CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

216285Orig1s000

NON-CLINICAL REVIEW(S)

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

PHARMACOLOGY/TOXICOLOGY NDA REVIEW AND EVALUATION

Application number:	216285
Supporting document/s:	SDN 1 (eCTD 0001)
Applicant's letter date:	August 30, 2021
CDER stamp date:	August 30, 2021
Product:	Drospirenone chewable tablet, 3.5 mg
Indication:	Contraception
Applicant:	Exeltis USA, Inc.
Review Division:	Division of Urology, Obstetrics, and Gynecology (DUOG)
Reviewer:	Andrea L. Benedict, PhD
Supervisor:	Kimberly P. Hatfield, PhD
Division Director:	Audrey Gassman, MD
Project Manager:	Jeannie Roule

Template Version: September 1, 2010

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1 Executive Summary

1.1 Introduction

Drospirenone (DRSP) 3.5 mg chewable tablet is a chewable progestin-only pill (POP) oral hormonal contraceptive containing 24 active tablets of 3.5 mg (b) (4) DRSP and 4 inert tablets (28 daily tablet regimen) for use by females of reproductive potential to prevent pregnancy.

DRSP 3.5 mg chewable tablet is a new chewable tablet dosage form that the Applicant describes as a line extension of SLYND (drospirenone) 4 mg tablet (NDA 211367, approval date May 23, 2019). SLYND also contains 24 active, white, film-coated tablets of DRSP 4 mg and 4 inactive, green placebo, film-coated tablets (28 daily tablet regimen), which is taken orally (swallowed) for use by females of reproductive potential to prevent pregnancy.

The SLYND application was a 505(b)(2) NDA submission that relied on the Agency's previous findings of safety for the Listed Drug YAZ® (NDA 21676). SLYND is currently listed in the FDA's Orange Book as a Reference Listed Drug (RLD) and Reference Standard (RS). DRSP 3.5 mg chewable tablet is proposed to be an alternative oral dosage form for oral contraceptive users who may have difficulty or a dislike for swallowing whole tablets.

The intended administration is one tablet daily: one active white tablet for 24 consecutive days followed by one inactive green tablet for 4 consecutive days, which are co-packaged in the same container closure system as is used for SLYND. The differences between the proposed DRSP 3.5 mg chewable tablet and SLYND are 1) the amount of DRSP, 2) inclusion of peppermint flavor (b) (4) and 3) (b) (4) excipients, microcrystalline cellulose and lactose monohydrate, (b) (4) respectively.

The Applicant intends to rely on the Agency's previous findings of safety for DRSP from the listed drug YAZ® to support the nonclinical module and inform Sections 8 and 13 of the labeling, and will also cross-reference their own data from the SLYND NDA (211367). To support the safety of non-compendial peppermint flavoring excipient, the Applicant has provided a quantitative listing of the composition, certificate of analysis (COA), and justification of specifications.

1.2 Brief Discussion of Nonclinical Findings

The Applicant has not conducted nonclinical studies with DRSP 3.5 mg chewable tablet and no additional nonclinical studies were required or requested by the Division to support an NDA application, pending an adequate scientific bridge was established through clinical comparative PK studies of DRSP 3.5 mg chewable tablet to SLYND.

Exeltis USA, Inc. is the Sponsor of NDA 211367 for SLYND, which was approved under 505(b)(2) pathway with reference to YAZ® as the listed drug product. The NDA referred to the Agency's previous findings of safety and efficacy for the nonclinical pharmacology, pharmacokinetics, and toxicology of the DRSP component of YAZ®

(NDA 21676) to support the nonclinical sections. The Applicant did not conduct any new nonclinical studies to support the SLYND NDA.

The scientific bridge between DRSP 3.5 mg chewable tablet and SLYND is provided by a comparative clinical bioavailability (BA) study (2020-FLE1-SLINC-PK-04). In the pivotal comparative BA study, the Applicant demonstrated that the DRSP exposure after single doses of DRSP 3.5 mg chewable tablet administered was less than or comparable to the reference drug (SLYND). Refer to the clinical pharmacology review submitted by Dr. Mohammad Akbar on May 21, 2022, for further information on the scientific bridge.

The nonclinical evidence supporting the safety of DRSP 3.5 mg chewable tablet is based on the Agency's determination of safety and efficacy for the Listed Drug product, YAZ®. SLYND was found to be adequately comparable to YAZ® under NDA 211367. YAZ® is an approved drug product (3 mg (b) (4) DRSP and 0.02 mg ethinyl estradiol tablets) that is indicated for use in the prevention of pregnancy in females of reproductive potential. Therefore, an acceptable bridge between DRSP 3.5 mg chewable tablet and SLYND provides reliance on the nonclinical safety information as provided in both the SLYND and YAZ® approved labeling.

1.3 Recommendations

1.3.1 Approvability

Nonclinical data support approval of Drospirenone (DRSP) 3.5 mg chewable tablet for the indication of prevention of pregnancy in females of reproductive potential.

1.3.2 Additional Nonclinical Recommendations

No additional nonclinical studies are recommended.

1.3.3 Labeling

The product labeling will be completed in a separate review.

2 Drug Information

2.1 Drug

CAS Registry Number
67392-87-4

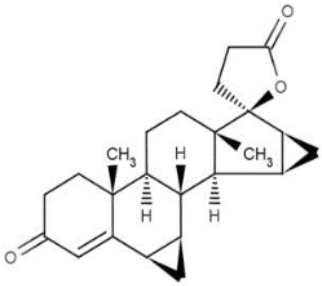
Generic Name
Drospirenone

Chemical Name
6β, 7β; 15β, 16β-dimethylene-3-oxo-17α-pregn-4-ene-21, 17-carbolactone

Molecular Formula/Molecular Weight
$C_{24}H_{30}O_3$ / 366.5 g/mol

Structure or Biochemical Description

Figure 1: Structure of Drospirenone



Pharmacologic Class
Progestin

2.2 Relevant INDs, NDAs, BLAs and DMFs

IND 146207	Drospirenone 3.5 mg chewable tablet, 24/4 regimen; Indication: Prevention of pregnancy; Sponsor: Exeltis USA, Inc. (affiliate of Laboratorios León Farma S.A.)
IND 111347	LF111 (drospirenone 4 mg tablet), 24/4 regimen; Indication: Prevention of pregnancy; Sponsor: Laboratorios León Farma S.A.
NDA 211367	SLYND (drospirenone 4 mg tablet), 24/4 regimen; Indication: Prevention of pregnancy; Sponsor: Exeltis USA, Inc. (affiliate of Laboratorios León Farma S.A.); Original Approval Date: May 23, 2019
NDA 21676	YAZ® (3 mg drospirenone and 0.02 mg ethinyl estradiol), 24/4 regimen; Indication: Prevention of pregnancy; Sponsor: Bayer HealthCare Pharmaceuticals Inc.; Original Approval Date: March 16, 2006
DMF	(b) (4)
DMF	
DMF	

2.3 Drug Formulation

Drospirenone 3.5 mg Chewable Tablets: The DRSP drug product is a 5 mm, round, unscored, film-coated, white tablet that must be chewed completely before swallowing for once daily oral administration. Each tablet contains 3.5 mg of DRSP and has a total target weight of 56.75 mg. The composition of the DRSP tablet is provided in Table 1.

Placebo Tablets: The placebo drug product is a 5 mm, round, unscored, film-coated, green tablet that is chewed completely before swallowing for once daily oral administration. Each tablet has a total target weight of 67.6 mg. The composition of the placebo tablet is provided in Table 2.

Table 1: Composition of Drospirenone 3.5 mg Chewable Tablet

Material	Function	Quantitative Composition (mg)	Content (% w/w)	Quality Standard	IIG Limit for Oral Route of Administration [e]		
					CAS Number	UNII	Max. Daily Exposure [f]
Core Tablet							
Drospirenone [a]	Active Pharmaceutical Ingredient	3.50	(b) (4)	USP	n.a.	n.a.	n.a
Microcrystalline cellulose			(b) (4)	NF			(b) (4)
Anhydrous Lactose				NF			
Colloidal silicon dioxide				NF			
Magnesium stearate				NF			
Peppermint (b) (4) Flavor [b]				In-house Monograph			
- Peppermint oil				-			
- Maltodextrin				-			
- Modified starch				-			
							(b) (4)
- Polyvinyl Alcohol-partially Hydrolyzed				USP			(b) (4)
- Titanium Dioxide				USP			
- Polyethylene Glycol (Macrogol) 3350				NF			
- Talc				USP			
							(b) (4)
TOTAL		**56.75**	**100.0**	-			

[a] Drospirenone (b) (4)

[b] Components present in Peppermint (b) (4) Flavor are peppermint oil (b) (4) and maltodextrin and modified starch (E 1450) (b) (4). Information is provided in [Section 3.2.P.4.1.3 Specifications - Peppermint (b) (4) Flavor *(Drospirenone 3.5mg Chewable Tablet)*]

[c] Components present (b) (4) are polyvinyl alcohol, titanium dioxide, polyethylene glycol (PEG) 3350, and talc. Detailed information is provided [Section 3.2.P.4.1.2 Specifications – (b) (4) (b) (4) *(Drospirenone 3.5mg Chewable Tablet)*]

[d] (b) (4)

[e] https://www.accessdata.fda.gov/scripts/cder/iig/index.cfm (access 04 August 2021)

[f] Maximum daily exposure for oral chewable tablet unless specified

[g] Maximum potency per unit dose for oral tablet

[h] Maximum potency per unit dose for oral chewable tablet

[i] Maximum daily exposure for oral capsule

Table 2: Composition of Placebo Tablet

Component	Functionality	Quantity per Tablet (mg)	Content (% w/w)	Quality Standard	IIG Limit for Oral Route of Administration [d]		
					CAS Number	UNII	Maximum Daily Exposure (MDE) [e]
(b) (4)							
Colloidal Silicon Dioxide				NF			(b) (4)
Magnesium Stearate				NF			
Peppermint (b) (4) Flavor [a]				In-house Monograph			
Peppermint oil				n.a.			
Maltodextrin							
Modified starch (E 1450)				n.a.			
(b) (4)							
- Hypromellose 2910				USP			(b) ( )
- Triacetin				USP			
- Polysorbate 80				NF			
- Titanium dioxide				USP			
- FD&C Blue No. 2 --Aluminum Lake				CFR 82.102			
- Ferric Oxide Yellow				NF			
							(b) ( )
TOTAL		67.60					

[a] Components present in Peppermint (b) (4) Flavor. Information is provided in [Section 3.2.P.4.1.3 Specifications - Peppermint (b) (4) Flavor *(Drospirenone 3.5mg Chewable Tablet)*]
[b] Components present (b) (4). Detailed information is provided in [Section 3.2.P.4.1.2 Specifications – (b) (4) *(Placebo Chewable Tablet)*]
[c] (b) (4)
[d] https://www.accessdata.fda.gov/scripts/cder/iig/index.cfm (access August 8, 2021)
[e] Maximum daily exposure for oral chewable tablet unless specified
[f] Maximum daily exposure for film coated tablet
[g] Maximum potency per unit dose for film coated tablet
[h] Maximum potency per unit dose for chewable tablet

2.4 Comments on Novel Excipients

Table 1 and Table 2 above include the daily amounts of each excipient in the DRSP and placebo tablet, respectively, as well as the maximum daily exposure for each excipient that was found in the FDA's Inactive Ingredient Report (IIG).

The listed excipients and the individual components of the film coating systems are excipients found in the FDA's IIG and are proposed at daily levels that are within those of previously approved drug products for the oral route of administration. All excipients are at acceptable levels.

2.5 Comments on Impurities/Degradants of Concern

There are no impurities or degradants of concern.

Proposed Impurity Specifications:

The individual and total impurity specifications for the DRSP drug substance (DMF (b) (4)) are in accordance with the acceptance criteria for total impurities in the current USP monograph for DRSP.

The impurity specifications for acceptance limits of individual unknown impurities at release (i.e., (b) (4)%) and on stability (i.e., (b) (4)) in the DRSP drug product are within the acceptance criteria for identification thresholds for drug products per the ICH Q3B(R2) guidance.

The impurity specifications for acceptance limits of total impurities at release and on stability of ≤(b) (4)% in the DRSP drug product is within the acceptance criteria for qualification thresholds for drug products per the ICH Q3B(R2) guidance.

2.6 Proposed Clinical Population and Dosing Regimen

DRSP 3.5 mg chewable tablet is a Progestin Only Pill (POP) containing 24 active tablets of DRSP (b) (4) and four inert placebo tablets (28 daily tablet regimen) for use by females of reproductive potential to prevent pregnancy.

The intended administration is one tablet daily taken orally; 1 white active tablet containing DRSP 3.5 mg for 24 consecutive days followed by 1 green inert placebo tablet for 4 consecutive days.

2.7 Regulatory Background

On May 23, 2019, SLYND drospirenone 4 mg tablets (NDA 211367) for oral (swallowed) route of administration was approved as the first drospirenone-containing progestin-only pill (POP) for the indication of prevention of pregnancy in females of reproductive potential. SLYND is owned by the current Applicant for NDA 216285.

The sponsor, Laboratorios León Farma S.A., was granted two pre-IND Written Response Only meetings with the Division under IND 146207, with preliminary responses provided on January 10, 2020, and March 25, 2021, respectively. The sponsor requested feedback from the Division regarding the overall development program of Drospirenone 3.5 mg chewable tablet to support an intended 505(b)(2) NDA for the indication of prevention of pregnancy in females of reproductive potential. Refer to the IND 146207 Nonclinical reviews dated May 22, 2020 and April 7, 2021.

3 Studies Submitted

3.1 Studies Reviewed

There were no nonclinical studies submitted with this NDA. The Applicant has not completed any nonclinical pharmacology, pharmacokinetics, or toxicology studies with DRSP 3.5 mg chewable tablet and no additional nonclinical studies were required or requested by the Division to support an NDA application. The Applicant has submitted a 505(b)(2) application relying on the Agency's previous determination of safety for the DRSP component of the approved Listed Drug YAZ® (NDA 21676) to support the nonclinical section of this NDA. The current Applicant's other approved DRSP POP drug product, SLYND, was approved on May 23, 2019, as a 505(b)(2) NDA which relied

on the Agency's findings of safety and efficacy for the Listed Drug YAZ®. All nonclinical pharmacology/toxicology information in the current submission cross references the SLYND NDA 211367 and was previously reviewed and evaluated under that submission. Refer to the Nonclinical Pharmacology/Toxicology Sections of the Multi-disciplinary Review and Evaluation for SLYND NDA 211367 by Dr. Andrea L. Benedict, dated May 23, 2019.

As the Applicant has adequately bridged their DRSP 3.5 mg chewable tablet to the SLYND 4 mg swallowed tablet, the Applicant may rely on the Agency's findings for the nonclinical safety information for drospirenone as it is reflected in the approved SLYND and YAZ® drug labeling.

3.2 Studies Not Reviewed

Not applicable.

3.3 Previous Reviews Referenced

NDA 211367 SLYND®; Nonclinical Pharmacology/Toxicology Sections of the Multi-disciplinary Review and Evaluation; Dr. Andrea L. Benedict, dated May 23, 2019

IND 146207 Drospirenone 3.5 mg chewable tablet; Nonclinical Reviews; Dr. Andrea L. Benedict, dated May 22, 2020, and April 7, 2021

11 Integrated Summary and Safety Evaluation

The Applicant, Exeltis USA Inc. (affiliate of Laboratorios Leon Farma S.A.), submitted NDA 216285 for DRSP 3.5 mg chewable tablets, a POP oral hormonal contraceptive containing 3.5 mg DRSP, for the indication of prevention of pregnancy in females of reproductive potential. Each 28-day cycle includes oral administration of one active tablet for 24 consecutive days followed by one inert tablet for 4 consecutive days (i.e., 24/4 for a total 28-day cycle regimen).

NDA 216285 is a 505(b)(2) application with YAZ® as the Listed Drug product. The scientific bridge between DRSP 3.5 mg chewable tablet and YAZ® is provided by a comparative clinical bioavailability (BA) study (2020-FLE1-SLINC-PK-04) between DRSP 3.5 mg chewable tablet and SLYND, which was found to be adequately comparable to YAZ® under NDA 211367. In the pivotal comparative BA study, the Applicant demonstrated that the DRSP exposure after single doses of DRSP 3.5 mg chewable tablet administered was less than or comparable to the reference drug SLYND. Therefore, it is appropriate for the applicant to rely on the Agency's previous findings of nonclinical safety for SLYND and YAZ® in support of this 505(b)(2) NDA.

This NDA submission contains no new nonclinical studies, and no additional nonclinical studies were necessary. An adequate scientific bridge has been established to SLYND and YAZ®, and the Agency's prior determination of safety of DRSP to support the nonclinical section of the NDA is appropriate.

Pharmacology/Toxicology supports approval of DRSP 3.5 mg chewable tablets for the indication of prevention of pregnancy in women under NDA 216285.

Andrea L. Benedict -S

Digitally signed by Andrea L. Benedict -S
Date: 2022.07.06 17:24:35 -04'00'

Kimberly P. Hatfield -S

Digitally signed by Kimberly P. Hatfield -S
Date: 2022.07.06 17:26:22 -04'00'

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/

ANDREA BENEDICT
07/06/2022 05:31:36 PM

KIMBERLY P HATFIELD
07/06/2022 05:34:00 PM

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

PHARMACOLOGY/TOXICOLOGY NDA REVIEW AND EVALUATION

Application number:	216285
Supporting document/s:	SDN 1 (eCTD 0001)
Applicant's letter date:	July 27, 2018
CDER stamp date:	July 27, 2018
Product:	Drospirenone chewable tablet, 3.5 mg
Indication:	Contraception
Applicant:	Exeltis USA, Inc.
Review Division:	Division of Urology, Obstetrics, and Gynecology (DUOG)
Reviewer:	Andrea L. Benedict, PhD
Supervisor:	Kimberly P. Hatfield, PhD
Division Director:	Audrey Gassman, MD
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Template Version: September 1, 2010

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1 Executive Summary

1.1 Introduction

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DRSP 3.5 mg chewable tablet is a new chewable tablet dosage form that the Applicant describes as a line extension of SLYND (drospirenone) 4 mg tablet (NDA 211367, approval date May 23, 2019). SLYND also contains 24 active, white, film-coated tablets of DRSP 4 mg and 4 inactive, green placebo, film-coated tablets (28 daily tablet regimen), which is taken orally (swallowed) for use by females of reproductive potential to prevent pregnancy.

The SLYND application was a 505(b)(2) NDA submission that relied on the Agency's previous findings of safety for the Listed Drug YAZ® (NDA 21676). SLYND is currently listed in the FDA's Orange Book as a Reference Listed Drug (RLD) and Reference Standard (RS). DRSP 3.5 mg chewable tablet is proposed to be an alternative oral dosage form for oral contraceptive users who may have difficulty or a dislike for swallowing whole tablets.

The intended administration is one tablet daily: one active white tablet for 24 consecutive days followed by one inactive green tablet for 4 consecutive days, which are co-packaged in the same container closure system as is used for SLYND. The differences between the proposed DRSP 3.5 mg chewable tablet and SLYND are 1) the amount of DRSP, 2) inclusion of peppermint flavor ((b) (4) (b) (4) , and 3) (b) (4) excipients, microcrystalline cellulose and lactose monohydrate, (b) (4) respectively.

The Applicant intends to rely on the Agency's previous findings of safety for DRSP from the listed drug YAZ® to support the nonclinical module and inform Sections 8 and 13 of the labeling, and will also cross-reference their own data from the SLYND NDA (211367). To support the safety of non-compendial peppermint flavoring excipient, the Applicant has provided a quantitative listing of the composition, certificate of analysis (COA), and justification of specifications.

1.2 Brief Discussion of Nonclinical Findings

The Applicant has not conducted nonclinical studies with DRSP 3.5 mg chewable tablet and no additional nonclinical studies were required or requested by the Division to support an NDA application, pending an adequate scientific bridge was established through clinical comparative PK studies of DRSP 3.5 mg chewable tablet to SLYND.

Exeltis USA, Inc. is the Sponsor of NDA 211367 for SLYND, which was approved under 505(b)(2) pathway with reference to YAZ® as the listed drug product. The NDA referred to the Agency's previous findings of safety and efficacy for the nonclinical pharmacology, pharmacokinetics, and toxicology of the DRSP component of YAZ®

(NDA 21676) to support the nonclinical sections. The Applicant did not conduct any new nonclinical studies to support the SLYND NDA.

The scientific bridge between DRSP 3.5 mg chewable tablet and SLYND is provided by a comparative clinical bioavailability (BA) study (2020-FLE1-SLINC-PK-04). In the pivotal comparative BA study, the Applicant demonstrated that the DRSP exposure after single doses of DRSP 3.5 mg chewable tablet administered was less than or comparable to the reference drug (SLYND). Refer to the clinical pharmacology review submitted by Dr. Mohammad Akbar on May 21, 2022, for further information on the scientific bridge.

The nonclinical evidence supporting the safety of DRSP 3.5 mg chewable tablet is based on the Agency's determination of safety and efficacy for the Listed Drug product, YAZ®. SLYND was found to be adequately comparable to YAZ® under NDA 211367. YAZ® is an approved drug product (3 mg (b) (4) DRSP and 0.02 mg ethinyl estradiol tablets) that is indicated for use in the prevention of pregnancy in females of reproductive potential. Therefore, an acceptable bridge between DRSP 3.5 mg chewable tablet and SLYND provides reliance on the nonclinical safety information as provided in both the SLYND and YAZ® approved labeling.

1.3 Recommendations

1.3.1 Approvability

Nonclinical data support approval of Drospirenone (DRSP) 3.5 mg chewable tablet for the indication of prevention of pregnancy in females of reproductive potential.

1.3.2 Additional Nonclinical Recommendations

No additional nonclinical studies are recommended.

1.3.3 Labeling

The product labeling will be completed in a separate review.

2 Drug Information

2.1 Drug

CAS Registry Number
67392-87-4

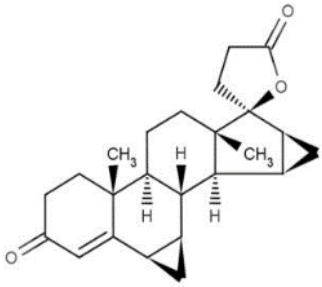
Generic Name
Drospirenone

Chemical Name
6β, 7β; 15β, 16β-dimethylene-3-oxo-17α-pregn-4-ene-21, 17-carbolactone

Molecular Formula/Molecular Weight
$C_{24}H_{30}O_3$ / 366.5 g/mol

Structure or Biochemical Description

Figure 1: Structure of Drospirenone



Pharmacologic Class
Progestin

2.2 Relevant INDs, NDAs, BLAs and DMFs

IND 146207	Drospirenone 3.5 mg chewable tablet, 24/4 regimen; Indication: Prevention of pregnancy; Sponsor: Exeltis USA, Inc. (affiliate of Laboratorios León Farma S.A.)
IND 111347	LF111 (drospirenone 4 mg tablet), 24/4 regimen; Indication: Prevention of pregnancy; Sponsor: Laboratorios León Farma S.A.
NDA 211367	SLYND (drospirenone 4 mg tablet), 24/4 regimen; Indication: Prevention of pregnancy; Sponsor: Exeltis USA, Inc. (affiliate of Laboratorios León Farma S.A.); Original Approval Date: May 23, 2019
NDA 21676	YAZ® (3 mg drospirenone and 0.02 mg ethinyl estradiol), 24/4 regimen; Indication: Prevention of pregnancy; Sponsor: Bayer HealthCare Pharmaceuticals Inc.; Original Approval Date: March 16, 2006
DMF	(b) (4)
DMF	
DMF	

2.3 Drug Formulation

Drospirenone 3.5 mg Chewable Tablets: The DRSP drug product is a 5 mm, round, unscored, film-coated, white tablet that must be chewed completely before swallowing for once daily oral administration. Each tablet contains 3.5 mg of DRSP and has a total target weight of 56.75 mg. The composition of the DRSP tablet is provided in Table 1.

Placebo Tablets: The placebo drug product is a 5 mm, round, unscored, film-coated, green tablet that is chewed completely before swallowing for once daily oral administration. Each tablet has a total target weight of 67.6 mg. The composition of the placebo tablet is provided in Table 2.

Table 1: Composition of Drospirenone 3.5 mg Chewable Tablet

Material	Function	Quantitative Composition (mg)	Content (% w/w)	Quality Standard	IIG Limit for Oral Route of Administration [e]		
					CAS Number	UNII	Max. Daily Exposure [f]
							(b) (4)
Drospirenone [a]	Active Pharmaceutical Ingredient	3.50	(b) (4)	USP	n.a.	n.a.	n.a
Microcrystalline cellulose			(b) (4)	NF			(b) (4)
Anhydrous Lactose				NF			
Colloidal silicon dioxide				NF			
Magnesium stearate				NF			
Peppermint (b) (4) Flavor [b]				In-house Monograph			
- Peppermint oil				-			
- Maltodextrin				-			
- Modified starch				-			
							(b) (4)
- Polyvinyl Alcohol-partially Hydrolyzed				USP			(b) (4)
- Titanium Dioxide				USP			
- Polyethylene Glycol (Macrogol) 3350				NF			
- Talc				USP			
							(b) (4)
TOTAL		**56.75**	**100.0**	-			

[a] Drospirenone (b) (4)

[b] Components present in Peppermint (b) (4) Flavor are peppermint oil (b) (4) and maltodextrin and modified starch (E 1450) (b) (4) Information is provided in [Section 3.2.P.4.1.3 Specifications - Peppermint (b) (4) Flavor *(Drospirenone 3.5mg Chewable Tablet)*]

[c] Components present (b) (4) are polyvinyl alcohol, titanium dioxide, polyethylene glycol (PEG) 3350, and talc. Detailed information is provided [Section 3.2.P.4.1.2 Specifications – (b) (4) *Drospirenone 3.5mg Chewable Tablet)*]

[d] (b) (4)

[e] https://www.accessdata.fda.gov/scripts/cder/iig/index.cfm (access 04 August 2021)

[f] Maximum daily exposure for oral chewable tablet unless specified

[g] Maximum potency per unit dose for oral tablet

[h] Maximum potency per unit dose for oral chewable tablet

[i] Maximum daily exposure for oral capsule

Table 2: Composition of Placebo Tablet

Component	Functionality	Quantity per Tablet (mg)	Content (% w/w)	Quality Standard	IIG Limit for Oral Route of Administration [d]		
					CAS Number	UNII	Maximum Daily Exposure (MDE) [e]
							(b) (4)
Colloidal Silicon Dioxide				NF			
Magnesium Stearate				NF			
Peppermint (b) (4) Flavor [a]				In-house Monograph			
Peppermint oil				n.a.			
Maltodextrin							
Modified starch (E 1450)				n.a.			
							(b) (4)
- Hypromellose 2910				USP			(b) (4)
- Triacetin				USP			
- Polysorbate 80				NF			
- Titanium dioxide				USP			
- FD&C Blue No. 2 --Aluminum Lake				CFR 82.102			
- Ferric Oxide Yellow				NF			
							(b) (4)
TOTAL		67.60					

[a] Components present in Peppermint (b) (4) Flavor. Information is provided in [Section 3.2.P.4.1.3 Specifications - Peppermint (b) (4) flavor *(Drospirenone 3.5mg Chewable Tablet)*]
[b] Components present (b) (4) Detailed information is provided in [Section 3.2.P.4.1.2 Specifications – (b) (4) *(Placebo Chewable Tablet)*]
[c] (b) (4)
[d] https://www.accessdata.fda.gov/scripts/cder/iig/index.cfm (access August 8, 2021)
[e] Maximum daily exposure for oral chewable tablet unless specified
[f] Maximum daily exposure for film coated tablet
[g] Maximum potency per unit dose for film coated tablet
[h] Maximum potency per unit dose for chewable tablet

2.4 Comments on Novel Excipients

Table 1 and Table 2 above include the daily amounts of each excipient in the DRSP and placebo tablet, respectively, as well as the maximum daily exposure for each excipient that was found in the FDA's Inactive Ingredient Report (IIG).

The listed excipients and the individual components of the film coating systems are excipients found in the FDA's IIG and are proposed at daily levels that are within those of previously approved drug products for the oral route of administration. All excipients are at acceptable levels.

2.5 Comments on Impurities/Degradants of Concern

There are no impurities or degradants of concern.

Proposed Impurity Specifications:

The individual and total impurity specifications for the DRSP drug substance (DMF [redacted] are in accordance with the acceptance criteria for total impurities in the current USP monograph for DRSP.

The impurity specifications for acceptance limits of individual unknown impurities at release (i.e., ≤[redacted]%) and on stability (i.e., ≤[redacted]%) in the DRSP drug product are within the acceptance criteria for identification thresholds for drug products per the ICH Q3B(R2) guidance.

The impurity specifications for acceptance limits of total impurities at release and on stability of ≤[redacted]% in the DRSP drug product is within the acceptance criteria for qualification thresholds for drug products per the ICH Q3B(R2) guidance.

2.6 Proposed Clinical Population and Dosing Regimen

DRSP 3.5 mg chewable tablet is a Progestin Only Pill (POP) containing 24 active tablets of DRSP [redacted] and four inert placebo tablets (28 daily tablet regimen) for use by females of reproductive potential to prevent pregnancy.

The intended administration is one tablet daily taken orally; 1 white active tablet containing DRSP 3.5 mg for 24 consecutive days followed by 1 green inert placebo tablet for 4 consecutive days.

2.7 Regulatory Background

On May 23, 2019, SLYND drospirenone 4 mg tablets (NDA 211367) for oral (swallowed) route of administration was approved as the first drospirenone-containing progestin-only pill (POP) for the indication of prevention of pregnancy in females of reproductive potential. SLYND is owned by the current Applicant for NDA 216285.

The sponsor, Laboratorios León Farma S.A., was granted two pre-IND Written Response Only meetings with the Division under IND 146207, with preliminary responses provided on January 10, 2020, and March 25, 2021, respectively. The sponsor requested feedback from the Division regarding the overall development program of Drospirenone 3.5 mg chewable tablet to support an intended 505(b)(2) NDA for the indication of prevention of pregnancy in females of reproductive potential. Refer to the IND 146207 Nonclinical reviews dated May 22, 2020 and April 7, 2021.

3 Studies Submitted

3.1 Studies Reviewed

There were no nonclinical studies submitted with this NDA. The Applicant has not completed any nonclinical pharmacology, pharmacokinetics, or toxicology studies with DRSP 3.5 mg chewable tablet and no additional nonclinical studies were required or requested by the Division to support an NDA application. The Applicant has submitted a 505(b)(2) application relying on the Agency's previous determination of safety for the DRSP component of the approved Listed Drug YAZ® (NDA 21676) to support the nonclinical section of this NDA. The current Applicant's other approved DRSP POP drug product, SLYND, was approved on May 23, 2019, as a 505(b)(2) NDA which relied

on the Agency's findings of safety and efficacy for the Listed Drug YAZ®. All nonclinical pharmacology/toxicology information in the current submission cross references the SLYND NDA 211367 and was previously reviewed and evaluated under that submission. Refer to the Nonclinical Pharmacology/Toxicology Sections of the Multi-disciplinary Review and Evaluation for SLYND NDA 211367 by Dr. Andrea L. Benedict, dated May 23, 2019.

As the Applicant has adequately bridged their DRSP 3.5 mg chewable tablet to the SLYND 4 mg swallowed tablet, the Applicant may rely on the Agency's findings for the nonclinical safety information for drospirenone as it is reflected in the approved SLYND and YAZ® drug labeling.

3.2 Studies Not Reviewed

Not applicable.

3.3 Previous Reviews Referenced

NDA 211367 SLYND®; Nonclinical Pharmacology/Toxicology Sections of the Multi-disciplinary Review and Evaluation; Dr. Andrea L. Benedict, dated May 23, 2019

IND 146207 Drospirenone 3.5 mg chewable tablet; Nonclinical Reviews; Dr. Andrea L. Benedict, dated May 22, 2020, and April 7, 2021

11 Integrated Summary and Safety Evaluation

The Applicant, Exeltis USA Inc. (affiliate of Laboratorios Leon Farma S.A.), submitted NDA 216285 for DRSP 3.5 mg chewable tablets, a POP oral hormonal contraceptive containing 3.5 mg DRSP, for the indication of prevention of pregnancy in females of reproductive potential. Each 28-day cycle includes oral administration of one active tablet for 24 consecutive days followed by one inert tablet for 4 consecutive days (i.e., 24/4 for a total 28-day cycle regimen).

NDA 216285 is a 505(b)(2) application with YAZ® as the Listed Drug product. The scientific bridge between DRSP 3.5 mg chewable tablet and YAZ® is provided by a comparative clinical bioavailability (BA) study (2020-FLE1-SLINC-PK-04) between DRSP 3.5 mg chewable tablet and SLYND, which was found to be adequately comparable to YAZ® under NDA 211367. In the pivotal comparative BA study, the Applicant demonstrated that the DRSP exposure after single doses of DRSP 3.5 mg chewable tablet administered was less than or comparable to the reference drug SLYND. Therefore, it is appropriate for the applicant to rely on the Agency's previous findings of nonclinical safety for SLYND and YAZ® in support of this 505(b)(2) NDA.

This NDA submission contains no new nonclinical studies, and no additional nonclinical studies were necessary. An adequate scientific bridge has been established to SLYND and YAZ®, and the Agency's prior determination of safety of DRSP to support the nonclinical section of the NDA is appropriate.

Pharmacology/Toxicology supports approval of DRSP 3.5 mg chewable tablets for the indication of prevention of pregnancy in women under NDA 216285.

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/

ANDREA BENEDICT
05/23/2022 03:20:12 PM

KIMBERLY P HATFIELD
05/23/2022 03:26:13 PM
I concur with the review and recommendations of Dr. Benedict.