# CENTER FOR DRUG EVALUATION AND RESEARCH

***APPLICATION NUMBER:***

# 208612Orig1s000

# CLINICAL REVIEW(S)

# CLINICAL REVIEW

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|---|---|
| Application Type | NDA |
| Application Number(s) | 208612 |
| Priority or Standard | Standard |
| Submit Date(s) | 3/16/2017 |
| Received Date(s) | 3/16/2017 |
| PDUFA Goal Date | 1/14/2018 |
| Division / Office | DBRUP/ODE III |
| Reviewer Name(s) | Abby F. Anderson, MD |
| Review Completion Date | January 9, 2018 |
| Established Name | Ethinyl Estradiol/ Levonorgestrel (EE/LNG) and Ferrous Bisglycinate |
| (Proposed) Trade Name | Balcoltra |
| Therapeutic Class | Combined Hormonal Contraceptive (CHC) |
| Applicant | Neuvosyn Laboratories |
| Formulation(s) | Tablet |
| Dosing Regimen | One tablet orally daily |
| Indication(s) | Prevention of pregnancy |
| Intended Population(s) | Females of reproductive potential |

Template Version:  March 6, 2009

APPEARS THIS WAY ON ORIGINAL

# Table of Contents

# Recommendations/Risk Benefit Assessment

## 1.1 Recommendation on Regulatory Action

I recommend approval of BALCOLTRA (ethinyl estradiol/levonorgestrel/ferrous bisglycinate) for the prevention of pregnancy. This recommendation is based on the fact that the product contains an approved combined hormonal contraceptive (CHC) product ethinyl estradiol/levonorgestrel (EE/LNG) packaged with inactive tablets containing a new excipient, ferrous bisglycinate (EE/LNG Fe). Hereafter, either BALCOLTRA or EE/LNG Fe will be used to refer to this product.

## 1.2 Risk Benefit Assessment

BALCOLTRA is a co-packaged product of the generic drug Falmina® (ANDA 090721) with iron placebo tablets containing ferrous bisglycinate, a novel excipient. Falmina was determined to be equivalent to the reference listed drug (RLD), Lutera® (ANDA 076625) via a single dose bioequivalence study under fasting conditions. Lutera was previously determined to be bioequivalent to the innovator product, Alesse® (NDA 020683), which was discontinued from marketing, not for reasons of safety or efficacy. The bioequivalence bridge that has been established is sufficient from a clinical pharmacology prospective to support efficacy and safety for the Applicant's proposed product. Ferrous bisglycinate, an iron containing novel excipient is not present in a dose that is considered to have therapeutic function. After review, no safety concerns with this excipient were identified by Pharmacology/Toxicology and Chemistry. Therefore, the risk/benefit of BALCOLTRA is expected to be similar to that of the approved Alesse product.

Based on this, my clinical review will focus on disciplines' reviews of the novel excipient, ferrous bisglycinate, and updating the Alesse labeling to the Division's current standards to provide information on the efficacy and safety of the product.

## 1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies

None

### 1.4 Recommendations for Postmarket Requirements and Commitments

None

# 2 Introduction and Regulatory Background

## 2.1 Product Information

BALCOLTRA is indicated to prevent pregnancy in women who chose an oral contraceptive as their method of contraception. The Applicant is proposing to co-package Falmina (ANDA 090721), which contains 0.02mg EE and 0.1mg LNG in each tablet, manufactured by Novast, with seven (b) (4) Ferrochel tablets (equivalent to 10 mg elemental iron) manufactured by (b) (4)[1]. Ferrochel, also referred to as ferrous bisglycinate chelate, was assigned to GRAS status in 1999. Because Ferrochel has no therapeutic purpose and has never been used in a drug application, it is considered a novel excipient. The regimen consists of continuous dosing of active tablets for 21 consecutive days followed by 7 days of inactive tablets.

BALCOLTRA is being submitted via the 505(b)(2) regulatory pathway. The originally proposed RLD, was Alesse (NDA 020683), which has the same dose and dosing regimen as EE/LNG Fe. Alesse has been discontinued and withdrawn from sale NOT for reasons of safety or effectiveness (published in the Federal Register March 11, 2010)[2]. Lutera (ANDA 076625) is now the RLD for the 0.02 mg EE/0.1mg LNG oral contraceptives. Falmina was determined to be bioequivalent to Lutera, received FDA approval in March 28, 2012 and is currently marketed in the US. The Applicant has obtained the right of reference (ROR) from Novast Holdings Ltd. to Falmina. The Applicant has also obtained the ROR from (b) (4) to Ferrochel.

## 2.2 Tables of Currently Available Treatments for Proposed Indications

There are numerous oral CHCs with EE and LNG. The table below lists combination oral contraceptives (COC) with 0.02 mg EE and 0.1 mg LNG approved for prevention of pregnancy found in the public database - drugs@FDA[3].

[1] (b) (4). was purchased by (b) (4). Prior to the purchase Ferrochel was manufactured at (b) (4) facility and packaged at (b) (4) facility. As of June 2017, Ferrochel is now manufactured and packaged a (b) (4) facility. NDA208612 Seq No 5. 6/9/2017.
[2] Federal Register, Volume 75, Issue 47 (March 11,2010)
[3] https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm?event=BasicSearch.process

Table 1: Approved EE/LNG COCs

| Proprietary Name | Status |
|---|---|
| Alesse | discontinued |
| Levlite | discontinued |
| Aviane | AB1 |
| Afirmelle | AB1 |
| Falmina | AB1 |
| Lessina | AB2 |
| Lutera | AB1 |
| Vienva | AB1 |
| Orsythia | AB1 |

## 2.3 Availability of Proposed Active Ingredient in the United States

The progestin, LNG has a long history of use in women's health and is a component of many products. The following table lists the approved indications and routes of administration for LNG.

Table 2: Approved Indications and Route of Administration for LNG

| Used in combination with an estrogen | |
|---|---|
| Indication | Route of Administration |
| Contraception | Oral |
| Emergency contraception | Oral |
| Vasomotor symptoms | Film - controlled release |
| Osteoporosis prevention | Patch |
| Used alone | |
| Indication | Route of Administration |
| Contraception | Intrauterine, Implant |
| Emergency contraception | Oral |
| Heavy menstrual bleeding (secondary indication) | Intrauterine |

Ethinyl estradiol also has a long history of use in women's health and is present in most oral CHCs marketed in the US. The following table lists the approved indications and routes of administration for EE.

Table 3: Approved Indications and Route of Administration for EE

| Used in combination with a progestin | |
|---|---|
| Indication | Route of Administration |
| Contraception | Film – controlled release (now referred to as transdermal contraceptive delivery system, TCDS), Oral, Vaginal ring |
| Emergency contraception | Oral |
| Vasomotor symptoms | Oral, Film – controlled release |
| Osteoporosis prevention | Patch |
| Premenstrual dysphoric disorder | Oral |
| Acne vulgaris | Oral |

## 2.4 Important Safety Issues with Consideration to Related Drugs

CHCs as a class that use ethinyl estradiol and levonorgestrel have several well-recognized safety issues. The safety concerns present in current contraceptive labeling are listed below.

- Vascular events, which may be fatal, include:
    - º Deep venous thrombosis, pulmonary embolism, retinal thrombosis, other venous thrombosis
    - º Myocardial infarction
    - º Cerebrovascular diseases
- Liver disease and Hepatic neoplasia including adenomas, nodular hyperplasia, cholestasis
- Elevated blood pressure
- Headache
- Bleeding irregularities and amenorrhea
- Carbohydrate and lipid metabolic effects
- Breast cancer or other estrogen- or progestin-sensitive cancer

***Reviewer comment: This previously approved product would not be expected to have a different safety profile from other products in this CHC class.***

## 2.5 Summary of Presubmission Regulatory Activity Related to Submission

Neuvosyn requested a type B meeting on April 4, 2014 to discuss their development plan for EE/LNG Fe using nonclinical and clinical information available in the public domain and their ROR to Falmina (ANDA 090721) to pursue a 505(b)(2) application. In the pre-IND meeting request, two contraceptive products were considered for development: (b) (4)

(b) (4)

The Division responded to Neuvosyn's questions with written responses on May 23, 2014. The Division agreed that ROR from Novast for Falmina (ANDA 090721) bioequivalence to Lutera (ANDA 090721) would established an appropriate scientific bridge to Alesse (NDA 020682).

The Applicant's product, EE 0.02mg/LNG 0.1mg tablets with (b) (4) would be a duplicate of a listed drug and thus eligible for approval under section 505(j) in the Office of Generic Drugs.

In the product using (b) (4) would be a novel excipient. Nonclinical information to provide adequate evidence of safety would be needed for approval of the proposed product. The nonclinical information could be provided by either published literature, ROR from the holder of the drug master file (DMF), or the Applicant could conduct the nonclinical studies needed. In addition, at the time of filing the application, full CMC information or a DMF with the appropriate Letter of Authorization (LOA) would be needed.

A teleconference between the Applicant and the Division occurred March 16, 2015 to discuss Neuvosyn's development of EE/LNG Fe through the 505(b)(2) pathway. The Applicant obtained the DMF LOA for Ferrochel tablets and proposed to use this as the iron in the product, given its generally regarded as safe (GRAS) listing, it's safe use as a dietary supplement, and the availability of nonclinical and clinical safety data.

During the teleconference, the Applicant and the Division discussed NDA requirements to support the submission and approval of a 505 (b)(2) NDA. The Applicant proposed to rely upon nonclinical and clinical information available in the public domain. Nonclinical and CMC information made available by (b) (4) (manufacturer of Ferrochel) is relied upon for safety of ferrous bisglycinate. The FDA's findings of safety and effectiveness for Alesse (NDA 020683) are relied upon via the ROR from Novast for Falmina bioequivalence to Lutera establishing an appropriate scientific bridge to Alesse. The Applicant has not conducted nor does the Applicant plan to conduct any clinical studies in support of the proposed product. The Division concurred that the Applicant did not need any clinical studies to support the proposed EE/LNG Fe product.

Neuvosyn submitted the application to NDA 208612 on October 13, 2015 and a user fee was submitted and processed March 16, 2017. Therefore, the PDUFA goal date is January 14, 2018.

# 4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

## 4.1 Chemistry Manufacturing and Controls

The CMC review mainly focused on the quality information with the inactive tablets, ferrous bisglycinate (Ferrochel) tablets. The quantity of iron contained in these placebo tablets is not considered therapeutic from a clinical perspective. The overall drug product package for both (LNG/EE and Ferrochel tablets) in light of the container closure and the storage condition and expiration dating was reviewed. Per the December 1, 2017 Quality NDA Review by Dr. Hong Cai [4]:

"

> Since the active LNGL/EE tablets, 0.1 mg/0.02 mg are the same as the approved product Falmina (ANDA #090-721), the active LNGL/EE tablets are deemed adequate without further review.
>
> Each inactive tablet contains (b) (4) Ferrochel (b) (4), equivalent to 36.5mg of ferrous bisglycinate or10 mg of elemental iron. Ferrochel is the main component in the placebo tablet and there is no cause for concern about the proposed dose in accordance to the communication with Pharm Tox Reviewer Dr. Leslie Mckinney (via email on 08/01/2017). Furthermore, the levels of all the excipients including the coloring agents in Ferrochel are within the FDA IIG for the oral dosage form. Therefore, they are acceptable from CMC perspective.

***Reviewer comment: I concur with the CMC reviewer that there are no outstanding CMC issues that preclude approval.***

## 4.3 Preclinical Pharmacology/Toxicology

The new excipient ferrous bisglycinate is reviewed as a novel excipient and is not considered an active ingredient. Per the March 16, 2017 Pharmacology/Toxicology NDA Review by Leslie McKinney, PhD [5]:

> "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

[4] http://panorama.fda.gov/document/view?ID=5a219b70000e7406b6152f19c116ec61
[5] http://darrts.fda.gov:9602/darrts/ViewDocument?documentId=090140af8046f8b4

> 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."

***Reviewer comment: I concur with the Pharm/Tox reviewer that there are no outstanding nonclinical issues with the novel excipient or drug product that would preclude approval.***

### 4.4 Clinical Pharmacology

The Clinical Pharmacology NDA Review by Li Li, PhD[6] dated Dec. 15, 2017 references the use of a single dose BE study under fasting condition to demonstrate Falmina bioequivalence to Lutera, the RLD at the time of Falmina approval. Dr. Li also notes:

> "There are no new clinical pharmacology studies in the current NDA. The only component of this NDA relevant for Clinical Pharmacology review is the Sponsor's proposed labeling."[6]

***Reviewer comment: I concur with the Clinical Pharm reviewer that there are no clinical issues with the bridging between the drug product and the RLD.***

#### 4.4.1 Mechanism of Action

The mechanism of action by which oral CHCs prevent pregnancy is primarily by suppressing ovulation. Other possible mechanisms include cervical mucus changes that inhibit sperm penetration and endometrial changes that reduce the likelihood of implantation. It is expected that the Applicant's product will have mechanisms of action similar to other approved CHCs and will be labeled as such.

## 5 Sources of Clinical Data

The Applicant is relying on the Agency's previous findings of efficacy and safety for Alesse Tablets (NDA 020683) and the Agency's previous findings of bioequivalence between Lutera (ANDA 077625) and Alesse and between Falmina (ANDA 090721) and Lutera. The Applicant did not conduct any clinical studies, but submitted a published report which describes the interim results from the pivotal clinical trial submitted for Alesse NDA to inform labeling. Safety updates for Alesse as well as postmarketing safety data were also submitted by the Applicant for this review.

[6] Li Li PhD, Clinical Pharmacology Review December 15, 2017, available at:http://darrts.fda.gov:9602/darrts/ViewDocument?documentId=090140af804717fa

Ferrous bisglycinate, an iron containing novel excipient is not present in a dose that is considered to have therapeutic function. Review of nonclinical and CMC submissions by Pharmacology/Toxicology and Chemistry did not identify any safety concerns with this novel excipient (Section 4).

# 6 Review of Efficacy

*Efficacy Summary*

Efficacy of EE/LNG Fe, is based on the Agency's previous findings of safety and effectiveness for Alesse (EE/LNG) Tablets (NDA 020683). The review of NDA 020683 by Phill Price, MD[7], dated February 26, 1997 concludes that acceptable efficacy is documented. The efficacy was based on one multi-center trial of 1477 subjects with use of the COC for up to 6 months. There were five (5) pregnancies and the Pearl Index (PI) is calculated to be 0.841. The Life-table analysis at cycle 6 showed the cumulative pregnancy rate is 0.0041 (0.4 women/women years of use became pregnant). After review of NDA 020683, the product was determined to have acceptable efficacy and approved on March 27, 1997. Based on my review of the postmarketing data, I do not identify any signals that would cause concern for efficacy issues with this product that has different placebo tablets as compared to Alesse.

## 6.1 Indication

The indication of EE/LNG Fe is for the prevention of pregnancy in women who elect to use oral contraceptives as a method of contraception. This indication is identical to those of other approved CHCs and to that of the approved NDA product that this product is bridged to (Alesse/ NDA 020683).

The inactive iron tablets containing ferrous bisglycinate are present to facilitate ease of drug administration in a 28-day regimen and do not serve any therapeutic purpose. It is not expected that the inactive iron tablets, in separate tablets from the EE/LNG tablets, will have any effect on the efficacy or safety of this product. Therefore, no additional efficacy claim regarding iron will be allowed in the indication.

# 7 Review of Safety

Safety Summary

To support the safety of their combination EE/LNG Fe COC, Neuvosyn relies on the Agency's previous findings of safety and efficacy for Alesse Tablets (NDA 020683). The original review of NDA 020683 (EE/LNG) by Phill Price, MD[5], dated February 26, 1997,

[7] https://www.accessdata.fda.gov/drugsatfda_docs/nda/97/20683_ALESSE%20TABLETS_MEDR.PDF

concluded there were no unusual adverse events (AE) seen. In addition, postmarketing safety update submissions do not reveal any new safety signals. To update the product safety labeling to be consistent with current requirements, the Applicant provided an article by Archer[8] et al to inform the safety labeling for EE/LNG Fe, specifically the Adverse Reaction and Clinical Studies sections of the label. This publication was an interim report of the Alesse pivotal trial. There were no unusual AEs for CHCs reported. AEs noted in > 5% of subjects were headache, metrorrhagia, dysmenorrhea, and nausea. AEs leading to discontinuation occurred in 9% of the subjects with headache and metrorrhagia being the most frequent (1% each).

***Reviewer's comment: I concur that the data from the article by Archer is sufficiently robust to support its use for labeling purposes in section 9.2.***

Ferrous bisglycinate, an iron containing novel excipient is not present in a dose that is considered to have therapeutic function. Ferrous bisglycinate has a GRAS listing and review of nonclinical and CMC submissions by Pharmacology/Toxicology and Chemistry did not identify any safety concerns with this excipient (Section 4). It is not expected that the packaging of the inactive iron tablets, in separate tablets from the EE/LNG tablets, will have any effect on the safety of this product.

Safety Updates

Included in the 10/13/15 submission (SN 1) were:

- Approved labeling for Alesse
- Literature search from Jan 2012 to Dec 2014
- FDA Adverse Event Reporting System 1st quarter 2011 to 4th quarter 2013

The 120 Day safety update report was submitted 7/12/2017 (SN 6) and contained:

- Literature search from December 2014 through May 2017

Postmarketing data report was submitted 11/22/2017 (SN 17) and contained:

- FDA Adverse Event Reporting System 1st quarter 2012 to 2nd quarter 2017

The clinical review of the most recent postmarketing safety updates and literature search will be discussed in sections 8 and 9 respectively.

## 7.3 Pediatrics and Assessment of Effects on Growth

This application does not trigger the Pediatric Research Equity Act (PREA) because BALCOLTRA (EE/LNG Fe) does not include a new dosage form, indication, route of administration, or dosing regimen.

# 8 Postmarket Experience

The Applicant submitted results in summary form of adverse event cases reported into the US FDA Adverse Event Reporting System (FAERS) database from 1st quarter 2012 through 2nd quarter 2017 using the search terms ethinyl estradiol AND levonorgestrel OR daysee OR introvale OR lo[-]seasonique OR quartette OR quasense OR seasonale OR seasonique OR setlakin OR altavera OR aviane[-]28 OR enpresse[-]28 OR falmina OR lutera OR kurvelo OR lessina[-]28 OR levonest OR levora OR marlissa OR myzilra OR nordette[-]28 OR orsythia OR portia[-]28 OR trivora[-]28 OR climara[-]pro. Postmenopausal patients, defined as ≥ 60 years of age, were excluded.

The findings for the 50 most common adverse events AEs are shown below.

Table 4: AEs in Applicant's Postmarketing Search 1st Quarter 2012- 2nd Quarter 2017

| **Adverse Events Included in the FAERS 50 Most Common Adverse Events Report** | | |
|---|---|---|
| **Adverse Event** | **Number of Cases** | **Percent of Total (N = 2549)** |
| Nausea | 210 | 8.2% |
| Headache | 164 | 6.4% |
| Fatigue | 157 | 6.2% |
| Vomiting | 140 | 5.5% |
| Drug ineffective | 139 | 5.5% |
| Pain, not specified | 130 | 5.1% |
| Dizziness | 107 | 4.2% |
| Depression | 96 | 3.8% |
| Pulmonary embolism | 93 | 3.6% |
| Anxiety | 89 | 3.5% |
| Diarrhoea | 85 | 3.3% |
| Dyspnoea | 83 | 3.3% |
| Abdominal pain | 77 | 3.0% |
| Malaise | 77 | 3.0% |
| Vaginal haemorrhage | 69 | 2.7% |
| Injection site pain | 68 | 2.7% |
| Arthralgia | 63 | 2.5% |
| Insomnia | 63 | 2.5% |
| Metrorrhagia | 63 | 2.5% |
| Feeling abnormal | 62 | 2.4% |

| | | |
|---|---|---|
| Rash | 58 | 2.3% |
| Deep vein thrombosis | 57 | 2.2% |
| Off label use | 57 | 2.2% |
| Injury | 56 | 2.2% |
| Pruritus | 56 | 2.2% |
| Pyrexia | 51 | 2.0% |
| Condition aggravated | 49 | 1.9% |
| Muscle spasms | 49 | 1.9% |
| Somnolence | 49 | 1.9% |
| Pain in extremity | 48 | 1.9% |
| Paraesthesia | 48 | 1.9% |
| Abdominal pain upper | 47 | 1.85 |
| Drug interaction | 47 | 1.8% |
| Asthenia | 43 | 1.7% |
| Back pain | 43 | 1.7% |
| Migraine | 43 | 1.7% |
| Nasopharyngitis | 43 | 1.7% |
| Chest pain | 42 | 1.6% |
| Injection site erythema | 42 | 1.6% |
| Urticaria | 41 | 1.6% |
| Weight decreased | 41 | 1.6% |
| Hypoaesthesia | 40 | 1.6% |
| Menorrhagia | 40 | 1.6% |
| Palpitations | 39 | 1.5% |
| Drug dose omission | 37 | 1.5% |
| Hot flush | 37 | 1.5% |
| Incorrect dose administered | 37 | 1.5% |
| Product use issue | 37 | 1.5% |
| Cough | 36 | 1.4% |
| Erythema | 36 | 1.4% |

Source: Modified from: NDA 208612 SN17 Table 2.7.4-1p 2 and Figure 2.7.4-1 p4

***Reviewer comment: The above search includes postmenopausal products containing EE/LNG. From my perspective, the adverse events observed with postmenopausal products are not relevant because the population using these products is significantly different from that using the contraceptive product. Therefore, my discussion of the safety profile for the Applicant's product will focus on data from the CHCs only.***

The Office of Surveillance and Epidemiology (DPV II) performed a similar search of FAERS which is shown below. DPV's findings among the 50 most common AEs included emotional distress, induced abortion, cerebral venous thrombosis, peripheral swelling, cerebrovascular accident, hypertension, menstrual irregularity, and mood altered.

Table 5: AEs in Agency's FAERs Search Jan. 2012- July 2017

| **Most Frequently Reported MedDRA Preferred Terms (PT) - TOP 50** | | |
|---|---|---|
| | | |
| **Event-Preferred Terms(PTs)** | **Total Cases** | **Percent of Total** |
| DRUG INEFFECTIVE | 137 | 37.43169399 |
| PREGNANCY ON ORAL CONTRACEPTIVE | 137 | 37.43169399 |
| ANXIETY | 120 | 32.78688525 |
| PAIN | 117 | 31.96721311 |
| EMOTIONAL DISTRESS | 113 | 30.87431694 |
| PARTNER STRESS | 113 | 30.87431694 |
| HEADACHE | 36 | 9.836065574 |
| ABORTION INDUCED | 23 | 6.284153005 |
| NAUSEA | 22 | 6.010928962 |
| MALAISE | 18 | 4.918032787 |
| PULMONARY EMBOLISM | 18 | 4.918032787 |
| METRORRHAGIA | 15 | 4.098360656 |
| VOMITING | 13 | 3.551912568 |
| DRUG DOSE OMISSION | 12 | 3.278688525 |
| INAPPROPRIATE SCHEDULE OF DRUG ADMINISTRATION | 12 | 3.278688525 |
| SOMNOLENCE | 12 | 3.278688525 |
| DIZZINESS | 11 | 3.005464481 |
| HAEMORRHAGE | 11 | 3.005464481 |
| DEPRESSION | 10 | 2.732240437 |
| RASH | 10 | 2.732240437 |
| ABDOMINAL PAIN | 9 | 2.459016393 |
| CEREBRAL VENOUS THROMBOSIS | 9 | 2.459016393 |
| FATIGUE | 9 | 2.459016393 |
| COELIAC DISEASE | 8 | 2.18579235 |
| DRUG INTERACTION | 8 | 2.18579235 |
| MIGRAINE | 8 | 2.18579235 |
| PARAESTHESIA | 8 | 2.18579235 |
| PYREXIA | 8 | 2.18579235 |

| | | |
|---|---|---|
| ASTHENIA | 7 | 1.912568306 |
| DYSPNOEA | 7 | 1.912568306 |
| EXPOSURE DURING PREGNANCY | 7 | 1.912568306 |
| MULTIPLE SCLEROSIS RELAPSE | 7 | 1.912568306 |
| MUSCLE SPASMS | 7 | 1.912568306 |
| PERIPHERAL SWELLING | 7 | 1.912568306 |
| VAGINAL HAEMORRHAGE | 7 | 1.912568306 |
| WEIGHT INCREASED | 7 | 1.912568306 |
| ABDOMINAL DISCOMFORT | 6 | 1.639344262 |
| ABDOMINAL PAIN UPPER | 6 | 1.639344262 |
| DECREASED APPETITE | 6 | 1.639344262 |
| DEEP VEIN THROMBOSIS | 6 | 1.639344262 |
| FEELING ABNORMAL | 6 | 1.639344262 |
| MENORRHAGIA | 6 | 1.639344262 |
| MOOD SWINGS | 6 | 1.639344262 |
| URTICARIA | 6 | 1.639344262 |
| WEIGHT DECREASED | 6 | 1.639344262 |
| ARTHRALGIA | 5 | 1.366120219 |
| CEREBROVASCULAR ACCIDENT | 5 | 1.366120219 |
| CHEST PAIN | 5 | 1.366120219 |
| DIARRHOEA | 5 | 1.366120219 |
| HYPERTENSION | 5 | 1.366120219 |
| INSOMNIA | 5 | 1.366120219 |
| IRRITABILITY | 5 | 1.366120219 |
| MENSTRUATION IRREGULAR | 5 | 1.366120219 |
| MOOD ALTERED | 5 | 1.366120219 |
| MYALGIA | 5 | 1.366120219 |
| PRODUCT USE IN UNAPPROVED INDICATION | 5 | 1.366120219 |
| PRURITUS | 5 | 1.366120219 |
| **Count of Cases for Top 50 PTs :** | 366 | |
| **This is only a partial display of the report generated** | | |
| **Percent of Total: Total may not be equal to 100%** | | |

Communication from M.Chehab, OSE/DPV reviewer, email communication 8/7/2017.

***Reviewer comment: The differences in the results are most likely due to the different search terms and populations summarized. The AEs found in both postmarketing summary reports are known AEs of CHCs and are relevant to labeling. I do not find any new AEs or safety trends for the EE/LNG products.***

***Although it is difficult to use postmarketing data to establish a causal relationship to drug exposure, the safety profile of AEs with CHCs are well known. Therefore, AEs related to CHCs that are consistent with class and identified in the postmarketing period will be placed in the postmarketing portion of the Applicant's label.***

# 9 Appendices

## 9.1 Literature Review/References

This literature review includes references related to EE/LNG but not ferrous bisglycinate. In addition to the Alesse label reference of Archer, et al.[8], the literature searches by the Applicant include four (4) articles between 2012 (the last time Lutera label was updated) and 2014 and eight (8) articles between January 2015 and May 2017.

The Alesse label references the clinical trial described in Archer's[8] 1997 report, "A New Low-Dose Monophasic Combination Oral Contraceptive (Alesse) with Levonorgestrel 100 µg and Ethinyl Estradiol 20 µg", and is presented as interim data from an ongoing clinical study. A total of 1477 subjects, aged 17-49 years, were enrolled with 792 subjects having completed 6 cycles of treatment at the time of the report. After excluding cycles where back up contraception was used and/or ≥3 consecutive active pills were missed, a total of 7,720 cycles were used for efficacy evaluation. With five (5) pregnancies, the Pearl Index (PI) reported was 0.84.

Archer's report noted a 28% withdrawal rate during the treatment period with 9% of subjects withdrawing due to AEs. AEs leading to discontinuation were headache, metrorrhagia, amenorrhea, depression, emotional lability, hypertension, acne, menorrhagia, nausea, hypercholesterolemia, weight gain, dysmenorrhea, and flatulence. Treatment related AEs were reported by 38% of the subjects with headache (14%), metrorrhagia (8%), dysmenorrhea (7%), and nausea (7%) being reported by greater than 5% of the subjects. Breakthrough bleeding and spotting occurred in 11% of all cycles.

***Reviewer comment: The findings from the above trial will be used to inform the label.***

The four articles describing adverse events with the use of LNG or EE/ LNG between 2012 and 2014 include two (2) articles on LNG as emergency contraception (EC)[9,10] and one (1) article on an extended cycle formulation of EE/ LNG with no placebo pills[11]. The emergency contraceptive articles compare LNG only (0.15 mg) to EE/LNG (0.1mg EE/0.5mg LNG). Treatment-emergent AEs noted in these studies and not noted in the

[8] *Archer* D, Maheux R, DelConte A, et al. A new low-dose monophasic combination oral contraceptive (Alesse™) with levonorgestrel 100 µg and ethinyl estradiol 20 µg. *Contraception*. 1997;55:139-144.
[9] Dunn S, Guilbert É, Burnett M, et al. Emergency contraception: no. 280. Int J Gynaecol Obstet. 2013;120(1):102-107.
[10] Farajkhoda T, Khoshbin A, Enjezab B, Bokaei M, Karimi Zarchi M. Assessment of two emergency contraceptive regimens in Iran: levonorgestrel versus the Yuzpe. Niger J Clin Pract. 2009 Dec;12(4):450-452.
[11] *Kroll* R, Seidman L, Ricciotti N, Howard B, Weiss H. A phase 1, multicentre, open-label study to evaluate ovarian follicular activity and hormone levels with an extended-regimen combined oral contraceptive with low-dose ethinyl estradiol supplementation. *Eur J Contracept Reprod Health Care*. 2014 Dec 19:1-10. [Epub ahead of print]

clinical trial above are vomiting, dizziness, fatigue, weakness, and hot flushes, with the majority occurring in the EE/LNG group. The article involving an extended cycle formulation of EE/LNG had one subject who was discontinued from the study with elevated liver function tests[9]. The AEs were attributed to the higher doses of EE and to a lesser extent, the higher dose of LNG used in EC. None of these AEs represent a new safety signal. The fourth article[12] describes a study comparing AEs experienced with 2 types of EE/LNG COCs and a EE/LNG patch. No new hormone-related AEs were noted.

The literature search from January 1, 2015 through May 31, 2017 found 8 relevant articles involving EE/LNG COCs similar to the approved EE/LNG product in the US.

Gersten et al[13] 2016 studied bone mass in adolescents for one year comparing an extended cycle oral COC with no placebo and a 28-day COC with 21 days of LNG 0.1mg/EE 0.02 mg and 7 days of placebo. Compared with a reference group not on hormonal contraceptives, the extended cycle COC had no decrease in BMD accrual while the EE/LNG with placebo had a statistically significant lower bone accrual at the end of one year use. There were no unexpected AEs in the contraceptive treatment groups.

A PK study involving Chinese women and EE 0.02 mg/LNG 0.1 mg showed no new findings (Xin)[14]. Three other PK studies involving EE 0.03 mg/LNG 1.5 mg showed no clinical relevant changes with the COC and coadministration with fostamatinib(Martin)[15], canagliflozin (Devineni)[16], or faldaprevir (Sabo)[17].

[12] Kaunitz A, Archer D, Mishell D Jr, Foegh M. Safety and tolerability of a new low-dose contraceptive patch in obese and nonobese women. Am J Obstet Gynecol. 2014 Sep 16. pii: S0002-9378(14)00944-2. doi: 10.1016/j.ajog.2014.09.014. [Epub ahead of print]
[13] Gersten J, Hsieh J, Weiss H, Ricciotti N. Effect of Extended 30 jlg Ethinyl Estradiol with Continuous Low-Dose Ethinyl Estradiol and Cyclic 20 jlg Ethinyl Estradiol Oral Contraception on Adolescent Bone Density: A Randomized Trial. J Pediatr Adolesc Gynecol. 20 16;29:635-642.
[14] Xin X, Wu Y, Liu X, Sun C, Gong T, Ding L. Pharmacokinetics of Oral Combination Contraceptive Drugs Containing Ethinyl Estradiol and Levonorgestrel in Health Female Chinese Volunteers. Drug Res. 2016;66:100-106.
[15] Martin P, Gillen M, Ritter J, et al. Effects of Fostamatinib on the Pharmacokinetics of Oral Contraceptive, Warfarin, and the Statins Rosuvastatin and Simvastatin: Results From Phase I Clinical Studies. Crossmark. 2016;16:93-107. Published online at Springerlink.com, doi: 10.1007 /s40268-015-0120-x.
[16] Devineni D, Manitpisitkul P, Vaccaro N, et al. Effect of canagliflozin, a sodium glucose cotransporter 2 inhibitor, on the pharmacokinetics of oral contraceptives, warfarin, and digoxin in healthy participants. J Clin Pharmacal. 2015;53(1):41-53.
[17] Sabo J, Lang B, Elgadi M, Huang F. Effect of the Hepatitis C Virus Protease Inhibitor Faldaprevir on the Pharmacokinetics of an Oral Contraceptive Containing Ethinylestradiol and Levonorgestrel in Health Female Volunteers. J Antimicrob Agents and Chemother. 2015;59(1):514-519. Published online at aac.asm.org, doi:10.1128/AAC03589-14.

Two studies using COCs with higher doses of LNG and EE showed no new findings with procoagulant parameters (Stocco)[18] and no negative impact on overall sexual function (Zethraeus)[19].

The last study referenced (Leung)[20] involved EE/LNG use in emergency contraception with EE 0.2 mg/LNG 1.0mg over 24 hours. No new AEs were noted in this study.

***Reviewer comment: Most of the above studies involve use of EE and/or LNG in higher doses that EE/LNG Fe. The other studies involve clinical research. None of the findings are new and/or present relevant information that would inform labeling for EE/LNG Fe.***

## 9.2 Labeling Recommendations

The most recent labeling supplement for Alesse (NDA 020683) was approved in January 2008 and the most recent labeling supplement for Lutera (ANDA 076625) was approved in July 2012. Lutera has identical labeling to Alesse.

The Applicant submitted draft labeling for EE/LNG Fe on October 13, 2015 which was in Physician Labeling Rule (PLR)[21] but contained outdated information that has been removed from recent CHC labels such as perfect vs. actual use and listing all adverse reactions noted with CHCs as a class in the Adverse Reaction section. The label also did not conform to the Pregnancy and Lactation Labeling Rule (PLLR)[22] effective June 30, 2015.

The Division requested the Applicant resubmit the label consistent with class labeling using Femcon, a recently approved label, as a format and general content guide. The Applicant submitted the revised label September 1, 2017 utilizing the Archer article to inform the Adverse Reaction and Clinical Studies sections of the label. The Division requested the Applicant provide Postmarketing Experience based on a FAERS-like search for EE/LNG CHCs between January 2012 through July 2017.

A summary of agreed upon label changes is below.

[18] Stocco B, Fumagalli H, Franceschini S, et al. Comparative Study of the Effects of Combined Oral Contraceptives in Hemostatic Variables: An ObservPLRational Preliminary Study. Medicine. 2015;94(4):1-6. Published online at md-journal.com, doi:10.1097/MD.0000000000000385.
[19] Zethraeus N, Dreber A, Ranehill E, et al. Combined Oral Contraceptives and Sexual Function in Women- a Double-Blind, Randomized, Placebo-Controlled Trial. J Clin Endocrinol Metab. 2016:1-8. Published online at press.endocrine.org/joumal/jcem, doi: 10.121 O/jc.20 16-2032.
[20] Leung V, Soon J, Lynd L, Marra C, Levine M. Population-based evaluation of the effectiveness of two regimens for emergency contraception. Intl J Gynecol and Obstet. 20 16; 133:342-346.
[21] https://www.fda.gov/OHRMS/DOCKETS/98fr/E6-846.pdf
[22] https://www.federalregister.gov/documents/2014/12/04/2014-28241/content-and-format-of-labeling-for-human-prescription-drug-and-biological-products-requirements-for

In places where wording was changed, new text is underlined and deleted text is scored through.

General changes made throughout the document:

- Product name, BALCOLTRA, inserted
- (b) (4) to describe the placebo tablet were changed to "inactive".
- Use of condoms or spermicide instead of both
- Replacement of "Ferrochel" with ferrous bisglycinate

Highlights of Prescribing Information

Removed under Dosage and Administration
(b) (4)

Added under Contraindications
Hypersensitivity of any of the components (4)

Added under Warnings and Precautions
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 (5.9)

Added under Adverse Reactions
Common adverse reactions (≥ 2% of women): headache (14%), metrorrhagia (8%), dysmenorrhea and nausea (7% each), abdominal pain and breast pain (4% each), emotional lability and acne (3% each), and depression, amenorrhea, and vaginal moniliasis (2% each) (6.1).

Dosage and Administration

The Division requested removal (b) (4) (b) (4).

5 Warnings and Precautions

Order rearrangement was performed so that the warning and precautions in the Highlights section are listed first in section 5: Warnings and Precautions.

5.8 Bleeding Irregularities and Amenorrhea
The incidences of unscheduled bleeding, spotting, and amenorrhea that was noted in the registration trial were added.

(b) (4) In clinical trial with levonorgestrel 0.1mg and ethinyl estradiol 0.02 mg tablets (b) (4) breakthrough bleeding and spotting was reported in 4% and 12% of cycles, respectively. Breakthrough bleeding and spotting occurred together during 11% of the cycles.

In the clinical trial, 2.6% of the evaluable cycles were amenorrheic.

5.9 (b) (4)

This section was removed and statements (b) (4) were placed in section 8.1 Pregnancy per PLLR format.

5.12 Monitoring

Recommendation (b) (4) was removed to align with USSPR for Contraceptive Use, 2016[23] as shown below.

A woman who is taking COCs should have her blood pressure checked periodically (b) (4) with her healthcare provider (b) (4)

Added additional section to Warnings and Precautions

5.9 FD&C Yellow No. 5

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

6 Adverse Reactions

The section was separated into 6.1 Clinical Trial Experience and 6.2 Postmarketing Experience.

6.1 Clinical Trial Experience

The trial results from Archer[8] were placed in a clear format with the common adverse events listed.

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice.

In a clinical trial with levonorgestrel 0.1 mg and ethinyl estradiol 0.02 mg tablets, a total of 1477 healthy women of child-bearing potential were enrolled and had 7870 cycles of exposure. Of these, 792 subjects had completed 6 cycles of treatment. The women ranged in age from 17-49 years and 87% were Caucasian.

*Common Adverse Reactions (≥ 2% of women):*

[23] USSPR Contraceptive Use, 2016 p 27.

- headache (14%)
- metrorrhagia (8%)
- dysmenorrhea (7%)
- nausea (7%)
- abdominal pain (4%)
- breast pain (4%)
- emotional lability (3%)
- acne (3%)
- depression (2%)
- amenorrhea (2%)
- vaginal moniliasis (2%)

At the time of the report, 133 (9%) subjects had withdrawn from the study due to adverse events. The most frequent were due to headache and metrorrhagia (1% each). Other adverse events occurring in < 1% of those who discontinued included amenorrhea, depression, emotional lability, hypertension, acne, menorrhagia, nausea, hypercholesterolemia, weight gain, dysmenorrhea, and flatulence. All other reasons for discontinuation were reported by 3 or fewer subjects.

## 6.2 Postmarketing Experience

The Applicant updated this section with results from their search of postmarketing reports of AEs reported with use of EE/LNG.

*Cardiac disorder*: chest pain, dyspnea, palpitations

*Gastrointestinal disorders*: abdominal pain, nausea, vomiting, diarrhea

*General disorders and administration site conditions*: chest pain, fatigue, pain, malaise, injection site pain or erythema, feeling abnormal, pyrexia, condition aggravated, asthenia

*Immune system disorders*: hypersensitivity reactions, including pruritus, rash, urticaria, erythema

*Injury, poisoning, and procedural complications*: injury

*Investigations*: weight decreased

*Musculoskeletal and connective tissue disorders*: pain in extremity, arthralgia, back pain, muscle spasm

*Nervous system disorders*: headache, migraine, dizziness, hypoesthesia, paresthesia

*Psychiatric disorders*: depression, insomnia, anxiety

*Reproductive system and breast disorders*: metrorrhagia, menorrhagia, hot flush, vaginal hemorrhage

*Respiratory, thoracic, and mediastinal disorders*: nasopharyngitis, cough

*Sleep disorders and disturbances*: somnolence

*Vascular disorders*: deep vein thrombosis, pulmonary embolism

## 7 Drug Interactions

The sections below were updated to conform to new safety labeling for CHCs

Consult the labeling of concurrently used drugs to obtain further information about interactions with hormonal contraceptives or the potential for enzyme alterations.

7.1 Effects of Other Drugs on Combined Oral Contraceptives

Substances decreasing the plasma concentrations of COCs and potentially diminishing the efficacy of COCs:

Drugs or herbal products that induce certain enzymes, including cytochrome P450 3A4 (CYP3A4), may decrease the plasma concentrations of COCs and potentially diminish the effectiveness of COCs or increase breakthrough bleeding. Some drugs or herbal products that may decrease the effectiveness of hormonal contraceptives include phenytoin, barbiturates, carbamazepine, bosentan, felbamate, griseofulvin, oxcarbazepine, rifampicin, topiramate, rifabutin, rufinamide, aprepitant, and products containing St. John's wort. Interactions between hormonal contraceptives and other drugs may lead to breakthrough bleeding and/or contraceptive failure. Counsel women to use an alternative method of contraception or a back-up method when enzyme inducers are used with COCs, and to continue back-up contraception for 28 days after discontinuing the enzyme inducer to ensure contraceptive reliability.

Colesevelam: Colesevelam, a bile acid sequestrant, given together with a COC, has been shown to significantly decrease the AUC of ethinyl estradiol (EE). The drug interaction between the contraceptive and colesevelam was decreased when the two drug products were given 4 hours apart.

Substances increasing the plasma concentrations of COCs:

Co-administration of atorvastatin or rosuvastatin and certain COCs containing EE increase AUC values for EE by approximately 20-25%. Ascorbic acid and acetaminophen may increase plasma EE concentrations, possibly by inhibition of conjugation. CYP3A4 inhibitors, such as itraconazole, fluconazole, grapefruit juice, or ketoconazole may increase plasma hormone concentrations.

Human immunodeficiency virus (HIV)/ Hepatitis C virus (HCV) protease inhibitors and non-nucleoside reverse transcriptase inhibitors:

Significant changes (increase or decrease) in the plasma concentrations of estrogen and/or progestin have been noted in some cases of co-administration with HIV/HCV protease inhibitors and non-nucleoside reverse transcriptase inhibitors (decrease [e.g., nelfinavir, ritonavir, darunavir/ritonavir, (fos)amprenavir/ritonavir, lopinavir/ritonavir,tipranavir/ritonavir, boceprevie, telaprevir, nevirapine and efavirenz] or increase [e.g., indinavir ~~and,~~ atazanavir/ritonavir and etravirine]) (b) (4) (b) (4).

7.2 Effects of Combined Oral Contraceptives on Other Drugs

Combined oral contraceptives containing EE may inhibit the metabolism of other compounds (e.g., cyclosporine, prednisolone, theophylline, tizanidine, and voriconazole) and increase their plasma concentrations. Combined oral contraceptives have been shown to decrease plasma concentrations of acetaminophen, clofibric acid, morphine, salicylic acid, temazepam and lamotrigine. Significant decrease in plasma concentration of lamotrigine has been shown, likely due to induction of lamotrigine glucuronidation. This may reduce seizure control; therefore, dosage adjustments of lamotrigine may be necessary.

Women on thyroid hormone replacement therapy may need increased doses of thyroid hormone because the serum concentration of thyroid-binding globulin increases with use of COCs *[see Warnings and Precautions (5.11)]*.

7.3 Concomitant Use with HCV Combination Therapy – Liver Enzyme Elevation

Do not co-administer BALCOLTRA with HCV drug combinations containing ombitasvir/ paritaprevir/ritonavir, with or without dasabuvir, due to potential for ALT elevations [*see Warnings and Precautions* (5.3)].

7.4 Interactions with Laboratory Tests

The use of contraceptive steroids may influence the results of certain laboratory tests, such as coagulation factors, lipids, glucose tolerance, and binding proteins.

# 8 Use in Specific Populations

## 8.1 Pregnancy

The Applicant and Division agreed on a new risk summary and human data statements to include as required under PLLR. Pharmacology/Toxicology removed the statement (b) (4) because the statement is non-informative and is not placed in CHC labels when human data is available to inform the label.

Risk Summary

BALCOLTRA is contraindicated in pregnancy because there is no reason to use combined hormonal contraceptives (CHCs) in pregnancy. Discontinue BALCOLTRA 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)*.

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.

## 8.2 Lactation

The Applicant agreed to the benefit/risk statement as required under PLLR.

Risk Summary
Combined hormonal contraceptives (CHCs) and/or metabolites are present in human milk and in breast-fed infants. CHCs, including BALCOLTRA, can reduce milk production in breast-feeding females. This reduction can occur at any time but is less likely to occur once breast-feeding is well-established. When possible, advise the nursing female to use other methods of contraception until she discontinues breast-feeding. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for BALCOLTRA and any potential adverse effects on the breast-fed child from BALCOLTRA or from the underlying maternal condition.

8.7 (b) (4)

This section was removed (b) (4) (b) (4) and no data was identified from the literature that was sufficient to update this section.

11 Description

The ingredients listed were updated by the Applicant to match components listed in the NDA.

The chemical formula and molecular weight were added. The molecular structures were revised with correct stereo bond drawings and same decimal place format.

***Reviewer's comment: This information was reviewed by the CMC review team and determined to be acceptable.***

12 Clinical Pharmacology

12.2 Pharmacodynamics

This section (12.2) was added with the following:

> No specific pharmacodynamics studies were conducted with BALCOLTRA.

12.3 Pharmacokinetics

The Applicant agreed to place the PK profiles based on the BE study under ANDA 090721 in this section and remove (b) (4) as requested by the Division as recommended by the Clinical Pharmacology team.

***Reviewer's comment: The Clinical Pharmacology team reviewed the PK information in the label and determined it to be acceptable.***

14 Clinical Studies

The Division requested an approximate pregnancy rate because the calculation of Pearl Index at time of study was most likely not calculated as today's standards. Demographics from the registration trial were added. The Division also requested removal of language (b) (4). The Applicant agreed to the requests.

In a clinical trial with levonorgestrel 0.1 mg and ethinyl estradiol 0.02 mg tablets, 1,477 (b) (4) women aged 17-49 years had 7,720 cycles of use. Eighty-seven percent (87%) of the women were Caucasian.

The average weight was 66.4 kg with a range of 38.0-154.2 kg. Among the women in the trial, 5.3% had never used COCs.

- (b) (4) -A total of 5 pregnancies were reported. This represents an overall pregnancy rate of (b) (4) approximately 1 pregnancy per 100 woman-years.

(b) (4)

Patient Information

The Patient Package Information and Instructions for Use documents were reviewed and reformatted by DMPP to reduce redundancy, to make patient information more consistent and concise, and to include the information necessary for patients to safely take their medication.

"What is BALCOLTRA?":

The warning that the COC does not protect again HIV is placed here for prominence.

TRADEMARK does **not** protect against HIV infections (AIDS) and other sexually transmitted infections.

"How does BALCOLTRA work for contraception?":

The following pregnancy data statement is added.

Based on the results of one clinical study of a 28-day regimen of levonorgestrel 0.1mg/ethinyl estradiol 0.02 mg tablets, about 1 out of 100 women may get pregnant within the first year they use TRADEMARK.

The Division requested removal of paragraph below because (b) (4) this information is no longer placed in contraceptive labels. The Applicant agreed.

(b) (4)

Do not take TRADEMARK if you:

Warning on allergies to ingredients in TRADEMARK was added.

are allergic to levonorgestrel, ethinyl estradiol, ferrous bisglycinate or any of the ingredients in BALCOLTRA. Some people who are allergic to aspirin may also be allergic to FD&C Yellow No. 5 (tartrazine). FD&C Yellow No. 5 (tartrazine) is an ingredient in BALCOLTRA which also may cause an allergic type reaction such as bronchial asthma. See the end of this Patient Information leaflet for a complete list of ingredients in BALCOLTRA.

Before you take BALCOLTRA:

Warning to discontinue BALCOLTRA prior to surgery was added.

• are scheduled for surgery. BALCOLTRA may increase your risk of blood clots after surgery. You should stop using your BALCOLTRA at least 4 weeks before you have surgery and not restart it until at least 2 weeks after your surgery

What are the possible serious side effects of TRADEMARK?:

High blood pressure monitoring was aligned with recommendation to have regular monitoring at any time.

• **high blood pressure.** You should see your healthcare provider (b) (4) to check (b) (4) your blood pressure regularly.

What are the most common side effects of BALCOLTRA?

The most common side effects of this CHC were aligned to section 6.1 and are shown below.

The most common side effects of TRADAENAME include:

- headache (including migraine)
- irregular vaginal bleeding (including absence of period)
- nausea and vomiting
- breast (b) (4)
  - tenderness, pain and discomfort
    (b) (4)
- abdominal (b) (4) pain
- pain with your periods (menstrual cycle)
- mood changes, including depression
- acne
- vaginal infections

(b) (4)

General Information about the safe and effects use of BALCOLTRA:

Additional warning against giving medication to other people was added to read:

Do not give BALCOLTRA to other people, even if they have the same symptoms that you have. It may harm them.

What should I know about my period when taking BALCOLTRA?:

(b) (4)-Some women may miss a period. Irregular vaginal bleeding or spotting may happen while you are taking BALCOLTRA, especially during the first few months of use. This usually is not a serious problem. If the irregular vaginal bleeding or spotting continues or happens again after you have had regular menstrual cycles call your healthcare provider. It is important to continue taking your pills on a regular schedule to prevent a pregnancy.

What if I miss my scheduled period when using BALCOLTRA?

This section was added for consistency with other hormonal products used to prevent pregnancy and the following information added.

Some women miss periods on hormonal birth control, even when they are not pregnant. However, if you go 2 or more months in a row without a period, or you miss your period after a month where you did not use all of your BALCOLTRA correctly, call you healthcare provider because you may be pregnant. Also call your healthcare provider if you have symptoms of pregnancy such as morning sickness or unusual breast tenderness. Stop taking BALCOLTRA if you are pregnant

What are the ingredients in BALCOLTRA?

This section was updated to be consistent with Section 16 of the PI.

**Instructions for Use**

Important Information about taking BALCOLTRA:

Remove (b) (4) from instructions on use to conform with PI

Both the orange pills and the blue pills ~~may~~ should be swallowed whole. (b) (4) (b) (4)

Clarification on missed periods during use

Some women miss periods on hormonal birth control, even when they are not pregnant. (b) (4) (b) (4) However, if you miss a period and have not taken BALCOLTRA according to directions, or miss **2** periods in a row, or feel like you may be pregnant, call your healthcare provider. If you have a positive pregnancy test, you should stop taking BALCOLTRA.

Warning on surgery and use of BALCOLTRA

Stop taking TRADNAME at least **4** weeks before you have major surgery and do not restart it until at least 2 weeks after your surgery. (b) (4) Be sure to use other forms of contraception (like condoms and spermicide) during this time period.

Clarification on using day label for BALCOLTRA pill pack

Find what day of the week you are to start taking pills. If your period begins on a day other than Sunday, place the day label strip that starts with the first day of your period. (b) (4) (b) (4) - For example, if your period begins on Monday, place the day label strip with Monday as the first day.

Carton and Blister label

The established name on the blister and carton labels were increased in size and the color scheme was modified to provide prominence of the established name.

The "Rx only" statement was added to the blister label in accordance with Section 503(b)(4)(A) of the Federal Food, Drug, and Cosmetic Act.

The carton label statement was changed to align with the Draft Guidance for Industry: Labeling for Combined Oral Contraceptives.

This product (b) (4) is intended to prevent pregnancy. It does not protect against HIV infection (AIDS) and other sexually transmitted diseases.

The carton label added a warning for serious cardiovascular events with smoking and use of CHCs, added the inactive ingredients of both tablets, and removed reference to Ferrochel.

The above changes in the Patient labeling reflect DMEPA recommendations listed below from their November 2017 review. A summary of these recommendations included:

1. 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
3. 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. 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".

***Reviewer's comment: I concur with the recommended changes to the label from DMEPA and DMPP.***

***Reviewer's summary comment: After labeling negotiations concluded, the Applicant submitted final labeling on January 9, 2018 I have reviewed the final label and determined that there are no identified errors in the clinical sections and patient package insert.***

## 9.3 Advisory Committee Meeting

An Advisory Committee meeting was not requested for this application as it does not represent a new molecular entity, novel indication or dosage form or have a novel safety or efficacy issue that would require expert input.

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**

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/s/

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ABBY F ANDERSON
01/09/2018

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