CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

209405Orig1s000

OTHER REVIEW(S)

MEMORANDUM

REVIEW OF REVISED LABEL AND LABELING

Division of Medication Error Prevention and Analysis (DMEPA)
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:	March 27, 2020
Requesting Office or Division:	Division of Urology, Obstetrics, and Gynecology (DUOG)
Application Type and Number:	NDA 209405
Product Name and Strength:	levonorgestrel and ethinyl estradiol tablets, 0.1 mg/0.02 mg
Applicant/Sponsor Name:	Exeltis USA Inc.
OSE RCM #:	2019-226-5
DMEPA Safety Evaluator:	Justine Kalonia, PharmD
DMEPA Team Leader:	Briana Rider, PharmD, CPPS

1 PURPOSE OF MEMORANDUM

The Applicant submitted revised container labels and carton labeling received on March 26, 2020 for levonorgestrel and ethinyl estradiol tablets. Division of Urology, Obstetrics, and Gynecology (DUOG) requested that we review the revised container labels and carton labeling for levonorgestrel and ethinyl estradiol tablets (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 and labeling memorandums. [abcde]

2 CONCLUSION

[a] Karpow C. Label and Labeling Review for levonorgestrel and ethinyl estradiol (NDA 209405). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2019 Oct 02. RCM No.: 2019-226.
[b] Karpow C. Label and Labeling Memorandum for levonorgestrel and ethinyl estradiol (NDA 209405). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2019 Nov 12. RCM No.: 2019-226-1.
[c] Karpow C. Label and Labeling Memorandum for levonorgestrel and ethinyl estradiol (NDA 209405). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2019 Dec 16. RCM No.: 2019-226-2.
[d] Kalonia, J. Label and Labeling Memorandum for levonorgestrel and ethinyl estradiol (NDA 209405). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2020 Feb 04. RCM No.: 2019-226-3.
[e] Kalonia J. Label and Labeling Review for levonorgestrel and ethinyl estradiol (NDA 209405). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2020 MAR 16. RCM No.: 2019-226-4.

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

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/s/

JUSTINE H KALONIA
03/27/2020 12:48:59 PM

DANIELLE M HARRIS on behalf of BRIANA B RIDER
03/27/2020 01:18:46 PM

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

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

Memorandum

Date: March 24, 2020

To: Nikia Morris
Regulatory Project Manager
Division of Bone, Reproductive and Urologic Products (DBRUP)

From: Jina Kwak
Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

CC: Matthew Falter
Team Leader, OPDP

Subject: **NDA 209405**
OPDP labeling comments for TRADENAME (levonorgestrel and ethinyl estradiol) tablets, for oral use

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In response to DBRUP consult request dated August 14, 2019, OPDP has reviewed the proposed product labeling (PI), Patient Package Insert (PPI), Instructions for Use (IFU) and carton and container labeling for TRADENAME (levonorgestrel and ethinyl estradiol) tablets, for oral use.

PI, PPI and IFU: OPDP's comments on the proposed labeling are based on the draft PI, PPI and IFU received by electronic mail from DBRUP (Nikia Morris) on March 12, 2020 and are provided below.

A combined OPDP and Division of Medical Policy Programs (DMPP) review was completed and comments on the proposed PPI and IFU were sent under separate cover on March 23, 2020.

Carton and Container Labeling: OPDP has reviewed the attached proposed carton and container labeling submitted by the Sponsor to the electronic document room on March 23, 2020 and we do not have any comments.

Thank you for your consult. If you have any questions, please contact Jina Kwak: 301-796-4809; Jina.Kwak@fda.hhs.gov

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/s/

JINA KWAK
03/24/2020 01:10:42 PM

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:	March 23, 2020
To:	Nikia Morris Regulatory Project Manager **Division of Bone, Reproductive and Urologic Products (DBRUP)**
Through:	LaShawn Griffiths, MSHS-PH, BSN, RN Associate Director for Patient Labeling **Division of Medical Policy Programs (DMPP)** Sharon W. Williams, MSN, BSN, RN Senior Patient Labeling Reviewer, Patient Labeling **Division of Medical Policy Programs (DMPP)**
From:	Lonice Carter, MS, RN, CNL Patient Labeling Reviewer **Division of Medical Policy Programs (DMPP)** Jina Kwak, PharmD Regulatory Review Officer **Office of Prescription Drug Promotion (OPDP)**
Subject:	Review of Patient Labeling: Patient Package Insert (PPI) and Instructions for Use (IFU)
Drug Name (established name):	TRADENAME (levonorgestrel and ethinyl estradiol)
Dosage Form and Route:	tablets, for oral use
Application Type/Number:	NDA 209405
Applicant:	Exeltis USA, Inc.

1 INTRODUCTION

On May 30, 2019, Exeltis USA, Inc. submitted for the Agency's review a New Drug Application (NDA) for TRADENAME (levonorgestrel and ethinyl estradiol) tablets, for oral use after a refusal to file letter dated March 8, 2019. This NDA proposes an indication for the prevention of 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 Bone, Reproductive and Urologic Products (DBRUP) on August 14, 2019, for DMPP and OPDP to review the Applicant's proposed Patient Package Insert (PPI), and Instructions for Use (IFU) for TRADENAME (levonorgestrel and ethinyl estradiol) tablets, for oral use.

2 MATERIAL REVIEWED

- Draft TRADENAME (levonorgestrel and ethinyl estradiol) PPI and IFU received on May 30, 2019, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on March 12, 2020.
- Draft TRADENAME (levonorgestrel and ethinyl estradiol) Prescribing Information (PI) received on May 30, 2019, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on March 12, 2020.
- Approved BALCOLTRA (levonorgestrel and ethinyl estradiol tablets and ferrous bisglycinate tablets) comparator labeling dated January 9, 2018.

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 are 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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/s/

LONICE J CARTER
03/23/2020 10:35:33 AM

JINA KWAK
03/23/2020 10:54:11 AM

SHARON W WILLIAMS
03/23/2020 10:55:15 AM

LASHAWN M GRIFFITHS
03/23/2020 11:25:35 AM

MEMORANDUM

REVIEW OF REVISED LABEL AND LABELING
Division of Medication Error Prevention and Analysis (DMEPA)
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:	March 16, 2020
Requesting Office or Division:	Division of Bone, Reproductive and Urologic Products (DBRUP)
Application Type and Number:	NDA 209405
Product Name and Strength:	levonorgestrel and ethinyl estradiol, tablets, 0.1 mg/0.02 mg
Applicant/Sponsor Name:	Exeltis USA Inc.
OSE RCM #:	2019-226-4
DMEPA Safety Evaluator:	Justine Kalonia, PharmD
DMEPA Team Leader:	Briana Rider, PharmD, CPPS

1 PURPOSE OF MEMORANDUM

The Sponsor submitted revised container (blister) labels and carton labeling received on March 10, 2020 for levonorgestrel and ethinyl estradiol tablets. The Division of Bone, Reproductive and Urologic Products (DBRUP) requested that we review the revised container labels and carton labeling for levonorgestrel and ethinyl estradiol tablets (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 and labeling memorandums.[abcd]

2 ASSESSMENT

[a] Karpow C. Label and Labeling Review for levonorgestrel and ethinyl estradiol (NDA 209405). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2019 Oct 02. RCM No.: 2019-226.
[b] Karpow C. Label and Labeling Memorandum for levonorgestrel and ethinyl estradiol (NDA 209405). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2019 Nov 12. RCM No.: 2019-226-1.
[c] Karpow C. Label and Labeling Memorandum for levonorgestrel and ethinyl estradiol (NDA 209405). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2019 Dec 16. RCM No.: 2019-226-2.
[d] Kalonia, J. Label and Labeling Memorandum for levonorgestrel and ethinyl estradiol (NDA 209405). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2020 Feb 04. RCM No.: 2019-226-3.

Table 1 below includes the identified medication error issues with the revised container (blister) labels and carton labeling, our rationale for concern, and the proposed recommendation to minimize the risk for medication error.

Table 1. 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, Patient Information, Instructions For Use (IFU), and container labels and carton labeling.	The proprietary name, (b) (4) was found unacceptable by DMEPA under NDA 209405 on March 13, 2020 due to potential name confusion with another proprietary name. We reference our March 16, 2020 Proprietary Name Request Denial letter informing you that the proposed proprietary name, (b) (4) was found unacceptable.	Remove the proprietary name, (b) (4) throughout the Prescribing Information, Patient Information, IFU, and container labels and carton labeling (including the braille lettering for (b) (4).
Container (Blister) Labels and Carton Labeling			
2.	In light of recommendation #1 above, the product will have the same name levonorgestrel and ethinyl estradiol tablets as other (b) (4) tablets with the same active ingredients.	May pose risk of product selection errors at the point of dispensing (b) (4)	(b) (4)

3 CONCLUSION

The revised container labels and carton labeling are unacceptable from a medication error perspective. We provide recommendations to Exeltis USA Inc. to address our concerns in Table 1 above. We ask that the Division convey Table 1 in its entirety to Exeltis USA Inc. so that recommendations are implemented prior to approval of this NDA.

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/s/

JUSTINE H KALONIA
03/16/2020 10:34:34 AM

BRIANA B RIDER
03/16/2020 10:40:11 AM

MEMORANDUM

REVIEW OF REVISED LABEL AND LABELING

Division of Medication Error Prevention and Analysis (DMEPA)

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:	February 4, 2020
Requesting Office or Division:	Division of Bone, Reproductive and Urologic Products (DBRUP)
Application Type and Number:	NDA 209405
Product Name and Strength:	(b) (4) (levonorgestrel/ethinyl estradiol), (b) (4) tablets, 0.1 mg/0.02 mg
Applicant/Sponsor Name:	Exeltis USA Inc.
OSE RCM #:	2019-226-3
DMEPA Safety Evaluator:	Justine Kalonia, PharmD
DMEPA Team Leader:	Briana Rider, PharmD, CPPS

1 PURPOSE OF MEMORANDUM

The Sponsor submitted revised container (blister) labels and carton labeling received on December 17, 2019 for levonorgestrel/ethinyl estradiol (b) (4) tablets containing the proposed proprietary name, (b) (4) which is currently under review. The Division of Bone, Reproductive and Urologic Products (DBRUP) requested that we review the revised container labels and carton labeling for levonorgestrel/ethinyl estradiol (b) (4) tablets (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 and labeling memorandums.[bcd]

2 ASSESSMENT

[a] Acceptability of the proposed proprietary name is currently under Agency review.

[b] Karpow C. Label and Labeling Review for (levonorgestrel/ethinyl estradiol) (NDA 209405). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2019 Oct 02. RCM No.: 2019-226.

[c] Karpow C. Label and Labeling Memorandum for (levonorgestrel/ethinyl estradiol) (NDA 209405). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2019 Nov 12. RCM No.: 2019-226-1.

[d] Karpow C. Label and Labeling Memorandum for (levonorgestrel/ethinyl estradiol) (NDA 209405). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2019 Dec 16. RCM No.: 2019-226-2.

Table 1. Identified Issues and Recommendations for Exeltis USA Inc. (entire table to be conveyed to Applicant)			
	IDENTIFIED ISSUE	**RATIONALE FOR CONCERN**	**RECOMMENDATION**
Trade and Sample Container Labels and Carton Labeling (All NDC)			
1.	The appearance of the established name (active ingredients and dosage form) and strength [that is, (b) (4) lacks prominence.	The established name lacks prominence commensurate with the proposed proprietary name and is not presented in accordance with 21 CFR 201.10(g)(2). As currently presented, the established name (active ingredients and dosage form) and strength are crowded on one line and are presented in (b) (4) font, which may not provide adequate contrast between it and the white background on some of the panels of the carton labeling and container labels.	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 placing the dosage form on the next line below the active ingredients. For example, (b) (4) We also recommend you improve the contrast between the background and the established name and strength and ensure the established name is at least half the size of the proprietary name.

3 CONCLUSION

The revised container labels and carton labeling are unacceptable from a medication error perspective. We provide a recommendation to address our concerns in Table 1.

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/s/

JUSTINE H KALONIA
02/04/2020 09:16:27 AM

BRIANA B RIDER
02/04/2020 12:55:39 PM

MEMORANDUM

REVIEW OF REVISED LABEL AND LABELING
Division of Medication Error Prevention and Analysis (DMEPA)
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:	November 12, 2019
Requesting Office or Division:	Division of Bone, Reproductive and Urologic Products (DBRUP)
Application Type and Number:	NDA 209405
Product Name and Strength:	(Levonorgestrel/Ethinyl Estradiol) (b) (4) tablets, 0.1 mg/0.02 mg
Applicant/Sponsor Name:	Exeltis USA Inc.
OSE RCM #:	2019-226-1
DMEPA Safety Evaluator:	Celeste Karpow, PharmD, MPH
DMEPA Team Leader:	Briana Rider, PharmD, CPPS

1 PURPOSE OF MEMORANDUM

The Applicant submitted revised container labels and carton labeling received on October 24, 2019 for levonorgestrel/ethinyl estradiol (b) (4) tablets. The Division of Bone, Reproductive and Urologic Products (DBRUP) requested that we review the revised container labels and carton labeling for levonorgestrel/ethinyl estradiol (b) (4) tablets (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 CONCLUSION

The revised container labels and carton labeling are unacceptable from a medication error perspective:

- The placeholder, "Tradename" is on the container labels and carton labeling, however, a proprietary name has not been submitted to the Agency;

[a] Karpow C. Label and Labeling Review for Levonorgestrel/ethinyl estradiol (b) (4) tablets (NDA 209405). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2019 OCT 02. RCM No.: 2019-226.

- The carton containing 6 individual blister cards (NDC 0642-7471-06) incorrectly states the net quantity on the principal display panel (PDP) as: (b) (4)

3 RECOMMENDATIONS FOR Exeltis USA Inc.

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

A. General Comments (Blister labels & Carton labeling)
    1. We note the presence of the placeholder "Tradename" on the container labels and carton labeling. However, a proprietary name has not been submitted to the Agency for review. Please note that if you intend to have a proprietary name for this application you are required to submit a request for proprietary name review. Requests for proprietary name review are completed within 90 days for NDAs per PDUFA Performance Goals for Proprietary Name Review. If you intend to market your proposed product without a proprietary name, remove the placeholder "Tradename" and resubmit the container labels and carton labeling to the Agency.

B. Carton Labeling (6 count; NDC 0642-7471-06)
    1. The carton containing 6 individual blister cards (NDC 0642-7471-06) incorrectly states the net quantity on the principal display panel (PDP) as: (b) (4) . Revise the net quantity statement on the PDP to read: "Contains: 6 blister cards of 28 tablets (b) (4)" for consistency with the side and back panels of the carton labeling and the Prescribing Information.

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/s/

CELESTE A KARPOW
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BRIANA B RIDER
11/12/2019 11:10:49 AM

LABEL AND LABELING REVIEW
Division of Medication Error Prevention and Analysis (DMEPA)
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:	October 2, 2019
Requesting Office or Division:	Division of Bone, Reproductive and Urologic Products (DBRUP)
Application Type and Number:	NDA 209405
Product Name and Strength:	(Levonorgestrel/Ethinyl Estradiol) (b) (4) tablets, 0.1 mg/0.02 mg
Product Type:	Multi-Ingredient Product
Rx or OTC:	Prescription (Rx)
Applicant/Sponsor Name:	Exeltis USA Inc.
FDA Received Date:	May 30, 2019
OSE RCM #:	2019-226
DMEPA Safety Evaluator:	Celeste Karpow, PharmD, MPH
DMEPA Team Leader (Acting):	Briana Rider, PharmD, CPPS

1 REASON FOR REVIEW

As part of the approval process for levonorgestrel/ethinyl estradiol (b) (4) tablets, NDA 209405, the Division of Bone, Reproductive and Urologic Products (DBRUP) requested that we review the proposed levonorgestrel/ethinyl estradiol prescribing information (PI), instructions for use (IFU), container labels, and carton labeling for areas of vulnerability that may lead to medication errors. NDA 209405 is a 505(b)(2) NDA and the listed drug product is Alesse, NDA 020683.

2 REGULATORY HISTORY

Exeltis USA Inc. previously submitted NDA 209405 on January 7, 2019. However, the Agency issued a refuse to file letter on March 18, 2019 for NDA 209405. The application was resubmitted on May 30, 2019.

3 MATERIALS REVIEWED

We considered the materials listed in Table 1 for this review. The Appendices provide the methods and results for each material 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
Human Factors Study	C – N/A
ISMP Newsletters*	D – N/A
FDA Adverse Event Reporting System (FAERS)*	E – N/A
Other	F – N/A
Labels and Labeling	G

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

4 OVERALL ASSESSMENT OF THE MATERIALS REVIEWED

Levonorgestrel/ethinyl estradiol 0.10 mg/0.02 mg (b) (4) tablets are provided in blister cards containing 28 tablets, consisting of 21 active tablets and 7 inactive tablets, indicated for use by females to prevent pregnancy.

Our review of the proposed blister labels, carton labeling, Prescribing Information (PI) and Instructions for Use (IFU), for levonorgestrel/ethinyl estradiol (b) (4) tablets identified the following areas of needed improvement that may contribute to medication errors:

Prescribing Information (PI)

1. The strength presentation of the levonorgestrel component is represented with a terminal zero, “levonorgestrel 0.10 mg”, which may pose risk of 10-fold misinterpretation.
2. The dosing instructions in the HPI and FPI can be improved for clarity.

Instructions for Use (IFU)

1. The graphic of the blister label in the IFU does not match the proposed blister label.

General Comments (Blister Labels & Carton Labeling)

1. “TRADENAME” appears in all capital letters; words written in all-capital letters are less legible than words written in mixed case letters.
2. Our review of the blister labels and carton labeling notes that the Sponsor refers to the dosage form as “tablets”. (b) (4)
3. The braille translation for the product will need to be revised pending review of a proprietary name.
4. There are multiple linear barcodes on the blister label and carton labeling and we cannot determine which barcode contains the NDC number.
5. The professional sample blister label was not submitted for agency review.

Blister Labels

1. The principle display panel (PDP) (b) (4)
2. The format of the expiration date can be improved.
3. The blister label contains the undefined abbreviations, “Wk 2,” “Wk 3,” “Wk 4.” We find use of this abbreviation could result in misinterpretation and confusion.

Carton Labeling

1. The route of administration is not present on the principle display panel, which could pose risk of wrong route of administration errors.
2. The net quantity appears immediately below the product strength and could lead to misinterpretation of strength.
3. The statement, (b) (4) is a negative statement and might be misinterpreted.
4. The usual dosage statement can be revised for consistency with the Prescribing Information.

Blister Envelope

1. A placeholder for the proprietary name is present on the blister envelope without the accompanying established name. Per 21 CFR 201.10 (g)(1), the established name shall accompany the proprietary name each time it is featured on the label or labeling.

We provide recommendations regarding these areas below in Section 5.1 and 5.2 to help minimize the potential for medication errors to occur with the use of the product.

5 CONCLUSION & RECOMMENDATIONS

We identified areas of the prescribing information, instructions for use, blister card label, and carton labeling where additional important information should be added to or revised to help ensure the safe use of the product. We provide recommendations below in sections 5.1 and 5.2 to address our concerns and we advise these recommendations be implemented prior to the approval of this application.

5.1 RECOMMENDATIONS FOR THE DIVISION

A. Prescribing Information

1. We note the strength presentation of the levonorgestrel component is represented with a terminal zero, "levonorgestrel 0.10 mg", which may pose risk of 10-fold misinterpretation. Revise the strength presentation throughout the PI to "levonorgestrel 0.1 mg" to avoid misinterpretation of the strength in accordance with our draft guidance[a] and ISMP's List of Error-Prone Abbreviations, Symbols, and Dose Designations[b].
2. The dosing instructions in the HPI and FPI can be improved. As currently presented, the PI states, (b) (4) [redacted] We recommend revising this statement for clarity. For example, you may wish to consider, "(b) (4) [redacted] "

[a] Draft Guidance for Industry: Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors. Food and Drug Administration. 2013. Available from: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM349009.pdf.

[b] ISMP's List of Error-Prone Abbreviations, Symbols, and Dose Designations [Internet]. Horsham (PA): Institute for Safe Medication Practices. 2017 [cited 2019 AUG 14]. Available from: https://www.ismp.org/tools/errorproneabbreviations.pdf.

B. Instructions for Use (IFU)

1. As currently presented, the image of the blister pack in Figure A does not match the proposed blister pack label. We recommend the image used in Figure A in the IFU match the intend to market blister pack label.

5.2 RECOMMENDATIONS FOR EXELTIS USA INC.

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

A. General Comments (Blister labels & Carton Labeling)

1. We note the placeholder "TRADENAME" appears in all capital letters. We recommend capitalizing only the first letter in the proprietary name because words written in all-capital letters are less legible than words written in mixed case letters[c]. For readability, consider utilizing mixed case letters for the proprietary name on the intend to market labels and labeling.
2. As currently presented, the dosage form on the blister labels and carton labeling is "tablets". (b) (4) Ensure the dosage form is correct throughout the labels and labeling.
3. As currently presented, the braille translation for your product is "tradename 0.1 mg/0.02 mg". If you choose to market your product under a proprietary name, ensure you revise your braille translation once a proprietary name is found conditionally acceptable.
4. As currently presented, there are multiple linear barcodes on the blister label and carton labeling. We cannot determine which linear barcode will contain the NDC. Ensure the linear barcode that contains the NDC is surrounded by sufficient white space to allow scanners to correctly read the barcode in accordance with 21 CFR 201.25(c)(i). We recommend you move the barcode(s) that does not contain the NDC number away from the barcode that does contain the NDC number and present it in a size that does not compete with or distract from the presentation of other required or recommended information on the label or labeling.
5. We note you did not submit the professional sample blister label. Consider submitting the professional sample blister label for agency review.

[c] Draft Guidance for Industry: Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors. Food and Drug Administration. 2013. Available from: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM349009.pdf.

B. Blister Labels

1. The principle display panel (PDP) [redacted]

2. As currently presented, the format for the expiration date on the blister label is "YYYY MM." FDA recommends that the human-readable expiration date on the drug package label include a year, month, and non-zero day. If space permits, consider revising the expiration date on the blister label to the following format: YYYY-MM-DD, consistent with the format utilized on the carton labeling.

3. We note the blister label contains undefined abbreviations, "Wk 2," "Wk 3," "Wk 4." However, we are concerned that users may not know what abbreviation, Wk, stands for. Consider replacing the abbreviation, Wk, with its intended meaning to prevent misinterpretation and confusion.

C. Carton Labeling

1. As currently presented, the route of administration is not present on the principle display panel (PDP). Please include the route of administration on the PDP in accordance with our draft guidance for industry[d].

2. As currently presented, the net quantity appears immediately below the product strength. From post-marketing experience, the risk of numerical confusion between the strength and net quantity increases when the net quantity statement is located in close proximity to the strength statement. Relocate the net quantity statement away from the product strength, such as to the bottom of the principal display panel.

3. The statement, [redacted] is a negative statement. Based on our post-marketing experience, negative statements (e.g. do not) may have the opposite of the intended meaning because the word "not" can be overlooked, and the warning may be misinterpreted as an affirmative action. In addition, it might diminish the prominence of the positive statement. Delete the statement, [redacted][e, c]

4. To ensure consistency with the physician labeling rule (PLR) formatted Prescribing Information, revise the statement, [redacted]

[d] Draft Guidance for Industry: Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors. Food and Drug Administration. 2013. Available from: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM349009.pdf.

[e] Institute for Safe Medication Practices. Affirmative warnings (do this) may be better understood than negative warnings (do not do that). ISMP Med Saf Alert Acute Care. 2010;15(16):1-3.

(b) (4)

to read “Recommended Dosage: (b) (4) . See prescribing information.”

D. Blister envelope

1. As currently presented, a placeholder for the proprietary name appears on the blister envelope without the established name. Per 21 CFR 201.10 (g)(1), the established name shall accompany the proprietary name each time it is featured on the label or labeling. Revise the blister envelope to include the established name.

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for Levonorgestrel/Ethinyl Estradiol received on May 30, 2019 from Exeltis USA Inc., and the listed drug (LD).

Table 2. Relevant Product Information for Levonorgestrel/Ethinyl Estradiol and the Listed Drug		
Product Name	Levonorgestrel/Ethinyl Estradiol	Alesse[f]
Initial Approval Date	N/A	03/27/1997
Active Ingredient	Levonorgestrel/Ethinyl Estradiol	Levonorgestrel/Ethinyl Estradiol
Indication	Prevention of pregnancy	Prevention of pregnancy
Route of Administration	oral	oral
Dosage Form	(b) (4) tablets	tablets
Strength	0.1 mg/0.02 mg	0.1 mg/0.02 mg
Dose and Frequency	Take one tablet by mouth once daily	Take one tablet by mouth once daily
How Supplied	Each blister card contains 28 tablets: 21 active tablets and 7 inactive tablets. NDC 0642-7471-01, one carton containing 1 blister card NDC 0642-7471-03, one carton containing 3 blister cards NDC 0642-7471-06, one carton containing 6 blister cards	Packages of 3 MINI-PACK™ dispensers containing 28 tablets; NDC 0008-2576-02: NDC 0008-0912, 21 active tablets NDC 0008-0650, 7 inert tablets
Storage	Store at controlled room temperature 20° to 25°C (68°to 77°F). (b) (4)	Store at controlled room temperature 20° to 25°C (68°to 77°F).
Container Closure	(b) (4) /Aluminum blister	N/A

[f] Alesse [Prescribing Information]. Drugs@FDA. U.S. Food and Drug Administration. 2018 MAR 27. Available from: https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/020683s012lbl.pdf.

APPENDIX B. PREVIOUS DMEPA REVIEWS

On August 16, 2019, we searched for previous DMEPA reviews relevant to this current review using the terms, “209405”. Our search identified no previous reviews.

APPENDIX G. LABELS AND LABELING

G.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,[g] along with postmarket medication error data, we reviewed the following Levonorgestrel/Ethinyl Estradiol labels and labeling submitted by Exeltis USA Inc..

- Blister card label received on May 30, 2019
- Carton labeling received on May 30, 2019
- Professional Sample Carton Labeling received on May 30, 2019
- Blister Envelope received on May 30, 2019
- Instructions for Use received on May 30, 2019
- Prescribing Information (Image not shown) received on May 30, 2019

G.2 Label and Labeling Images

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

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

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/s/

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