CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

208612Orig1s000

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:	December 22, 2017
Requesting Office or Division:	Division of Bone, Reproductive, and Urologic Products (DBRUP)
Application Type and Number:	NDA 208612
Product Name and Strength:	Levonorgestrel/ethinyl estradiol USP and ferrous bisglycinate tablets 0.1 mg/0.02 mg and 36.5 mg
Applicant/Sponsor Name:	Neuvosyn Laboratories, LLC
Submission Date:	December 19, 2017
OSE RCM #:	2017-1324-2
DMEPA Safety Evaluator:	Denise V. Baugh, PharmD, BCPS
DMEPA Team Leader:	Lolita G. White, PharmD

1 PURPOSE OF MEMO

The Division of Bone, Reproductive, and Urologic Products requested that we review the revised blister label and carton labeling for levonorgestrel/ethinyl estradiol USP and ferrous bisglycinate tablets (Appendix A) to determine if it is acceptable from a medication error perspective. The revisions were made to reflect the addition of the alternative proposed proprietary name, Balcoltra*** which is being reviewed by DMEPA separately. We did not identify any additional areas for improvement of the blister label or carton labeling.

2 CONCLUSION

The revised blister label and carton labeling for levonorgestrel/ethinyl estradiol USP and ferrous bisglycinate tablets is acceptable from a medication error perspective. We have no further comment.

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/s/

DENISE V BAUGH
12/22/2017

LOLITA G WHITE
12/22/2017

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:	December 18, 2017
Requesting Office or Division:	Division of Bone, Reproductive, and Urologic Products (DBRUP)
Application Type and Number:	NDA 208612
Product Name and Strength:	levonorgestrel/ethinyl estradiol USP and ferrous bisglycinate tablets 0.1 mg/0.02 mg and 36.5 mg
Applicant/Sponsor Name:	Neuvosyn Laboratories, LLC
Submission Date:	December 8, 2017
OSE RCM #:	2017-1324-1
DMEPA Safety Evaluator:	Denise V. Baugh, PharmD, BCPS
DMEPA Team Leader:	Lolita G. White, PharmD

1 PURPOSE OF MEMO

The Division of Bone, Reproductive, and Urologic Products requested that we review the revised blister label and carton labeling (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.[a]

2 CONCLUSION

The revised blister label and carton labeling for 'levonorgestrel/ethinyl estradiol tablets, USP 0.1 mg/0.02 mg and ferrous bisglycinate tablets, 36.5' mg is acceptable from a medication error perspective. We have no further recommendations at this time.

[a] Baugh, D. Label and Labeling Review for Levonorgestrel and Ethinyl Estradiol tablets, USP 0.1 mg/0.02 mg and Ferrous Bisglycinate tablets, 36.5 mg (NDA 208612). Silver Spring (MD): Food and Drug Administration, Center for Drug Evaluation and Research, Office of Surveillance and Epidemiology, Division of Medication Error Prevention and Analysis (US); 2017 November 29. RCM No.: 2017-1324.

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/s/

DENISE V BAUGH
12/18/2017

LOLITA G WHITE
12/19/2017

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:	December 12, 2017
To:	Hylton V. Joffe, M.D. Director **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)** Marcia Williams, PhD Team Leader, Patient Labeling **Division of Medical Policy Programs (DMPP)**
From:	Sharon W. Williams, MSN, BSN, RN Patient Labeling Reviewer **Division of Medical Policy Programs (DMPP)** Lynn Panholzer, 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):	levonorgestrel and ethinyl estradiol and ferrous bisglycinate
Dosage Form and Route:	tablets, for oral administration
Application Type/Number:	NDA 208612
Applicant:	Neuvosyn Laboratories, LLC

1 INTRODUCTION

On October 9, 2016, Neuvosyn Laboratories, LLC submitted for the Agency's review a New Drug Application (NDA) for levonorgestrel and ethinyl estradiol and ferrous bisglycinate tablets, for oral administration indicated 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 Urology Products (DBRUP) on June 20, 2017, for DMPP and OPDP to review the Applicant's proposed PPI and IFU for levonorgestrel and ethinyl estradiol and ferrous bisglycinate tablets, for oral administration.

DMPP conferred with the Division of Medication Error, Prevention, and Analysis (DMEPA) and their comments were included in this review.

2 MATERIAL REVIEWED

- Draft levonorgestrel and ethinyl estradiol and ferrous bisglycinate PPI and IFU received on October 9, 2016, and received by DMPP and OPDP on December 5, 2017.
- Draft levonorgestrel and ethinyl estradiol and ferrous bisglycinate Prescribing Information (PI) received on October 9, 2016, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on December 5, 2017.

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. In our review of the PPI and IFU the target reading level is at or below an 8th grade 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.

In our collaborative review of the PPI and IFU we have:

- 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)

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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/s/

SHARON W WILLIAMS
12/12/2017

LYNN M PANHOLZER
12/12/2017

LASHAWN M GRIFFITHS
12/12/2017

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

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

Memorandum

Date: December 11, 2017

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

From: Lynn Panholzer, PharmD, Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

CC: Matthew Falter, PharmD, Team Leader, OPDP

Abby Anderson, MD, Medical Officer, DBRUP

Subject: OPDP Labeling Comments for levonorgestrel and ethinyl estradiol tablets, and ferrous bisglycinate tablets, for oral administration

NDA: 208612

In response to DBRUP's consult request dated July 14, 2017, OPDP has reviewed the proposed product labeling (PI), patient package insert (PPI), and carton and container labeling for the original NDA submission for levonorgestrel and ethinyl estradiol tablets, and ferrous bisglycinate tablets, for oral administration.

PI and PPI: OPDP's comments on the draft PI are based on the version dated 11/29/17 in Sharepoint (accessed 12/10/17), and are provided below.

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

Carton and Container Labeling: OPDP has reviewed the attached proposed carton and blister labels submitted by the sponsor on 12/8/17, available in the EDR, and our comment on the blister label is provided below. We have no comments on the carton label.

Thank you for your consult. If you have any questions, please contact Lynn Panholzer at (301) 796-0616 or lynn.panholzer@fda.hhs.gov.

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/s/

LYNN M PANHOLZER
12/11/2017

MEMORANDUM

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

DATE: 12/1/17

TO: Allen Fields, Neuvosyn Laboratories, Inc

THROUGH: Denise Baugh, DMEPA
Hong Cai, CMC

FROM: Jennifer Dao

SUBJECT: NDA 208612-- Carton and Container Information Request

APPLICATION/DRUG: NDA 208612- levonorgestrel and ethinyl estradiol and Ferrous bisclycinate tablets

The following email was sent to the Applicant on 12/1/17. The comments were received from DMEPA and CMC.

From: Dao, Jennifer
To: "Allen Fields"
Subject: NDA 208612--Carton and Container Information Request
Date: Friday, December 01, 2017 10:52:08 AM
Importance: High

Hi Allen,
We refer to your New Drug Application mentioned above. The following comments below are in regards to the Carton and Container labels. We ask that you respond and send us revised labels by next Friday, Dec. 8th. Please let me know if you won't be able to meet this date.

For the Immediate Container Label (the blister pack containing 28 tablets):

1. To be consistent with PI, please remove "USP" notation from the established name.
2. Add the statement "Contains FD&C Yellow No. 5 (tartrazine) as a color additive" per 21 CFR201.20 (a).
3. The name and place of the manufacturer/distributor should be consistent with the information provided in carton label.
4. The established name lacks prominence commensurate with the proposed proprietary

name. We recommend you 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). In addition, we recommend you revise the established name to be at least half the size of the proprietary name in accordance with 21 CFR 201.10(g)(2).

5. Add the "Rx Only" statement in accordance with Section 503(b)(4)(A) of the Federal Food, Drug, and Cosmetic Act. Ensure that its prominence is presented in accordance with our Guidance for Industry: Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors, April, 2013; "https://www.fda.gov/downloads/drugs/guidances/ucm349009.pdf

For the Carton Label:

6. Refer to the comment 1&4 for the immediate container label.

7. Remove the statement: (b) (4)

8. Provide the list of the inactive ingredients.

9. Provide the lot number and expiration date.

10. We find the statement (b) (4) (b) (4) (b) (4) is not in accordance with the Draft Guidance for Industry: Labeling for Combined Oral Contraceptives and may cause confusion. Additionally, this may be misleading because it is a broad statement about the therapeutic class which includes products that have additional indications besides pregnancy (e.g. treatment of acne vulgaris, management of dysmenorrhea). We recommend you revise the statement from: (b) (4) (b) (4) to read: "This product is intended to prevent pregnancy. It does not protect against HIV infection (AIDS) and other sexually transmitted diseases".

General Comment:

11. We are concerned with the visibility of the letters as proposed. Specifically, these letters are presented in (b) (4) font on a yellow background on the carton labeling and they are presented in (b) (4) font on a white background on the blister label. This presentation makes this part of the name difficult to read. We recommend improving the color contrast to increase the readability of the name.

Please confirm the receipt of this email.
Thank you,
Jennifer

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/s/

JENNIFER M DAO
12/01/2017

LABEL, LABELING, AND PACKAGING 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:	November 29, 2017
Requesting Office or Division:	Division of Bone, Reproductive, and Urologic Products (DBRUP)
Application Type and Number:	NDA 208612
Product Name and Strength:	Levonorgestrel and Ethinyl Estradiol tablets, USP 0.1 mg/0.02 mg and Ferrous Bisglycinate tablets, 36.5 mg
Product Type:	Multi-ingredient product
Rx or OTC:	Rx
Applicant/Sponsor Name:	Neuvosyn Laboratories, LLC
Submission Date:	October 12, 2017
OSE RCM #:	2017-1324
DMEPA Primary Reviewer:	Denise V. Baugh, PharmD, BCPS
DMEPA Team Leader:	Lolita G. White, PharmD

1 REASON FOR REVIEW

The Division of Bone, Reproductive, and Urologic Products (DBRUP) has requested the Division of Medication Error Prevention and Analysis (DMEPA) review the blister label, carton labeling, and prescribing information (PI) for NDA 208612 to determine if it is acceptable from a medication error perspective.

2 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 for our label and labeling reviews unless we are aware of medication errors through our routine post-market safety surveillance

3 OVERALL ASSESSMENT OF THE MATERIALS REVIEWED

Our review of the proposed blister label, carton labeling, and prescribing information (PI) identified the following areas of needed improvement that may lead to medication errors:

Blister label and Carton labeling

a. The established name ('levonorgestrel and ethinyl estradiol tablets USP, 0.1 mg/0.02 mg and ferrous bisglycinate tablets, 36.5 mg') lacks prominence commensurate with the proposed proprietary name. This is required in accordance with 21 CFR 201.10(g)(2) to decrease the risk of an error in product selection.

b. The 'Rx Only' statement on the blister label is missing and therefore not in accordance with Section 503(b)(4)(A) of the Federal Food, Drug, and Cosmetic Act.

c. The carton labeling includes a statement which is overly broad and not in accordance with the Draft Guidance for Industry: Labeling for Combined Oral Contraceptives.

We provide recommendations regarding these areas below in Section 4.1 in order to help minimize the potential for medication errors with this product.

4 CONCLUSION & RECOMMENDATIONS

We identified areas on the container label and carton labeling where the readability of drug-identifying information can be improved to help ensure the safe use of the product. We provide recommendations in Section 4.1 to address our concerns. We request implementation of these recommendations prior to approval of this product.

4.1 RECOMMENDATIONS FOR NEUVOSYN LABORATORIES, LLC

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

A. Blister Label

1. The established name lacks prominence commensurate with the proposed proprietary name . We recommend you 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). In addition, we recommend you revise the established name to be at least half the size of the proprietary name in accordance with 21 CFR 201.10(g)(2).

2. Add the "Rx Only" statement in accordance with Section 503(b)(4)(A) of the Federal Food, Drug, and Cosmetic Act. Ensure that its prominence is presented in accordance with our Guidance for Industry: Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors, April, 2013; "https://www.fda.gov/downloads/drugs/guidances/ucm349009.pdf

B. Carton Labeling

1. See recommendation A.1 above.

2. We find the statement (b) (4) (b) (4) (b) (4) is not in accordance with the Draft Guidance for Industry: Labeling for Combined Oral Contraceptives and may cause confusion. Additionally, this may be misleading because it is a broad statement about the therapeutic class which includes products that have additional indications besides pregnancy (e.g. treatment of acne vulgaris, management of dysmenorrhea). We recommend you revise the statement from: (b) (4) (b) (4) (b) (4) to read: "This product is intended to prevent pregnancy. It does not protect against HIV infection (AIDS) and other sexually transmitted diseases".

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for levnorgestrel and ethinyl estradiol tablets, USP and ferrous bisglycinate tablets that Neuvosyn Laboratories, LLC submitted on October 12, 2017.

Table 2. Relevant Product Information for Levonorgestrel and Ethinyl Estradiol tablets, USP and ferrous bisglycinate tablets	
Initial Approval Date	N/A
Active Ingredient	Levonorgestrel and ethinyl estradiol and ferrous bisglycinate
Indication	Pregnancy prevention
Route of Administration	oral
Dosage Form	tablet
Strength	0.1 mg/0.02 mg and 36.5 mg
Dose and Frequency	One tablet orally once daily
How Supplied	Blister pack contains 28 tablets arranged in 3 rows of 7 active tablets and 1 row of inert tablets; one carton contains one blister pack
Storage	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]

APPENDIX B. PREVIOUS DMEPA REVIEWS

B.1 Methods

On July 20, 2017, we searched the L: drive and AIMS using the terms, “Ferrochel” and “NDA 208612” to identify reviews previously performed by DMEPA.

B.2 Results

Our search identified no previous reviews relevant to this review.

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,[a] along with post-market medication error data, we reviewed the following levonorgestrel and ethinyl estradiol tablets, USP, and ferrous bisglycinate tablets labels and labeling submitted by Neuvosyn Laboratories, LLC on October 12, 2017.

- Blister label
- Carton labeling
- Prescribing Information (Image not shown)

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

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/s/

DENISE V BAUGH
11/29/2017

LOLITA G WHITE
11/29/2017