CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

208612Orig1s000

PRODUCT QUALITY REVIEW(S)

Recommendation: ***APPROVAL***

NDA 208612

Levonorgestrel and Ethinyl Estradiol Tablets, and Ferrous Bisglycinate Tablets

Review #1

Drug Name/Dosage Form	Levonorgestrel and Ethinyl Estradiol Tablets, and Ferrous Bisglycinate Tablets
Strength	0.1 mg / 0.02 mg and 36.5 mg
Route of Administration	Oral
Rx/OTC Dispensed	Rx
Applicant	Neuvosyn Laboratories, LLC
US agent, if applicable	-

SUBMISSION(S) REVIEWED	DOCUMENT DATE	DISCIPLINE(S) AFFECTED
Original (0000)	10/13/15	All
(User Fee Payment)	03/14/17	-
Amendment (0003)	05/15/17	Product
Correspondence (0005)	06/09/17	Facilities
Amendment (0007)	07/20/17	Biopharm.
Amendment (0008)	08/10/17	Product, Process
Amendment (0009)	08/23/17	Product, Biopharm.
Labeling (0010)	09/01/17	Product
Amendment (0011)	09/05/17	Product, Process
Amendment (0013)	09/29/17	Product
Amendment (0014)	10/12/17	Product
Amendment (0018)	11/29/17	Product
Amendment (0019)	11/30/17	Product
Labeling (0020)	12/08/17	Product
Labeling (0022)	12/19/17	Product

Quality Review Team

Discipline	Primary Reviewer	Office / Division
Drug Substance	Jeffrey Medwid	OPQ/ONDP/DNDPAPI/BII
Drug Product	Hong Cai	OPQ/ONDP/DBRUP/BV
Process	Zhao (Joe) Wang	OPQ/OPF/DPAII/BV
Microbiology	Zhao (Joe) Wang	OPQ/OPF/DPAII/BV
Facility	Xiaohui (Sherry) Shen	OPQ/OPF/DIA/BIII
Biopharmaceutics	An-Chi (Angela) Lu / Vidula Kolhatkar	OPQ/ONDP/DB/B2
RBPM	Thao Vu	OPQ/OPRO/RBPMI/BI
ATL	Mark Seggel	OPQ/ONDP/BV
Laboratory (OTR)	-	-
Environmental	Hong Cai	OPQ/ONDP/DBRUP/BV

Quality Review Data Sheet

1. RELATED/SUPPORTING DOCUMENTS

A. DMFs:

DMF #	Type	Holder	Item Referenced	Status	Date Review Completed	Comments
(b) (4)	Type III		(b) (4)	NA		See 3.2.P.7
	Type III			NA		See 3.2.P.7
	Type IV			NA		

is enough data in not need to be reviewed

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

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
Application and associated reviews	ANDA 90721	LNG and EE 0.1 mg/0.02 mg tablets; AP 03/28/12
Application and associated reviews	NDA 20683	Alesse® (Ethinyl Estradiol and Levonorgestrel Tablets) AP 03/27/97
Meeting packages and associated responses	pre-IND 122407	pre-IND and pre-NDA meetings

2. CONSULTS

DISCIPLINE	STATUS	RECOMMENDATION	DATE	REVIEWER
Biostatistics	n/a			
Pharmacology/ Toxicology	Complete	Approval of application. No safety concerns associated with ferrous bisglycinate.	12/08/17	L. McKinney
CDRH	n/a			
Clinical	n/a			
Other	n/a			

Executive Summary

I. Recommendations and Conclusion on Approvability

Neuvosyn's 505(b)(2) New Drug Application #208612, for a kit consisting of Levonorgestrel and Ethinyl Estradiol Tablets and Ferrous Bisglycinate Tablets, is recommended for APPROVAL from the OPQ perspective.

The progestin / estrogen combination oral contraceptive (CHC) component of the kit was approved March 28, 2012 under ANDA 90721 (Falmina™ (levonorgestrel and ethinyl estradiol tablets) 0.1 mg/0.02 mg; Novast Laboratories, Ltd.).

The chemistry, manufacturing and controls (CMC) of the ferrous bisglycinate tablets, as well as the co-packaging of these therapeutically inactive tablets with the COC tablets, are adequately documented in NDA 208612, as amended.

Overall, sufficient information and supporting data have been provided in accordance with 21 CFR 314.50 to ensure the identity, strength, quality, purity, potency and bioavailability of the kit components. As revised, the drug product labeling complies with the requirements under 21 CFR 201.

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

The container and carton labels, as well as the package insert, as revised, are complete, accurate and conform to the relevant sections of 21 CFR 201.

II. Summary of Quality Assessments

A. Product Overview

Proposed Indication(s) including Intended Patient Population	Women of reproductive potential seeking prevention of pregnancy.
Duration of Treatment	As needed.
Maximum Daily Dose	• Levonorgestrel 0.1 mg and ethinyl estradiol 0.02 mg per day for 21 days. • Therapeutically inactive ferrous bisglycinate 36.5 mg per day for 7 days.
Alternative Methods of Administration	Not applicable.

The Orange Book lists 53 combination estrogen/progestin oral contraceptive (COC) products containing ethinyl estradiol (EE) and levonorgestrel (LNG) that are currently marketed and another 18 products that have been discontinued. New Drug Application #208612 provides

yet another option for an LNG + EE combination oral contraceptive. In this instance, the proposed COC kit is based on the approved generic product, Falmina, approved under Novast Laboratories' ANDA 90721 on March 28, 2012. Falmina consists of 21 orange levonorgestrel and ethinyl estradiol tablets, 0.1 mg/0.02 mg and 7 white inactive, iron-free tablets that serve solely as 'reminders' to facilitate the correct dosing regimen. The applicant is relying on the Agency's previous findings of safety and efficacy for Alesse Tablets (NDA 20683), the now discontinued reference listed drug (RLD).

In addition to the same 21 orange levonorgestrel and ethinyl estradiol tablets, 0.1 mg/0.02 mg, as found in Falmina, the proposed kit includes 7 therapeutically inactive, blue film-coated tablets containing ferrous bisglycinate. It appears that the kit would thus be the first LNG plus EE combination oral contraceptive kit to include inactive tablets containing a ferrous salt. Of the currently marketed COC kits, only those with norethindrone (or norethindrone acetate) and ethinyl estradiol include therapeutically inactive tablets containing a ferrous salt, namely ferrous fumarate.

Ferrous bisglycinate, in the form of Ferrochel®, is present as a component in a variety of dietary supplements. Each inactive, placebo tablet contains 36.5 mg of ferrous bisglycinate, the equivalent of 10 mg of elemental iron. The glycine chelate of iron is reported to be "less reactive and better absorbed than the free ionic metal."

The only unique aspect of the proposed drug product kit is the inclusion of inactive tablets containing ferrous bisglycinate, thus the only potential new risks introduced with the use of the kit will be those associated with the inactive tablets. And those risks are expected to be minimal.

B. Quality Assessment Overview

Levonorgestrel and Ethinyl Estradiol Tablets

The chemistry, manufacturing and controls of the levonorgestrel and ethinyl estradiol tablets, 0.1 mg/0.02 mg, is exactly as described in Novast's approved ANDA 90721, for which Neuvosyn has a written Right of Reference. The COC's present in Novast's product and in Neuvosyn's COC kit are identical in all aspects.

The manufacture of the COC by Novast has already been reviewed and approved by OGD. However, because the COC has low drug loads, the manufacturing process was briefly re-evaluated to ensure that content uniformity requirements are met.

The chemistry, manufacturing and controls for the active ingredients, levonorgestrel and ethinyl estradiol, are documented in Type II DMF's (b) (4), respectively. The continued adequacy of both DMFs has been confirmed.

Ferrous Bisglycinate Tablets and Kit

Ferrous Bisglycinate

Ferrous bisglycinate is a "ferrous amino acid chelate formed by 2 glycine molecules bound to a ferrous cation, resulting in a stable double heterocyclic ring compound." It has been used in numerous dietary supplements and fortified foods since 1989. Neuvosyn notes that, "in 1999 FDA assigned generally regarded as safe (GRAS) status to ferrous bisglycinate chelate (GRAS Notice GRN 000019), based on the self-affirmation process." Dr. Leslie McKinney, Pharmacology/Toxicology reviewer, has determined that there are no safety concerns associated with ferrous bisglycinate.

Ferrous bisglycinate is supplied as Ferrochel®, a mixture of ferrous bisglycinate, citric acid, glycine, water, maltodextrin, and silica. The chemistry, manufacturing and controls of Ferrochel®, is documented in NDA 208612.

Ferrochel is manufactured by (b) (4)
(b) (4)

A retest period of (b) (4) months has been established when Ferrochel is stored at 25°C.

This NDA is recommended for approval from the CMC drug substance perspective.

Note that ferrous bisglycinate is not a USAN-designated name. However, per Dr. David Lewis, FDA representative on the USAN council, such designation is not required in this instance.

Ferrous Bisglycinate Tablets

Each inert, therapeutically inactive, placebo tablet contains (b) (4) Ferrochel®, equivalent to 36.5 mg ferrous bisglycinate or 10 mg iron. In addition to citric acid, glycine, maltodextrin and silica, the inert tablets contain microcrystalline cellulose, croscarmellose sodium magnesium stearate and colloidal silicon dioxide. The tablets are film-coated with (b) (4) (b) (4). This non-functional film-coat contains hypromellose, titanium dioxide, polyethylene glycol 400, FD&C Red #40 Aluminum Lake, FD&C Yellow #6 Aluminum Lake and FD&C Blue #1 Aluminum Lake. The tablets are debossed with "N" on one side. (*Note: the inert, ferrous salt-free tablets in Falmina are debossed with "N" on one side and "P" on the other side. However, these tablets have a white film-coat.*) All excipients are of suitable quality.

The inert tablets are manufactured by Novast Laboratories, Nantong, China, which is the same facility where the active COC tablets are manufactured. The manufacturing process

involves relatively straightforward operations: (b) (4) (b) (4). The inert tablets and active COC tablets are then co-packaged in blister packs.

The product specification includes tests for appearance, identification, assay, content uniformity by weight variation, water content, residual solvents, and dissolution. The specification fits its intended purpose to ensure the consistency of the drug product quality at release and over the shelf life. Per the Process review (see below), microbial limits testing is not necessary.

Ferrous bisglycinate tablets and the LNG + EE tablets are co-packaged in (b) (4) (b) (4) foil blister cards. The packaging components and packaging process are essentially the same as employed for Falmina. The blister materials are of acceptable quality and provide a suitable barrier to moisture.

An expiration dating period of 24-months for ferrous bisglycinate tablets (b) (4) (b) (4) when stored at 25°C is supported by the available stability data. The approved expiration dating period for Falmina is 24 months.

Overall, there are minimal risks to inert ferrous bisglycinate tablet has minimal risk associated with product quality and. From the drug product perspective, NDA 208612, as amended, is recommended for approval.

Process and Microbiology

The manufacturing process for the placebo tablets is relatively straightforward. Because the ferrous bisglycinate content of the inert tablets is (b) (4), content uniformity (b) (4)

(b) (4)

Biopharmaceutics

While the dissolution rate of the therapeutically inactive ferrous bisglycinate tablets cannot, by definition, impact the efficacy of the oral contraceptive kit, it can serve as a measure of product quality and consistency. Ferrous bisglycinate is highly soluble across physiological pHs. The inactive tablets dissolve completely within (b) (4) minutes under a variety of conditions. Ultimately the method selected is the same as that specified in the monograph for Ferrous Fumarate Tablets, USP. An acceptance criterion of Q = (b) (4)% at 30 minutes has been established.

From the Biopharmaceutics perspective, this NDA is Adequate as amended.

Facilities

The (b) (4) manufacturing sites for levonorgestrel and ethinyl estradiol, respectively, have acceptable CGMP status.

(b) (4) the manufacturer of ferrous bisglycinate, in the form of Ferrochel, was last inspected as a human food and dietary supplement manufacturer in March 2015. Because ferrous bisglycinate is considered a therapeutically inactive ingredient in the kit, it was determined that an inspection was not necessary.

Novast Laboratories, Nantong, China, currently manufactures COCs including Falmina under ANDA 90721. The facility also has extensive experience with the manufacture of other oral contraceptives. Because this facility has a compliant inspectional history for solid dosage oral contraceptive products manufacturing and the active tablets will be the same as the approved drug Falmina, a pre-approval inspection was not requested. This facility is considered acceptable to perform manufacturing functions as the sponsor proposed.

An overall inspection recommendation of Approve has been issued by the Division of Inspectional Assessment in the Office of Process and facilities, OPQ.

Environmental Assessment

Neuvosyn claims a categorical exclusion from the requirement to submit an environmental assessment under 21 CFR 25.31(a). Approval of the application will not increase use of the active moieties and no extraordinary circumstances are known to exist. The categorical exclusion is therefore granted.

Labeling

Several deficiencies in the labels and labeling were identified and communicated to the application. The issues included use of Ferrochel® as the proprietary name for the inactive tablets, incorrect identification of the iron-containing component, as well as the strength thereof, in the inactive tablets, inadequate description of the identifying characteristics of the

dosage forms, inadequate description of the active ingredients, levonorgestrel and ethinyl estradiol, and incomplete listing of inactive ingredients.

All of the issues identified have been addressed by the applicant. The revised labels and labeling as submitted on December 19, 2017 are accurate and complete from the product quality perspective.

The proposed proprietary names (i.e., trademarks) including (b) (4) (b) (4) were found unacceptable from the DMEPA/OSE perspective. The proprietary name Balcoltra is currently under review. Note that an acceptable proprietary name is not a requisite for approval and marketing of the drug product.

C. Special Product Quality Labeling Recommendations

Not Applicable

D. Final Risk Assessment (see Attachment I)

E. List of Deficiencies for Complete Response

Not Applicable

Application Technical Lead Name and Date:

Mark R. Seggel, Ph.D.
Acting CMC Lead for DBRUP

Mark Seggel

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BIOPHARMACEUTICS

Product Background:

NDA/ANDA:208612

Drug Product Name / Strength: (b) (4) **tablet, Levonorgestrel and ethinyl estradiol tablets 0.1mg/0.02mg and ferrous bisglycinate tablets 36.5 mg**

Route of Administration: oral

Applicant Name: Neuvosyn Laboratories, LLC

Review Recommendation: Adequate

Review Summary:

Pursuant to section 505(b)(2) pathway, the Applicant submits an NDA for (b) (4) (levonorgestrel 0.1-mg and ethinyl estradiol 0.02-mg tablets and Ferrochel [ferrous bisglycinate] (b) (4) tablets) for the prevention of pregnancy. The proposed product is a fixed-dose combination of an oral contraceptive containing levonorgestrel 0.1-mg and ethinyl estradiol 0.02-mg tablets copackaged with 7 nonhormonal (placebo) iron tablets each containing 36.5mg ferrous bisglycinate . The dosing regimen consists of continuous dosing for 21 consecutive days followed by 7 days on placebo tablets. The iron placebo tablets are present to facilitate ease of drug administration in a 28-day regimen and do not serve any therapeutic purpose. Each placebo tablet contains 10 mg of elemental iron. This application relies on the Agency's previous findings of safety and effectiveness for the listed drug, Alesse® Tablets, manufactured by Wyeth Pharmaceuticals, Inc., under NDA 020683. The Agency's Approved Drug Products with Therapeutic Equivalence Evaluations cites Lutera® Tablets (ANDA 076625) as the reference standard (RS) for combination oral contraceptive products containing levonorgestrel 0.1 mg and ethinyl estradiol 0.02 mg because Alesse® tablets are discontinued (not due to safety/efficacy).

Novast Laboratories, Ltd. (Novast), received FDA approval for Falmina™ (levonorgestrel and ethinyl estradiol tablets, United States Pharmacopeia [USP]), 0.1 mg/0.02 mg (ANDA 090721) on March 28, 2012 to be bioequivalent to the RLD, Lutera Tablets. The Applicant, Neuvosyn, obtained a right of reference from Novast to ANDA 090721.

Formulation Development

There is no difference between the proposed commercial formulation and the development formulation. The dosage form of the Levonorgestrel/Ethinyl Estradiol

(LNGL/EE) tablets and the Ferrochel (Ferrous Bisglycinate, Ferrous Bisglycinate Chelate, FBC) placebo tablets are of immediate release (IR) tablets. The compositions of the active LNGL/EE tablets, 0.1 mg/0.02 mg, for the commercial product of Falmina (ANDA 90721) are listed below in Table 1:

Table 1: Composition of LNGL/EE Tablets, 0.1 mg/ 0.02 mg

Ingredient	Function	Quality Standard	mg/tablet	% (w/w) [b]
Core Tablets				
Levonorgestrel	Active	USP	0.10	(b) (4)
Ethinyl Estradiol	Active	USP	0.02	
Lactose Monohydrate (b) (4)	(b) (4)	NF	(b) (4)	
Pregelatinized Starch (		NF		
Magnesium Stearate		NF		
(b) (4)		HPLC		
Alcohol [a]		USP		
				(b) (4)

lets, (b) (4) are listed

Table 2: Composition of Ferro (b) (4)

Ingredient	Function	Quality Standard	mg/tablet	% (w/w)
Core Tablets				
Ferrochel				(b) (4)
Microcrystalline Cellulose, M102				
Croscarmellose Sodium				
Magnesium Stearate				
Colloidal Silicon Dioxide				
(b) (4)				
Hypromellose, type 2910, (b) (4)				
Titanium Dioxide				
Polyethylene Glycol 400				
FD&C Red #40 Aluminum Lake				
FD&C Yellow #6 Aluminum Lake				
FD&C Blue #1 Aluminum Lake				
(b) (4)				
Total				
		(b) (4)		

Dissolution Testing

1. For Levonorgestrel/Eth mg/0.02 mg, all the CMC information is referred to ANDA 90721. There is no new information submitted for the LNGL/EE Tablets. The approved dissolution method is as follows:

Apparatus:	2 (Paddle)
Speed of Rotation:	75 rpm
Medium:	5µg per g Tween 80 in water
Volume:	500 mL
Temperature:	37±0.5°C

The approved dissolution specification is NLT (b)(4)% (Q) of Levonorgestrel and Ethinyl Estradiol in 60 minutes.

2. For Ferrochel (Ferrous Bisglycinate, Ferrous Bisglycinate Chelate, FBC) Tablets, (b)(4):

The proposed dissolution method is as follows:

- Apparatus: USP-2, Paddles
- Volume: 900 mL
- Temperature: 37 ± 0.5°C
- RPM: 75
- Media: 0.1 N HCl with 0.5% SLS

The proposed dissolution method is acceptable.

The original proposed specification is NLT (b)(4)% (Q) at (b)(4) min. The specification is considered broad. An IR was sent to the sponsor on 8/17/2017 to request the applicant to tighten the specification to the following:

Not less than (b)(4)% (Q) at 30 minutes

The applicant acknowledged and accepted the recommended acceptance criterion on 8/23/2017.

List Submissions being reviewed (table):
Application 208612 - Sequence 0000 - 0000 (1) 10/13/2015 ORIG-1 /Multiple Categories/Subcategories
Application 208612 - Sequence 0009 - 0009 (10) 08/23/2017 ORIG-1 /Multiple Categories/Subcategories

BCS Designation

Reviewer's Assessment: No BCS classification can be determined

Solubility: 400 mg/mL in water

Permeability: Not provided

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(b) (4)

Please refer to Drug Product review for validation of analytical method.

The following IR was sent on 8/17/2017 to tighten the dissolution acceptance criterion:

Your proposed dissolution specification for ferrous bisglycinate tablets of NLT (b) (4)% (Q) at (b) (4)min is too liberal. The following acceptance criteria are recommended based on the dissolution data submitted: Not less than (b) (4)% (Q) at 30 minutes.

We request that you acknowledge your acceptance of the recommended dissolution acceptance criteria. Implement the recommended dissolution acceptance criteria for the proposed drug product, and provide the revised specifications table with the updated acceptance criterion for the dissolution test.

The applicant responded on 8/23/2017 by acknowledging the recommended dissolution acceptance criterion. The revised specification (product code 334, version 03) and analytical procedure (STM FP-050, version 03) were updated in section 3.2.P.5. In addition, the stability protocol (PL-STAB-15001, version 04) and stability summary data (24M) which contain the specification for FBC tablets have also been revised accordingly and provided in the updated section 3.2.P.8.1 and 3.2.P.8.3.

Clinical relevance of dissolution method & acceptance criteria (e.g., IVIVR, IVIVC, In Silico Modeling, small scale in vivo)

Reviewer's Assessment: ***No IVIVC was performed.***

Application of dissolution/IVIVC in QbD

Reviewer's Assessment: *N/A*

MODIFIED RELEASE ORAL DRUG PRODUCTS –In-Vitro Alcohol Dose Dumping

Reviewer's Assessment: *N/A*

In-Vitro Soft-food Interaction Study

Reviewer's Assessment: *N/A*

Bridging of Formulations

Reviewer's Assessment: ***{Adequate }***
The batch size for the exhibit batches at pilot scale is (b) (4) tablets. The proposed commercial batch is (b) (4) tablets. The scale-up is (b) (4) of the exhibit batch, and is acceptable since it is (b) (4)

Biowaiver Request

Reviewer's Assessment: ***There is no Biowaiver requested for this NDA submission.***

R Regional Information

Comparability Protocols

Reviewer's Assessment: *N/A*

Post-Approval Commitments (For NDA only)

Reviewer's Assessment: *N/A*

Lifecycle Management Considerations

List of Deficiencies: None

Primary Biopharmaceutics Reviewer Name and Date:

An-Chi Lu, Pharm.D., 8/24/2017

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

Vidula Kolhatkar, Ph.D.; October 27, 2017

An-Chi Lu

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Vidula Kolhatkar

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LABELING

I. PI

1. Highlights of Prescribing Information

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use (b) (4) safely and effectively. See full prescribing information for (b) (4)

(b) (4) (levonorgestrel and ethinyl estradiol tablets, USP, 0.1mg/0.02mg and ferrous bisglycinate tablets, 36.5mg), for oral administration
Initial U.S. Approval: 1997

(b) (4) ----------DOSAGE FORMS AND STRENGTHS----------
(b) (4) consists of 28 tablets in the following order (3):

- 21 orange tablets (active), each containing 0.1 mg levonorgestrel and 0.02 mg ethinyl estradiol.
- 7 blue tablets ((b) (4) placebo), each containing ferrous bisglycinate 36.5mg. The ferrous bisglycinate tablets do not serve any therapeutic purpose. (3)

Item	Information Provided in NDA	Reviewer's Assessment
Product Title (Labeling Review Tool and 21 CFR 201.57(a)(2))		
Proprietary name and established name	(b) (4) **(levonorgestrel and ethinyl estradiol tablets, USP, 0.1mg/0.02mg and ferrous bisglycinate tablets, 36.5mg)**	**Not satisfactory** Revise to Tradename (levonorgestrel and ethinyl estradiol tablets and ferrous bisglycinate tablets).
Dosage form, route of administration	tablets for oral administration	**Satisfactory**
Controlled drug substance symbol (if applicable)	N/A	N/A
Dosage Forms and Strengths (Labeling Review Tool and 21 CFR 201.57(a)(8))		
Summary of the dosage form and strength	(b) (4) consists of 28 tablets in the following order (3): • 21 orange tablets (active), each containing 0.1 mg	**Satisfactory**

	levonorgestrel and 0.02 mg ethinyl estradiol. • 7 blue tablets ([redacted] placebo), each containing ferrous bisglycinate 36.5mg. The ferrous bisglycinate tablets do not serve any therapeutic purpose. (3)	

2. *FULL PRESCRIBING INFORMATION*

1. *Section 3 Dosage Forms And Strengths:*

3 DOSAGE FORMS AND STRENGTHS

(b) (4) (levonorgestrel and ethinyl estradiol tablets, and ferrous bisglycinate tablets), is available in a 28 tablet compact blister card with:

- 21 orange (active) tablets containing levonorgestrel 0.1 mg and ethinyl estradiol 0.02 mg
- 7 blue ((b) (4) placebo) tablets containing ferrous bisglycinate 36.5mg.

The ferrous bisglycinate tablets do not serve any therapeutic purpose.

Item	Information Provided in NDA	Reviewer's Assessment
(Refer to Labeling Review Tool and 21 CFR 201.57(c)(4))		
Available dosage forms	• 21 orange (active) tablets containing levonorgestrel 0.1 mg and ethinyl estradiol 0.02 mg • 7 blue ((b) (4) placebo) tablets containing ferrous bisglycinate 36.5mg.	**Satisfactory** The dosage form is correctly expressed as tablets.
Strengths: in metric system	• 21 orange (active) tablets containing levonorgestrel 0.1 mg and ethinyl estradiol 0.02 mg • 7 blue ((b) (4) placebo) tablets containing ferrous bisglycinate 36.5mg.	**Satisfactory** Strengths are expressed correctly.
Active moiety expression of strength with equivalence statement (if applicable)	N/A	N/A The established name of the drug product does not contain any salt form of the active ingredient.
A description of the identifying characteristics of the dosage forms, including shape, color, coating, scoring, and imprinting, when applicable.	(b) (4) (levonorgestrel and ethinyl estradiol tablets, and ferrous bisglycinate tablets), is available in a 28 tablet compact blister card with: • 21 orange (active) tablets containing levonorgestrel 0.1 mg and ethinyl estradiol 0.02 mg • 7 blue ((b) (4) placebo) tablets containing ferrous bisglycinate 36.5mg.	**Not Satisfactory** Revise to: Tradename (levonorgestrel and ethinyl estradiol tablets, and ferrous bisglycinate tablets), is available in a 28 tablet compact blister card with: • 21 orange, round biconvex tablets (active) debossed with "A3" on one side and each containing levonorgestrel 0.1 mg and ethinyl estradiol 0.02 mg • 7 blue, round biconvex tablets (inactive placebo) debossed with "N" on one side and each containing ferrous bisglycinate 36.5mg.

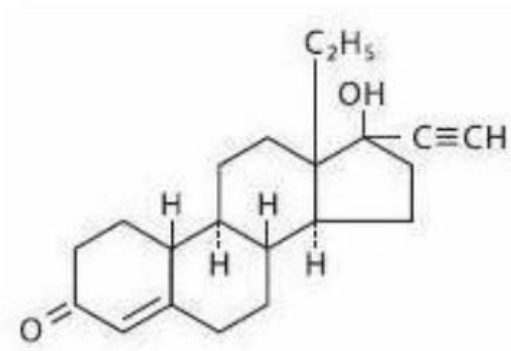
2. *Section 11 Description:*

11 DESCRIPTION

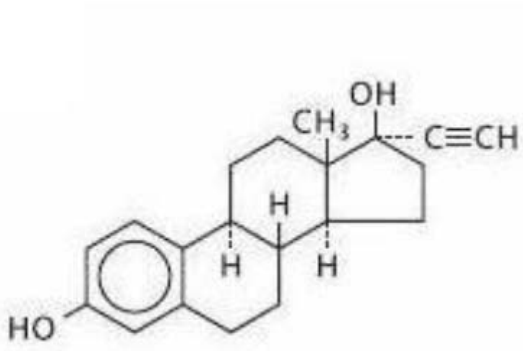
21 orange active tablets each containing 0.1 mg of levonorgestrel, d(-)-13β-ethyl-17α-ethinyl-17β-hydroxygon-4-en-3-one, a totally synthetic progestogen, and 0.02 mg of ethinyl estradiol, 17α-ethinyl-1,3,5(10)-estratriene-3, 17β-diol.

The inactive ingredients present are FD&C Yellow #5 Aluminum Lake, FD&C Yellow #6 Aluminum Lake, FD&C Red #40 Aluminum Lake, titanium dioxide, polyvinyl alcohol, talc, macrogol/polyethylene glycol 3350 NF, lecithin (soya), iron oxide black, lactose monohydrate, magnesium stearate and pregelatinized corn starch.

Each inactive, blue tablet (b) (4) contains the following inactive ingredients: (b) (4) (ferrous bisglycinate, citric acid (b) (4) glycine, maltodextrin (b) (4) water, colloidal silicon dioxide NF), microcrystalline cellulous NF, magnesium stearate NF, croscarmellose sodium NF, colloidal, silicon dioxide NF, (b) (4) (b) (4)



Levonorgestrel



Ethinyl Estradiol

$C_{21}H_{28}O_2$ MW 312.4 (b) (4)

$C_{20}H_{24}O_2$ MW 296.4

Item	Information Provided in NDA	Reviewer's Assessment
(Refer to Labeling Review Tool and 21 CFR 201.57(c) (12), 21 CFR 201.100(b)(5)(iii), 21 CFR 314.94(a)(9)(iii), and 21 CFR 314.94(a)(9)(iv))		
Proprietary name and established name	Not included.	**Not Satisfactory** Include the proprietary name and established name.
Dosage form and route of administration	Tablets	**Satisfactory.**
Active moiety expression of strength with equivalence statement (if applicable)	N/A	N/A
For parenteral, otic, and ophthalmic dosage forms, include the quantities of all inactive ingredients [see 21 CFR 201.100(b)(5)(iii), 21 CFR 314.94(a)(9)(iii), and 21 CFR 314.94(a)(9)(iv)], listed by USP/NF names (if any) in alphabetical order (USP <1091>)	(21 orange active tablets) The inactive ingredients present are FD&C Yellow #5 Aluminum Lake, FD&C Yellow #6 Aluminum Lake, FD&C Red #40 Aluminum Lake, titanium dioxide, polyvinyl alcohol, talc, macrogol/polyethylene glycol 3350 NF, lecithin (soya), iron oxide black, lactose monohydrate, magnesium stearate and pregelatinized corn starch. Each inactive, blue tablet (b) (4) contains the following inactive ingredients: (b) (4) (ferrous bisglycinate, citric acid (b) (4) glycine, maltodextrin NF, water, colloidal silicon dioxide NF), microcrystalline cellulous NF, magnesium stearate NF, croscarmellose sodium NF, colloidal, silicon dioxide NF, (b) (4) (b) (4) (b) (4)	**Not Satisfactory** 1. Remove "," from the statement "colloidal, silicon dioxide NF) to "colloidal silicon dioxide NF". 2. Correct the spelling "microcrystalline cellulous NF" to "microcrystalline cellulose". 3. Remove the statement for (b) (4) 4. Remove (b) (4) and list the components in (b) (4) 5. List the (b) (4)

		(b) (4) FD&C yellow #6 per 21 CFR 201. 20 (c).
Statement of being sterile (if applicable)	N/A	N/A
Pharmacological/ therapeutic class	21 orange active tablets each containing 0.1 mg of levonorgestrel, d(-)-13β-ethyl-17α-ethinyl-17β-hydroxygon-4-en-3-one, a totally synthetic progestogen, and 0.02 mg of ethinyl estradiol, 17α-ethinyl-1,3,5(10)-estratriene-3, 17β-diol.	**Not Satisfactory**. Include the pharmacological class for ethynyl estradiol, an estrogenic compound.
Chemical name, structural formula, molecular weight	21 orange active tablets each containing 0.1 mg of levonorgestrel, d(-)-13β-ethyl-17α-ethinyl-17β-hydroxygon-4-en-3-one, a totally synthetic progestogen, and 0.02 mg of ethinyl estradiol, 17α-ethinyl-1,3,5(10)-estratriene-3, 17β-diol.  Levonorgestrel  Ethinyl Estradiol $C_{21}H_{28}O_2$ MW 312.4 (b) (4) $C_{20}H_{24}O_2$ MW 296.4	**Not Satisfactory** Provide the correct bond configuration format for the chirality of ethinyl group of Levonorgestrel in the drawing. Indicate the chiral centers of both molecules with wedge and dash bond notations. MW should be presented in the same numerical format (decimal places) for both molecules.
If radioactive, statement of important nuclear characteristics.	N/A	N/A
Other important chemical or physical properties (such as pKa or pH)	Not provided.	**Satisfactory**

3. ***Section 16 How Supplied/Storage and Handling***

16 HOW SUPPLIED/STORAGE AND HANDLING

16.1 How Supplied

(b) (4) is available in a blister pack containing 28 tablets arranged in 3 rows of 7 active tablets and 1 row of (b) (4) tablets, as follows:

- 21 active tablets: orange, round tablet debossed with "A3" on one side; each tablet containing levonorgestrel 0.1 mg and ethinyl estradiol 0.02 mg
- 7 (b) (4) tablets: blue, round tablet debossed with "N" on one side; each tablet containing ferrous bisglycinate 36.5mg.

(b) (4) is available in the following:

Carton of 1 blister pack (NDC 75854-000-28)

16.2 Storage Conditions

- Store at 20° to 25°C (68° to 77°F); excursions permitted to 15° to 30°C (59° to 86°F). [See USP controlled room temperature].
- Protect from light

Keep out of the reach of children.

Item	Information Provided in NDA	Reviewer's Assessment
(Refer to Labeling Review Tool and 21 CFR 201.57(c)(17))		
Strength of dosage form	•21 active tablets: orange, round tablet debossed with "A3" on one side; each tablet containing levonorgestrel 0.1 mg and ethinyl estradiol 0.02 mg • 7 (b) (4) tablets: blue, round tablet debossed with "N" on one side; each tablet containing ferrous bisglycinate 36.5mg.	**Satisfactory**.
Available units (e.g., bottles of 100 tablets)	(b) (4) is available in a blister pack containing 28 tablets arranged in 3 rows of 7 active tablets and 1 row of (b) (4) tablets,… (b) (4) is available in the following: Carton of 1 blister pack (NDC 75854-000-28)	**Satisfactory**
Identification of dosage forms, e.g., shape, color, coating, scoring, imprinting, NDC number	(b) (4) s available in a blister pack containing 28 tablets arranged in 3 rows of 7 active tablets and 1 row of (b) (4) tablets, as follows: • 21 active tablets: orange, round tablet debossed with "A3" on one side; each tablet containing levonorgestrel 0.1 mg and ethinyl estradiol 0.02 mg • 7 (b) (4) tablets: blue, round tablet debossed with "N" on one side; each tablet containing ferrous bisglycinate 36.5mg.	**Satisfactory**

	(b) (4) is available in the following: Carton of 1 blister pack (NDC 75854-000-28)	
Special handling (e.g., Dispense in tight and light resistant container as defined in USP)	N/A	**Satisfactory**
Storage conditions	• Store at 20° to 25°C (68° to 77°F); excursions permitted to 15° to 30°C (59° to 86°F). [See USP controlled room temperature]. • Protect from light	**Satisfactory**
Manufacturer/distributor name (21 CFR 201.1(h)(5))	Not Provided.	**Not Satisfactory** Provide the manufacturer/distributor name and place of business.

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Item	Information Provided in NDA	Reviewer's Assessment
Proprietary name, established name (font size and prominence (21 CFR 201.10(g)(2))	(b) (4) levonorgestrel and ethinyl estradiol tablets, USP, 0.1 mg/0.02 mg and ferrous bisglycinate tablets, 36.5 mg	**Not Satisfactory** To be consistent with PI, remove (b) (4) notation from the established name. The presentation format of the established name and dosage strength should be as: Levonorgestrel and ethynyl estradiol tablets and ferrous bisglycinate tablets, 0.1mg/0.02mg and 36.5 mg.
Dosage strength Active moiety expression of strength with equivalence statement (if applicable), if space is available	(b) (4) levonorgestrel and ethinyl estradiol tablets, USP, 0.1 mg/0.02 mg and ferrous bisglycinate tablets, 36.5 mg	**Satisfactory.** Not applicable for salt equivalence statement.
Net contents	28 tablet blister card	**Satisfactory**
"Rx only" displayed prominently on the main panel	Not provided.	**Not Satisfactory**
NDC number	Not Provided.	**Satisfactory** It is not requested per the revised CFR21 in April, 2016.
Lot number and expiration date (21 CFR 201.17)	Provided.	**Satisfactory.**
Storage conditions Special handling, e.g., "Dispense in tight and light resistant container as defined in USP".	**Storage:** Store at 20° to 25°C (68° to 77°F) [See USP Controlled Room Temperature].	**Satisfactory** "Protect from Light" is not included, but it is acceptable with the consideration of the limited space.
Bar code (21CFR 201.25)	Provided	**Satisfactory.**
Name of manufacturer/distributor	Mfd. For Neuvosyn Laboratories, LLC., Alpharetta, GA 30022	**Not Satisfactory.** The name and place of the manufacturer/distributor should be consistent with the information provided in Carton.

And others, if space is available		

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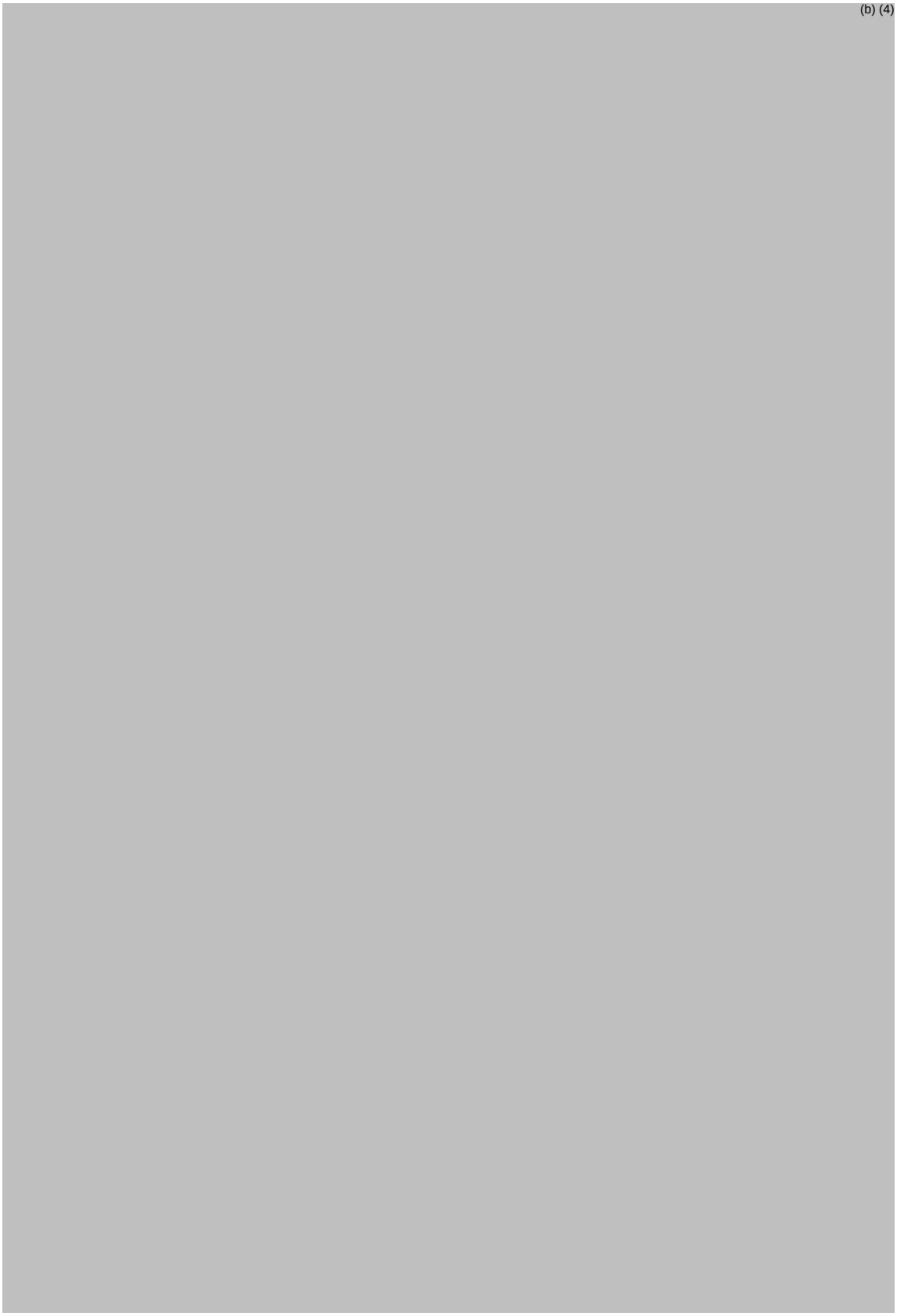

(b) (4)

Item	Information Provided in NDA	Reviewer's Assessment
Proprietary name, established name (font size, prominence)	(b) (4) levonorgestrel and ethinyl estradiol tablets, USP, 0.1 mg/0.02 mg and ferrous bisglycinate (b) (4) tablets, 36.5 mg (b) (4)	**Not Satisfactory** To be consistent with PI, remove (b) (4) notation from the established name. The presentation format of the established name and the dosage strength should be as: Levonorgestrel and ethynyl estradiol tablets and ferrous bisglycinate tablets, 0.1mg/0.02mg and 36.5 mg. The size of established name should be at least 50% of the tradename. Remove" (b) (4)
Dosage strength Active moiety expression of strength with equivalence statement (if applicable) in the side panel.	(b) (4) levonorgestrel and ethinyl estradiol tablets, USP, 0.1 mg/0.02 mg and ferrous bisglycinate (b) tablets, 36.5 mg Each orange tablet (21) contains levonorgestrel 0.1 mg and ethinyl estradiol 0.02 mg. Each blue tablet contains ferrous bisglycinate* 36.5 mg.	**Not Satisfactory** The dosage strength is correct for both active and inactive. The presentation format is not correct. See the comments in the Proprietary name section.
Net quantity of dosage form	1 blister Pack, 28 tablets.	**Satisfactory**

“Rx only” displayed prominently on the main panel	Rx only	**Satisfactory**
Lot number and expiration date	Not Provided.	**Not Satisfactory** Provide the lot number and expiration date.
Storage conditions Special handling, e.g., “Dispense in tight and light resistant container as defined in USP”.	**Storage:** Store at 20° to 25°C (68° to 77°F); Excursions permitted to 15° to 30° C (59° to 86° F). [See USP controlled room temperature.] Protect from light. Keep out of the reach of	**Satisfactory**
Bar code (21CFR 201.25)		**Satisfactory**
NDC number (21 CFR 207.35(b)(3)(i))		**Satisfactory**
Manufacturer/distributor's name	(b) (4)	**Not Satisfactory** Include the street address per 21 CFR201.1 (i). The manufacturer/distributor information should be consistent with PI.
Quantitative ingredient information (injectables)	provided.	**Not Satisfactory** Provide the list of the inactive ingredients. This is an oral dosage form and the quantitative information is not required.
Statement of being sterile (if applicable)	N/A	N/A

"See package insert for dosage information"	Usual Dosage: One orange tablet daily for 21 consecutive days followed by one blue placebo tablet for 7 consecutive days according to prescribed schedule. See enclosed prescribing information.	**Satisfactory**
"Keep out of reach of children" (Required for OTC in CFR. Optional for Rx drugs)	**CAUTION:** Keep out of the reach of children. Contains color additives including FD&C Yellow No. 5 (tartrazine).	**Satisfactory**

List of Deficiencies:

I. <u>Regarding PI</u>

A. In **"HIGHLIGHTS OF PRESCRIBING INFORMATION"** section:

1. Revise the product title to "Tradename (levonorgestrel and ethinyl estradiol tablets, and ferrous bisglycinate tablets)".

B. In the **Full prescribing information:**

1. Add the following statement in "Precautions" section per 21CFR201.20(b): ""This product contains FD&C Yellow No. 5 (tartrazine) which may cause allergic-type reactions (including bronchial asthma) in certain susceptible persons. Although the overall incidence of FD&C Yellow No. 5 (tartrazine) sensitivity in the general population is low, it is frequently seen in patients who also have aspirin hypersensitivity."

2. In **Dosage forms and strengths (Section 3),**

Revise the dosage strength and description statement to the following:

"• 21 orange, round biconvex (active) tablets debossed with "A3" on one side and each containing levonorgestrel 0.10 mg and ethinyl estradiol 0.02 mg

• 7 blue, round biconvex ([redacted (b) (4)] placebo) tablets debossed with "N" on one side and each containing ferrous bisglycinate 36.5mg."

3. In **Description** (Section 11),

a. Include the proprietary name and established name.
b. Include the dosage form and route of administration.
c. Remove "," from the statement "colloidal, silicon dioxide NF) to "colloidal silicon dioxide NF".
d. Correct the spelling "microcrystalline cellulous NF" to "microcrystalline cellulose".

e. Remove Trademark (b) (4) from this section and revise the inactive ingredient list to remove the redundant ones.
f. Replace the (b) (4) with its components to ensure the consistent presentation of the (b) (4) components of the inactive ingredients in both active and inactive tablets. Additionally, FD&C Yellow No.6 should be stated per CFR21201.20 (c).
g. Remove the statement (b) (4) (b) (4)
h. To be consistent with the inactive ingredients list of active orange tablet in PI, revise Table 2 (Composition of LNGL/EE Tablets, 0.1mg/0.02mg in section 3.2.P.1) in NDA to include the component list (b) (4).

4. In **HOW SUPPLIED/STORAGE AND HANDLING** (Section 16):

    a. Provide the manufacturer/distributor name and place.

Note: The comments related to PI were conveyed together with the OND comments to the applicant through tracked changes.

II. Regarding Container and Carton labels:

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

1. To be consistent with PI, Remove (b) (4) notation from the established name.
2. The established name should be at least half the size of the proprietary name.
3. Add “Rx only”
4. Add the statement "Contains color additives including FD&C Yellow No. 5 (tartrazine)" per 21 CFR201.20 (a).
5. The name and place of the manufacturer/distributor should be consistent with the information provided in the Carton.

For the Carton Label:

1. Refer to the comment 1&2 for the immediate container label.
2. Remove the statement: (b) (4)
3. Provide the list of the inactive ingredients.
4. Provide the lot number and expiration date.

Note: The above review comments is based on the related labeling/label materials submitted on October 12, 2017 (SN0014).

The applicant submitted an amendment (SN0020) with the revised Carton and Container labels on December 8, 2017 (See the label images below) for the immediate container (the blister pack) and the Carton in accordance to FDA comments conveyed on 12/1/2017. Additionally, the applicant requested to use the (b) (4) descriptor next to the nonproprietary name levonorgestrel and ethynyl estradiol tablets in PI and Carton and Container labels. This is acceptable based on the referenced ANDA090721 PI. However, its use should be limited to the section #3, #11 and #16. The (b) (4) should not be included in the Product Title per FDA Labeling Review Tool (February, 2017).

The following comments should be conveyed to the applicant for the Carton and Container Labels submitted on December 8, 2017 (SN0020):

For both Carton and Container (blister pack) labels:

1. Present the product title and the strength as following for both Carton and Container (blister pack) labels:

   "Tradename

   (levonorgestrel and ethinyl estradiol tablets, USP, and ferrous bisglycinate tablets)

   0.1mg/0.02mg and 36.5mg"
2. The Manufacturer/Distributor information should be consistent with PI.

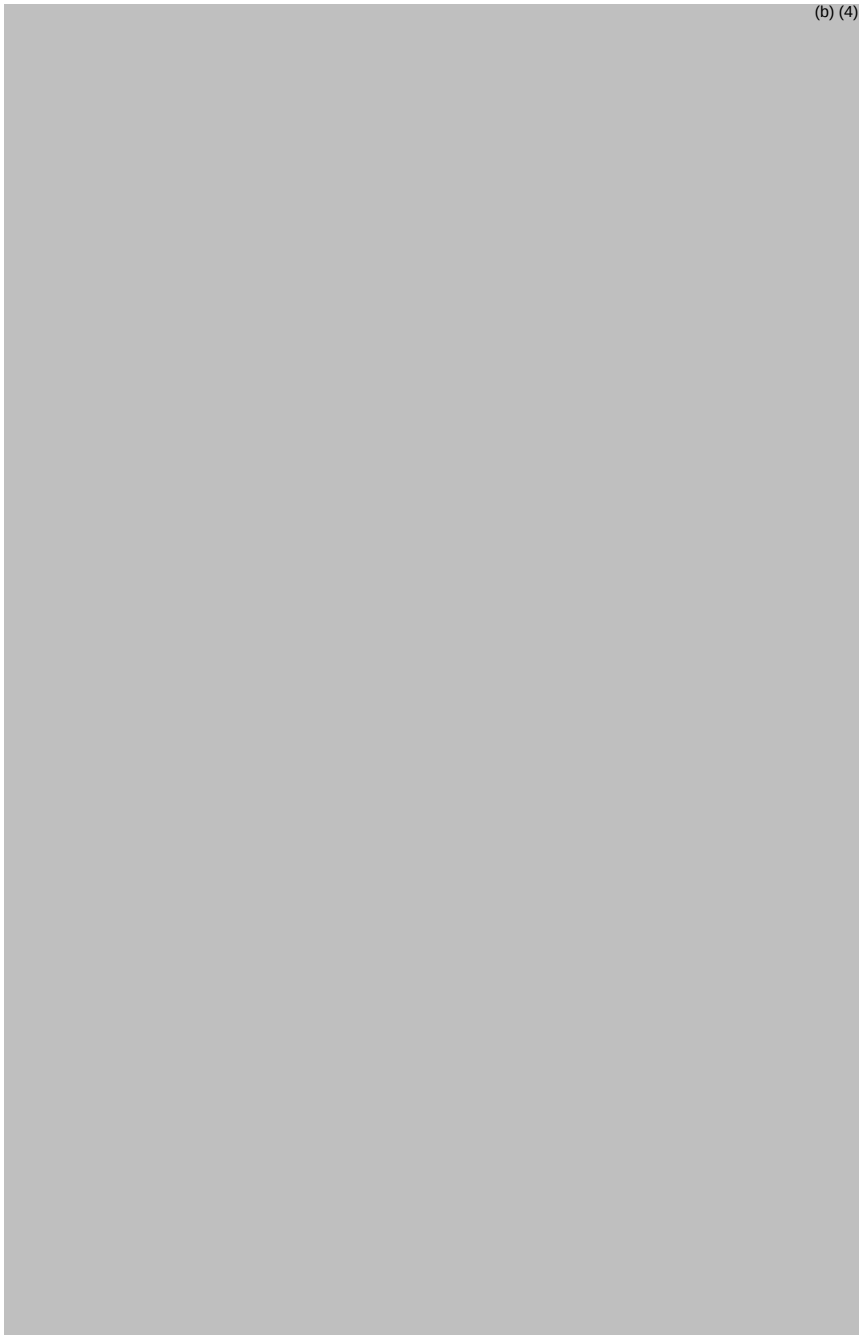
For the Carton label:

1. The list of the inactive ingredients for the inactive blue ferrous bisglycinate tablets should be consistent with the list in section #11 of PI.
2. Remove (b) (4) from the statement (b) (4) (b) (4)

For the Container (blister pack) label:

1. Remove the proprietary name for the inactive ingredient (b) (4).


(b) (4)



Overall Asse

The following materials related to labeling/label have been reviewed submitted on October 12, 2017 (SN0014) and the revised Carton and Container (the blister pack) labels submitted on December 8, 2017 (SN0020):

- Highlights of Prescribing Information: Names and Dosage Forms and Strengths.

- Full Prescribing Information: Sections: #3 DOSAGE FORMS AND STENGTHS; #11 (DESCRIPTION) and #16 (HOW SUPPLIED/STORAGE AND HANDLING)

- Blister Pack, and the Carton labels (SN0014 and SN0020)

From the ONDP perspective, this application is ***not*** recommended for approval per 314.125(b)(6) until the deficiencies delineated above are satisfactorily resolved. It is also noted that the Proprietary name (b) (4) are not approved. Therefore, Trademame is pending for approval at the time of this review.

Primary Labeling Reviewer Name and Date:

Hong Cai, Ph.D.
Reviewer, Branch V
DNDP II/ONDP

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

I concur with Dr. Cai's assessment and her recommendation that this NDA is not ready for approval as of this review.

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

Hong Cai

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Moo Jhong Rhee

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Memorandum

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

Date: January 2, 2018

From: Hong Cai, Ph.D.
Drug Product Reviewer, Branch V
Division of New Drug Products II
Office of New Drug Products

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

To: Labeling Review #1 of NDA 208612

Subject: Finalized Label/labeling of CMC Sections

At the time when Labeling Review of this application was completed (12/15/2017), this NDA was not recommended for approval due to unresolved CMC label/labeling issues. To resolve the outstanding label/labeling issues, the applicant submitted amendments to the NDA that provide the revised package insert (PI) and the container and carton labels (SN0022 on 12/19/2017). The revised labels/labeling have adequately addressed all the CMC labeling issues with the exception of a few formatting errors (number format for consistency of the molecular weight expression in Section #11 of PI and the word spacing in the carton label). It is also noted at the time of this review, the trade name "Balcoltra™" is pending for FDA approval. See **Attachment-1** for PI CMC related sections reviewed and **Attachment-2** for the container and carton labels.

Recommendation:

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

Hong Cai, Ph.D.
Drug Product Reviewer
Branch V, Division II, ONDP

Moo-Jhong Rhee, Ph.D.
Branch Chief
Branch V, Division II, ONDP

Attachment-1:

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use BALCOLTRA™ safely and effectively. See full prescribing information for BALCOLTRA™.

BALCOLTRA™ (levonorgestrel and ethinyl estradiol tablets and ferrous bisglycinate tablets) for oral administration
Initial U.S. Approval: 1997

----------**DOSAGE FORMS AND STRENGTHS**----------
Balcoltra consists of 28 tablets in the following order (3):

- 21 orange tablets (active), each containing 0.10 mg levonorgestrel and 0.02 mg ethinyl estradiol.
- 7 blue tablets (inactive placebo) each containing ferrous bisglycinate36.5 mg. The ferrous bisglycinate tablets do not serve any therapeutic purpose. (3)

FULL PRESCRIBING INFORMATION

3 DOSAGE FORMS AND STRENGTHS

Balcoltra (levonorgestrel and ethinyl estradiol tablets, USP, and ferrous bisglycinate tablets) is available in a 28-tablet compact blister card with:

- 21 orange, round biconvex tablets (active) debossed with "A3" on one side and each containing levonorgestrel 0.10 mg and ethinyl estradiol 0.02 mg
- 7 blue, round biconvex tablets (inactive placebo) debossed with "N" on one side and each containing ferrous bisglycinate 36.5mg

The ferrous bisglycinate tablets do not serve any therapeutic purpose.

11 DESCRIPTION

Balcoltra (levonorgestrel and ethinyl estradiol tablets, USP, and ferrous bisglycinate tablets) provides an oral contraceptive regimen consisting of 21 orange active tablets and 7 blue inactive tablets.

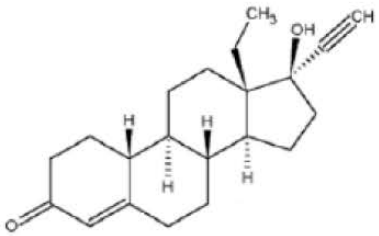
- 21 orange active tablets each containing 0.10 mg of levonorgestrel, d(-)-13β-ethyl-17α-ethinyl-17β-hydroxygon-4-en-3-one, a totally synthetic progestogen, and 0.02 mg of ethinyl estradiol, 17α-ethinyl-1,3,5(10)-estratriene-3, 17β-diol, an estrogenic compound
- 7 blue inactive tablets each containing 36.5 mg ferrous bisglycinate

The inactive ingredients present in orange active tablet are FD&C Yellow #5 Aluminum Lake, FD&C Yellow #6 Aluminum Lake, FD&C Red #40 Aluminum Lake, titanium dioxide, polyvinyl alcohol, talc, macrogol/polyethylene glycol 3350 NF, lecithin (soya), iron oxide black, lactose monohydrate, magnesium stearate and pregelatinized starch.

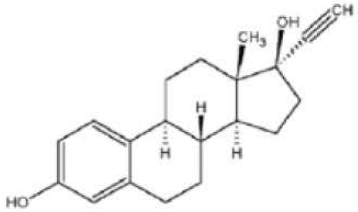
Each inactive blue tablet contains the following inactive ingredients: ferrous bisglycinate, citric acid, glycine, water, maltodextrin , silica, microcrystalline cellulose NF, magnesium stearate NF, croscarmellose sodium NF, colloidal silicon dioxide NF, hypromellose, type 2910, (b) (4) titanium dioxide, polyethylene glycol 400, FD&C Red #40 Aluminum Lake, FD&C Yellow #6 Aluminum Lake and FD&C Blue #1 Aluminum Lake.

Levonorgestrel has the empirical formula of $C_{21}H_{28}O_2$ and the molecular weight of 312.4 (b) (4) and ethinyl estradiol has the empirical formula of $C_{20}H_{24}O_2$ and the molecular weight of 296.40.

The molecular structures are provided below:



Levonorgestrel
$C_{21}H_{28}O_2$ MW: 312.4



Ethinyl Estradiol
$C_{20}H_{24}O_2$ MW: 296.4

16 HOW SUPPLIED/STORAGE AND HANDLING

16.1 How Supplied

Balcoltra is available in a blister pack containing 28 tablets arranged in 3 rows of 7 active tablets and 1 row of inactive tablets, as follows:

- 21 active tablets: orange, round tablet debossed with "A3" on one side; each tablet containing levonorgestrel 0.10 mg and ethinyl estradiol 0.02 mg
- 7 inactive tablets: blue, round tablet debossed with "N" on one side; each tablet containing ferrous bisglycinate 36.5 mg

Balcoltra is available as a Carton of 1 blister pack (NDC 75854-000-28)

16.2 Storage Conditions

- Store at 20° to 25°C (68° to 77°F); excursions permitted to 15° to 30°C (59° to 86°F). [See USP controlled room temperature].
- Protect from light

Keep out of the reach of children.

Manufactured for: Neuvosyn Laboratories, LLC., 11675 Great Oak Way, Ste 120, Alpharetta, GA 30022

Manufactured by: Novast Laboratories, Ltd., Nantong, China 226009

Date: 12/2017

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

Hong Cai

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Moo Jhong Rhee

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Date: 1/02/2018 04:22:01PM
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ATTACHMENT I: Final Risk Assessments

A. Final Risk Assessment and Lifecycle Knowledge Management

a) Drug Product

'Kit' consisting of 21 orange Levonorgestrel and Ethinyl Estradiol Tablets 0.1 mg/ 0.02 mg and 7 blue Ferrous Bisglycinate Tablets, 36.5 mg

'Kit'

From Initial Risk Identification			Assessment		
Attribute/ CQA	**Factors that can impact the CQA**	**Initial Risk Ranking**		**Final Risk Evaluation**	
Packaging Integrity	• Process parameters • Scale/equipment • Site • CGMP	Moderate	(b) (4)	Adequate	(b) (4)

Ferrous Bisglycinate Tablets, 36.5 mg

From Initial Risk Identification			Assessment		
Attribute/ CQA	**Factors that can impact the CQA**	**Initial Risk Ranking**		**Final Risk Evaluation**	**Lifecycle Considerations/ Comments**
Appearance	• Formulation • Raw materials • Process parameters • Scale/equipment	Low	(b) (4)	Adequate	
Identification	• Raw materials • CGMP	Low		Adequate	
Ferrous Bisglycinate Assay	• Process parameters • Scale/equipment • Site	Low		Adequate	
Content Uniformity	• Process parameters • Scale/equipment • Site	Low		Adequate	
Related Substances Impurities / Degradants	• Formulation • Raw materials • Process parameters • Scale/equipment • Site	Low		Adequate	No tox issues with any of the components or potential degradants
Product Performance / Dissolution	• Formulation • Raw materials • Process parameters • Scale/equipment • Site	Low		Adequate	
Moisture Content	• Raw Materials • Site	Low		Adequate	
Microbial Limits	• Formulation • Raw materials • Process parameters • Scale/equipment • Site	Low		Adequate	

Levonorgestrel and Ethinyl Estradiol Tablets 0.1 mg/ 0.02 mg

See ANDA 90721 and associated CMC reviews. The COC tablets have low drug loads of highly active hormonal compounds. Ensuring content uniformity is thus critical to safety and efficacy.

######

Mark
Seggel

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