CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

216285Orig1s000

OTHER REVIEW(S)

PHARMACOLOGY/TOXICOLOGY LABELING REVIEW

NDA #	216285
Supporting Document(s)	SDN1 (eCTD 0001)
Submit Date	August 30, 2021
Received Date	August 30, 2021
PDUFA Goal Date	June 30, 2022
Established/Proper Name	Drospirenone
(Proposed) Trade Name	Drospirenone Chewable Tablets
Pharmacologic Class	Progestin
Code Name	DRSP
Applicant	Exeltis USA, Inc
Dosage Form	Chewable oral tablet
Applicant Proposed Dosing Regimen	Drospirenone 3.5 mg chewable tablets once daily for 24 days followed by one inactive chewable tablet once daily for 4 days
Applicant Proposed Indication(s)/Population(s)	Prevention of Pregnancy/Females of reproductive potential

Introduction

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

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

The nonclinical review of drospirenone chewable tablets was presented in a separate review dated May 23, 2022. The current document is for labeling only.

Labeling Review

There are no proposed changes to Sections 8.1, 8.2, 12.1 or 13 of the prescription label as compared to the previously approved labeling for SLYND (version dated May 23, 2019). No additional changes are recommended to these sections of the proposed prescription label for drospirenone chewable tablets from the nonclinical Pharmacology/Toxicology perspective.

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/s/

ANDREA BENEDICT
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KIMBERLY P HATFIELD
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Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology
Office of Pharmacovigilance and Epidemiology

Pharmacovigilance Memorandum

Date:	May 20, 2022
Reviewer:	Miriam Chehab, PharmD, BCPPS Division of Pharmacovigilance II
Team Leader:	Lynda McCulley, PharmD, BCPS Division of Pharmacovigilance II
Product Names:	Drospirenone 4 mg tablet and 3.5 mg chewable tablet
Subject:	All adverse events
Application Type/Number:	NDA 211367 and NDA 216285
Applicant/Sponsor:	Exeltis USA, Inc
OSE RCM #:	2021-1774

1 INTRODUCTION

This Division of Pharmacovigilance (DPV) memorandum documents the cursory screening of postmarketing adverse events retrieved from the FDA Adverse Event Reporting System (FAERS) database for any new or unlabeled safety concerns with drospirenone through January 24, 2022. A FAERS search was requested by the Division of Urology, Obstetrics, and Gynecology (DUOG), within the Office of Rare Diseases, Pediatrics, Urologic and Reproductive Medicine/Office of New Drugs, during the filing meeting on October 13, 2021, for drospirenone 3.5 mg chewable tablet (NDA 216285).[a] Of note, the Applicant for the aforementioned NDA currently under review by DUOG is also the same Applicant for the already FDA approved drospirenone 4 mg tablet, Slynd (NDA 211367).

The purpose of this DPV memorandum is to assist DUOG in the identification of any new or unlabeled safety concerns that can be incorporated into their review of drospirenone 3.5 mg chewable tablet (NDA 216285).

2 METHODS AND MATERIALS

DPV searched the FAERS database with the strategy described in **Table 1**.

Table 1. FAERS Search Strategy*	
Date of search	January 25, 2022
Time period of search	May 23, 2019† – January 24, 2022
Search type	DSAD Quick Search
Product terms	PAI: Drospirenone
MedDRA search terms (Version 24.1)	All adverse event terms
* See **Appendix A** for a description of the FAERS database. † U.S. approval date for Slynd. **Abbreviations:** DSAD = Drug Safety Analytics Dashboard, MedDRA = Medical Dictionary for Regulatory Activities, PAI = Product Active Ingredient, U.S. = United States	

3 RESULTS

The FAERS search from **Table 1** yielded 199 reports. **Table 2** lists the most frequently reported MedDRA preferred terms (PTs). Although only PTs with a frequency ≥ 5 are listed in the table, we reviewed all PTs for new potential safety signals. A case-level analysis was not performed on all reports. Of note, report counts may include duplicate reports for the same patient from multiple reporters (e.g., manufacturer, family member, physician, pharmacist, nurse), miscoded reports, or unrelated reports. A single report may contain more than one MedDRA PT.

[a] Of note, a brand/trade name has not yet been approved for this NDA.

Table 2. Most Frequently Reported MedDRA PTs With N ≥ 5 With Drospirenone, Received by FDA From May 23, 2019 – January 24, 2022, Sorted by Decreasing Number of FAERS Reports per PT	
MedDRA PT	**Number of FAERS Reports***
Off label use	20
Nausea	19
Heavy menstrual bleeding	17
Intermenstrual bleeding	16
Depressed mood	14
Arthralgia	13
Pulmonary embolism	13
Abdominal distension	12
Drug ineffective	12
Headache	12
Drug interaction	11
Irritability	11
Abdominal pain lower	10
Epilepsy	10
General physical health deterioration	10
Impaired work ability	10
Micturition urgency	10
Petit mal epilepsy	10
Pregnancy on oral contraceptive	10
Amenorrhoea	9
Condition aggravated	9
Deep vein thrombosis	8
Migraine	8
Pain in extremity	8
Depression	7
Fatigue	7
Intentional product use issue	7
Crying	6
Weight increased	6
Acne	5
Product use in unapproved indication	5
Suppressed lactation	5
Urticaria	5
Vomiting	5
* A single report may contain more than one MedDRA PT. **Abbreviations:** MedDRA = Medical Dictionary for Regulatory Activities, PT = Preferred Term	

The FAERS cases summarized below were identified as potential cases of interest during our screening of the PTs reported with drospirenone use. No additional relevant new safety findings were identified as the remainder of the PTs screened were: (1) related to an alternative explanation(s) (disease-related, indication-related, or concomitant medication-related), (2) were determined to be uninformative, or (3) were expected/labeled adverse events.

FAERS Case # 17049338 (Version 2); Non-Expedited; Manufacturer Control # US-EX USA HOLDINGS-EXHL20192429; United States; Initial FDA Received Date – November 19, 2019; Outcome – Non-Serious
Reported PTs – *Urticaria, Rash, Pruritus*

A 15-year-old female was prescribed Slynd (drospirenone 4 mg tablet). After ingestion of her first dose, the patient developed pruritis and a rash on her neck. Diphenhydramine was then ingested at home. After ingestion of her second dose of Slynd, urticaria was noted "throughout the patient's body, primarily on her trunk." She was taken to the emergency room, monitored for "several hours," was treated with an unspecified intravenous steroid, and then discharged with oral steroids. No airway or respiratory involvement occurred. Slynd was discontinued and symptom resolution was noted within 24 – 48 hours. The patient's medical history was significant for an ibuprofen allergy. No information was provided regarding concomitant medications.

FAERS Case # 18742769 (Version 3); Non-Expedited; Manufacturer Control # US-INSUD PHARMA-2101US00001; United States; Initial FDA Received Date – January 14, 2021; Outcome – Non-Serious
Reported PTs – *Urticaria, Hypersensitivity*
A female of unknown age was prescribed Slynd (drospirenone 4 mg tablet). She then developed "severe hives" at an unspecified time after the initiation of therapy. Diphenhydramine was ingested and Slynd was discontinued. The event was noted to have resolved the following day. The patient's medical history was significant for herpes labialis and allergies to cephalosporins, penicillins, and sulfa-containing medications. Concomitant medications included valacyclovir.

FAERS Case # 19944133 (Version 1); Non-Expedited; Manufacturer Control # US-INSUD PHARMA-2110US02204; United States; Initial FDA Received Date – October 11, 2021; Outcome – Non-Serious
Reported PTs – *Rash*
A female in her mid-to-late 30s was prescribed Slynd (drospirenone 4 mg tablet). Within a "few days" after the initiation of therapy, she developed a rash "all over her body." The patient went to urgent care and was given an unspecified "steroid injection and topical." Slynd was discontinued. No information was provided regarding the outcome of the patient's reaction. No information was provided regarding her medical history or concomitant medications.

FAERS Case # 20080307 (Version 1); Non-Expedited; Manufacturer Control # US-INSUD PHARMA-2111US02715; United States; Initial FDA Received Date - November 17, 2021; Outcome – Non-Serious
Reported PTs – *Urticaria, Burning sensation*
A 28-year-old female was prescribed Slynd (drospirenone 4 mg tablet). Approximately six days after the initiation of therapy, the patient "felt like her arms and legs were on fire." She then took an unspecified antihistamine and went to sleep. The next night, the patient ingested her routine Slynd dose and experienced the same reaction as the previous night. Her arms and legs were also reported to be "covered in hives." It was noted that the patient did not eat anything different and did not change detergents or get new sheets. Slynd was discontinued and her reaction was reported to be improving. No information was provided regarding her medical history or concomitant medications. It was reported that the patient had previously used medroxyprogesterone but had experienced unspecified mood changes.

Reviewer Comments: All four of these cases describe the development of symptoms related to a hypersensitivity reaction (i.e., pruritis, rash, urticaria) after the ingestion of drospirenone. The

temporal association and discontinuation of drospirenone (with a positive dechallenge in three cases, albeit with treatment) support a potential drug-event association between drospirenone use and hypersensitivity reactions.

4 SUMMARY AND CONCLUSION

In conclusion, DPV identified four potential cases of interest reporting hypersensitivity reactions with drospirenone use. No language regarding the occurrence of hypersensitivity reactions was proposed in the prescribing information submitted by the Applicant for drospirenone 3.5 mg chewable tablet (NDA 216285). Additionally, there is no language in the current prescribing information for Slynd (drospirenone 4 mg tablet), which was approved by FDA on May 23, 2019.[1] These cases were shared with the DUOG clinical team via email on March 1, 2022, for labeling consideration. At the drospirenone 3.5 mg chewable tablet labeling meeting on April 27, 2022, the DUOG clinical team noted that language regarding hypersensitivity reactions will be recommended for inclusion in the ADVERSE REACTIONS, *Postmarketing Experience*, section for both drospirenone products.

5 REFERENCES

[1] Slynd (drospirenone tablets, 4 mg) [package insert]. Florham Park, NJ: Exeltis USA, Inc.; May 2019. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/211367s000lbl.pdf

6 APPENDICES

6.1 APPENDIX A. FDA ADVERSE EVENT REPORTING SYSTEM (FAERS)

FDA Adverse Event Reporting System (FAERS)

FAERS is a database that contains information on adverse event and medication error reports submitted to FDA. The database is designed to support FDA's postmarketing safety surveillance program for drug and therapeutic biological products. The informatic structure of the database adheres to the international safety reporting guidance issued by the International Council on Harmonisation. Adverse events and medication errors are coded to terms in the Medical Dictionary for Regulatory Activities terminology. The suspect products are coded to valid tradenames or active ingredients in the FAERS Product Dictionary.

FAERS data have limitations. First, there is no certainty that the reported event was actually due to the product. FDA does not require that a causal relationship between a product and event be proven, and reports do not always contain enough detail to properly evaluate an event. Further, FDA does not receive reports for every adverse event or medication error that occurs with a product. Many factors can influence whether or not an event will be reported, such as the time a product has been marketed and publicity about an event. Therefore, FAERS data cannot be used to calculate the incidence of an adverse event or medication error in the U.S. population.

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MEMORANDUM

REVIEW OF REVISED LABEL AND LABELING
Division of Medication Error Prevention and Analysis 2 (DMEPA 2)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

Date of This Memorandum:	May 9, 2022
Requesting Office or Division:	Division of Urology, Obstetrics, and Gynecology (DUOG)
Application Type and Number:	NDA 216285
Product Name and Strength:	Drospirenone chewable tablets, 3.5 mg
Applicant/Sponsor Name:	Exeltis USA, Inc.
OSE RCM #:	2021-1776-2
DMEPA 2 Safety Evaluator:	Justine Kalonia, PharmD
DMEPA 2 Acting Team Leader:	Stephanie DeGraw, PharmD

1 PURPOSE OF MEMORANDUM

The Applicant submitted revised carton labeling received on May 5, 2022 for Drospirenone chewable tablets. The Division of Urology, Obstetrics, and Gynecology (DUOG) requested that we review the revised carton labeling for Drospirenone chewable tablets (Appendix A) to determine if it is acceptable from a medication error perspective. The revisions are in response to recommendations that we made during a previous label and labeling review and memorandum.[a,b]

2 CONCLUSION

The Applicant implemented all of our recommendations and we have no additional recommendations at this time.

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[a] Kalonia, J. Label and Labeling Review for drospirenone chewable tablets (NDA 216285). Silver Spring (MD): FDA, CDER, OSE, DMEPA 2 (US); 2022 JAN 10. RCM No.: 2021-1776.
[b] Kalonia, J. Label and Labeling Review for drospirenone chewable tablets (NDA 216285). Silver Spring (MD): FDA, CDER, OSE, DMEPA 2 (US); 2022 APR 19. RCM No.: 2021-1776-1.

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Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Medical Policy

PATIENT LABELING REVIEW

Date:	May 3, 2022
To:	Jeannie Roule Chief, Project Management Staff **Division of Urology, Obstetrics, and Gynecology (DUOG)**
Through:	LaShawn Griffiths, MSHS-PH, BSN, RN Associate Director for Patient Labeling **Division of Medical Policy Programs (DMPP)** Nyedra W. Booker, PharmD, MPH Senior Patient Labeling Reviewer **Division of Medical Policy Programs (DMPP)**
From:	Lonice Carter, MS, RN, CNL, NHDP-BC Patient Labeling Reviewer **Division of Medical Policy Programs (DMPP)** Elvy Varghese, Pharm.D. Regulatory Review Officer **Office of Prescription Drug Promotion (OPDP)**
Subject:	Review of Patient Labeling: Patient Package Insert (PPI) and Instructions for Use (IFU)
Established name:	Drospirenone Chewable Tablets
Dosage Form and Route:	for oral use
Application Type/Number:	NDA 216285
Applicant:	Exeltis USA, Inc.

1 INTRODUCTION

On August 30, 2021, Exeltis USA, Inc. submitted for the Agency's review a New Drug Application (NDA) 216285 for Drospirenone Chewable Tablets, for oral use. This NDA proposes an indication for use by females of reproductive potential to prevent pregnancy.

This collaborative review is written by the Division of Medical Policy Programs (DMPP) and the Office of Prescription Drug Promotion (OPDP) in response to a request by the Division of Urology, Obstetrics, and Gynecology (DUOG) on September 8, 2021, for DMPP and OPDP to review the Applicant's proposed Patient Package Insert (PPI) and Instructions for Use (IFU) for Drospirenone Chewable Tablets, for oral use.

2 MATERIAL REVIEWED

- Revised draft Drospirenone Chewable Tablets, for oral use PPI and IFU received on April 11, 2022, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on April 27, 2022.
- Revised draft Drospirenone Chewable Tablets, for oral use Prescribing Information (PI) received on April 11, 2022, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on April 27, 2022.
- Approved SLYND (drospirenone) tablets, for oral use comparator labeling dated May 23, 2019.

3 REVIEW METHODS

To enhance patient comprehension, materials should be written at a 6th to 8th grade reading level, and have a reading ease score of at least 60%. A reading ease score of 60% corresponds to an 8th grade reading level.

Additionally, in 2008 the American Society of Consultant Pharmacists Foundation (ASCP) in collaboration with the American Foundation for the Blind (AFB) published *Guidelines for Prescription Labeling and Consumer Medication Information for People with Vision Loss*. The ASCP and AFB recommended using fonts such as Verdana, Arial or APHont to make medical information more accessible for patients with vision loss. We reformatted the PPI and IFU documents using the Arial font, size 10.

In our collaborative review of the PPI and IFU we:

- simplified wording and clarified concepts where possible
- ensured that the PPI and IFU are consistent with the Prescribing Information (PI)
- removed unnecessary or redundant information

- ensured that the PPI and IFU are free of promotional language or suggested revisions to ensure that it is free of promotional language
- ensured that the PPI and IFU meet the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)
- ensured that the PPI and IFU are consistent with the approved comparator labeling where applicable.

4 CONCLUSIONS

The PPI and IFU are acceptable with our recommended changes.

5 RECOMMENDATIONS

- Please send these comments to the Applicant and copy DMPP and OPDP on the correspondence.
- Our collaborative review of the PPI and IFU is appended to this memorandum. Consult DMPP and OPDP regarding any additional revisions made to the PI to determine if corresponding revisions need to be made to the PPI and IFU.

Please let us know if you have any questions.

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FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion

****Pre-decisional Agency Information****

Memorandum

Date: May 3, 2022

To: Ionna A. Comstock, /Clinical Reviewer, M.D.
Division of Urology, Obstetrics, and Gynecology (DUOG)

Jeannie M. Roule, Regulatory Project Manager, DUOG

From: Elvy Varghese, Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

CC: James Dvorsky, Team Leader, OPDP

Subject: OPDP Labeling Comments for DROSPIRENONE CHEWABLE TABLETS, for oral use

NDA: 216285

In response to DUOG's consult request dated September 8, 2021 OPDP has reviewed the proposed product labeling (PI), patient package insert (PPI), Instructions For Use (IFU) and carton and container labeling for the original NDA submission for DROSPIRENONE CHEWABLE TABLETS, for oral use (drosperinone chewable tablets).

Labeling: OPDP's comments on the proposed labeling are based on the draft labeling received by electronic mail from DUOG (Jeannie Roule) on April 27, 2022, and are provided below.

A combined OPDP and Division of Medical Policy Programs (DMPP) review will be completed, and comments on the proposed PPI and IFU will be sent under separate cover.

Carton and Container Labeling: OPDP has reviewed the attached proposed carton and container labeling submitted by the Sponsor to the electronic document room on April 11, 2022, and our comments are provided below.

Thank you for your consult. If you have any questions, please contact Elvy Varghese at (240) 402-0080 or Elvy.Varghese@fda.hhs.gov.

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ELVY M VARGHESE
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MEMORANDUM

REVIEW OF REVISED LABEL AND LABELING
Division of Medication Error Prevention and Analysis 2 (DMEPA 2)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

Date of This Memorandum:	April 19, 2022
Requesting Office or Division:	Division of Urology, Obstetrics, and Gynecology (DUOG)
Application Type and Number:	NDA 216285
Product Name and Strength:	drospirenone chewable tablets, 3.5 mg
Applicant/Sponsor Name:	Exeltis USA, Inc.
OSE RCM #:	2021-1776-1
DMEPA 2 Safety Evaluator:	Justine Kalonia, PharmD
DMEPA 2 Acting Team Leader:	Stephanie DeGraw, PharmD

1 PURPOSE OF MEMORANDUM

The Applicant submitted revised prescribing information (PI), patient information (PPI), container labels and carton labeling received on April 11, 2022 for drospirenone chewable tablets (NDA 216285). The Division of Urology, Obstetrics, and Gynecology (DUOG) requested that we review the revised container labels and carton labeling for NDA 216285 (Appendix A) to determine if they are acceptable from a medication error perspective. The revisions are in response to recommendations that we made during a previous label and labeling review.[a]

2 OVERALL ASSESSMENT

We note that Exeltis submitted two proposed proprietary names for this product that we found unacceptable.[b,c] Thus, Exeltis responded that they intend to submit a new proprietary name for review after NDA approval, and therefore, submitted new labels and labeling (b) (4) (b) (4) replacing it with the established name,

[a] Kalonia, J. Label and Labeling Review for drospirenone chewable tablets (NDA 216285). Silver Spring (MD): FDA, CDER, OSE, DMEPA 2 (US); 2022 JAN 10. RCM No.: 2021-1776.

(b) (4)

"DROSPIRENONE CHEWABLE TABLETS, 3.5 MG"[d] throughout the revised labels and labeling including the PI and PPI.

We note the Sponsor stated that they implemented most of our recommendations. However, two revisions (i.e., to the (b) (4) statement, and addition of the 2D data matrix barcode) were not implemented as intended. Therefore we provide clarification on these recommendations to the Sponsor below in Section 4.

3 CONCLUSION

We find the revisions to the container labels, blister sleeve, and sample carton labeling acceptable. However, the revised trade carton labeling is unacceptable from a medication error perspective. Thus, for the trade carton labeling, we provide two clarifications to our prior recommendations below.

4 RECOMMENDATIONS FOR EXELTIS USA, INC.

We recommend the following be implemented prior to approval of this NDA:

A. Trade Carton Labeling

a. We note you have implemented our recommendation to revise the (b) (4) statement to read "Recommended Dosage: one tablet daily for 28 days or as directed by physician. Must chew before swallowing. See prescribing information. This package is not child resistant." However, we find that the 3rd sentence in this statement was not revised on the Trade Carton Labeling, which still states "(b) (4) Revise this sentence to read "See prescribing information." to align with your other labels and labeling.

b. We note you stated that you added a "2D data matrix barcode" to the trade carton labeling as your machine-readable portion of the product identifier, however, it appears that you have instead added a (b) (4) code. Replace the (b) (4) code with an appropriate 2D data matrix barcode. Please refer to the following for more information:

i. Per the guidance (Product Identifiers Under the Drug Supply Chain Security Act Questions and Answers), (b) (4) (b) (4)

[d] Response to DMEPA Labeling Comments Dated 12 January 2022 (NDA 216285 drospirenone chewable tablets). Florham Park (NJ): Exeltis USA, Inc.; 2022 APR 11. Available from: \\CDSESUB1\evsprod\nda216285\0011\m1\us\111-information-amendment\1114-multi-module-info-amendment.pdf

(b) (4) As such, a (b) (4) code cannot replace the 2D data matrix barcode on packages or the linear or 2D data matrix barcode on homogenous cases as required under the DSCSA."

1. * See GS1 General Specifications (Release 18, Ratified, January 2018), Section 2.1.6 Healthcare primary packaging (https://www.gs1.org/sites/default/files/docs/barcodes/GS1_General_Specifications.pdf).
2. See our guidance available from: https://www.fda.gov/media/116304/download

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LABEL AND LABELING REVIEW
Division of Medication Error Prevention and Analysis 2 (DMEPA 2)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

*** This document contains proprietary information that cannot be released to the public***

Date of This Review:	January 10, 2022
Requesting Office or Division:	Division of Urology, Obstetrics, and Gynecology (DUOG)
Application Type and Number:	NDA 216285
Product Name and Strength:	drospirenone chewable tablets, 3.5 mg
Product Type:	Single Ingredient Product
Rx or OTC:	Prescription (Rx)
Applicant/Sponsor Name:	Exeltis USA, Inc.
FDA Received Date:	August 30, 2021 and September 3, 2021
OSE RCM #:	2021-1776
DMEPA 2 Safety Evaluator:	Justine Kalonia, PharmD
DMEPA 2 Acting Team Leader:	Stephanie DeGraw, PharmD

1 REASON FOR REVIEW

As part of the approval process for drospirenone chewable tablets, the Division of Urology, Obstetrics, and Gynecology (DUOG) requested that we review the proposed drospirenone chewable tablets prescribing information (PI), patient information, instructions for use (IFU), container labels, and carton labeling for areas of vulnerability that may lead to medication errors.

2 MATERIALS REVIEWED

Table 1. Materials Considered for this Label and Labeling Review

Material Reviewed	Appendix Section (for Methods and Results)
Product Information/Prescribing Information	A
Previous DMEPA Reviews	B – N/A
ISMP Newsletters*	C – N/A
FDA Adverse Event Reporting System (FAERS)*	D – N/A
Other	E – N/A
Labels and Labeling	F

N/A=not applicable for this review
*We do not typically search FAERS or ISMP Newsletters for our label and labeling reviews unless we are aware of medication errors through our routine postmarket safety surveillance

3 CONCLUSION AND RECOMMENDATIONS

The proposed prescribing information (PI), patient information, instructions for use (IFU), container labels, and carton labeling may be improved to promote the safe use of this product from a medication error perspective. We provide the identified medication error issues, our rationale for concern, and our proposed recommendations to minimize the risk for medication error in Section 4 for the Division and in Section 5 for Exeltis USA, Inc.

4 RECOMMENDATIONS FOR DIVISION OF UROLOGY, OBSTETRICS, AND GYNECOLOGY (DUOG)

Table 2. Identified Issues and Recommendations for Division of Urology, Obstetrics, and Gynecology (DUOG)

	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
Prescribing Information, Patient Information, and Instructions for Use – General Issues			
1.	The proposed proprietary name, (b) (4) is used throughout the Prescribing Information (PI), Patient Information, and Instructions for Use (IFU), and container labels and carton labeling.	The proprietary name, (b) (4), was found unacceptable by DMEPA.	We recommend removing the proposed proprietary name, (b) (4), throughout the Prescribing Information, Patient Information, and IFU. Until a new name is found to be conditionally acceptable, the placeholder "TRADENAME" may be used. Then replace "TRADENAME" with the proprietary name that is eventually found conditionally acceptable.
2.	The strength statement in the header of the PI lacks adequate spacing between the numerical dose and unit of measure.	Lack of adequate spacing may impact readability and result in wrong strength medication errors.	To improve readability, we recommend placing adequate space between the numerical dose and unit of measure (e.g., 3.5 mg instead of 3.5mg).
Highlights of Prescribing Information (HPI)			
1.	The statement under DOSAGE AND ADMINISTRATION does not clearly convey the administration warning to chew the tablet completely.	This language may be improved for clarity and readability and to highlight the warning that the tablets must be chewed and should not be swallowed whole.	Consider separating the dosage and administration statements into 2 bullet points and revise to read: • Chew one tablet daily for 28 days; one white active chewable tablet daily during the first 24 days and one green inactive chewable tablet daily during the 4 following days. • Tablets must be chewed completely before

Table 2. Identified Issues and Recommendations for Division of Urology, Obstetrics, and Gynecology (DUOG)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
			swallowing. Do NOT swallow whole.
2.	The strength statement under DOSAGE FORMS AND STRENGTHS in the HPI says that each active tablet contains "(b) (4) ; however, this is inconsistent with the rest of the labels and labeling submitted, which say the strength is 3.5 mg of drospirenone.	Inconsistent strength statements may lead to confusion.	Revise the strength statements to be consistent throughout the labels and labeling.
Full Prescribing Information – Section 3 Dosage Forms and Strengths			
1.	We note that the proposed colors and imprints on the tablets are similar to another progestin only birth control tablet currently marketed by the same sponsor (i.e., Slynd (drospirenone) 4 mg tablets).	Per our Guidance for Industry: *Safety Considerations for Product Design to Minimize Medication Errors*,* "The imprint code may be critical to identifying the product when the dosage form is separated from the commercial product packaging. It is important to avoid the use of similar imprint codes and to consider how the codes are imprinted on multiple products within product lines." *Guidance available from: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM331810.pdf	We recommend that the Sponsor considers using a different imprints and colors, to further differentiate the tablets and revises the PI accordingly.

Table 2. Identified Issues and Recommendations for Division of Urology, Obstetrics, and Gynecology (DUOG)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
Full Prescribing Information – Section 16 How Supplied/Storage and Handling			
1.	Some of the appropriate information to facilitate identification of the dosage form is missing from Section 16 of the PI. Specifically, the imprinting and scoring information found in Section 3 of the PI is not present in Section 16 of the PI.	To facilitate identification of the dosage form, the imprinting and scoring must be included in Section 16 of the PI per 21 CFR 201.51(c)(17)(iii).	Revise Section 16 to include the imprinting and scoring information.

5 RECOMMENDATIONS FOR EXELTIS USA, INC.

Table 3. Identified Issues and Recommendations for Exeltis USA, Inc. (entire table to be conveyed to Applicant)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
General Recommendations (All Labels and Labeling)			
1.	The proposed proprietary name, (b) (4) is used throughout the Prescribing Information (PI), Patient Information, Instructions for Use (IFU), and container labels and carton labeling, and sleeve.	The proprietary name, (b) (4), was found unacceptable by DMEPA.	Remove the proposed proprietary name, (b) (4) throughout the Prescribing Information, Patient Information, IFU, and container labels and carton labeling. Until a new name is found to be conditionally acceptable, the placeholder "TRADENAME" may be used. Then replace "TRADENAME" with the proprietary name that is eventually found conditionally acceptable.
2.	The drug-identifying information for your product (established	Inability to identify this information may lead to product selection errors.	Revise the font type to improve readability. For example, increase spacing

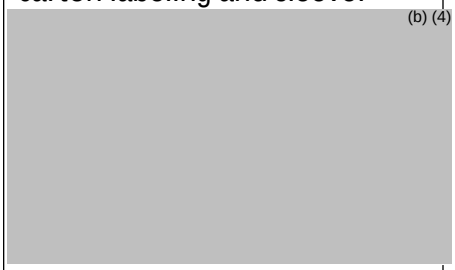
Table 3. Identified Issues and Recommendations for Exeltis USA, Inc. (entire table to be conveyed to Applicant)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
	name, dosage form, and strength) is difficult to read. The important drug-identifying information is presented in a thin and closely spaced font on the carton labeling, container labels, and sleeve.		between letters, or consider using an alternative font type.
3.	The appearance of the established name (active ingredients and dosage form) lacks prominence commensurate with the proposed proprietary name on the carton labeling, container labels, and sleeve.	This is not presented in accordance with 21 CFR 201.10(g)(2). As currently presented, the established name and strength are presented in a light grey font, which may not provide adequate contrast between it and the white background.	Increase the prominence of the established name taking into account all pertinent factors, including typography, layout, contrast, and other printing features in accordance with 21 CFR 201.10(g)(2). We recommend you improve the contrast between the background and the established name and strength.
4.	The Usual Dosage statement can be improved on the carton labeling and sleeve.	To ensure consistency with the Physician Labeling Rule (PLR) formatted Prescribing Information labeling.	We recommend you revise the Usual Dosage statement on the carton labeling and sleeve: (b) (4)  to read: "Recommended Dosage: one tablet daily for 28 days or as directed by physician. Must chew before swallowing. See prescribing information. This package is not child resistant."

Table 3. Identified Issues and Recommendations for Exeltis USA, Inc. (entire table to be conveyed to Applicant)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
Container Labels and Carton Labeling			
1.	The format for expiration date is not defined.	Clearly define the expiration date will minimize confusion and risk for deteriorated drug medication errors.	Identify the expiration date format you intend to use. FDA recommends that the human-readable expiration date on the drug package label include a year, month, and non-zero day. FDA recommends that the expiration date appear in YYYY-MM-DD format if only numerical characters are used or in YYYY-MMM-DD if alphabetical characters are used to represent the month. If there are space limitations on the drug package, the human-readable text may include only a year and month, to be expressed as: YYYY-MM if only numerical characters are used or YYYY-MMM if alphabetical characters are used to represent the month. FDA recommends that a hyphen or a space be used to separate the portions of the expiration date.
Container Label(s)			
1.	We note that the linear barcode on the container labels is in a location where it may not remain intact under normal conditions of use.	As currently presented, it appears that important identifying information, including the linear barcode will be damaged when the tablets are removed from the blister. Per 21 CFR 201.25(c)(1)(ii), the barcode should be placed in an area	Ensure the barcode is placed in an area where it will not be damaged under normal conditions of use (for example, during tablet removal from the blister).

Table 3. Identified Issues and Recommendations for Exeltis USA, Inc. (entire table to be conveyed to Applicant)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
		where it will not be damaged.	
Carton Labeling			
1.	As currently presented, there is no machine readable (2D data matrix barcode) product identifier on the carton labeling.	In September 2018, FDA released draft guidance on product identifiers required under the Drug Supply Chain Security Act (DSCSA)*. The Act requires manufacturers and repackagers, respectively, to affix or imprint a product identifier to each package and homogenous case of a product intended to be introduced in a transaction in(to) commerce beginning November 27, 2017, and November 27, 2018, respectively. * The draft guidance is available from: https://www.fda.gov/ucm/groups/fdagov-public/@fdagov-drugs-gen/documents/document/ucm621044.pdf	We recommend that you review the draft guidance. If you determine that the product identifier requirements apply to your product's labeling, we request you add a placeholder for the machine readable (2D data matric barcode) product identifier to the carton labeling.
Blister Sleeve			
1.	The sleeve does not contain the NDC.	Per 21 CFR 201.2, the NDC is "requested but not required to appear on all drug labels and in all drug labeling", however, FDA strongly encourages the NDC appear on all drug labels and in all drug labeling.	Consider including the NDC for your product on the sleeve to help facilitate identification of the product.

APPENDICES: METHODS & RESULTS FOR EACH MATERIAL REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 4 presents relevant product information for drospirenone chewable tablets that Exeltis USA, Inc. submitted on September 3, 2021.

Table 4. Relevant Product Information for drospirenone chewable tablets	
Initial Approval Date	N/A
Active Ingredient	drospirenone
Indication	prevent pregnancy
Route of Administration	oral (chew (do not swallow whole))
Dosage Form	tablets
Strength	3.5 mg
Dose and Frequency	Chew and swallow 1 tablet daily.
How Supplied	Each carton contains one blister card containing 28 chewable tablets. Each blister card holds 24 active chewable tablets each containing 3.5 mg of drospirenone, followed by 4 inert tablets that do not contain drospirenone.
Storage	Store at 20°C to 25°C (68°F to 77°F); excursions permitted from 15°C to 30°C (59°F to 86°F) [see USP Controlled Room Temperature].
Container Closure	PVC-PVDC/Aluminum blister card

APPENDIX F. LABELS AND LABELING

F.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,[a] along with postmarket medication error data, we reviewed the following drospirenone chewable tablets labels and labeling submitted by Exeltis USA, Inc.

- Container label received on August 30, 2021
- Carton labeling received on August 30, 2021
- Professional sample container label received on August 30, 2021
- Professional sample carton labeling received on August 30, 2021
- Prescribing Information, Patient Information, and Instructions for Use (Image not shown)
    - PDF version received on August 30, 2021 available from \\CDSESUB1\evsprod\nda216285\0001\m1\us\114-labeling\draft\labeling\11413-draft-labeling-text.pdf
    - Word version received on September 3, 2021, available from \\CDSESUB1\evsprod\nda216285\0002\m1\us\114-labeling\draft\labeling\11413-draft-labeling-text.docx

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

[a] Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

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/s/

JUSTINE H KALONIA
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STEPHANIE L DEGRAW
01/10/2022 08:16:01 PM

M E M O R A N D U M

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

DATE: 12/27/2021

TO: Division of Urology, Obstetrics, and Gynecology (DUOG)
Office of Rare Diseases, Pediatrics, Urology and Reproductive Medicine (ORPURM)

FROM: Division of New Drug Study Integrity (DNDSI)
Office of Study Integrity and Surveillance (OSIS)

SUBJECT: **Decline to conduct an on-site inspection**

RE: NDA 216285

The Division of New Drug Study Integrity (DNDSI) within the Office of Study Integrity and Surveillance (OSIS) determined that an inspection is not warranted at this time for the site listed below. The rationale for this decision is noted below.

Rationale

The Office of Regulatory Affairs (ORA) inspected the site in August 2019, which falls within the surveillance interval. The inspection was conducted under the following submissions: ANDAs non-responsive .

The final classification for the inspection was No Action Indicated (NAI).

Therefore, based on the rationale described above, an inspection is not warranted at this time.

Inspection Site

Facility Type	Facility Name	Facility Address
Clinical	Blueclinical, Ltd.	Blueclinical Phase I, Hospital da Prelada, 3rd Floor and East Wing of 4th Floor, Rua de Sarmento de Beires, 153, 4250-449 Porto, Portugal

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M E M O R A N D U M

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

DATE: 12/27/2021

TO: Division of Urology, Obstetrics, and Gynecology (DUOG)
Office of Rare Diseases, Pediatrics, Urology and Reproductive Medicine (ORPURM)

FROM: Division of New Drug Study Integrity (DNDSI)
Office of Study Integrity and Surveillance (OSIS)

SUBJECT: **Decline to conduct an on-site inspection**

RE: NDA 216285

The Division of New Drug Study Integrity (DNDSI) within the Office of Study Integrity and Surveillance (OSIS) determined that an inspection is not warranted at this time for the site listed below. The rationale for this decision is noted below.

Rationale

OSIS inspected the site in (b) (4) which falls within the surveillance interval. The inspection was conducted under the following submissions: ANDAs non-responsive .

The final classification for the inspection was No Action Indicated (NAI).

Therefore, based on the rationale described above, an inspection is not warranted at this time.

Inspection Site

Facility Type	Facility Name	Facility Address
Analytical		(b) (4)

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