handling

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

1.2.6 Manufacturing Information After Section 17 (for drug products)

(b) (4)

Item	Items in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments (If an item is Inadequate, provide more details on the issues, as appropriate)
Manufacturing Information After Section 17		
Name and location of business (street address, city, state, and zip code) of the manufacturer, distributor, and/or packer	Adequate	Adequate

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

QUALITY ASSESSMENT

Item	Items in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments about Carton Labeling (If an item is Inadequate, provide more details on the issues, as appropriate)
Established name[2], (font size and prominence)	Adequate	
Strength(s) in metric system	Adequate	
Route(s) of administration	Adequate	
If the active ingredient is a salt, include the equivalency statement per Salt Guidance and MAPP.	N/A	
Net contents (e.g., tablet count, volume of liquid)	Adequate	
"Rx only" displayed on the principal display	Adequate	
NDC	Adequate	
Lot number and expiration date	Adequate	
Storage conditions. If applicable, include a space on the carton labeling for the user to write the new beyond-use-date (BUD).	Adequate	
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, and these products require a "Not for direct infusion" statement.	N/A	
For parenteral injectable dosage forms, include the name and quantities of all active and inactive ingredients in alphabetical order. For ingredients added to adjust the pH or make isotonic, include the name and statement of effect.	N/A	
If alcohol is present, must provide the amount of alcohol in terms of percent volume of absolute alcohol	N/A	
Linear Bar code	Adequate	

[2] Established name = [Drug] [Route of Administration] [Dosage Form]

QUALITY ASSESSMENT

Item	Items in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments about Carton Labeling (If an item is Inadequate, provide more details on the issues, as appropriate)
Name of manufacturer/distributor /packer	Adequate	
If there is a Medication Guide, must include a statement about dispensing a Medication Guide to each patient.	N/A	
No text on Ferrule and Cap overseal, unless a cautionary statement is required.	N/A	
If there is a USP monograph for the drug product and it contains a labeling requirement, ensure the labeling requirement is fulfilled.	N/A	
When a drug product differs from the relevant USP standard of strength, quality, or purity, as determined by the application of the tests, procedures, and acceptance criteria set forth in the relevant compendium, its difference shall be plainly stated on its label.	N/A	
And others, if space is available.	N/A	

Assessment of Carton and Container Labeling: *Adequate*

The C/C labels were revised on May 5, 2022 based on the DMEPA comments. They are adequate from the CMC perspective.

The PI contains all necessary information, however, some of the CMC sections need to be revised as shown in the list of deficiencies below.

List of Deficiencies:

The following comments were sent to the applicant regarding the PI.

1. Sec. HIGHLIGHTS OF PRESCRIBING INFORMATION

   Revise the drug product title as shown below.

   DROSPIRENONE chewable tablets, for oral use
   Initial U. S. Approval: 2021

   Revise DOSAGE FORMS AND STRENGHTS section as shown below.

   ----------**DOSAGE FORMS AND STRENGTHS**----------
   Drospirenone Chewable Tablets consists of 28 tablets in the following order (3):
   - 24 white active chewable tablets each containing 3.5 mg of drospirenone
   - 4 green inert chewable tablets

2. FULL PRESCRIPTION INFORMATION

   Revise Sec. 3 DOSAGE FORMS AND STRENGHTS as shown below

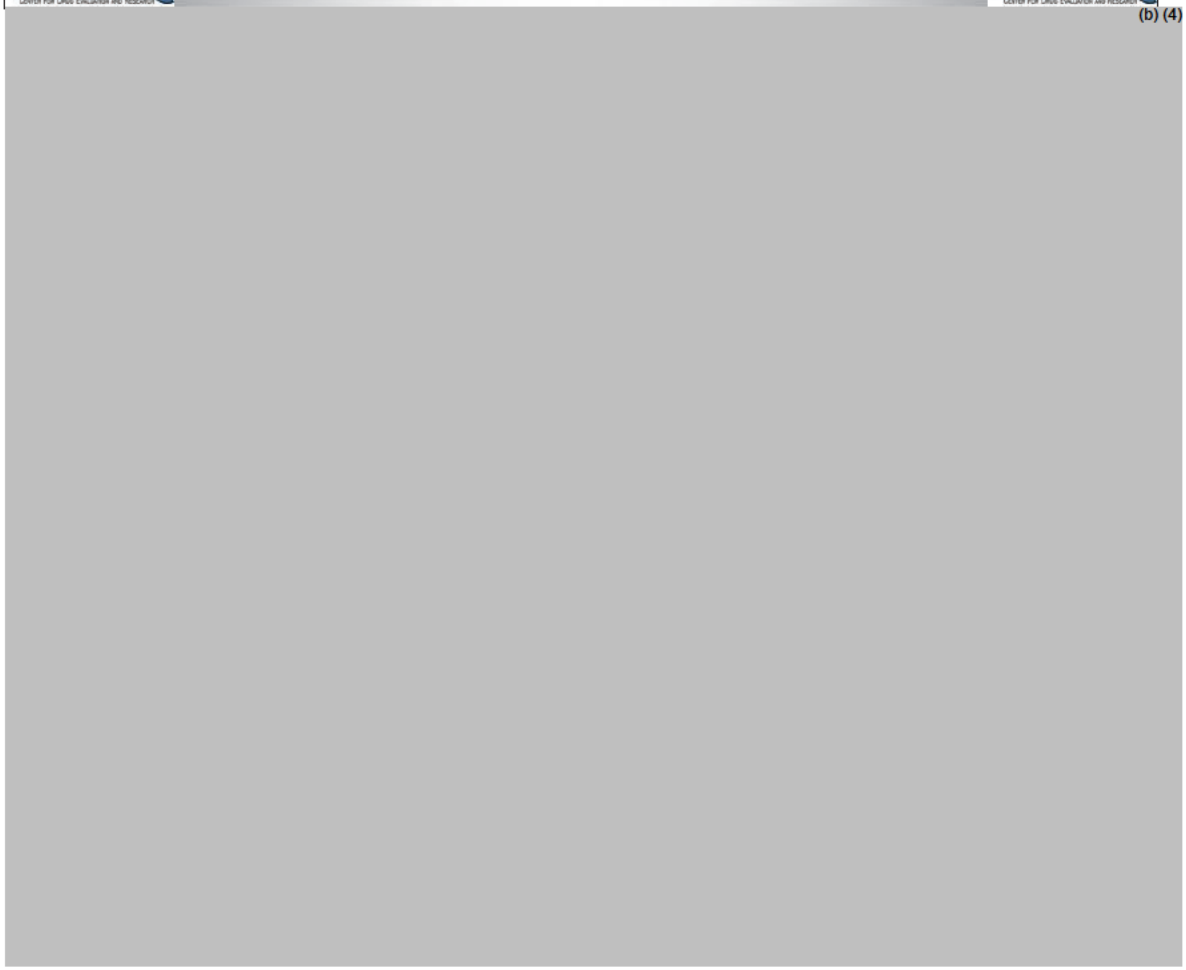
   3 DOSAGE FORMS AND STRENGTHS
   Drospirenone Chewable Tablets is supplied in a blister card with 28 round, film-coated and unscored chewable tablets in the following order:
   - 24 white active chewable tablets each containing 3.5 mg of drospirenone debossed with a "C" on one side and a "D" on the other side
   - 4 green inert chewable tablets debossed with a "E" on one side and a "C" on the other side

3. Revise Sec. 11 DESCRIPTION as shown below

   11 DESCRIPTION
   Drospirenone Chewable Tablets is an oral contraceptive. Drospirenone chewable tablets is supplied in a blister card with 28 round, film-coated and unscored chewable tables in the following order:
   - 24 white active chewable tablets each containing 3.5 mg of drospirenone debossed with a "C" on one side and a "D" on the other side
   - 4 green inert chewable tablets debossed with a "E" on one side and a "C" on the other side

   Drospirenone is a white to almost white or slightly yellow crystalline powder. It is a progestin and neutral molecule with slight solubility in water. Drospirenone is chemically described as (6R,7R,8R,9S,10R,13S,14S,15S,16S,17S)-1,3',4',6,6a,7,8,9,10,11, 12,13,14,15,15a,16-hexadecahydro10,13-dimethylspiro-[17H-dicyclopropa- [6,7:15,16]cyclopenta[a]phenanthrene-17,2'(5'H)-furan]-3,5'(2H)-dione). It has a molecular weight of 366.49, a molecular formula of $C_{24}H_{30}O_3$, and the structural formula below:

(b) (4)



4. Revise Sec. 16 HOW SUPPLIED/STORAGE AND HANDLING as shown below.

16 HOW SUPPLIED/STORAGE AND HANDLING

16.1 How Supplied

Drospirenone chewable tablets is packaged in clear to a slightly opaque PVC-PVDC/Aluminum blister cards. Each blister card holds 28 5-mm round, film-coated and unscored chewable tables in the following order:

- 24 white active chewable tablets each containing 3.5 mg of drospirenone debossed with a "C" on one side and a "D" on the other side
- 4 green inert chewable tablets debossed with a "E" on one side and a "C" on the other side

DROSPIRENONE CHEWABLE TABLETS is supplied in cardboard carton containing a blister card of 28 chewable tablets: NDC 0642-7478-01

16.2 Storage and Handling

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

QUALITY ASSESSMENT

Overall Assessment and Recommendation:

The NDA is not ready for approval in its present form per CFR 314.125(b)(6) until the outstanding labeling issues listed in the **List of Deficiencies** are satisfactorily resolved.

Primary Labeling Assessor Name and Date:
Hitesh Shroff, PhD
OPQ/ONDP/DNDP II/ Branch IV
05-10-2022

Secondary Assessor Name and Date (and Secondary Summary, as needed):
Hong Cai, Ph.D.
Chief, Branch 4
OPQ/ONDP/DNDP II

Hitesh Shroff

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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: **June 15, 2022**

From: **Hitesh Shroff, Ph.D.**
Senior CMC Reviewer, ONDP/Division II/Branch IV

Through: **Hong Cai, Ph.D.**
Branch Chief, ONDP/Division II/Branch IV

To: **Labeling Review of NDA 216285: Drospirenone Chewable Tablets, 3.5 mg**

Subject: **Final Recommendation for Labeling/Labels**

On June 13, 2022, the applicant submitted revised PI and PPI. The CMC related deficiencies identified in the previous labeling review have been adequately addressed in the revised PI and PPI. The revised PI is provided in the Attachment. The PI and PPI are satisfactory from the CMC perspective.

Recommendation:
This NDA is **now** recommended for **Approval** from the labeling perspective.

Primary Labeling Assessor Name and Date:
Hitesh Shroff, PhD
Senior CMC Reviewer
ONDP/Division II/Branch IV
June 15, 2022

Secondary Reviewer Name and Date:
Hong Cai, Ph.D.
Branch Chief
ONDP/Division II/Branch IV
June 15, 2022

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

Hitesh Shroff

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Hong Cai

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BIOPHARMACEUTICS

Product Background:

The current submission is for the approval of [redacted] (drospirenone). [redacted] are indicated for use by females of reproductive potential to prevent pregnancy.

NDA-216285-ORIG-1

Drug Product Name / Strength: [redacted] (drospirenone) / 3.5 mg

Route of Administration: Oral

Applicant Name: Exeltis USA, Inc.

Review Summary: Adequate

Drospirenone can be considered a low solubility, high permeability Biopharmaceutics Classification System (BCS) Class 2 compound. No bridging of formulations is necessary. No biowaiver is necessary. The discriminating ability of the method was adequately demonstrated with respect to particle size [redacted] NDA 216285 is adequate from a biopharmaceutics perspective and recommended for approval.

List Submissions being reviewed (table):

08/30/2021	NDA 216285/Sequence 0001/Original Submission
04/13/2022	NDA 216285/Sequence 0012/Response to Information Request

BCS Designation

Reviewer's Assessment: BCS Class 2

Solubility:

The solubility of drospirenone is shown in Table 1.

Table 1. Solubility of Drospirenone in aqueous and organic solvents

Solvent	Solubility [a] (mg/mL) (b) (4)	Solubility Classification [b]
		Slightly soluble
		Practically insoluble
		Practically insoluble
		Practically insoluble
		Sparingly soluble
		Slightly soluble
		Sparingly soluble

[a] At 25 ± 5 °C
[b] Definition of solubility: < 0.1 mg/mL: practically insoluble, 0.1-1 mg/mL: very slightly soluble, 1-10 mg/mL: slightly soluble, 10-33 mg/mL: sparingly soluble, 33-100 mg/mL: soluble, 100-1000mg/mL: freely soluble.

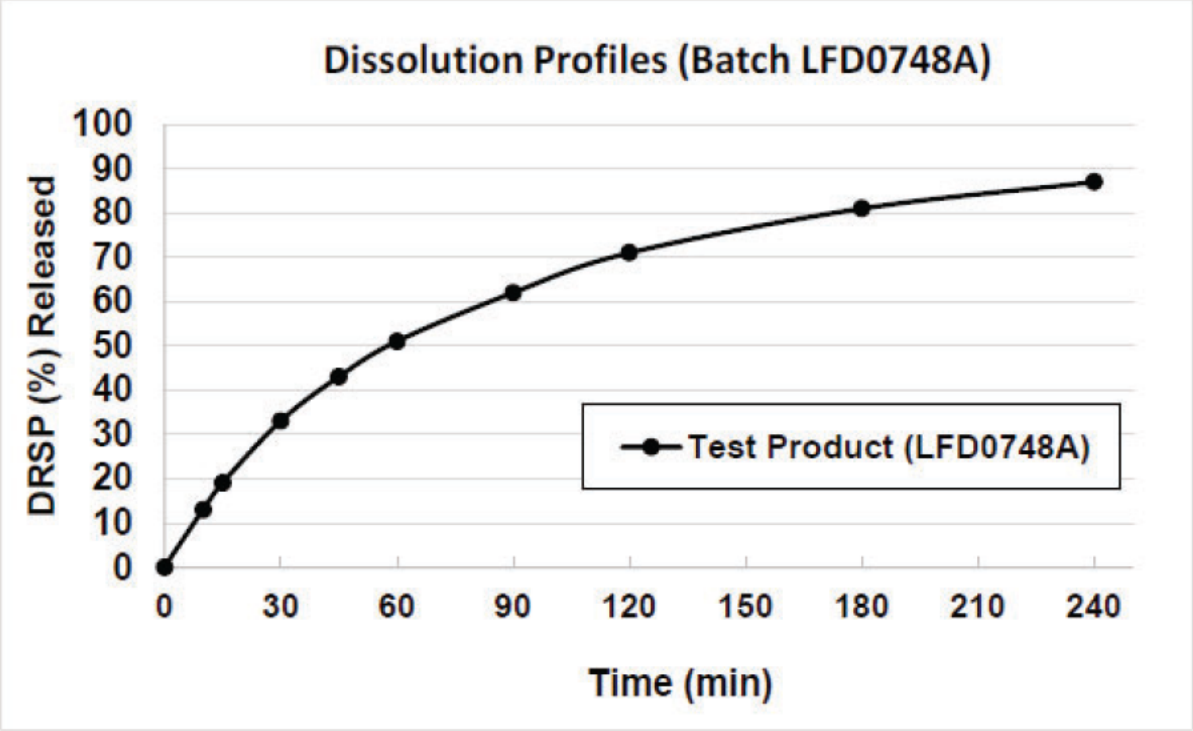
Permeability:

The Applicant stated that drospirenone is a poorly soluble, highly permeable Biopharmaceutics Classification System (BCS) Class 2 compound without reporting permeability data.

Dissolution:

A dissolution profile of biobatch dissolution is shown in Figure 1.

Figure 1. Dissolution of the biobatch



The conditions used were 900 mL purified water with 0.06 % Tween 20, 100 rpm, Apparatus 2 at 37 ºC ± 0.5 ºC. It can be concluded that dissolution is complete (> (b) (4)%) in four hours (b) (4) .

Dissolution Method

The solubility of drospirenone is shown in Table 1 above. (b) (4)

Drospirenone 3.5 mg chewable tablets were shown to be bioequivalent versus Slynd (drospirenone) 4 mg tablet in the study No. 2020-FLE1-SLINC-PK-04 (BLCL-DRS-FDA-04). This study will be assessed by clinical pharmacology team. Therefore, the development of the dissolution method for Drospirenone 3.5 mg chewable tablets started using the same method as Slynd (drospirenone) 4 mg tablets.

(b) (4)

(b) (4) The discriminating ability of the method was adequately demonstrated with respect to particle size (b) (4) See Appendix 1. . The final QC method uses the following conditions: purified water with 0.06 % Tween 20, 100 rpm, Apparatus 2 at 37 ºC ± 0.5 ºC

Acceptance Criteria

These selected time points are based on the FDA guidance for poorly water soluble drugs, "Dissolution Testing of Immediate Release Solid Oral Dosage Forms" where it is mentioned that "for slowly dissolving or poorly water soluble drugs (BCS class 2), a two-point dissolution specification, one at 15 minutes to include a dissolution range (a dissolution window) and the other at a later point (30, 45, or 60 minutes) to ensur (b) (4) dissolution, is recommended to characterize the quality of the product".

Dissolution acceptance criteria were updated compared to Slynd as shown in Table 2.

Table 2: Slynd acceptance criteria and proposed acceptance criteria

Current Specification for Slynd Drospirenone 4 mg tablets (method at 75 rpm)	Proposal Specification for Drospirenone 3.5 mg Chewable Tablets (method at 100 rpm)
L: (b) (4)% (15min)	L: (b) (4)% (30min)
Q: (b) (4)% (180min)	Q: (b) (4)% (240min)

This shift is proposed since Drospirenone 3.5mg chewable tablets show slower dissolution profile than Slynd (Drospirenone 4mg tablets) (b) (4) The 30-minute timepoint has been selected instead of 15-minute (b) (4). Additionally, the proposed acceptance criteria at 30-minute timepoint for Drospirenone 3.5 mg chewable tablets is similar to the limits at 15-minute for Slynd (Drospirenone 4mg tablets) which is (b) (4)%. The proposed range for Drospirenone 3.5 mg chewable tablets is established considering the biobatch (batch No. LFD0748A) values ±10%. Regarding the 240-minute timepoint, it is selected as it is the minimum timepoint where biobatch (LFD0748A) achieves values above (b) (4)%.

Reviewer's Assessment:

Method development resulted in a robust method that achieved greater than (b) (4)% dissolution in four hours. The acceptance criteria are adequate.

Bridging of Formulations

Batch LFD0748, which is to-be-marketed formulation, was used in all three pivotal studies (BLCL-DRS-FDA-04 (bioequivalence study), BLCL-DRS-FDA-06 (food effect) and BLCL-DRS-FDA-06 (irritation study)). Therefore, no bridging of formulations is necessary

Reviewer's Assessment:

No bridging of formulations is necessary

Biowaiver Request

There is no biowaiver request

Reviewer's Assessment:

No biowaiver request is necessary, since there is only one strength and a bioequivalence study was conducted using that strength.

Primary Biopharmaceutics Reviewer Name: Bryan Ericksen, Ph.D.

Secondary Reviewer Name: Tapash Ghosh, Ph.D.

APPENDIX 1

Dissolution Data Tables

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Bryan Ericksen

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Tapash Ghosh

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