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APPLICATION NUMBER:

208612Orig1s000

NON-CLINICAL REVIEW(S)

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

PHARMACOLOGY/TOXICOLOGY NDA REVIEW AND EVALUATION

Application number:	20816
Supporting document/s:	SDN25
Applicant's letter date:	January 9, 2018
CDER stamp date:	January 9, 2018
Product:	Ethinyl Estradiol / Levonorgestrel and Ferrous Bisglycinate
Indication:	Prevention of pregnancy
Applicant:	Neuvosyn Laboratories LLC
Review Division:	Division of Bone, Reproductive, and Urologic Drug Products (DBRUP)
Reviewer:	Leslie McKinney, PhD
Supervisor/Team Leader:	Mukesh Summan, PhD, DABT
Division Director:	Hylton Joffe, MD, MMSc
Project Manager:	Jennifer Dao

Memo to file for labeling:

I have reviewed the label for this product and concur with final wording. The label has been updated for PLLR and follows standard labeling for oral contraceptives. There are no nonclinical data in the label.

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/s/

LESLIE C MCKINNEY
01/09/2018

MUKESH SUMMAN
01/09/2018

**DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
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PHARMACOLOGY/TOXICOLOGY NDA REVIEW AND EVALUATION

Application number:	208612
Supporting document/s:	SDN2
Applicant's letter date:	March 16, 2017
CDER stamp date:	March 16, 2017
Product:	Ethinyl Estradiol / Levonorgestrel and Ferrous Bisglycinate
Indication:	Prevention of pregnancy
Applicant:	Neuvosyn Laboratories LLC
Review Division:	Division of Bone, Reproductive and Urologic Products (DBRUP)
Reviewer:	Leslie McKinney, PhD
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Division Director:	Hylton Joffe, MD, MMSc
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1 Executive Summary

1.1 Introduction

TRADENAME® is a fixed-dose combination of an oral contraceptive containing levonorgestrel 0.1-mg and ethinyl estradiol 0.02-mg tablets co-packaged with 7 nonhormonal (placebo) iron tablets each containing (b) (4) Ferrochel® (ferrous bisglycinate). The placebo iron 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 (0.16 mg/60 kg adult).

For this product, Ferrochel® is considered to be a novel excipient. It is comprised of ferrous bisglycinate, citric acid, glycine, water, maltodextrin, and silica. Following oral ingestion, ferrous bisglycinate dissociates in the acid environment of the stomach to release free iron and glycine. Ferrochel® has been used in both the dietary supplement market and the pharmaceutical market as an iron supplement since 1989. In 1999 FDA assigned generally regarded as safe (GRAS) status to ferrous bisglycinate chelate (GRAS Notice GRN 000019), and it is currently used to fortify a number of commercial food products (Hertrampf and Olivares, 2004). In 2003, the Joint Food and Agriculture Organization/World Health Organization (FAO/WHO) Expert Committee on Food Additives (JECFA) approved the use of Ferrochel® as a source of iron for supplementation and fortification purposes, provided that the total intake of iron does not exceed the provisional maximum tolerable daily intake of 0.8 mg/kg body weight (JECFA, 2004; EFSA, 2006).

For the part of the application specific to the contraceptive (levonorgestrel and ethinyl estradiol), the application has cross-referenced two approved products: Alesse® (NDA 020683), which is no longer marketed, and Falmina® (ANDA 090721). Falmina® is bridged to Lutera® (ANDA 076625) as the reference listed drug.

For the part of the application specific to Ferrochel®, the sponsor relies on published literature and nonclinical study reports obtained from (b) (4) the manufacturer of Ferrochel®. The Division agreed that literature and nonclinical information obtained (b) (4) would be sufficient for NDA filing at the preNDA meeting on 3-26-2015.

1.2 Brief Discussion of Nonclinical Findings

A 3-month repeat dose toxicity studies in the rat showed no toxicity of Ferrochel® at up to 500 mg/kg/d (~600X the proposed human dose on a mg/kg basis and ~100X on a mg/m² basis). A multigenerational dietary toxicity study conducted in breeding sows utilizing various chelating agents also showed no toxicity. In that study, the average dose of iron was 482 mg/day.

1.3 Recommendations

1.3.1 Approvability

From a PharmTox perspective the application is approvable.

1.3.2 Additional Non Clinical Recommendations

None.

1.3.3 Labeling

Regarding the active ingredients, ethinyl estradiol and levonorgestrel, relevant sections of the label follow the Alesse® label and are based on clinical experience with the active ingredients. No nonclinical data are included. Because the Alesse® label had not been updated for PLLR, the label for TRADENAME® has a newly generated risk summary for use during pregnancy:

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

TRADENAME is contraindicated in pregnancy because there is no reason to use combined hormonal contraceptives (CHCs) in pregnancy. Discontinue TRADENAME if pregnancy occurs. Based on epidemiologic studies and meta-analyses, there is little or no increased risk of birth defects in the children of females who inadvertently use COCs during early pregnancy (*See Data*). [REDACTED] (b) (4).

In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2 to 4 percent and 15 to 20 percent, respectively.

Human Data

Epidemiologic studies and meta-analyses have not found an increased risk of genital or nongenital birth defects (including cardiac anomalies and limb-reduction defects) following exposure to COCs before conception or during early pregnancy.

Pharm Tox recommends deleting the following sentence

[REDACTED] (b) (4)

[REDACTED] (b) (4)

Regarding the new excipient, Ferrochel®, the review team has determined that it should be treated equivalently to oral contraceptives containing ferrous fumarate and is exempt from the requirement for labeling of iron-containing products. The text below is excerpted from an email from the clinical reviewers explaining the exemption.

21 CFR 310.518 requires that iron-containing drug products include the following warning in labeling: "WARNING: Accidental overdose of iron-containing products is a leading cause of fatal poisoning in children under 6. Keep this product out of reach

of children. In case of accidental overdose, call a doctor or poison control center immediately.”

Oral contraceptive pills are exempt from the labeling requirements of 21 CFR 310.518 under the provision in paragraph (b): “The iron-containing inert tablets supplied in monthly packages of oral contraceptives are categorically exempt from the requirements of paragraph (a) of this section.”

The reason that oral contraceptive pills are exempt from these labeling requirements has been stated as: “The agency observes that the inert tablets in oral contraceptive products contain up to 75 mg of ferrous fumarate (equivalent to 25 mg of iron), and therefore a 1-month supply of oral contraceptives containing 7 inert tablets will contain up to 175 mg of iron. The total amount of iron in a 1-month supply of oral contraceptives is only 70 percent of the amount (250 mg) that experts have stated is sufficient to produce symptoms of poisoning in a 10 kg child (see discussion above).

Each ferrous bisglycinate tablet in NDA 208612 contains 36.5 mg of ferrous bisglycinate, equivalent to 10 mg of elemental iron. The amount of iron per tablet is below the threshold level for unit-dose packaging of 30 mg of iron per dosage unit.

2 Drug Information

2.1 Drug

Drug Ferrochel®, also known as ferrous glycinate, ferrous bisglycinate chelate, ferrous glycinate, iron (II) amino acid chelate, bis-glycino iron II, and bisglycino-iron (II) chelate

CAS Registry Number: 20150-34-9

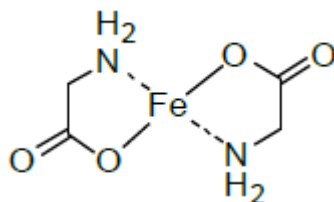
Generic Name There is no compendial name

Code Name manufacturer's number: 03550

Chemical Name Iron, bis(glycinate-N,O)

Molecular Formula/Molecular Weight: $\text{Fe}(\text{CO}_2\text{CH}_2\text{NH}_2)_2$ 203.96

Structure



Pharmacologic Class: amino acid iron chelate

Manufacturer: The Ferrochel® manufacturer is (b) (4) and the drug product manufacturer is Novast.

2.2 Relevant INDs, NDAs, BLAs and DMFs

NDA 020683 Alesse®

ANDA 090721 Falmina

ANDA 076625 Lutera®

DMFs (b) (4)

2.3 Drug Formulation

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

All inactive ingredients except for the Ferrochel® in the placebo tablet are below the highest level listed in the Inactive Ingredients Database for oral administration (Table 2.6.1-5).

Table 2.6.1-5. Excipients in a Ferrochel Placebo Tablet Compared to Approved Orally Administered Products in the Inactive Ingredients Database			
Name	Specification Amount (%)	Amount (mg)	Inactive Ingredients Database Maximum (mg)
Ferrochel			
Microcrystalline cellulose, NF			
Magnesium stearate, NF			
Croscarmellose sodium, NF			
Colloidal silicon dioxide, NF			
NA = not applicable.			

2.4 Comments on Novel Excipients

Ferrochel® is a novel excipient. The inactive components of Ferrochel® are present at quantities below the maximum amounts listed in FDA's Inactive Ingredients Database (Table 2.6.1-4).

Ferrochel Excipients

Table 2.6.1-4. Excipients in (b) (4) of Ferrochel Compared to Approved Orally Administered Products in the Inactive Ingredients Database			
Name	Specification Amount (%)	Maximum Amount (mg)	Inactive Ingredients Database Maximum (mg)
Ferrous bisglycinate	(b) (4)		
Citric acid, NF			
Glycine			
Water			
Maltodextrin, NF			
Colloidal silicon dioxide, NF			

2.5 Comments on Impurities/Degradants of Concern

Excerpted from sponsor's text: "Residual amounts of (b) (4) are present as impurities in Ferrochel® with specification limits of (b) (4) respectively. The maximum amount of (b) (4) in Ferrochel is (b) (4) which is less than the (b) (4) listed in the FDA's Inactive Ingredients Database and less than the (b) (4) that is included in the approved drug product AURYXIA®. The maximum amount of residual (b) (4) in Ferrochel is (b) (4) which is less than the (b) (4) in INFeD® and the (b) (4) in VENOFER®, which are approved parenteral drug products."

2.6 Proposed Clinical Population and Dosing Regimen

Women of reproductive potential. The dosing regimen consists of continuous dosing for 21 consecutive days followed by 7 days on placebo tablets.

2.7 Regulatory Background

Sponsor's summary:

"On April 4, 2014, Neuvosyn submitted a pre-IND meeting request for levonorgestrel/ethinyl estradiol tablets to be co-packaged with (b) (4) Tablets. The written responses to the pre-IND 122407 meeting information package, received on May 23, 2014, indicated that (b) (4) is considered a novel excipient and that data would be needed to support the safety of (b) (4). In consideration of the Agency's response and that no nonclinical toxicology or clinical safety data were available (b) (4), Neuvosyn elected to use Ferrochel® in the placebo tablet as the source of iron in place of (b) (4). This decision was based on the generally recognized as safe (GRAS) listing of Ferrochel as a dietary supplement, its safe use as a dietary supplement since 1989, and the availability of nonclinical and clinical safety data."

A type B (pre-NDA) meeting was held with the Division on March 16, 2015. During this meeting it was agreed that the application should be submitted via the 505(b)(2) pathway.

3 Studies Submitted

3.1 Studies Reviewed

The sponsor submitted three nonclinical studies to the NDA. The acute single-dose study was completed in 1993 and utilized Ferrochel® as the test agent. The 3-month rat toxicity study was completed in 1997 and utilized Ferrochel® as the test agent. Results of these studies have been published (Jeppsen and Borzelleca, 1999). The long-term multi-generational pig study utilized various chelating agents to administer several different elemental supplements, including iron, magnesium, zinc, manganese, copper, cobalt, and potassium. The results of this study as it pertains to iron chelates have been published (Jeppsen, 2001). These studies are briefly described under Section 6.

Table 2.6.6-1. Overview of the Completed Nonclinical Safety Studies with Ferrochel					
Report	Study Type, Duration	Species	Route	Doses^a (mg/kg)	GLP Status
Acute Single-Dose Toxicity Study					
<i>BSR 043-002</i>	Acute oral toxicity (LD ₅₀) safety assessment	Rat CD® [CrI:CD®(SD)]	Oral (gavage)	0 (vehicle) 770 (150) 1500 (300) 3100 (600) 6200 (1200)	GLP
90-Day Repeat-Dose (Diet) Subchronic Toxicity Study in Rats					
<i>HLS 96-2503</i>	90-Day repeat-dose subchronic study in rats (diet)	Rat CD[CrI:CD(BR)]	Oral (diet)	0 (vehicle) 100 (19.5) 250 (48.7) 500 (97.4)	GLP
Multigenerational Dietary Supplement Feeding Study in Breeder Sows					
<i>Metalosate: long-term pig study</i>	Chronic oral (diet) toxicity (multigenerational repeat-dose toxicity study)	Swine (York-Landrace-Hemp-Dorac)	Oral (diet)	Average 482 mg of iron per day.	Non-GLP
GLP = Good Laboratory Practice; LD ₅₀ = median lethal dose. ^a = Ferrochel; mg/kg (iron; mg/kg).					

3.2 Studies Not Reviewed

N/A

3.3 Previous Reviews Referenced

None

6 General Toxicology

6.1 Single-Dose Toxicity

An acute oral toxicity study with ferrous bisglycinate was conducted in male and female rats. The LD₅₀, expressed on the basis of iron content, was 560 mg iron per kilogram body weight. Because ferrous bisglycinate contains approximately 20% iron, the LD₅₀ is equivalent to 2800 mg/kg.

6.2 Repeat-Dose Toxicity

A rat 14-day oral toxicity study was completed with ferrous bisglycinate to establish the most appropriate doses for the 90-day subchronic toxicity study. There was no mortality in this study. One female that received ferrous bisglycinate at 500 mg/kg/day was reported to have a red focus in the glandular portion of the stomach and thick black material in the cecum. There were no other findings in this female. There were no abnormal findings in the other 2 females at this level or in any of the other treated animals. A conservative no observed adverse effect level (NOAEL) for this 14-day range-finding study was 300 mg/kg/day for the females. Based on these findings, the highest dose selected for the 90-day subchronic study was 500 mg/kg/day.

In the subchronic oral toxicity study, SD rats (20/sex/group) were given ferrous bisglycinate in the diet at concentrations of 0, 100, 250, or 500 mg/kg/day for a period of 13 weeks. There was no mortality in any group. There was no evidence of test-article-related, dose-dependent adverse effects on cage-side observations, physical examinations, ophthalmoscopy examinations, body weight gains, food consumption, absolute organ weights or organ ratios, clinical chemistry, hematology, gross pathology, or histopathology.

There were statistically significant increases compared to control values in the mean hepatic nonheme iron concentrations of males dosed with 250 and 500 mg/kg/day and females dosed with 500 mg/kg/day. Values were slightly higher in males dosed with 100 mg/kg/day and females dosed with 100 and 250 mg/kg/day; however, the increases were not statistically significant compared to control values. These increases in liver stores of iron indicate that the test material, which is an iron chelate, was absorbed by the animals. The increases in hepatic nonheme iron were not linear with respect to dose, reflecting the complex physiological control over iron absorption and distribution.

The NOAEL of 500 mg/kg/day for Ferrochel® in rats corresponds to ~100 mg iron per kilogram body weight per day. An NOAEL of 500 mg/kg represents an exposure margin of approximately 600-fold on a mg/kg basis (i.e., based on 50 mg Ferrochel in a 60-kg human) and approximately 100-fold on a mg/m².

9 Reproductive and Developmental Toxicology

Sponsor's summary:

"An assessment of the effects of long-term supplementation of iron amino acid chelate was made through a multi-generational animal study conducted by Jeppsen" (1993, *book chapter pdf submitted to the NDA*). "In this trial, 2 pig farms in the Province of Ontario, Canada, which were similar in feeding and management styles, were selected. One farm not using mineral supplements served as the control, while the farm using Metalosates in their everyday husbandry served as the test farm. Base feeds, inoculations, vaccinations, etc, were similar on each farm. The test farm received a feed supplement as Iron Metalosate, (b) (4) animal grade of iron amino acid chelate. The difference between this product and Ferrochel is that Ferrochel is made with United States Pharmacopeia (USP)-grade materials, whereas the animal equivalent is made with feed grade materials. This supplementation with the iron amino acid chelate occurred for a period of 5 filial generations. Mortality and other medical problems were recorded for each animal. In addition, any teratogenic effects were noted.

Animals representing the second (F2), third (F3), and fourth (F4) filial generation from each farm were sacrificed and necropsies were performed. Brain, blood, duodenum, jejunum, ileum, large bowel, muscle, heart, liver, spleen, bone marrow, mesenteric lymph node, kidney, and ovary tissue samples were taken and preserved in 10% buffered formalin. A board-certified veterinary pathologist completed a thorough histopathological assessment of the above tissues from each filial generation. The pathologist who examined both the control and test animals was blinded as to the treatment group. The pathologist noted no histopathological abnormalities associated with iron amino acid chelate supplementation.

No teratogenic effects were observed after long-term supplementation. This included a lack of siderosis (deposition of iron) in the tissues examined. The meat of the carcasses was graded by a veterinarian employed by the Canadian government. There were no significant differences in the quality of the carcasses. Upon analysis of the blood, there were no significant differences between red blood cell counts, white blood cell counts, hemoglobin content, packed cell volume, mean red cell volume, protein content, immature neutrophils, mature neutrophils, monocytes, lymphocytes, eosinophils, and basophils. Most of the hematology values were within the normal ranges listed and the few slightly aberrant values came from both control and treated groups in roughly equal numbers; as such, no statistical analysis was completed. All blood clinical chemistry and hematology values were within normal and expected ranges.

The only noticeable differences between the 2 groups were improvements in the test herd, such as increased piglet weight at weaning, lower piglet mortality, etc. The authors of the study concluded that there were no histopathological tissue alterations which could be attributable to the amino acid chelates nor were there any significant gross or microscopic differences between the test and control groups (Jeppsen, 1993). The pigs in the treated group were fed an average of 482 mg of iron per day. The dose of elemental iron in the Ferrochel placebo tablet is 10 mg."

11 Integrated Summary and Safety Evaluation

There are no toxicological concerns for any of the components of Ferrochel®. Each ferrous bisglycinate tablet in NDA 208612 contains 36.5 mg of ferrous bisglycinate, equivalent to 10 mg of elemental iron. This amount is below the RDA for non-pregnant females 19-50 yo of 18 mg and well below the tolerable upper intake level (maximum daily intake unlikely to cause adverse health effects) for the same population of 45 mg/day. From a PharmTox perspective there are no safety concerns.

12 Appendix/Attachments

Hertrampf, E. and Olivares, M. Iron Amino Acid Chelates. *Int. J. Vitam. Ntr. Res.* 74(6):435-443. 2004.

Jeppsen, RB and JF Borzelleca. Safety Evaluation of Ferrous Bisglycinate Chelate. *Food and Chemical Toxicology* 37:723-731. 1999.

Jeppsen, RB. Toxicology and safety of Ferrochel and other iron amino acid chelates. *Arch Latinoam Nutr.* 51(1 Suppl 1):26-34. 2001.

Opinion of the Scientific Panel on Food Additives, Flavourings, Processing Aids and materials in Contact with Food on a request from the Commission related to Ferrous bisglycinate as a source of iron for use in the manufacturing of foods and in food supplements. *The EFSA Journal* (2006) 299, 1-17. 2006.

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/s/

LESLIE C MCKINNEY
12/08/2017

MUKESH SUMMAN
12/08/2017
I concur