CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

214154Orig1s000

PRODUCT QUALITY REVIEW(S)

U.S. FOOD & DRUG ADMINISTRATION

RECOMMENDATION

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

NDA 214154
NEXTSTELLIS (drospirenone and estetrol tablets)
Assessment #1

Drug Product Name	drospirenone and estetrol tablets
Dosage Form	tablets
Strength	drospirenone 3 mg estetrol 14.2 mg (anhydrous); 15 mg as monohydrate
Route of Administration	Oral
Rx/OTC Dispensed	Rx
Applicant	Mayne Pharma LLC, Greenville, NC
US agent, if applicable	-
Application Type	505(b)(2)
NDA Classification Code*	Type 1,4 (NME [estetrol] and new combination (physical))
Combination Product**	na

* Previously referred to as the "Chemistry Classification Code."
** e.g., drug-device combination product

Submission(s) Assessed	Document Date	Discipline(s) Affected
Original (0001)	04/15/2020	All
Quality/Response (0005)	06/04/2020	OPMA
Quality/Response (0007)	06/08/2020	OPMA
Quality/Response (0008)	06/09/2020	OPMA
Labeling (0010)	07/17/2020	Labeling
Quality/Response (0014)	08/14/2020	Product, Biopharm.
Labeling/Labels (0014)	08/14/2020	Labeling
Quality/Response (0016)	08/21/2020	OPMA
Quality/Response (0017)	09/04/2020	All
Quality Response (0019)	09/28/2020	All
Labeling/Labels (0021)	10/08/2020	Labeling
Labeling/Labels (0024)	11/09/2020	Labeling
Labeling/Labels (0024)	11/25/2020	Labeling
Labeling/Labels (0025)	12/04/2020	Labeling

Labeling (0030)	01/08/2021	Labeling
Labeling (0037)	04/06/2021	Labeling
Labeling (0038)	04/09/2021	Labeling

QUALITY ASSESSMENT TEAM

Discipline	Primary Assessment	Secondary Assessment
Drug Substance	Friedrich Burnett	Donna Christner
Drug Product / Labeling	Michael Theodorakis	Wendy Wilson-Lee
Manufacturing / Microbiology	Youmin Wang	Jean Tang
Biopharmaceutics	Kalpana Paudel	Vidula Kolhatkar
RBPM	Marquita Burnett	
ATL	Mark Seggel	
Laboratory (OTR)	N/A	N/A
Environmental	Jim Laurenson	-

EXECUTIVE SUMMARY

I. RECOMMENDATIONS AND CONCLUSION ON APPROVABILITY

As amended, Mayne Pharma's 505(b)(2) New Drug Application 214154 for NEXTSTELLIS (drospirenone and estetrol) tablets, 3 mg/14.2 mg, is recommended for APPROVAL from the OPQ perspective. [Note: the strength of estetrol, a new molecular entity, is based on the anhydrous basis. Outside of the US, it is based on the monohydrate (i.e., 15 mg).]

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

The carton label and the blister card label as submitted on December 4, 2020 and November 9, 2020, respectively, are adequate from the product quality perspective. The prescribing information (PI) submitted April 9, 2021, and revised April 12, 2021, is accurate, complete and complies with the requirements under 21 CFR 201. The patient package insert (PPI) submitted April 9, 2021, and revised April 12, 2021, is acceptable from the product quality perspective.

All drug substance and product-related manufacturing, packaging and testing facilities have acceptable drug CGMP status. An overall manufacturing inspection recommendation of APPROVE was issued on November 30, 2020. The recommendation remains current as of this review. Note: Product manufacturing was (b) (4) as initially proposed by the original IND sponsor, Estetra SPRL.

An expiration dating period of 36 months for product stored in the at 20°C to 25°C is granted.

The claimed categorical exclusion from the environmental assessment requirements under 21 CFR Part 25.31(b) is acceptable.

II. SUMMARY OF QUALITY ASSESSMENTS

A. Product Overview

NEXTSTELLIS is a new fixed-dose combination product for the prevention of pregnancy. Each 28-day blister card includes 24 once-daily active tablets containing 3 mg drospirenone (DRSP), a progestin, and 14.2 mg estetrol (anhydrous basis), an estrogen structurally related to estradiol and estriol (see Attachment 1 of this Executive Summary), and 4 once-daily inactive, placebo tablets. Estetrol (E4) is a new molecular entity (NME).

The listed drug referenced by the Applicant is YAZ (drospirenone and ethinyl estradiol) tablets, 3 mg / 0.02 mg, approved March 16, 2006 under Bayer NDA 21676. Drospirenone is an active ingredient in approved products containing DRSP alone, and in combination with estradiol, ethinyl estradiol, or ethinyl estradiol and levomefolate.

The Applicant describes estetrol as "a naturally occurring estrogen produced by the human fetal liver. It is only produced during pregnancy and reaches the maternal circulation through the placenta." Estetrol is considered a weak estrogen, but because it is "tolerated in very high concentrations in fetal and maternal tissue," it was selected for development for use in combination with a suitable progestin. The combination of synthetic estetrol and drospirenone was selected for development as efficacious and safe alternative to approved products, with an acceptable bleeding profile and less pronounced effects on metabolic parameters.

The manufacture, packaging and controls for NEXTSTELLIS are consistent with those for other combined oral contraceptives containing low doses of potent active ingredients. Control of content uniformity and prevention of packaging errors are critical for ensuring the safety and efficacy of this novel combined oral contraceptive.

Proposed Indication(s) including Intended Patient Population	"NEXTSTELLIS is a combination of drospirenone, a progestin, and estetrol, an estrogen, indicated for use by females of reproductive potential to prevent pregnancy."
Duration of Treatment	As needed.
Maximum Daily Dose	• 1 active tablet daily for 24 days: 3 mg drospirenone and 14.2 mg estetrol (anh.) • 1 inert, placebo tablet daily for 4 days
Alternative Methods of Administration	Not applicable.

B. Quality Assessment Overview

Drug Substance: Adequate

Estetrol (E4)

The chemistry, manufacturing and controls for estetrol is documented in (b) (4) Type II DMF (b) (4). Estetrol, an estrogen, is (b) (4) .

The white to off-white crystalline solid is very slightly soluble in water and aqueous solutions. The monohydrate is otherwise soluble in methanol, ethanol, sparingly soluble in acetone and slightly soluble in ethyl acetate and acetonitrile (USP solubility definitions). It has an octanol/water partition coefficient (log P_{ow}) of (b) (4).

Polymorphs of estetrol have been identified. (b) (4)

A retest period of (b) (4) months at (b) (4) RH has been established for estetrol as manufactured by (b) (4)

The CMC information on the API provided in DMF (b) (4) is found to be adequate in support of NDA 214154 (see F. Burnett's review of DMF (b) (4) dated 05/26/2020).

Drospirenone (DRSP)

The CMC information for DRSP, a synthetic progestin, is documented in (b) (4) Type II DMF (b) (4) Drospirenone is manufactured at (b) (4) facility. It is (b) (4) No polymorphic forms of DRSP are known. (b) (4) DRSP has a (b) (4) month retest period when stored at (b) (4) The CMC information on the API provided in DMF (b) (4) is found to be adequate in support of NDA 214154 (see F. Burnett's review of DMF (b) (4) dated 05/29/2020).

See IQA Chapter I for additional notes.

Drug Product: Adequate

NEXTSTELLIS (drospirenone and estetrol tablets) 3 mg/14.2 mg, is a novel combined oral contraceptive containing the previously approved

active drospirenone and the NME estetrol. NEXTSTELLIS is supplied in a (b) (4) aluminum foil blister card with 24 once-daily active tablets and 4 inert, placebo tablets. In addition to DRSP and E4, the active tablets contain corn starch, lactose monohydrate, magnesium stearate, povidone, and sodium starch glycolate. The tablets are embossed with a drop-shaped logo and have (b) (4) pink film-coating consisting of hydrogenated cottonseed oil, hydroxypropyl cellulose, hypromellose, iron oxide red (b) (4), talc, and titanium dioxide.

The white film-coated, hormone-free, (b) (4) inactive / inert placebo tablets serve as reminders over the last 4 days. The placebo tablet core is composed of corn starch, lactose monohydrate, and magnesium stearate. The tablets are embossed with a drop-shaped logo and have (b) (4) white film-coating consisting of hydrogenated cottonseed oil, hydroxypropyl cellulose, hypromellose, talc, and titanium dioxide. All inactive ingredients meet USP/NF compendial requirements and are suitable for the intended use.

The overall control strategy for ensuring the identity, strength, quality, purity, potency, and bioavailability of the finished drug product is relatively straightforward with adequate raw material controls, in-process controls, and finished product specification. The active tablet specification includes tests for identification of DRSP and E4, assay and content uniformity of DRSP and E4, degradation products, (b) (4), and in vitro dissolution. The proposed acceptance criteria for related substances / impurities are consistent with ICH Q3B(R2): Limits for specified impurities do not exceed the qualification threshold. Limits for any single-unidentified impurity do not exceed the identification threshold. The specification for the placebo tablets includes a test to ensure the absence of DRSP and E4.

Based on risk assessments, routine testing for elemental impurities and (b) (4) in the finished product is not required. Testing of the placebo tablets is performed to ensure the absence of the active ingredients. The analytical procedures have been adequately validated. Appropriate acceptance criteria have been established.

Long-term (25ºC/60% RH) and intermediate (30ºC/75% RH) stability data from 2 registration stability batches through 36 months and 1 batch through 24 months, and 6-months accelerated (40ºC/75% RH) data were submitted. All batches met the acceptance criteria for all testing intervals at long-term (25°C/60% RH) and intermediate (30°C/75% RH) storage for 24 to 36 months, and at accelerated storage conditions (40°C/75% RH) for 6 months. No significant trends were observed in the data at any storage condition or time. The data support a 36-month expiration dating

period for product stored at 20ºC to 25ºC. No relevant degradation was observed following exposure to light per ICH Q1B. No significant changes were observed during storage of (b) (4)

See IQA Chapter II for details.

Environmental Assessment: Adequate

The Applicant's claim for a categorical exclusion from an environmental assessment (EA) in accordance with 21 CFR 25.31(b), which is for substances that increase in use but result in an expected introduction concentration (EIC) of less than (<) 1 ppb. No extraordinary circumstances are known to the Applicant (21 CFR 25.15). The applicant also submitted EA data to support the exclusion claim based on recent FDA guidance (USFDA, 2016, Environmental Assessment: Questions and Answers Regarding Drugs with Estrogenic, Androgenic, or Thyroid Activity). The FDA EA Team reviewed the data and agreed that approval of this application would not result in a significant environmental impact. Therefore, the claim for an exclusion from an EA is acceptable.

Labeling: Adequate

The established name of the drug product is 'drospirenone and estetrol tablets.' The active ingredients are separated with 'and,' not a slash '/,' as proposed by the Applicant. The strength of estetrol, 14.2 mg, is expressed on the anhydrous basis. Outside of the US, the strength of estetrol is based on the monohydrate (15 mg). For COCs, by convention, the progestin component is followed by the estrogen component. The inactive ingredients in the active tablets and of the placebo tablets are clearly differentiated, and are listed. The storage statement follows current practice.

The carton label and the blister card label as submitted on December 4, 2020 (SN 0025) and November 9, 2020 (SN 0023), respectively, are adequate from the product quality perspective. The prescribing information (PI) submitted April 9, 2021 (SN 0038), and revised April 12, 2021, is accurate, complete and complies with the requirements under 21 CFR 201. The patient package insert (PPI) submitted April 9, 2021, and revised April 12, 2021, is acceptable from the product quality perspective.

Other labeling components include:
IFU (SN 0037, 04/06/2021)
Calendar sticker (SN 0021, 10/08/2020)
Pocket (blister card sleeve) (SN 0004, 05/18/2020)

Integrated Manufacturing: Adequate

Facilities (Adequate)
Note: Product manufacturing was (b) (4) as initially proposed by the original IND sponsor, Estetra SPRL.

All drug substance- and drug product-related manufacturing, packaging and testing facilities received “Approve Facility” recommendations based on either District recommendation or based on file review. No inspections were requested or completed. Latest Overall Manufacturing Inspection Recommendation Approve Completion Date: (b) (4). All facilities remain compliant as of the date of this review (see Attachment 2 of the Executive Summary.

Process (Adequate)

(b) (4)

(b) (4)

See IQA Chapter V for details.

Biopharmaceutics: Adequate

The Biopharmaceutics review focused on the evaluation and acceptability of the dissolution method and dissolution acceptance criterion. of bridging of formulations. The following dissolution method and acceptance criterion for the release of estetol and drospirenone from the fixed-dose combination tablets are deemed acceptable:
USP Apparatus 2 (Paddle) at 50 rpm and a medium consisting of 900 mL phosphate buffer pH 6.8 at 37ºC. The acceptance criteria of Q = (b) (4)% in 30 minutes for both E4 and DRSP. Phosphate buffer solution pH 6.8 was selected (b) (4)

The discriminating ability of the method was characterized. The dissolution rate of E4 slightly decreased with higher particle sizes or with (b) (4) drug substance. (b) (4) . Although estetol is only very slightly soluble in aqueous solvents, it can be considered BCS 1 because it is present in the product in a low dose. (b) (4)

The dissolution rate of DRSP is significantly impacted by the particle size of the DRSP used for the tablet batch manufacturing. The impact of film-coat weight is only observed during the first 10 minutes. Variation in sodium starch glycolate and (b) (4) (magnesium stearate) levels did not adversely impact dissolution.

Dissolution of E4 is rapid and > (b) (4)% is achieved within 15 min. However, for DRSP, dissolution is slightly slower and > (b) (4)% dissolution is achieved

in 30 min. Based on the results obtained for DRSP, the acceptance criterion for both components was set at > (b) (4)% in 30 min.

The final to-be-marketed product is the same product used in the pivotal clinical studies (Phase 3 and thereafter some Phase 1 and 2 studies).

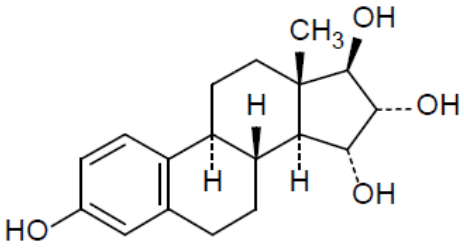
From Biopharmaceutics perspective, NDA 214154 for drospirenone and estetrol tablets, 3 mg/14.2 mg, is recommended for APPROVAL.

Microbiology (if applicable): Adequate

See Integrated Manufacturing Summary.

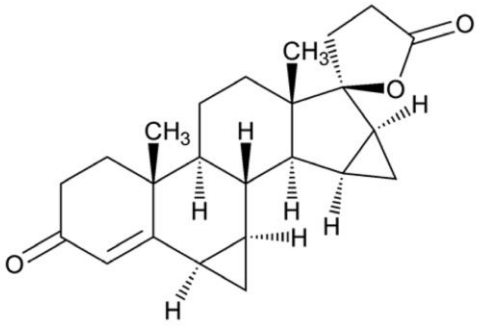
Attachment 1: Structures

Estetrol (estra-1,3,5(10)-triene-3,15α,16α,17β-tetrol)

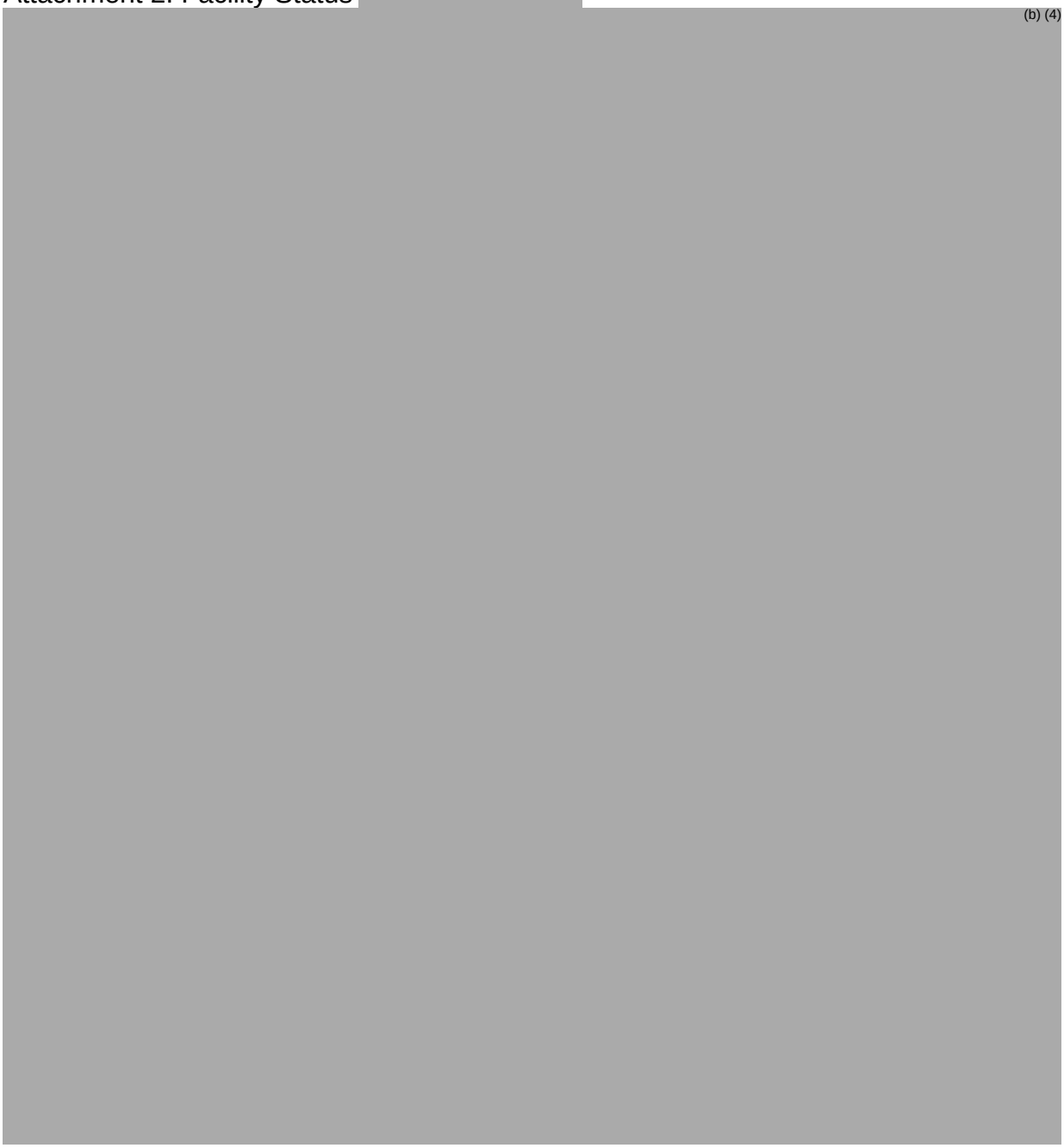


(b) (4)

Drospirenone



Attachment 2: Facility Status (b) (4)



C. Risk Assessment

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**
Identity	• CGMPs	Low	(b) (4)	Adequate	
Appearance	• Manufacturing equipment and process • Container/closure system (CCS)	Low		Adequate	
Assay / Stability	• Formulation • Raw materials • Process parameters • Scale/equipment • Site • CCS	Low		Adequate	
Related Substances Impurities / Degradants	• Process parameters • Container/closure system • Storage conditions	Low		Adequate	
Physical Stability	• Formulation • Process parameters • Storage conditions	Low		Adequate	
Content Uniformity	• Raw materials • Formulation • Process parameters • Scale/equipment • Site	Medium		Adequate	Drug load: (b) (4)% E4, (b) (4)% DRSP
Dissolution	• Formulation • Process parameters • Scale/equipment • Site	Low		Adequate	Although both actives are only very slightly soluble in aqueous systems, because of the low doses, the tablets meet BCS solubility criteria
(b) (4)		Low		Adequate	
(b) (4)	• Quality of raw materials • Process (b) (4) • Mfg. environment and equipment	Low		Adequate	
(b) (4)	• Raw materials	Low		Adequate	
Elemental Impurities	• Raw materials • Manufacturing Equipment • CCS	Low		Adequate	

D. List of Deficiencies for Complete Response

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

na

2. Drug Substance Deficiencies

na

3. Drug Product Deficiencies

na

4. Labeling Deficiencies

na

5. Manufacturing Deficiencies

na

6. Biopharmaceutics Deficiencies

na

7. Microbiology Deficiencies

na

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

na

######

***Application Technical Lead Name and Date**:*

Mark R. Seggel, Ph.D. April 12, 2021
Chemist
OPQ/ONDP/DNDPII/Br4

{see electronic signature page}

QUALITY ASSESSMENT DATA SHEET

1. RELATED/SUPPORTING DOCUMENTS

A. DMFs:

DMF #	Type	Holder	Item Referenced	Status	Date Assessment Completed	Comments
(b) (4)	II		(b) (4)	Adequate	F. Burnett 05/31/2020	
	II			Adequate	F. Burnett 05/29/2020	
	IV			N/A		
	IV			N/A	See also Review #2, 06/17/2010	
	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 during the current review cycle.

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

Application Number	Document(s)	Description
IND 110682	IND submissions, reviews and meeting minutes	IND for estetrol and drospirenone COC Ownership transferred from Estetra S.P.R.L. to Mayne Pharma LLC (04/03/2020)
NDA 21676	Listed drug	YAZ (drospirenone 3 mg and ethinyl estradiol 0.02 mg)

2. CONSULTS

Discipline	Status	Recommendation	Date	Assessor
Biostatistics	na			
Nonclinical	na			
CDRH-OPEQ	na			
Clinical	na			
Other	na			

CHAPTERS: Primary Quality Assessment

CHAPTER I: Drug Substance

CHAPTER II: Drug Product

CHAPTER III: Environmental Assessment (see Chapter II)

CHAPTER IV: Labeling

CHAPTER V: Manufacturing Integrated Assessment

CHAPTER VI: Biopharmaceutics

CHAPTER VII: Microbiology (see Chapter V)

CHAPTER VIII: Additional Quality Disciplines (Not applicable)

Mark Seggel

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CHAPTER IV: LABELING

IQA NDA Assessment Guide Reference

List of Submissions Reviewed and Discipline Reviews Cited:

Document Reviewed (eCTD #)	Date Received	Subject
eCTD-0023 (SDN-23) (ORIG-1)	2020-11-09	Latest Carton Labels
eCTD-0021 (SDN-21) (ORIG-1)	2020-10-08	Carton Labels
eCTD-0014 (SDN-14) (ORIG-1)	2020-08-14	Packaging Primary, secondary, (b) (4)
eCTD-0010 (SDN-10) (Multiple Submissions)	2020-07-17	Prescribing Information
eCTD-0007 (SDN-7) (ORG-1)	2020-06-08	Container Closure
eCTD-0004 (SDN-4) (GI-1)	2020-05-18	Proprietary Name
eCTD-0001 (SDN-1) (ORIG-1)	2020-04-15	Labeling

1.0 PRESCRIBING INFORMATION

The quality related aspects of the prescribing information are provided in the submission listed above. On 07/15/2020 DMEPA approved conditionally the proprietary name NEXTSTELLIS.

1.1 HIGHLIGHTS OF PRESCRIBING INFORMATION

1. TITLE:

NEXTSTELLIS (drospirenone and estetrol tablets) for oral use.
Initial U.S. Approval: 20YY

2. DOSAGE FORMS AND STRENGTHS

(b) (4)

4 white tablets.

Item	Information Provided in the NDA	Assessor's Comments
Product Title in Highlights: Drug product name §201.57(a)(2)		
Proprietary name	NEXTSTELLIS	**Adequate**, it has been approved by DMEPA
Established name(s)	(drospirenone and estetrol tablets) for oral use	**Adequate**
Route(s) of administration	Oral	**Adequate**
Dosage Forms and Strengths Heading in Highlights (21 CFR §201.57(a)(8))		
Summary of the dosage form(s) and strength(s) in metric system.	24 pink tablets each containing 3 mg of drospirenone and 15 mg estetrol monohydrate. 4 white inert tablets	**Adequate**
Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state "functionally scored"	N/A The tablets are not scored	N/A
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

1.2 FULL PRESCRIBING INFORMATION

1.2.1 Section 2 (DOSAGE AND ADMINISTRATION)

Item	Information Provided in the NDA	Assessor's Comments
DOSAGE AND ADMINISTRATION section		
Special instructions for product preparation (e.g., reconstitution and resulting concentration, dilution, compatible diluents, storage conditions needed to maintain the stability of the reconstituted or diluted product)	N/A	N/A

1.2.2. Section 3 (DOSAGE FORMS AND STRENGTHS)

Each blister card contains 24 pink tablets and 4 white tablets. The pink tablet contains 3 mg drospirenone and 15 mg of estetrol monohydrate. The white tablet is inactive. The tablets are taken once a day orally. The patient will start using the pink tablets for 24 days and then will switch to using the white tablets for 4 days.

Item	Information Provided in the NDA	Assessor's Comments
DOSAGE FORMS AND STRENGTHS section		
Available dosage form(s)	Pink tablet with two APIs, drospirenone and estetrol monohydrate White inert tablet	**Adequate**
Strength(s) in metric system	Pink tablet: 3 mg drospirenone and (b)(4) White tablet: inert	**Adequate** The active tablets contain (b)(4) .

If the active ingredient is a salt, apply the USP Salt Policy per FDA Guidance	N/A	N/A
A description of the identifying characteristics of the dosage forms, including shape, color, coating, scoring, and imprinting	The drug product consists of 28 tablets of which 24 tablets are pink and 4 tablets are white. The pink tablets contain 3 mg of drospirenone and (b) (4) mg of estetrol monohydrate (b) (4) The white tablets are inert. (b) (4) Both the pink and white tablets are 6 mm round, film coated tablets. Both the pink and white tablets are embossed on one side with a drop-shaped logo.	**Adequate**
Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state "functionally scored"	N/A	N/A
For injectable drug products for parental administration, use appropriate labeling term (e.g., single-dose, multiple-dose, single-patient-use). Other package type terms include	N/A	N/A

pharmacy bulk package and imaging bulk package.		

1.2.1 Section 11 DESCRIPTION

Section 11 Description in the PI should be revised to read as follows:

NEXTSTELLIS™ (drospirenone and estetrol tablets) is an oral contraceptive. It is (b) (4) in transparent PVC/aluminum blister cards containing 28 tablets ((b) (4)

(b) (4)

Drospirenone is a white to almost white or slightly yellow crystalline powder. It is (b) (4) neutral molecule with slight solubility in water.

(b) (4)

Estetrol monohydrate is a white to off-white crystalline solid, (b) (4) poorly soluble in water and aqueous solutions. Soluble in methanol, ethanol, sparingly soluble in acetone and slightly soluble in ethyl acetate and acetonitrile.

The active tablet is a 6 mm round film-coated pink tablet which contains 3 mg of drospirenone and 15 mg of estetrol monohydrate, equivalent to 14.2 mg estetrol, (b) (4) The pink film-coating has the following inactive ingredients: (b) (4) Each tablet is embossed on one side with a drop shaped logo.

The inert tablet is a 6 mm round (b) (4) white tablet which contains the inactive ingredients (b) (4). Each tablet is embossed on one side with a drop-shaped logo. The (b) (4) film-coating has the following inactive ingredients: (b) (4)

Item	Information Provided in the NDA	Assessor's Comments
DESCRIPTION section		
Proprietary and established name(s)	NEXTSTELLIS (drospirenone and estetrol tablets)	**Adequate e**
Dosage form(s) and route(s) of administration	Tablets, oral	**Adequate**
If the active ingredient is a salt, apply the USP Salt Policy and include the equivalency statement per FDA Guidance.	N/A	N/A Drospirenone and Estetrol Monohydrate are not salts

List names of all inactive ingredients. Use USP/NF names. Avoid Brand names.	**1. Drospirenone and Estetrol Tablet inactive ingredients:** lactose monohydrate, sodium starch glycolate, corn starch, povidone and magnesium stearate **2. Pink film coating inactive ingredients:** hypromellose, hydroxypropyl cellulose, talc, hydrogenated cottonseed oil, titanium dioxide, and iron oxide red. **3. Inactive Tablet ingredients**: lactose monohydrate and corn starch. 4**. White film coating ingredients**: hypromellose, hydroxypropyl cellulose, talc, hydrogenated cottonseed oil, and titanium dioxide.	**Adequate**
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
Statement of being sterile (if applicable)	N/A	N/A

Pharmacological/therapeutic class	**Estetrol** inhibits ovulation and affects the endometrium. **Drospirenone** inhibits the maturation of follicles and inhibits ovulation, preventing pregnancy. . Established Pharmacologic Class [EPC] – Progestin.	**Adequate**

Section 11 (DESCRIPTION) Continued

Item	Information Provided in the NDA	Assessor's Comments
For oral prescription drug products, include gluten statement if applicable	N/A	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	N/A

Assessment of Section 11 (DESCRIPTION): {Adequate}

1. Section 11 will be revised during reviewing team labeling meetings as described on pages 5 and 6 of this review document.

1.2.2 Section 16 (HOW SUPPLIED/STORAGE AND HANDLING)

Section 16 should be revised.

(b) (4)

Revision of Section 16.

NEXTSTELLIS (drospirenone and estetrol tablets) (b) (4)

NEXTSTELLIS is supplied in cardboard cartons containing 1 blister card (b) (4)

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

Item	Information Provided in the NDA	Assessor's Comments
HOW SUPPLIED/STORAGE AND HANDLING section		
Available dosage form(s)	Pink film coated active tablets, and white film coated inactive tablets	**Adequate**
Strength(s) in metric system	Pink film coated active tablets contain 3 mg of drospirenone and (b) (4) of estetrol monohydrate. White film coated inactive tablets (b) (4)	**Adequate**
Available units (e.g., bottles of 100 tablets)	Blister cards of 28 tablets (24 pink and 4 white tablets). Blister cards are packaged in carton containers with 1 (b) (4) blister cards.	**Adequate**
Identification of dosage forms, e.g., shape, color, coating, scoring, imprinting, NDC number	Both the pink and white film coated tablets are round with 6 mm diameter and embossed on one side with a drop-like logo. Blister cards of 28 tablets (24 pink and 4 white tablets) are packaged in carton containers with packaging configuration of 1 (b) (4) blister cards per carton container. The respective NDC numbers are: [51862-258-01], (b) (4)	**Adequate** Note: the Applicant's eCTD-0021 (SDN-21) received on 2020-10-08 did not include carton label for packaging (b) (4)
Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state "functionally scored"	N/A	N/A

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

Section 16 (HOW SUPPLIED/STORAGE AND HANDLING) (Continued)

Item	Information Provided in the NDA	Assessor's Comments
Special handling about the supplied product (e.g., protect from light, refrigerate). If there is a statement to "Dispense in original container," provide reason why (e.g. to protect from light or moisture, to maintain stability, etc.)	N/A	N/A
If the product contains a desiccant, ensure the size and shape differ from the dosage form and desiccant has a warning such as "Do not eat."	N/A	N/A
Storage conditions. Where applicable, use USP storage range rather than storage at a single temperature.	The Applicant did not include the storage conditions in the package insert	**Not Adequate** The storage statement "Store at 20°C to 25°C (68°F to 77°F), excursions permitted to 15°C to 30°C (59°F to 86°F) [see USP Controlled Room Temperature]" should be included in the HOW SUPPLIED/STORAGE AND HANDLING section of the package insert.

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	N/A
Include information about child-resistant packaging.	The Applicant did not provide information if the blister packaging is child resistant.	**Not Adequate** The Applicant should provide information about child resistant blister packaging for NEXTSTELLIS tablets.

Assessment of Section 16 (How Supplied/Storage and Handling): {Not Adequate}

1. Section 16 will be revised during reviewing team labeling meetings as described on page 9 of this labeling review.
2. The storage statement "Store at 20°C to 25°C (68°F to 77°F), excursions permitted to 15°C to 30°C (59°F to 86°F) [see USP Controlled Room Temperature]" should be included in Section 16.
3. (b) (4)
4. The Applicant should verify that the blister packaging is child resistant.

Any deficiencies should be listed at the end in the "ITEMS FOR ADDITIONAL ASSESSMENT."

1.2.3 Other Sections of Labeling

There may be other sections of labeling that contain product-quality related information. For example, there are specific required/recommended warnings for certain inactive ingredients [e.g., aspartame, aluminum in large and small volume parenterals, sulfites, FD&C Yellow Number 5 (tartrazine), and benzyl alcohol]. Please notify the prescription drug division if the product contains any of these inactive ingredients.

Please include your comments about other sections of labeling if they contain product quality information.

Assessment: Adequate
NEXTSTELLIS (drospirenone and estetrol tablets) does not contain any of the ingredients listed in Section 1.2.3. above.

1.2.6 Manufacturing Information After Section 17 (for drug products)

Item	Information Provided in the NDA	Assessor's Comments
Manufacturing Information After Section 17		
Name and location of business (street address, city, state and zip code) of the manufacturer, distributor, and/or packer	(b) (4) (b) (4) Mayne Pharma LLC 1240 Sugg Parkway Greenville, NC 27834	**Adequate**

Assessment: Adequate

2.0 PATIENT LABELING

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

3.0 CARTON and CONTAINER LABELING

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

Item	Information Provided in the NDA	Assessor's Comments about Carton Labeling
Proprietary name, established name, and dosage form (font size and prominence [21 CFR § 210.10(g)(2).	NEXTSTELLIS (drospirenone and estetrol tablets)	**Adequate**
Dosage strength	3 mg drospirenone/14.2 mg estetrol	**Adequate**
Route of administration	Oral	**Adequate**
If the active ingredient is a salt, include the equivalency statement per FDA Guidance	N/A	N/A
Net contents (e.g. tablet count)	(b) (4)	**Adequate**
"Rx only" displayed on the principal display	It is displayed on the principal display panel	**Adequate**
NDC number	NDC 51862-258-01. It is displayed on the blister card (primary container) and on the carton's (secondary) container principal display panel (PDP).	**Adequate**
Lot number and expiration date	They appear on the blister card (primary container).	**Adequate**
Storage conditions. If applicable, include a space on the carton labeling for the user to write the new BUD.	N/A	N/A
For injectable drug products for parental administration, use appropriate package type term (e.g., single-dose, multiple-dose, single-patient-use)	N/A	N/A
Other package terms include pharmacy bulk package and imaging bulk package which require "Not for direct infusion" statement.	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

Item	Information Provided in the NDA	Assessor's Comments about Carton Labeling
Proprietary name, established name, and dosage form (font size and prominence [21 CFR § 210.10(g)(2).	NEXTSTELLIS (drospirenone and estetrol tablets)	**Adequate**
Dosage strength	3 mg drospirenone/14.2 mg estetrol	**Adequate**
Route of administration	Oral	**Adequate**
If the active ingredient is a salt, include the equivalency statement per FDA Guidance	N/A	N/A
Net contents (e.g. tablet count)	(b) (4)	**Adequate**
"Rx only" displayed on the principal display	It is displayed on the principal display panel	**Adequate**
NDC number	NDC 51862-258-01. It is displayed on the blister card (primary container) and on the carton's (secondary) container principal display panel (PDP).	**Adequate**
Lot number and expiration date	They appear on the blister card (primary container).	**Adequate**
Storage conditions. If applicable, include a space on the carton labeling for the user to write the new BUD.	N/A	N/A
For injectable drug products for parental administration, use appropriate package type term (e.g., single-dose, multiple-dose, single-patient-use)	N/A	N/A
Other package terms include pharmacy bulk package and imaging bulk package which require "Not for direct infusion" statement.	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

Bar code: 21 CFR 201.25(c)(2)	A linear barcode that contains the National Drug Code (NDC) has been added to the immediate container (blister card) label and on the side panel of the carton container.	**Adequate**:

Item	Information Provided in the NDA	Assessor's Comments about Carton Labeling
Name of manufacturer/ distributor	(b) (4) Distributed by: Mayne Pharma LLC 1240 Sugg Parkway Greenville, NC 2783	**Adequate** (b) (4) appear on the back display panel of the carton container.
Medication Guide (if applicable)	The package insert has a medication guide	**Adequate**
No text on Ferrule and Cap overseal	N/A	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	N/A
And others, if space is available	N/A	N/A

Assessment of Carton and Container Labeling: {Not Adequate}

1. The Primary Container (Blister) Label is adequate.
2. The Secondary Container (Carton) Label needs minor revisions as follows:
   a. On the back display panel revise the statement to read "Each active tablet contains 3 mg drospirenone and 14.2 mg estetrol".

b. On the back panel the addresses of the manufacturer and distributor should appear as follows:

Distributed by:
Mayne Pharma LLC
1240 Sugg Parkway
Greenville, NC 2783

Any deficiencies should be listed at the end in the "ITEMS FOR ADDITIONAL ASSESSMENT."

ITEMS FOR ADDITIONAL ASSESSMENT ITEMS FOR ADDITIONAL ASSESSMENT

1. (b) (4)

2. Clarify whether the proposed blister packaging is child resistant.

3. The secondary container (carton) label needs revisions as follows:
   a. On the back display panel revise the statement to read "Each active tablet contains 3 mg drospirenone and 14.2 mg estetrol".
   b On the back panel the addresses of the manufacturer and distributor should appear as follows:

(b) (4)

Distributed by:
Mayne Pharma LLC
1240 Sugg Parkway
Greenville, NC 2783

4. (b) (4)

Overall Assessment and Recommendation:

Primary Labeling Assessor Name and Date:

As of this review, NDA 214154 is deemed not ready for approval per 21 CFR §314.125(b)(6) from the CMC labeling perspective. The CMC labeling deficiencies listed above should be rectified.

Michael C. Theodorakis, Ph.D.
Chemistry Reviewer
Branch IV/DNDP II/ONDP

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

Wendy I Wilson-Lee, Ph.D.
Division Director
CDER/OPQ/ONDP/DNDPII

Michael Theodorakis

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Date: 12/03/2020 08:06:58PM
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Wendy Wilson- Lee

Digitally signed by Wendy Wilson- Lee
Date: 11/24/2020 03:19:49PM
GUID: 50816dbc000085595ca3284bbca465a8

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

Date: **2/24/2021**

From: **Michael C. Theodorakis,** Ph.D.
Drug Product Reviewer
Branch IV Division of New Drug Products II
Office of New Drug Products

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

To: Labeling Review #1 of NDA 214154, NEXTSTELLIS (drospirenone and estetrol tablets) 3 mg/14.2 mg.

Subject: Finalized label/labeling of CMC Sections. Addendum to Labeling Review #1

At the time when labeling review of this application was completed (12/10/2020), this NDA was not recommended for approval due to unresolved CMC label/labeling issues. On 03/02/2021, the applicant submitted revised labels and labeling which satisfactorily addressed all CMC label/labeling issues that have been identified (see **Attachment** below).

Recommendation:

The outstanding CMC label/labeling issues have been resolved, and therefore, this application is now recommended for **approval** from the labeling perspective.

Michael C. Theodorakis, Ph.D.
Drug Product Reviewer
Branch IV, Division II, ONDP

Wendy I. Wilson-Lee, Ph.D.
Director
Division II, ONDP

Attachment

The following comments were included in my labeling review dated 1/4/2021.

Comment 1:

(b) (4)

Applicant's Response:
Section #16 "HOW SUPPLIED/STORAGE AND HANDLING states that E4/DRSP is supplied in a cardboard carton containing 1 blister card..." See eCTD -0030 (SDN-30) (ORIG-1) 2021-01-08.

Comment 2:
Clarify whether the proposed blister packaging is child resistant.

Applicant's Response:
The blister package is NOT child resistant. The statement "This package is not child resistant" has been added on the carton container label**.** See eCTD -0025 (SDN-25) (ORIG-`1) 2020-12-04.

Comment 3
The secondary container (carton) label needs revisions as follows:

a. On the back display panel revise the statement to read "Each active tablet contains 3 mg drospirenone and 14.2 mg estetrol".

b On the back panel the addresses of the manufacturer and distributor should appear as follows:

(b) (4)

Distributed by:
Mayne Pharma LLC
1240 Sugg Parkway
Greenville, NC 2783[4]

Applicant's Response:

a. The Applicant included in the back panel of the carton container the statement "Each active tablets contains 3 mg drospirenone and 14.2 mg estetrol". The Applicant provided an updated carton proof,

b. The Applicant provide the following response: **"**The qualifying statement has been updated to satisfy the requirements of 21 CFR 201.1 by including the distributor information. The country of origin statement "Product of Germany" has also been added to satisfy the US Customs and Border Protection ("CPB") requirement related to the source country and complies with 19 USC 1304. Reference is made to the updated carton proof. (Note: (b) (4)

Comment 4

The Applicant should clarify (b) (4) It should be noted that the Applicant submitted carton container labeling for the 1 blister card packaging configuration.

Applicant's Response:

See Applicant's response to Comment 1 above. The Applicant (b) (4)

Michael Theodorakis

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Date: 2/26/2021 04:55:35PM
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Wendy Wilson- Lee

Digitally signed by Wendy Wilson- Lee
Date: 2/26/2021 05:02:15PM
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BIOPHARMACEUTICS

Product Background:

NDA: NDA-214154-ORIG-1

Drug Product Name / Strength: Estetrol monohydrate (E4)/Drospirenone (DRSP) (15 mg/3 mg) Tablet (15 mg of estetrol monohydrate is equivalent to 14.2 mg of estetrol (anhydrous))

Route of Administration: Oral

Applicant Name: Mayne Pharma LLC

Proposed indication: Prevention of pregnancy

Dose: One tablet is administered daily for 24 days followed by one placebo (inert) tablet administered daily for four days.

Review Recommendation: **ADEQUATE**

Review Summary:
Estetrol monohydrate 15 mg/drospirenone 3 mg (E4/DRSP 15/3 mg) is a new combined oral contraceptive (COC) containing steroid hormones estetrol monohydrate (E4, an estrogen) in combination with drospirenone (DRSP, a progestogen). E4 is a new chemical entity (NME). E4 is a naturally occurring estrogen produced by the human fetal liver. E4 displays a high selectivity for estrogen receptors (ERs) and binds to both ERα and ERβ, with a preference for ERα. The proposed treatment regimen of the COC consists of one E4/DRSP 15/3 mg fixed-dose combination tablet daily taken for 24 days followed by one placebo tablet daily taken for four days.

Biopharmaceutics review is focused on the evaluation and acceptability of bridging of formulations, dissolution method, and dissolution acceptance criterion.

In Vitro Dissolution Method and Acceptance Criterion: ADEQUATE
The following dissolution method and acceptance criterion for the release of estetrol and drospirenone from the FDC tablets are deemed acceptable:

USP Apparatus	Speed (RPMs)	Medium/Temperature	Volume (mL)	Acceptance criterion
2 (Paddle)	50	Phosphate Buffer pH 6.8 /37°C ± 0.5°C	900	Q = (b) (4)% in 30 minutes for both E4 and DRSP

Bridging of clinical formulations: ADEQUATE
The final to-be-marketed product is the same product used in the pivotal clinical studies (Phase 3 and thereafter some Phase 1 and 2 studies).

Biowaiver Request: Not requested
Only one strength of the FDC drug product is developed.

List of Submissions reviewed:
Sequence 0001_Original submission
Sequence 0014_Response to IR1
Sequence 0017_Response to IR2

Highlight Key Outstanding Issues from Last Cycle: The Applicant was requested to provide solubility data in 3 different media (b) (4)

Concise Description of Outstanding Issues Remaining: None.

From Biopharmaceutics perspective, NDA 214154 for Estetrol monohydrate and Drospirenone Tablets (15 mg and 3 mg) is recommended for APPROVAL.

BCS Designation

Reviewer's Assessment:
The Applicant has not requested any BCS classification for their drug product. The Applicant, however, noted that estetrol monohydrate is a BCS 1 compound with high solubility and high permeability. DRSP can be considered as either Class 1 or Class 3 (based on solubility data). The details of these discussions are provided in the links below
\\CDSESUB1\evsprod\nda214154\0001\m3\32-body-data\32p-drug-prod\e4drsp-fct-haupt-pharma\32p2-pharm-dev\32p2-pharm-dev-active.pdf
\\CDSESUB1\evsprod\nda214154\0001\m2\27-clin-sum\summary-biopharm.pdf

Solubility
Estetrol is very slightly soluble in aqueous solvents as per Ph. Eur. and USP criteria, however it is a low dose in the drug product, and at the dose level E4 can be considered a BCS class 1. Estetrol monohydrate is (b) (4) at physiological pH, and no significant pH dependency of solubility was observed. The highest dose of 15 mg of E4 is soluble in 250 mL of water, hydrochloric acid, acetate buffer and in phosphate buffer, and therefore E4 can be considered highly soluble per the BCS guidance. The pH solubility profile is presented below.

Table 1: Solubility Estetrol monohydrate at 37°C (n = 3)

Media	Estetrol monohydrate (E4)
Water	76.9 mg / 250 mL RSD 0.1% (0.308 mg/mL)
Hydrochloric acid pH 1.0	76.2 mg / 250 mL RSD 0.7% (0.305 mg/mL)
Acetate buffer pH 4.5	75.8 mg / 250 mL RSD 0.5% (0.303 mg/mL)
Phosphate buffer pH 6.8	77.2 mg / 250 mL RSD 0.7% (0.309 mg/mL)

Although the water solubility of drospirenone is poor (Ph. Eur./USP: practically insoluble in water), the solubility according to BCS classification guidance is high. The highest dose of 3 mg of DRSP is soluble in 250 mL of water, acetate buffer, and phosphate buffer.

Drospirenone is (b) (4) at physiological pH. Per the Applicant, the lower amount of DRSP solubilized in acidic media (Table 2) (b) (4)

(b) (4)

Table 2: Solubility of Drospirenone at 37°C (n = 3)

	Drospirenone (DRSP)
Water	4.1 mg / 250 mL RSD 1.0% (16.46 µg / mL)
Hydrochloric acid pH 1.0	1.4 mg / 250 mL RSD 0.3% (5.67 µg / mL)
Acetate buffer pH 4.5	3.8 mg / 250 mL RSD 0.6% (15.19 µg / mL)
Phosphate buffer pH 6.8	4.2 mg / 250 mL RSD 0.3% (16.97 µg / mL)

Permeability

The Applicant noted that the apical to basolateral permeability of E4 across Caco-2 cell monolayers was 1.80^{-5} cm/sec, indicating high *in vitro* permeability. The mean value of the basolateral to apical permeability was 5.34^{-5} cm/sec for all E4 concentrations and the efflux ratio is > 2, suggesting that E4 is a substrate of an efflux transporter. This information was not reviewed in detail.

Permeability data are not available for drospirenone. Per the Applicant based on the PK data provided in study report "MIT-Es0001-C103", it could be assumed that the permeability of DRSP is relatively high.

Dissolution: Please see below.

1. Composition of proposed drug product

The quantitative composition of each component of the proposed FDC drug product is listed in table 3.

Table 3: Composition of Estetrol monohydrate 15 mg / drospirenone 3 mg Film-coated Tablet

Component	Quality Standard	Function	Quantity (%)	Quantity (mg)/tablet
Core Tablet				
Estetrol monohydrate[1]	In house	Active ingredient		(b) (4)
Drospirenone	Ph. Eur. / USP-NF[2]	Active ingredient		
Lactose monohydrate	Ph. Eur. / USP-NF	(b) (4)		
Sodium starch glycolate (b) (4)	Ph. Eur. / USP-NF			
(b) (4) corn starch	Ph. Eur. / USP-NF			
Povidone (b) (4)	Ph. Eur. / USP-NF			
(b) (4)				
Magnesium stearate	Ph. Eur. / USP-NF			
		(b) (4)		
Total				

[1] Corresponding to 14.2 mg anhydrous estetrol

(b) (4)

2. In vitro dissolution method and acceptance criterion

Reviewer's Assessment: ADEQUATE

The biopharmaceutics review is focused on the evaluation of dissolution method and acceptance criteria for Estetrol monohydrate/Drospirenone tablets. The following dissolution method and acceptance criterion were proposed for dissolution testing of FDC tablets.

Table 4: Dissolution method for estetrol monohydrate and drospirenone

USP Apparatus	Speed (RPMs)	Medium/Temperature	Volume (mL)	Acceptance criterion
2 (Paddle)	50	Phosphate Buffer pH 6.8 /37°C ± 0.5°C		Q = (b) (4)% in 30 minutes for both E4 and DRSP

Dissolution method development

The details of the dissolution method development are provided in the pharmaceutical development report (Page 47/73). A summary of the method development is provided below.

(b) (4)

[redacted]

Figure 1: Dissolution of E4 in Phosphate Buffer (pH 6.8), 50 rpm

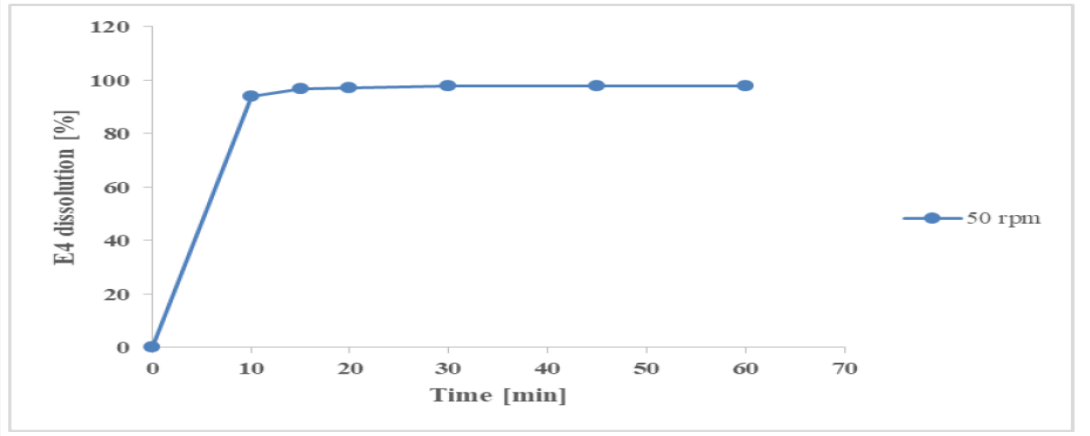
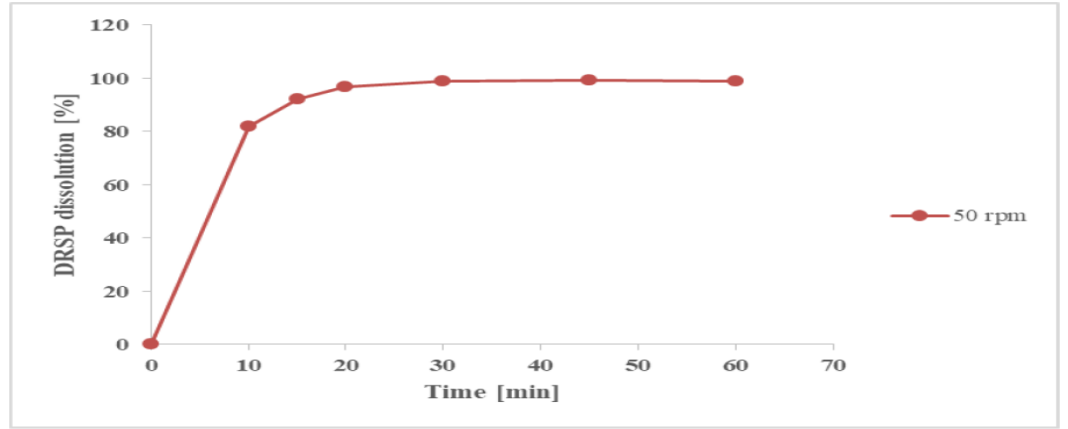


Figure 2: Dissolution of DRSP in Phosphate Buffer (pH 6.8), 50 rpm



Discriminating ability of the dissolution method

(b) (4) E4 monohydrate and (b) (4) DRSP is used for the manufacture of the drug product. The Applicant has provided data to show discriminating ability of the proposed dissolution method for film-coated tablets prepared with drug substances of different particle size distributions. The details are provided in pharmaceutical development report (Page 51/73). Table 6 below shows drug product batches with various particle size distributions of estetrol monohydrate and drospirenone and figures below show dissolution profiles of these batches.

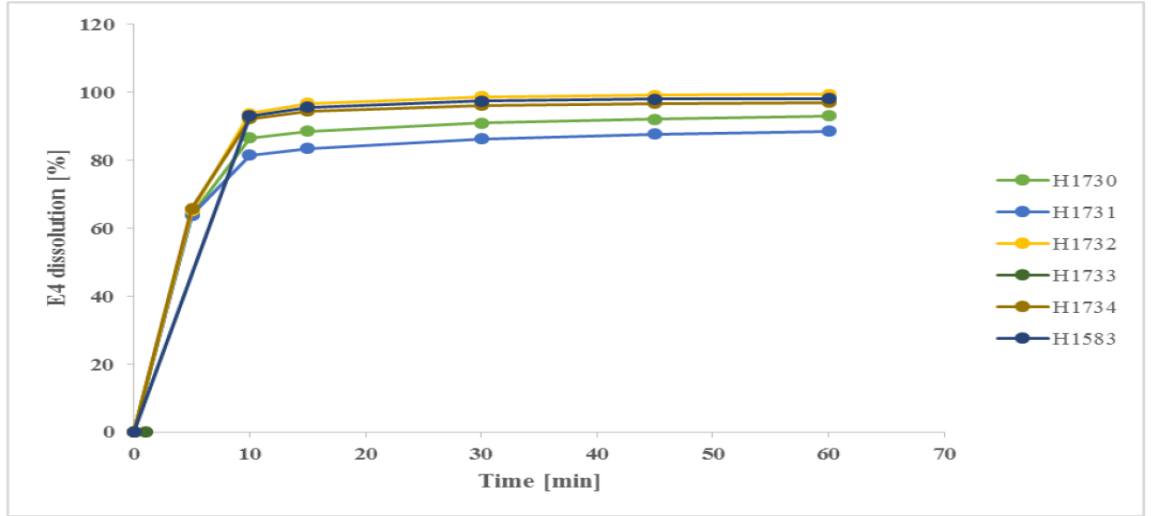
Table 6: List of Batches Tested to Demonstrate the Discriminatory ability of Estetrol monohydrate 15 mg/ drospirenone 3 mg film-coated tablets

Tablets batch	Drug substance batch contained in the tablets		Particle size distribution		Abbreviation used in discussion of this study	
	E4	DRSP	E4 [1)]	DRSP [2)]	E4	DRSP
H1730	E102mLS	9037MO00715	(b) (4)			
H1731	52268E002	9037MO00715				
H1732	32391C101	9037MO60116P				
H1733	32391C101	9037MlsO0017				
H1734	32391C101	9037AO00116				
H1583	52391E002	9037MO00715				

[1)] Current specification described in 3.2.S.4.1 for E4
[2)] Current specification described in 3.2.S.4.1 for DRSP

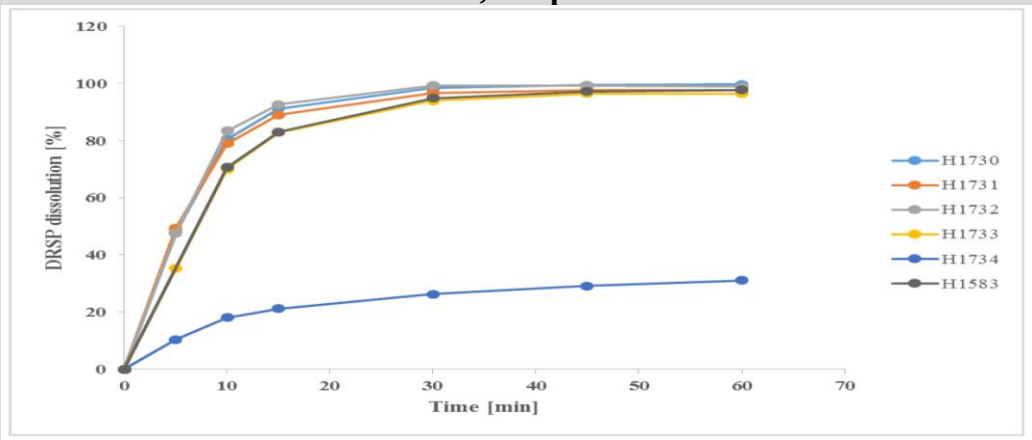
The dissolution rate of E4 slightly decreased with higher particle sizes (H1730) or with (b) (4) drug substance (H1731) in the tablets (figure 3). No difference in dissolution profiles of E4 was observed in different E4 batches having the same particle size distribution as used routinely (H1732, H1733, H1734, and H1583).

Figure 3: Dissolution of E4 with Different Particle Size Distributions in Phosphate Buffer pH 6.8, 50 rpm



The dissolution rate of DRSP is significantly impacted by the particle size of the DRSP used for the tablet batch manufacturing (figure 4). The usage of (b) (4) DRSP drug substance (H1734) shows a significantly slower dissolution compared to tablets with (b) (4) DRSP. All batches manufactured with (b) (4) (H1730, H1731 and H1583) show the same rapid dissolution behavior. No significant change of the dissolution rate is visible when DRSP batches with particle sizes at the (b) (4) (H1733) and at the (b) (4) limit (H1732) of the particle size specification ranges are used.

Figure 4: Dissolution of DRSP with Different Particle Size Distributions in Phosphate Buffer pH 6.8, 50 rpm



(b) (4)

Dissolution method validation

The dissolution method was fully validated by performing the specificity, system suitability, range, linearity, accuracy, precision, intermediate precision (Ruggedness), robustness, filter test, and solution stability. The analytical method validation will be reviewed by Drug Product reviewer. The details of the validation are provided in the link below:

\\CDSESUB1\evsprod\nda214154\0001\m3\32-body-data\32p-drug-prod\e4drsp-fct-haupt-pharma\32p5-contr-drug-prod\32p53-val-analyt-proc\32p53-val-analyt-proc-annex-dissolution-report.pdf

\\CDSESUB1\evsprod\nda214154\0001\m3\32-body-data\32p-drug-prod\e4drsp-fct-haupt-pharma\32p5-contr-drug-prod\32p53-val-analyt-proc\32p53-val-analyt-proc-annex-diss-report-suppl1.pdf

In vitro dissolution acceptance criterion

Dissolution data obtained from the 3 pivotal clinical batches (H1581, H1582 and H1583) with the proposed dissolution method is shown below. These dissolution profile data were used to establish the dissolution acceptance criterion for E4 and DRSP component in FDC tablet. The dissolution data and profiles are provided in \\CDSESUB1\evsprod\nda214154\0001\m3\32-body-data\32p-drug-prod\e4drsp-fct-haupt-pharma\32p5-contr-drug-prod\32p56-justif-spec\32p56-just-of-specifications-active.pdf

Figure 6: E4 dissolution profile from the 3 pivotal batches in Phosphate Buffer (pH 6.8), 50 rpm

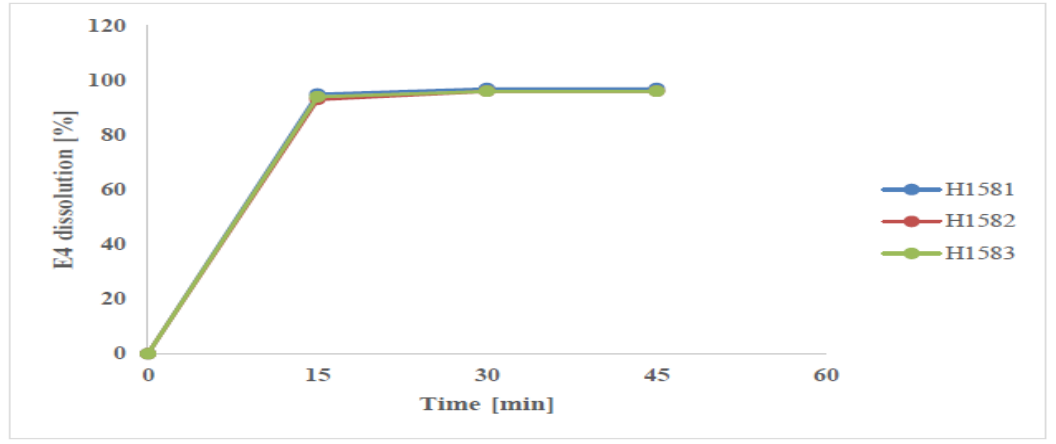
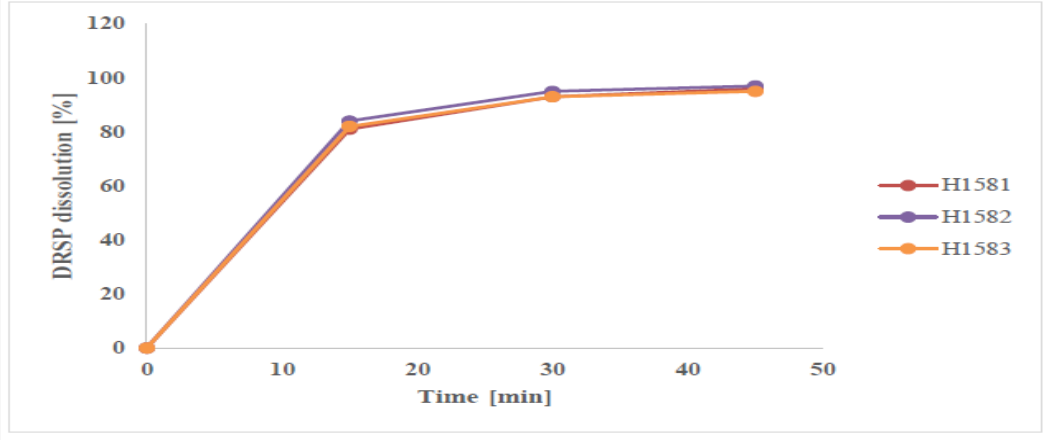


Figure 7: DRSP dissolution profile from the 3 pivotal batches in Phosphate Buffer (pH 6.8), 50 rpm



(b) (4)

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(b) (4)

Reviewer's assessment:

- The Applicant has developed and validated a dissolution method using Apparatus II (paddles) and 900 mL of Phosphate Buffer pH 6.8 at a rotation speed 50 rpm. The Applicant has provided method development report. The dissolution method is acceptable.
- The Applicant's proposed dissolution acceptance criterion *Q*= (b) (4) *% in 30 minutes* for both E4 and DRSP is acceptable based on the data provided.
- (b) (4)

3. Bridging of Clinical Formulations

Bridging of clinical formulations: ADEQUATE

The final to-be-marketed product is the same product used in the pivotal Phase 3 clinical studies. In addition to the Phase 3 clinical trials, several Phase 1/2 trials were conducted using the final formulation.

4. Biowaiver Request

The Applicant has not requested any biowaiver. There is only one strength of the FDC drug product proposed.

5. Conclusions and recommendation

From Biopharmaceutics perspective, NDA 214154 is recommended for APPROVAL.

Appendix 1

List of deficiencies communicated during the review cycle

Information Request 1 (IR 1)

1. Provide individual unit dissolution data for Figure 14 and Figure 15 in *Pharmaceutical development report* (page 52).

Reviewer's comments

The Applicant provided data as per the Agency request and is provided in the link below:
\\CDSESUB1\evsprod\nda214154\0014\m1\us\111-information-amendment\info-request-28jul2020.pdf

Information Request 2 (IR 2)

In the Pharmaceutical development report, you have provided information about the solubility of Estetrol monohydrate (E4); clarify which polymorphic form was used to determine the solubility. Provide solubility of Estetrol monohydrate (b) (4)

Reviewer's comments

The Applicant provided requested information in the link below which has been discussed in the appropriate section above.
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Primary Biopharmaceutics Reviewer Name: Kalpana Paudel, Ph.D.
Secondary Reviewer Name: Vidula Kolhatkar, Ph.D.

Kalpana Paudel

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Vidula Kolhatkar

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