CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

208612Orig1s000

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

Clinical Pharmacology Review	
NDA Number:	208612
Submission Date:	10/13/2015, 03/16/2017
Brand Name:	TRADENAME
Generic Name:	Levonorgestrel/Ethinyl Estradiol and Ferrous Bisglycinate
OCP Reviewer:	Li Li, Ph.D
OCP Team Leader:	Doanh Tran, Ph. D
OCP Division:	Division of Clinical Pharmacology III
OND Division:	Division of Bone Reproductive and Urologic Products
Sponsor:	Neuvosyn Laboratories LLC
Submission Type:	Original
Formulation and Dosing regimen:	Once daily of Levonorgestrel/Ethinyl Estradiol tablet for 21 days followed by once daily of iron placebo tablet for 7 days
Indication:	Prevention of Pregnancy

Executive Summary

The Sponsor submitted an original New Drug Application (NDA) for (b) (4) under 505(b)(2) for prevention of pregnancy. (b) (4) is a fixed-dose combination of an oral contraceptive tablet containing levonorgestrel (LNG) 0.1 mg and ethinyl estradiol (EE) 0.02 mg co-packaged with non-hormonal (placebo) iron tablets containing (b) (4) Ferrochel® (equivalent to 10 mg elemental iron). The dosing regimen consists of continuous dosing of contraceptive tablets for 21 consecutive days followed by 7 days on placebo iron tablets.

From regulatory perspective, (b) (4) is a co-packaged product of generic drug Falmina™ (LNG 0.1 mg/ EE 0.02 mg under ANDA 090721) with iron placebo tablets. Falmina™ was approved by the Office of Generic Drug (OGD) on March 28th 2012. Under ANDA 090721, Falmina ™ was demonstrated to be bioequivalent (BE) to the reference standard (RS) Lutera® via a single dose BE study under fasting condition. Lutera® (ANDA 076625) was used as the RS for this BE study because the innovator product Alesse® (NDA 020683 approved on March 27th 1997) was discontinued from marketing in the United States. The Sponsor did not conduct any human clinical studies to support this NDA, but plans to rely on the Agency's previous findings of safety and effectiveness for the listed drug, Alesse® under NDA 020683.

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.

Recommendations

The Office of Clinical Pharmacology/ Division of Clinical Pharmacology 3 (OCP/DCP3) finds NDA 208612 acceptable provided that agreement is reached between the Sponsor and the Division regarding the language in the package insert.

Detailed Labeling Recommendations

Labeling statements to be removed are shown in ~~red strikethrough font~~ and suggested labeling to be included is shown in underline red font

7 DRUG INTERACTIONS

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, voriconazole, 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, (b) (4) tipranavir/ritonavir, boceprevir, telaprevir, nevirapine and efavirenz] or increase [e.g., indinavir, (b) (4) -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~~12~~)].

7.3 Concomitant Use with HCV Combination Therapy – Liver Enzyme Elevation

Do not co-administer TRADENAME 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

(b) (4)

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Combination oral contraceptives lower the risk of becoming pregnant primarily by suppressing ovulation. Other possible mechanisms may include cervical mucus changes that inhibit sperm penetration and endometrial changes that reduce the likelihood of implantation.

12.2 Pharmacodynamics

No specific pharmacodynamics studies were conducted with TRADENAME.

12.3 Pharmacokinetics

Absorption

No specific investigation of the absolute bioavailability of levonorgestrel and ethinyl estradiol tablets USP) in humans has been conducted. However, literature indicates that levonorgestrel is rapidly and completely absorbed after oral administration (bioavailability about 100%) and is not subject to first-pass metabolism. Ethinyl estradiol is rapidly and almost completely absorbed from the gastrointestinal tract but, due to first-pass metabolism in gut mucosa and liver, the bioavailability of ethinyl estradiol is between 38% and 48%.

(b) (4)

After a single dose of two levonorgestrel and ethinyl estradiol tablets to 34 women under fasting conditions, the mean (±SD) plasma area under the concentration time curve (AUC) and maximum concentration (Cmax) of levonorgestrel were 41.7 ± 18.0 ng*hour/mL and 4.4 ± 1.8 ng/mL, respectively, with a median time to maximum concentration (Tmax) of 1.0 hours. The mean (±SD) plasma AUC and Cmax of ethinyl estradiol were 1167 ± 367 pg*hour/mL and 115 ± 37 pg/mL, respectively, with a median Tmax of 1.5 hours. The plasma levonorgestrel and ethinyl estradiol pharmacokinetic profiles following a single dose of two levonorgestrel and ethinyl estradiol tablets are shown in **Figure 2**.

Figure 2. Mean (b) (4) SD) Levonorgestrel and Ethinyl Estradiol (b) (4) lasma Concentrations in (b) (4) 34 Subjects Receiving two (b) (4) 0.1 mg Levonorgestrel an 0.02 mg Ethinyl Estradiol Tablets

Distribution
Levonorgestrel in serum is primarily bound to SHBG. Ethinyl estradiol is about 97% bound to plasma albumin. Ethinyl estradiol does not bind to SHBG, but induces SHBG synthesis.

Metabolism
Levonorgestrel: The most important metabolic pathway occurs in the reduction of the Δ4-3-oxo group and hydroxylation at positions 2α, 1β, and 16β, followed by conjugation. Most of the metabolites that circulate in the blood are sulfates of 3α, 5β-tetrahydro-levonorgestrel, while excretion occurs predominantly in the form of glucuronides. Some of the parent levonorgestrel also circulates as 17β-sulfate. Metabolic clearance rates may differ among individuals by several-fold, and this may account in part for the wide variation observed in levonorgestrel concentrations among users.

Ethinyl estradiol: Cytochrome P450 enzymes (CYP3A4) in the liver are responsible for the 2 hydroxylation that is the major oxidative reaction. The 2-hydroxy metabolite is further transformed by methylation and glucuronidation prior to urinary and fecal excretion. Levels of Cytochrome P450 (CYP3A) vary widely among individuals and can explain the variation in rates of ethinyl estradiol 2-hydroxylation. Ethinyl estradiol is excreted in the urine and feces as glucuronide and sulfate conjugates, and undergoes enterohepatic circulation.

Excretion

The elimination half-life for levonorgestrel is approximately (b) (4)34 ± (b) (4)14 hours (b) (4) Levonorgestrel and its metabolites are primarily excreted in the urine (40% to 68%) and about 16% to 48% are excreted in feces. The elimination half-life of ethinyl estradiol is (b) (4)17 ± 5.7 (b) (4) hours (b) (4) (b) (4)

Reviewer's Comment:
The Sponsor needs to add standard deviation (SD) bars to Figure 2 and remove the additional markers for LNG PK profile.

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