CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

211367Orig1s000

PRODUCT QUALITY REVIEW(S)

QUALITY ASSESSMENT

Recommendation: ***As of this review, this 505(b)(2) NDA is Not Ready for Approval in its present form per 21 CFR 314.125(b)(8).***

NDA 211367
Review # 1

SLYND (drospirenone) tablets

Drug Name/Dosage Form	drospirenone tablets
Strength	4 mg
Route of Administration	Oral
Rx/OTC Dispensed	Rx
Applicant	Exeltis USA Inc.
US agent, if applicable	-

SUBMISSION(S) REVIEWED	DOCUMENT DATE	DISCIPLINE(S) AFFECTED
Original (0001)	07/27/18	All
Amendment (0006)	10/05/18	Drug Product; Biopharmaceutics
Amendment (0014)	01/09/19	Process; Biopharmaceutics
Amendment (0015)	01/18/19	Process/Microbiology
Amendment (0016)	01/30/19	Drug Product
Amendment (0018)	02/15/19	Drug Product
Amendment (0022)	03/11/19	Labeling
Amendment (0023)	03/13/19	Process
Amendment (0024)	03/22/19	Process
Amendment (0025)	04/01/19	Process; Labeling

Quality Review Team

Discipline	Reviewer	OPQ Division / Branch
Drug Substance	Soumya Mitra	ONDP / DNDAPI / NDBII
Drug Product, Labeling, EA	Hamid Shafiei	ONDP / DNDPII / NDPBV
Process, Microbiology, Facility	Michael Klapal	OPF / DIA / IABIII
Biopharmaceutics	Bryan Ericksen	ONDP / DB / BBII
RBPM	Grafton Adams	OPRO / DRBPMI / RBPMBI
Application Technical Lead	Mark Seggel	ONDP / DNDPII / NDPBV

Quality Review Data Sheet

1. RELATED/SUPPORTING DOCUMENTS

A. DMFs:

DMF #	Type	Holder	Item Referenced	Status	Date Review Completed	Comments
(b) (4)	II		(b) (4)	ADEQUATE	08/28/2018 M. Ethirajan	
	III			N/A		
	III			N/A		
	III			N/A		
	III			N/A		

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

B. Other Documents: *IND, RLD, or sister applications*

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
IND submissions and associated reviews	IND 111347	Drospirenone 4 mg tablets

2. CONSULTS

DISCIPLINE	STATUS	RECOMMENDATION	DATE	REVIEWER
Biostatistics	na			
Pharmacology/Toxicology	na			
CDRH	na			
Clinical	na			
Other	na			

na: not applicable

Executive Summary

I. Recommendations and Conclusion on Approvability

In its present form, Exeltis USA Inc.'s 505(b)(2) New Drug Application #211367 for Slynd (drospirenone) tablets, 4 mg, is not ready for approval. Labeling (prescribing information and container/carton labels) negotiations have not been completed, and in its present form, the labeling does not comply with the requirements under 21 CFR 201.

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

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

The claimed categorical exclusion from the requirement for preparation of an environmental assessment in accordance with 21 CFR 25.31(b) is acceptable based on a calculated Expected Introduction Concentration (EIC-aquatic) significantly below 1 ppb and supporting data.

POSTMARKETING COMMITMENTS

Not Applicable

II. Summary of Quality Assessments

A. Product Overview

Proposed Indication(s) including Intended Patient Population	(b) (4)
Duration of Treatment	(b) (4)
Maximum Daily Dose	
Alternative Methods of Administration	Not applicable

Drospirenone (DRSP) is a synthetic "fourth generation" progestin that is structurally related to spironolactone.

Currently, drospirenone is only available in fixed-dose combination products with either estradiol or ethinyl estradiol. Tablets containing drospirenone (0.25 mg and 0.5 mg) and estradiol are approved for the treatment of vulvar and vaginal atrophy symptoms and / or vasomotor symptoms due to menopause. Tablets containing 3 mg drospirenone in

combination with ethinyl estradiol (e.g., Yaz, Yasmin) are approved for the prevention of pregnancy.

The proposed drug product is a 28-day regimen consisting of 24 immediate-release, white film-coated drospirenone tablets (4 mg) and 4 green film-coated inert, placebo tablets. The tablets are dispensed in a blister card. The progestin-only pill (POP) provides an alternative to the combined progestin-estrogen oral contraceptives (COC) which contain ethinyl estradiol with associated cardiovascular risks.

Because of the low solubility of drospirenone (b) (4) in the active tablets, there are potential risks to product quality related to content uniformity and in vitro dissolution. The mitigation strategy to minimize product quality defects that could impact safety and efficacy includes (b) (4) (b) (4) (b) (4) The drug substance specification includes tests for particle size distribution (PSD) and specific surface area (SSA). These tests will ensure that the active ingredient has the optimum physical properties requisite for dissolution of the otherwise low solubility material.

The drug product specification includes test for content uniformity and in vitro dissolution. A two-tier approach to the dissolution test has been established (sampling at 15 minutes and at 3 hours) to ensure consistent performance of the drug product.

B. Quality Assessment Overview

Drug Substance:

Drospirenone is a synthetic progestin. The chemistry, manufacturing and controls for drospirenone drug substance are documented in (b) (4) Type II Drug Master File (DMF) (b) (4) The data provided in the DMF and in the NDA has been found adequate to support the use of the active pharmaceutical ingredient (API) in the manufacture of the drug product. Drospirenone is isolated as a white to off-white crystalline powder, but it does not present polymorphic forms. It has low aqueous solubility but high permeability. The drug substance meets the requirements of the USP monograph for drospirenone including related substances and residual solvents.

In addition to the USP monograph requirements, the NDA drug substance specification includes requirements for Specific Surface Area (SSA) and Particle Size Distribution (PSD). PSD and SSA are critical to performance of the drug product and directly impact product dissolution. The desired SSA and PSD are obtained (b) (4) (b) (4) The PSD test was revised (b) (4) (b) (4) to a three-tier test (d10, d50 and d90) (see IQA Attachment III for final drug substance regulatory specification) to provide additional assurance that the requisite dissolution behavior will be consistently achieved.

From the drug substance / API review perspective the information on the drug substance is Adequate to support APPROVAL of the NDA (see IQA Chapter I, Drug Substance for additional details).

Drug Product:

Drospirenone tablets are dispensed in a blister card containing 24 white, film-coated immediate-release active tablets and 4 green inert tablets. The active tablets contain 4 mg drospirenone, which accounts for (b) (4)% w/w of the total formulation. Inactive ingredients include microcrystalline cellulose, lactose, colloidal silicon dioxide, and magnesium stearate. The tablets have a (b) (4) white coating consisting of partially hydrolyzed polyvinyl alcohol, titanium dioxide, polyethylene glycol (b) (4) (b) (4). All excipients are of USP/NF compendial grade. (b) (4) (b) (4)

The inert placebo tablets contain lactose monohydrate, corn starch, povidone (b) (4) colloidal silicon dioxide (b) (4) magnesium stearate (b) (4) (b) (4) hypromellose (b) (4) triacetin, polysorbate (b) (4) titanium dioxide, FD&C Blue 2 Aluminum Lake, yellow ferric oxide, (b) (4) All components of the placebo tablet comply with USP/NF and with requirements of 21 CFR 82.102. (b) (4) (b) (4)

The drug product regulatory specification includes tests to provide further assurance that drospirenone tablets will have the requisite the identity, strength, quality, purity, and bioavailability. The acceptance criterion for total degradation products in the tablets was revised from not more than (NMT) (b) (4)% to NMT (b) (4)% at the request of the nonclinical review team (see IQA Attachment IV for final drug product regulatory specification). Individual related substances are controlled at NMT (b) (4)%. Of note is the dissolution test which includes sampling at 15 minutes and at 3 hours. Such a two-tiered approach is particularly useful for ensuring that immediate-release tablets with a low solubility active ingredient perform adequately. The acceptance criteria were established based on dissolution test results from clinical batches (see IQA Chapter VII, Biopharmaceutics and discussion below).

Long-term and accelerated stability studies support a 36-month expiration dating period for drug product stored at 25°C and packaged in the commercial aluminum foil / PVC-PVdC blisters.

This application is recommended for APPROVAL from the drug product perspective (see IQA Chapter II, Drug Product for the detailed assessment).

Environmental Analysis:

The applicant has claimed a categorical exclusion from the environmental assessment (EA) requirements in accordance with 21 CFR Part 25.31(b). This exclusion covers increases in use of the active moiety where, however, the expected introduction concentration (EIC) is less than 1 ppb. Because drospirenone is hormonally active, the applicant supported their claimed categorical exclusion with an environmental risk assessment for drospirenone that had been conducted for the European Union. The CDER EA Team reviewed the data and concluded that the results were indicative of no environmental impact, and thus support the applicant's categorical exclusion. See IQA Chapter II, Drug Product, for details.

Labeling:

Labeling deficiencies and recommendations have been identified (see IQA Chapter IV, Labeling). Labeling negotiations are ongoing. An addendum to the OPQ IQA will be filed upon resolution of all remaining labeling issues.

Process:

The drug product manufacturing process involves (b) (4)

(b) (4)

Overall, the product manufacturing process and in-process controls are adequately defined and are suitable for the manufacture of product with the requisite quality. This NDA is recommended for APPROVAL from the manufacturing process review perspective (see IQA Chapter V, Process, for details).

Facilities:

All facilities associated with the manufacture, testing and packaging of the drug substance and the drug product have acceptable CGMP status. The Office of Process and Facilities issued an overall manufacturing inspection recommendation of APPROVE on March 8, 2019. See IQA Chapter VI, Facilities for details.

Biopharmaceutics:

Consistent performance is critical to the safe and efficacious use of drospirenone tablets. Assurance of bioavailability is provided by a robust manufacturing process and use of a discriminatory in vitro dissolution test method. (b) (4) (b) (4)

The dissolution test ultimately selected employs USP Apparatus II (paddle) at 75 rpm and a medium consisting of 900 mL water with 0.6% Tween 20. The applicant's proposed acceptance criteria of (b) (4)% at 15 minutes and Q = (b) (4)% at 3 hours. The (b) (4) range at 15 minutes is problematic, although it is supported by data from clinical batches.

This NDA is recommended for APPROVAL from the Biopharmaceutics perspective (see IQA Chapter VII, Biopharmaceutics for details).

Microbiology:

Microbial growth is not supported by the formulation of this solid oral dosage form. Nevertheless, control of microbiological contamination is achieved through suitable control of the microbiological quality of the raw materials (b) (4) (b) (4) and maintenance of a suitable manufacturing environment. In addition, the applicant will conduct non-routine microbial testing (TAMC, TYMC, and absence of E. coli) on the finished product (one in 10 tablet batches, and at least once a year) as well as on stability. The applicant's strategy for control of microbial quality of the product is acceptable (see IQA Chapter V, Process for details).

Analytical Methods Verification:

Analytical Methods Verification by CDER's St. Louis laboratory was not requested because the analytical procedures are relatively straightforward and drospirenone is not an NME.

C. Special Product Quality Labeling Recommendations

Not Applicable

D. Final Risk Assessment (see Attachment I)

OVERALL ASSESSMENT AND SIGNATURES:

Application Technical Lead Name:
Mark R. Seggel, Ph.D.
CMC Lead (acting)

{see electronic signature page}

CHAPTERS: Primary Quality Assessment

CHAPTER I: Drug Substance
CHAPTER II: Drug Product
CHAPTER III: Environmental Assessment *(See Chapter II, Drug Product)*
CHAPTER IV: Labeling
CHAPTER V: Process
CHAPTER VI: Facilities
CHAPTER VII: Biopharmaceutics
CHAPTER VIII: Microbiology *(see Chapter V, Process)*
CHAPTER IX: Additional Quality Discipline *(Not Applicable)*
Attachment I: Final Risk Assessment / Life Cycle Management
Attachment II: List of Deficiencies for Complete Response (*Not Applicable*)
Attachment III: Final Drug Substance Specification
Attachment IV: Final Drug Product Specification

ATTACHMENT I: Final Risk Assessments

A. Final Risk Assessment and Lifecycle Knowledge Management

a) Drug Product

Final Risk Assessment for NDA 211367 Drospirenone Tablets, 4 mg (film-coated, immediate-release tablets)***

From Initial Risk Identification			Review Assessment		
Attribute/ CQA	**Factors that can impact the CQA**	**Initial Risk Ranking***	**Risk Mitigation Approach**	**Final Risk Evaluation**	**Lifecycle Considerations/ Comments****
Assay / Stability	• Formulation • Raw materials • Process parameters • Scale/equipment • Site • Container/closure system	8	(b) (4)	Acceptable	Limited degradation over shelf-life 36-months expiry at 25 C established
Related Substances Impurities / Degradants	• Process parameters • Container/closure system	12		Acceptable	Limit for Total revised per Pharm/Tox request. Limit for individual degradants below ICH Q3B(R2)
Physical stability (solid state)	• Raw material • Formulation • Process	4		Acceptable	
(b) (4)	• API • Container/closure system	8		Acceptable	
Uniformity of Dosage Units	• Raw materials • Formulation • Process parameters • Scale/equipment • Site	36		Acceptable	Any changes (b) (4) (b) (4) (b) (4) should be carefully evaluated for impact (b) (4) (b) (4)
Microbial Limits	• Raw materials • Manufacturing environment • Process • Moisture content	8		Acceptable	Skip lot testing acceptable, but impact of raw material or mfg. changes should be evaluated
Dissolution	• Formulation • Raw materials • Process parameters • Scale/equipment • Site	32		Acceptable	Highly variable at 15 minutes

*Risk ranking applies to product attribute/CQA

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

*** See Chapter 5, Process for details of process-related risks

ATTACHMENT II: List of Deficiencies for Complete Response

Not Applicable.

ATTACHMENT III: Final Drug Substance Specification

ectd sn 0014, 01/09/2019

Test	Method	Acceptance Criteria
Appearance	Visual assessment, USP monograph Drospirenone	White to light yellow powder.
Identification	IR, USP <197M>	Positive, consistent with reference standard
	HPLC, USP monograph Drospirenone	Positive, consistent with reference standard
Specific optical rotation	USP <781S>	(b) (4) °
Melting range	USP <741>	(b) (4) C
Water content	USP <921>	Not more than (b) (4) %
Residue on ignition	USP <281>	Not more than %
(b) (4)	USP <233>	Not more than (b) (4) ppm
Assay	HPLC, USP monograph Drospirenone	(b) (4) % (b) (4)
Purity	Residual Solvents (GC): (b) (4)	(b) (4) Not more than ppm Not more than ppm Not more than ppm Not more than ppm Not more than 0 ppm Not more than ppm Not more than ppm Not more than ppm
		Not more than (b) (4) ppm
	Related substances [1], USP monograph: (b) (4)	Not more than (b) (4) % Not more than % Not more than % Not more than % Not more than % Not more than % Not more than % Not more than % Not more than % Not more than % Not more than %
	• Any unspecified impurity • Total impurities	Not more than % Not more than %

Test	Method	Acceptance Criteria
Particle Size	USP <429>	d_{10}: Less than or equal to (b) (4) µm d_{50}: (b) (4) µm d_{90}: Greater than or equal to (b) (4) µm
Specific Surface Area	USP <846>	(b) (4) m^2/g

1. Individual known impurities for Drospirenone:

(b) (4)

ATTACHMENT IV: Final Drug Product Specification

ectd sn 0018, 02/15/2019

TESTS	ANALYTICAL METHOD	ACCEPTANCE LIMITS (UNITS)	
		RELEASE	STABILITY
APPEARANCE	Visual assessment	Round, white tablets with D and E debossed on opposite sides	Round, white tablets with D and E debossed on opposite sides
AVERAGE WEIGHT	In-house [3] USP <905>.	(b) (4) mg (Theoretical weight (b) (4) mg)	N/A
DROSPIRENONE IDENTIFICATION (UPLC)	In-house [3]	Matches retention time of reference standard	Matches retention time of reference standard
DROSPIRENONE IDENTIFICATION (UV)	In-house [3]	Matches spectrum of reference standard	N/A
DROSPIRENONE ASSAY (UPLC)	In-house [3]	(b) (4) %	(b) (4) %
(b) (4)		(b) (4) %	(b) (4) %
DROSPIRENONE DISSOLUTION (HPLC)	In-house [3]	$L_{(15\ min)}$ = (b) (4) % $Q_{(3h)}$ = (b) (4) %	$L_{(15\ min)}$ = (b) (4) % $Q_{(3h)}$ = (b) (4) %
DROSPIRENONE CONTENT UNIFORMITY (UPLC)	In-house [3] USP <905>	(b) (4) tablets AV≤ (b) (4) tablets AV ≤ Range (b) (4) M	N/A
DROSPIRENONE RELATED SUBSTANCES (UPLC) - Unknown Individual Impurities - Total Impurities	In-house [3]	≤ (b) (4) % ≤ % ≤ %	≤ (b) (4) % ≤ % ≤ %
MICROBIAL CONTROL [1] • **TAMC** (Total Aerobic Microbial Count) • **TYMC** (Total Yeast and Mold Count) • ***E. coli***	USP <61> USP <62>	≤ (b) (4) CFU / g ≤ CFU / g Absence in (b) (4) g	[2] ≤ (b) (4) CFU / g ≤ CFU / g Absence in (b) (4) g
RESIDUAL SOLVENTS	USP <467>	Complies with (b) (4) <USP 467>	N/A

[1] Microbial test is a non-routine test. It shall be conducted in one of each 10 batches, and at least once a year.
[2] Testing frequency according to stability protocol
[3] Analytical method is described in section 3.2.P.5.2. Analytical Procedures (Drospirenone 4 mg Tablet).

#######

Mark Seggel

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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: **May 22, 2019**

From: **Mark R. Seggel, Ph.D.**
Application Technical Lead
Office of New Drug Products
Branch V/DNDP II

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

To: **OPQ IQA #1 for NDA 211367**
SLYND (drospirenone) tablets

Subject: **Final Recommendation - APPROVAL**

Summary:

The OPQ Integrated Quality Assessment (IQA) dated May 9, 2019, concluded that this 505(b)(2) NDA was Not Ready for Approval in its present form per 21 CFR 314.125(b)(8). Specifically, it was noted that labeling (prescribing information (PI), container/carton) negotiations had not been completed, and in its present form, the labeling did not comply with the requirements under 21 CFR 201. The NDA was otherwise complete and adequate from the OPQ perspective.

Recommended revisions to the prescribing information and to the blister and carton labels have been conveyed to the applicant. Revision of the product title (Highlights) was requested. Revisions to enhance the clarity of Section 3, Dosage Form and Strength, were proposed. Deficiencies in Section 11, Description, included incorrect pharmacological/ therapeutic class and lack of information about inactive ingredients. Deficiencies in Section 16, How Supplied, included missing dosage form strength information, inclusion of inactive ingredients (belonged in Section 11), and insufficient information about the packaging system.

The proposed blister cards lacked NDC numbers, storage statements, and barcodes. The font size and prominence of the established name relative to the proprietary name was inadequate. This deficiency was also noted on the carton label. Needed revisions to the description of the net contents and storage statements on the carton were identified.

The revised labeling (PI, blister and carton) submitted May 20, 2019 (sn 0028) adequately addresses the deficiencies identified in the OPQ IQA #1 labeling review and outlined above. See Dr. Hamid Shafiei's attached labeling review addendum for details.

Additional Comments:

The OPDP-proposed revision of the storage statement in the patient labeling from "Store TRADENAME at room temperature between 59°F to 86°F (15°C to 30°C)" to "Store SLYND at room temperature between 68°F to 77°F (20°C to 25°C)" is appropriate from the CMC-perspective. The May 20, 2019 labeling submission adequately incorporates this change.

The May 20, 2019 version of the PI Highlights includes the statement, [redacted] (b) (4) [redacted] (b) (4) However, the initial approval of drospirenone, albeit in a fixed-dose combination with ethinyl estradiol, occurred in 2001, [redacted] (b) (5) [redacted] (b) (5) DBRUP has been advised of this discrepancy.

######

Recommendation:

This NDA is now recommended for **Approval** from the OPQ perspective.

Application Technical Lead Signature:

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

{see digital signature page}

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Seggel

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

DATE: **May 21, 2019**

FROM: **Hamid R. Shafiei, Ph.D.**
Review Chemist (Branch V/DNDP II/ONDP)

Moo-Jhong Rhee, Ph.D.
Branch Chief (Branch V/DNDP II/ONDP)

TO: **Prescribing Information (PI), Immediate Container, and Carton Labels Review # 1 for NDA 211367**

SUBJECT: **Final ONDP Recommendation from the Labeling/Label Review Perspective**

In the Review # 1 of NDA 211367, this application was not recommended for approval in the form it was presented due to the CMC deficiencies noted in PI labeling as well as immediate container (blister card) and carton labels.

The CMC labeling-label deficiencies identified in the Review # 1 have been satisfactorily addressed in the amendment submitted by the applicant on May 20, 2019 (**Attachment I**).

Recommendation: This application is now recommended for **approval** from the ONDP labeling-labels perspective.

Attachment I: Final PI and Labels

A. PI

a) Highlight Section

(b) (4)

SLYND consists of 24 white tablets each containing 4 mg of drospirenone and 4 green inert tablets. (3)

b) Full Prescribing Information

#3: Dosage Forms and Strengths

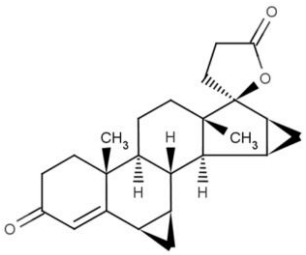
SLYND is supplied in blister cards, each containing 24 round, film-coated, unscored white tablets and 4 round, film-coated, unscored green tablets.

- Each white tablet contains 4 mg of drospirenone. White tablets are debossed with an "E" on one side and a "D" on the other side
- Each green tablet is inert and does not contain drospirenone. Green tablets are debossed with an "E" on one side and a "4" on the other side.

#11: Description

SLYND (drospirenone) is for use as an oral contraceptive. It is supplied as clear to a slightly opaque PVC-PVDC/Aluminum blister cards, each holding of 24 white tablets each containing 4 mg of drospirenone, a synthetic progestational compound and 4 green inert tablets.

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-[17Hdicyclopropa-[6,7:15,16]cyclopenta[a]phenanthrene-17,2' (5H)-furan]-3,5' (2H)-dione). It has a molecular weight of 366.5, a molecular formula of C24H30O3, and the structural formula below:



Drospirenone is a white to almost white or slightly yellow crystalline powder. It is a progestin and neutral molecule with slight solubility in water.

The active tablet is a 5 mm, round, unscored, film-coated, white tablet that contains 4mg of drospirenone as the active ingredient, and microcrystalline cellulose NF, anhydrous lactose NF, colloidal silicon dioxide NF, magnesium stearate NF, polyvinyl alcohol partially hydrolyzed NF, talc NF, titanium dioxide NF, and polyethylene glycol NF as the inactive ingredients. Each tablet is debossed with the letter "E" on one side and the letter "D" on the other sides.

The inert tablet is a 5 mm, round, unscored, film-coated, green tablet that does not contain drospirenone. Each inert green tablet contains the following inactive ingredients: Lactose monohydrate NF, corn starch NF, povidone 30000 NF, colloidal silicon dioxide NF, magnesium stearate NF, hypromellose NF, talc NF, titanium dioxide USP, polysorbate 2910 NF, triacetin NF, FD&C blue 2 aluminum lake and yellow ferric oxide.

#16: HOW SUPPLIED/STORAGE AND HANDLING

SLYND (drospirenone) tablets is packaged in clear to a slightly opaque PVC- PVDC/Aluminum blister cards. Each blister card holds 24 white round active film-coated tablets, each containing 4mg of drospirenone and 4 green round inert film-coated tablets that do not contain drospirenone. Trade Name is supplied in cardboard cartons containing 1, 3, or 6 blister cards as provided below:

SLYND 1 blister card (1 x 28 tablets) NDC 0642-7470-01

SLYND 3 blister cards (3 x 28 tablets) NDC 0642-7470-03

SLYND 6 blister cards (6 x 28 tablets) NDC 0642-7470-06

Storage and Handling

Store at 25ºC (77ºF); excursions permitted from 15 to 30ºC (59 to 86ºF) [*see USP Controlled Room Temperature*].

B. Container/Carton Labels:

a. Immediate container labels: Blister Card

b. Carton Labels

Carton Containing 1 Blister Card

Carton Containing 3 Blister Cards

(b) (4)

Carton Containing 6 Blister Cards

(b) (4)

Hamid Shafiei

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Moo Jhong Rhee

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BIOPHARMACEUTICS

Product Background: This Section 505(b)(2) submission is for LF111 (Drospirenone) Tablets (4 mg), for the indication of contraception. The listed drug products that are the bases for the submission are (b) (5) Yaz (NDA 021676, approved 03/16/2006). (b) (5)

NDA: 211367-ORIG-1

Drug Product Name / Strength: LF111 (Drospirenone) Tablets/ 4 mg

Route of Administration: Oral

Applicant Name: Exeltis USA, Inc.

Review Summary: Adequate

The applicant provided a dissolution method development report that justified the method parameters chosen. (b) (4) The discriminating ability of the dissolution method was demonstrated using a variety of variant batches.

Approved dissolution method and acceptance criteria for Drospirenone tablets

USP Apparatus	Speed (rpm)	Medium/Temperature	Volume (mL)	Acceptance criteria
2 (Paddle)	75	Water with 0.6% Tween 20/ 37 ± 0.5°C	900 mL	15 min: (b) (4) % 3 h: Q = (b) (4) %

List Submissions being reviewed (table):

07/27/2018	NDA 211367/Sequence 0001/Original Submission
10/05/2018	NDA 211367/Sequence 0006/Response to Information Request
01/09/2019	NDA 211367/Sequence 0014/Response to Information Request
01/18/2019	NDA 211367/Sequence 0015/Response to Information Request
03/13/2019	NDA 211367/Sequence 0023/Response to Information Request

Highlight of Key Outstanding Issues from Last Cycle: N/A

Concise Description of Outstanding Issues:

None

BCS Designation

Reviewer's Assessment: Drospirenone **can be considered BCS Class 2**

Drospirenone is not found in the BCS database (http://www.ddfint.net/search.cfm). According to the Pharmaceutical Development Report in Module 3.2.P.2, Drospirenone is a poorly soluble, highly permeable BCS Class 2 compound.

Solubility:

The Applicant presented a solubility study in Module 3.2.P.2, Annex 1. The test of solubility was performed (b) (4) (b) (4) (b) (4) Results are shown in Tables 2 and 3, below.

Table 2.- Solubility results

Medium	Solubility (µg/mL)
(b) (4)	

(b) (4)

Table 3.- Solubility results

(b) (4)

It can be concluded from these studies that Drospirenone is poorly soluble (b) (4) (b) (4)

Permeability:

Permeability data were not presented in the Pharmaceutical Development Report in Module 3.2.P.2 or elsewhere in the application. (b) (4) (b) (4)

(b) (4) The data were not submitted to FDA for evaluation.

Dissolution:

As was detailed in the Dissolution Method Development Report in Module 3.2.P.2, Annex 4, the (b) (4) final dissolution medium selected was water with 0.6% Tween 20. Various lower concentrations of Tween 20 were tested, (b) (4) (b) (4) The discriminating ability of the method was evaluated in these same experiments, which is discussed further in the Dissolution Method section below.

Dissolution Method and Acceptance Criteria

Reviewer's Assessment:

Method development was detailed in the Dissolution Method Development Report in Module 3.2.P.2, Annex 4. Several experiments compared two batches with different particle size distribution (PSD) and specific surface area (SSA) values, as shown in the table below:

Table 5. Quantitative composition and description of formulation of Drospirenone tablets, 4.0 mg, batches LFD0088A and LFD0141A.

Finished Product Batch No.	LFD0088	LFD0141
(b) (4)		

Method development experiments explored (b) (4) (b) (4)

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(b) (4)

Dissolution of Clinical Batches

In response to an information request, the Applicant submitted dissolution data from all 13 batches used in Phase 3 clinical studies in Module 3.2.P.5.4 of either Sequence 0014 on 01/09/2019 or Sequence 0015 on 01/18/2019.

See Appendix 1.

Dissolution Acceptance Criteria

There appears to be higher than usual variation in dissolution data. The results are problematic for the selection of acceptance criteria. The applicant selected 15-minute and 3-hour time-points. Dissolution data demonstrated higher variability at the 15-minute time-point. Hypothetically, a different time point could be chosen for the earlier time-point, but in this dataset the (b) (4) minute time points would not be improvements over the 15 minute time point. (b) (4) (b) (4) The applicant has provided data obtained from batches used in Phase 3 studies. Per email communication with Clinical team (Dr. Ronald Orleans and Dr. Gerald Willett) there are no clinical concerns with this NDA.

Considering that there are no concerns from the clinical perspective the Applicant's proposed range of (b)(4)% at the 15 minute time point is acceptable.

In response to an information request, the Applicant proposed a three-tier particle size specification in Sequence 0014, Module 3.2.S.4.1:

- D10: less than or equal to (b)(4) µm
- D50: (b)(4) µm
- D90: greater than or equal to (b)(4) µm

(b)(4)

Approved dissolution method and acceptance criteria for Drospirenone tablets

USP Apparatus	Speed (rpm)	Medium/Temperature	Volume (mL)	Acceptance criteria
2 (Paddle)	75	Water with 0.6% Tween 20/ 37 ± 0.5°C	900 mL	15 min: (b)(4)% 3 h: Q = (b)(4)%

Bridging of Formulations

Reviewer's Assessment:

On 10/05/2008 in Sequence 0006, the Applicant provided a table that listed all batches used in clinical trials and the formulation of each batch. On 01/09/2019, in Sequence 0014, the Applicant further clarified this table:

Table 10. List of Bio-batches and Product Code Involved in Clinical Studies for Development of LF111

Batch No.	Product Code (Formulation)	Strength
LFD0038A	101364	DR 3 mg
LFD0040A	101363	DR 3 mg
LFD0039A	101365	DR 3 mg
LFD0069A	701569	DR 4 mg
LFD0088A	701641	DR 4 mg
LFD0114A	701641	DR 4 mg
LFD0118A	701641	DR 4 mg
LFD0141A	701641	DR 4 mg
LFD0146A	702009	DR 2.8 mg
LFD0149B	701641	DR 4 mg
LFD0150B	701641	DR 4 mg
LFD0158A	701641	DR 4 mg
LFD0187A	701641	DR 4 mg
LFD0217A	701641	DR 4 mg
LFD0228A	701641	DR 4 mg
LFD0238A	701641	DR 4 mg
LFD0257A	701641	DR 4 mg
LFD0281A	701641	DR 4 mg
LFD0314A	701641	DR 4 mg
LFD0315A	701641	DR 4 mg
LFD0393A	701641	DR 4 mg

Note that six different formulations are listed. In Sequence 0014, the Applicant also provided dissolution data for batches LFD0149B, LFD0150B, LFD0187A, LFD0217A, and LFD0228A. All five of these batches have the same formulation, 701641.

In Sequence 0001, Module 5.2, the Applicant provided a tabular listing of Clinical Studies. Four Phase 3 (pivotal) studies are listed: CF111/301, 302, 303 and 304. Each study report body provided a listing of batch numbers used in that study. Study 301 used batch numbers LFD0114A, LFD0141A, LFD0149B, and LFD0150B. All four of these batches have the same formulation, 701641. Study 302 used batch numbers LFD0158A, LFD0187A, and LFD0217A, LFD0228A. All four of these batches have the same formulation, 701641. Study 303 used batch numbers LFD0218A, LFD0257A, LFD0314A, LFD0315A and LFD0393A. LFD0218A is not listed in the above table or in the table given in Sequence 0006. It is a typographical error. The correct batch number is LFD0281A, according to the Applicant's Response to Information Request in Sequence 0023, submitted 03/13/2019. All five batches used in Study 303 have the same formulation, 701641. Study 304 used batch numbers LFD0257A and LFD0315A. Both of these batches have the same formulation, 701641.

In conclusion, all batches used in the Phase 3 clinical trials are of the same formulation as the dissolution data presented in Sequence 0014. Therefore, no formulations need to be bridged.

List of Deficiencies: None

Primary Biopharmaceutics Reviewer Name:

Bryan Ericksen, Ph.D.

Secondary Reviewer Name (and Secondary Summary, as needed):

Vidula Kolhatkar, Ph.D.

Appendix 1: **Dissolution of Clinical Batches**

In response to an information request, the Applicant submitted dissolution data from all 13 batches used in Phase 3 clinical studies in Module 3.2.P.5.4 of either Sequence 0014 on 01/09/2019 or Sequence 0015 on 01/18/2019.

\\cdsesub1\evsprod\nda211367\0015\m3\32-body-data\32p-drug-prod\drospirenone-tab-leon\32p5-contr-drug-prod\32p54-batch-analys\annex-32p54-13-ind-diss-data-v01.xlsx

Bryan Ericksen

Digitally signed by Bryan Ericksen
Date: 5/09/2019 02:54:09PM
GUID: 59285fba002134adea4d6f405770a2b2

Vidula Kolhatkar

Digitally signed by Vidula Kolhatkar
Date: 5/09/2019 09:19:39AM
GUID: 5424aeae00c3274f93e50573f7ca407e

LABELING

R. Regional Information

1.14 Labeling

I. Package Insert

1. HIGHLIGHTS OF PRESCRIBING INFORMATION

1) Title

Tradename (drospirenone) (b) (4)

Initial U.S. Approval: XXXX

2) DOSAGE FORMS AND STRENGTHS

Tradename consists of 24 white tablet (b) (4) 4 mg of drospirenone and 4 green inert tablets. (3)

Item	Information Provided in NDA	Reviewer's Comment and Recommendations
Drug name (201.57(a)(2))		
Proprietary name and established name	Tradename (drospirenone)	Provided. **Satisfactory**
Dosage form, route of administration	tablet (b) (4)	Need to revise (b) (4) (b) (4) **Unsatisfactory**
Controlled drug substance symbol (if applicable)	Not applicable	Not applicable
Dosage Forms and Strengths (201.57(a)(8))	Tradename consists of 24 white tablet (b) (4) 4 mg of drospirenone and 4 green inert tablets	Provided. **Satisfactory**
Whether the drug product is scored	Not applicable	Not applicable

Revise (b) (4)

2. "FULL PRESCRIBING INFORMATION

1) #3: DOSAGE FORM AND STRENGTHS

(b) (4)

(b) (4)

Item	Information Provided in NDA	Reviewer's Comment and Recommendations
Available dosage forms	(b) (4)	Provided. **Satisfactory**
Strengths: in metric system	(b) (4)	Provided. But needs some revision for clarity. **Unsatisfactory**
Active moiety expression of strength with equivalence statement (if applicable)	• Each white tablet contains 4 mg of drospirenone • Each green tablet does not contain (b) (4)	Provided. **Satisfactory**
A description of the identifying characteristics of the dosage forms, including shape, color, coating, scoring, and imprinting, when applicable.	• Each white tablet contains 4 mg of drospirenone; (b) (4) (b) (4) • Each green tablet does not contain (b) (4) (b) (4)	Provided **Satisfactory**

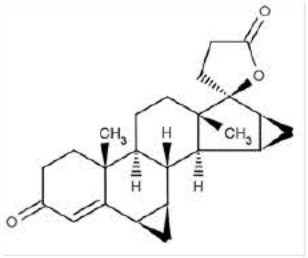
The dosage form and strength should be revised for clarity. The following revisions are recommended:

Tradename is in supplied in blister cards, each containing 24 round, film-coated, unscored white tablets and 4 round, film-coated, unscored green tablets.

- Each white tablet contains 4 mg of drospirenone. White tablets are debossed with an "E" on one side and a "D" on the other side
- Each green tablet is inert and does not contain drospirenone. Green tablets are debossed with an "E" on one side and a "4" on the other side.

2) #11: DESCRIPTION

(b) (4)



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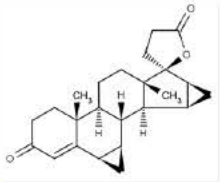
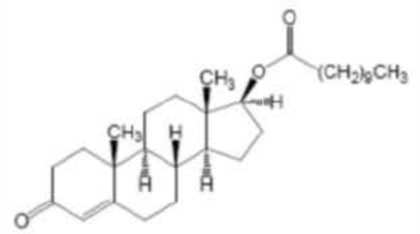
Item	Information Provided in NDA	Reviewer's Comment and Recommendations
Proprietary name and established name	(b) (4)	Provided. But needs revision to clarify the established name. **Unsatisfactory**
Dosage form and route of administration		Provided. **Satisfactory**
Active moiety expression of strength with equivalence statement (if applicable)	Not applicable	Not applicable.
Inactive ingredient information (quantitative, if injectables 21CFR201.100(b)(5)(iii)), listed by USP/NF names (if any) in alphabetical order (USP <1091>)	Not provided	Not provided. **Unsatisfactory**
Statement of being sterile (if applicable)	Not applicable	Not applicable
Pharmacological/ therapeutic class	oral contraceptive is a synthetic progestational compound	Not provided. It is a progestin. **Unsatisfactory**
Chemical name, structural formula, molecular weight	(b) (4) 	Provided. **Satisfactory**
If radioactive, statement of important nuclear characteristics.	Not applicable	Not applicable
Other important chemical or physical properties (such as pKa or pH)	Not provided	Not Provided. **Unsatisfactory**

This section should be revised to include, established name, information regarding the active ingredients, and other important chemical or physical properties of the drug. The following revisions is suggested:

Tradename (drospirenone) tablets is for use as an oral contraceptive. It is supplied as clear to a slightly opaque PVC-PVDC/Aluminum blister cards, each holding of 24 white tablets each containing 4 mg of drospirenone, a synthetic progestational compound and 4 green inert tablets.

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'(5H)-furan]-3,5'(2H)-dione). It has a molecular weight of 366.5, a molecular formula of $C_{24}H_{30}O_3$, and the structural formula below:



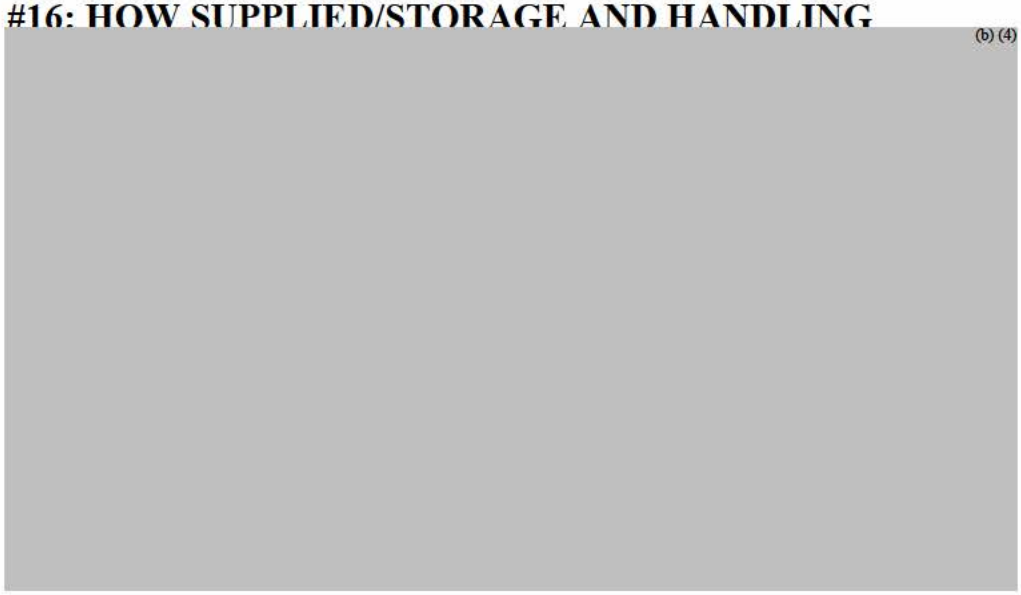
Drospirenone is a white to almost white or slightly yellow crystalline powder. It is a progestin and a neutral molecule with slight solubility in water

The active tablet is a 5 mm, round, unscored, film-coated, white tablet that contains 4mg of drospirenone as the active ingredient, and microcrystalline cellulose NF, anhydrous lactose NF, colloidal silicon dioxide NF, magnesium stearate NF, polyvinyl alcohol partially hydrolyzed NF, talc NF, titanium dioxide NF, and polyethylene glycol NF as the inactive ingredients. Each tablet is debossed with the letter "E" on one side and the letter "D" on the other sides.

The inert tablet is a 5 mm, round, unscored, film-coated, green tablet that does not contain drospirenone. Each inert green tablet contains the following inactive ingredients: Lactose monohydrate NF, corn starch NF, povidone 30000 NF, colloidal silicon dioxide NF, magnesium stearate NF, hypromellose NF, talc NF, titanium dioxide USP, polysorbate 2910 NF, triacetin NF, FD&C blue 2 aluminum lake and yellow ferric oxide.

3) #16: HOW SUPPLIED/STORAGE AND HANDLING

(b) (4)



TRADENAME 1 blister card (1 x 28 tablets) NDC 0642-7470-01

TRADENAME 3 blister cards (3 x 28 tablets) NDC 0642-7470-03

TRADENAME 6 blister cards (6 x 28 tablets) NDC 0642-7470-06

16.2 **Storage and Handling**

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

Item	Information Provided in NDA	Reviewer's Comment and Recommendations
Strength of dosage form	Not provided	Not provided. **Unsatisfactory**
Available units (e.g., bottles of 100 tablets)	(b) (4)	Provided. But needs revision. **Satisfactory**
Identification of dosage forms, e.g., shape, color, coating, scoring, imprinting, NDC number		Provided. But need to be revised. **Satisfactory**
Special handling (e.g., protect from light)	Not applicable	Not applicable
Storage conditions	Store at 25°C (77°F); excursions permitted to 15 to 30°C (59 to 86°F) [see USP Controlled Room Temperature].	Provided. **Satisfactory**
Manufacturer/distributor name (21 CFR 201.1(h)(5))	Manufactured for: Exeltis USA, Inc. Florham Park, NJ 07932 Manufactured by: Laboratorios León Farma, S. A., Navatejera, Spain 24008	Provided at the end of the PI. **Satisfactory**

This section must be revised to include strength of the dosage form, remove the description (b) (4) and a better description of the packaging. The following revision is recommended:

Trade Name (drospirenone) tablets is packaged in clear to a slightly opaque PVC-PVDC/Aluminum blister cards. Each blister card holds 24 white round active film-coated tablets, each containing 4mg of drospirenone and 4 green round inert film-coated tablets that do not contain drospirenone. Trade Name is supplied in cardboard cartons containing 1, 3, or 6 blister cards as provided below:

TRADENAME 1 blister card (1 x 28 tablets) NDC 0642-7470-01

TRADENAME 3 blister cards (3 x 28 tablets) NDC 0642-7470-03

TRADENAME 6 blister cards (6 x 28 tablets) NDC 0642-7470-06

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

II. Labels

1. IMMEDIATE CONTAINER

Blister Card

QUALITY ASSESSMENT

Item	Information Provided in NDA	Reviewer's Comment and Recommendations
Proprietary name, established name (font size and prominence (21 CFR 201.10(g)(2))	The trade name and established name are displayed.	Provided. Established name font size and prominence are inadequate. **Unsatisfactory**
Dosage strength	4mg	Provided. **Satisfactory**
Net contents	(b) (4) Oral Use	Provided. Should be revised and reference (b) (4) should be removed. (b) (4) should be changed to 28. **Unsatisfactory**
"Rx only" displayed prominently on the main panel	Displayed.	**Satisfactory**
NDC number (21 CFR 207.35(b)(3)(i))	Not provided	**Unsatisfactory**
Lot number and expiration date (21 CFR 201.17)	The location for lot number and expiration is displayed.	Provided. **Satisfactory**
Storage conditions	Not displayed.	Not provided. **Unsatisfactory**
Bar code (21CFR 201.25)	Not displayed.	Not provided **Unsatisfactory**
Name of manufacturer/distributor	Displayed.	Provided. **Satisfactory**
And others, if space is available	Not applicable	Not applicable

The following changes to the blister card label should be made:

- Adjust the font size and prominence of the established name to be consistent with 21 CFR 201.10(g)(2).
- Revised the net content to 28 tablets and remove all references (b) (4) (b) (4)
- Add the NDC number
- Add the storage conditions
- Add the bar code

2. CARTON LABELS:

Carton containing 1 blister card:

(b) (4)

Carton containing 3 blister cards:

Carton containing 6 blister cards:

(b) (4)

Item	Information Provided in NDA	Reviewer's Comment and Recommendations
Proprietary name, established name (font size and prominence (21 CFR 201.10(g)(2))	Displayed.	Provided. Established name font size and prominence are inadequate. **Unsatisfactory**
Dosage strength	4mg	Provided. **Satisfactory**
Net contents	(b) (4) Oral Use Oral Use Oral Use	• (b) (4) should be removed. • (b) (4) should be changed to 1 blister card, 3 blister cards, or 6 blister cards with 28 tablets per blister card. **Unsatisfactory**
"Rx only" displayed prominently on the main panel	Displayed	Displayed. **Satisfactory**
NDC number (21 CFR 207.35(b)(3)(i))	Displayed	Displayed. **Satisfactory**
Lot number and expiration date (21 CFR 201.17)	The location on the carton where the lot number and expiration will be placed has been designated.	Provided. **Satisfactory**
Storage conditions	Store at 25°C (77° F)	Provided. It should be revised to: Store at 25°C (77°F); excursions permitted to 15 to 30°C (59 to 86°F) **Unsatisfactory**
Bar code (21CFR 201.25)	Displayed	Displayed. **Satisfactory**
Name of manufacturer/distributor	Manufactured by : Laboratorios León Farma, S.A. c/ La Vallina s/n. Pol. Ind. Navatejera 24008 Navatejera, León, Spain Distributed by : Exeltis USA, Inc., Florham Park, NJ 07932 www.exeltisUSA.com	Displayed. **Satisfactory**
And others, if space is available	Not applicable	Not applicable

The following changes to the carton labels should be made:

- Adjust the font size and prominence of the established name to be consistent with 21 CFR 201.10(g)(2).
- Remove (b) (4) and revise the net content as provided below:
  - 1 blister card with 28 tablets
  - 3 blister cards with 28 tables per blister card

- 6 blister cards with 28 tables per blister card
- Add the storage conditions

III. LIST OF DEFICIENCIES:

A. Regarding PI

Highlights

- Need to revise (b) (4) (b) (4)

Full Prescribing Information

#3: Dosage Forms and Strengths

Revised this section as recommended below:

Tradename is supplied in blister cards, each containing 24 round, film-coated, unscored white tablets and 4 round, film-coated, unscored green tablets.

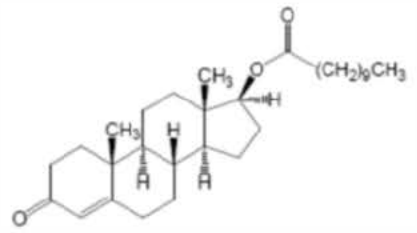
- Each white tablet contains 4 mg of drospirenone. White tablets are debossed with an "E" on one side and a "D" on the other side
- Each green tablet is inert and does not contain drospirenone. Green tablets are debossed with an "E" on one side and a "4" on the other side.

#11: Description

Revise this section as recommended below:

Tradename (drospirenone) is for use as an oral contraceptive. It is supplied as clear to a slightly opaque PVC-PVDC/Aluminum blister cards, each holding of 24 white tablets each containing 4 mg of drospirenone, a synthetic progestational compound and 4 green inert tablets.

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'(5H)-furan]-3,5'(2H)-dione). It has a molecular weight of 366.5, a molecular formula of $C_{24}H_{30}O_3$, and the structural formula below:



Drospirenone is a white to almost white or slightly yellow crystalline powder. It is a progestin and neutral molecule with slight solubility in water

The active tablet is a 5 mm, round, unscored, film-coated, white tablet that contains 4mg of drospirenone as the active ingredient, and microcrystalline cellulose NF, anhydrous lactose NF, colloidal silicon dioxide NF, magnesium stearate NF, polyvinyl alcohol partially hydrolyzed NF, talc NF, titanium dioxide NF, and polyethylene glycol NF as the inactive ingredients. Each tablet is debossed with the letter "E" on one side and the letter "D" on the other sides.

The inert tablet is a 5 mm, round, unscored, film-coated, green tablet that does not contain drospirenone. Each inert green tablet contains the following inactive ingredients: Lactose monohydrate NF, corn starch NF, povidone 30000 NF, colloidal silicon dioxide NF, magnesium stearate NF, hypromellose NF, talc NF, titanium dioxide USP, polysorbate 2910 NF, triacetin NF, FD&C blue 2 aluminum lake and yellow ferric oxide.

#16: How Supplied/Storage and Handling

Revise this section as recommended below:

Trade Name (drospirenone) tablets is packaged in clear to a slightly opaque PVC-PVDC/Aluminum blister cards. Each blister card holds 24 white round active film-coated tablets, each containing 4mg of drospirenone and 4 green round inert film-coated tablets that do not contain drospirenone. Trade Name is supplied in cardboard cartons containing 1, 3, or 6 blister cards as provided below:

TRADENAME 1 blister card (1 x 28 tablets) NDC 0642-7470-01

TRADENAME 3 blister cards (3 x 28 tablets) NDC 0642-7470-03

TRADENAME 6 blister cards (6 x 28 tablets) NDC 0642-7470-06

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

B. Regarding of the Container/Carton Labels:

a) Immediate container labels:

The following changes should be made to the blister card label:

- Adjust the font size and prominence of the established name to be consistent with 21 CFR 201.10(g)(2).
- Revised the net content to 28 tablets and remove (b) (4)
- Add the NDC number
- Add the storage conditions
- Add the bar code

b) Carton labels:

The following changes to the carton labels should be made:

- Adjust the font size and prominence of the established name to be consistent with 21 CFR 201.10(g)(2).
- Remove all references (b) (4) and revise the net content as provided below:
  - 1 blister card with 28 tablets
  - 3 blister cards with 28 tables per blister card
  - 6 blister cards with 28 tables per blister card
- Add the storage conditions

IV. OVERALL ASSESSMENT AND RECOMMENDATION:

- Multiple PI labeling deficiencies have been noted.
- The carton labels require revisions.

Recommendation:

From the ONDP perspective, this application is ***not*** recommended for approval per 21 CFR 314.125(b)(6) until the deficiencies delineated above are satisfactorily resolved.

Primary Labeling Reviewer Name:

Hamid Shafiei, Ph.D.
Reviewer, Branch V
DNDP II/ONDP/OPQ

Secondary Reviewer Name:

I concur with Dr. Shafiei's assessment and his recommendation that the labels and labeling are ***not*** ready for approval in its present form per 21 CFR 314.125 (b)(6) from the ONDP perspective.

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

Hamid Shafiei

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Date: 2/15/2019 11:05:11AM
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Moo Jhong Rhee

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Date: 3/20/2019 02:14:03PM
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