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APPLICATION NUMBER:

204654Orig1s000

SUMMARY REVIEW

Cross-Discipline Team Leader Review

Date	July 24, 2013
From	Lisa M. Soule, M.D.
Subject	Cross-Discipline Team Leader Review
NDA/BLA #	204-654
Applicant	Warner Chilcott Company, LLC
Date of Submission	September 28, 2012
PDUFA Goal Date	July 28, 2013
Proprietary Name / Established (USAN) names	Lo Minastrin Fe Ethinyl estradiol (EE)/Norethindrone acetate (NETA), EE alone, and ferrous fumarate (FF) tablets
Dosage forms / Strength	EE 10 µg/NETA 1 mg chewable tablet and EE 10 µg tablet to be swallowed
Dose Regimen	1 EE/NETA chewable tablet daily for 24 days, followed by 2 days of EE-alone (swallowed) and 2 days of FF tablets (swallowed)
Proposed Indication(s)	Prevention of pregnancy
Recommended:	***Approval***

1. Introduction

This NDA seeks approval for a chewable combination oral contraceptive (COC) containing norethindrone acetate (NETA) and ethinyl estradiol (EE); the COC is intended to be bioequivalent (BE) to the COC Lo Loestrin Fe, approved under NDA 22-501. The dose regimen is the same as that for Lo Loestrin Fe aside from chewing the combination tablets, and consists of :

- Days 1-24: one mint-flavored combination EE/NETA tablet (chewed)
- Days 25-26: one 10 µg EE-alone tablet (swallowed)
- Days 27-28: one inactive tablet containing ferrous fumarate (FF, swallowed).

Tablets may be taken without regard to meals.

There are several approved NDAs for chewable COCs; those currently marketed are Femcon Fe (NDA 21-490) and Generess Fe (NDA 22-573).

2. Background

2.1 DESCRIPTION OF PRODUCT

NETA and EE are well-characterized progestin and estrogen products, respectively, that are widely used in combined hormonal contraceptive products. These products reduce the risk of pregnancy mainly via the effect of the progestin on suppressing ovulation, along with changes in cervical mucus that inhibit sperm motility and endometrial changes that may inhibit implantation. The estrogen component may make some contribution to the contraceptive action, and mainly acts to maintain cycle control and provide an acceptable bleeding profile.

The Applicant has several approved COC products that contain EE and NETA. The Loestrin family of products had its initial approval in 1976, and includes Loestrin products containing 30 µg EE/1.5 mg NETA or 20 µg EE/1 mg NETA administered in a 21/7 regimen; Loestrin 24 Fe, which contains 20 µg EE/1 mg NETA and is administered in a 24/4 day regimen with four days of FF, and Lo Loestrin Fe, which contains 10 µg EE/1 mg NETA and is administered in a 24/2/2 day regimen with two days of EE-alone and two days of FF. Lo Loestrin Fe contains the lowest EE dose in any approved COC, and is the reference drug for the current chewable tablet.

Of the chewable formulations (most manufactured by another sponsor), Femcon Fe was approved in 2003 and contains 35 µg EE/400 µg NETA administered in a regimen of 21 days of active combination tablets and 7 days of FF tablets. A lower dose version, Generess, was approved in 2010; it contains 25 µg EE/800 µg NETA, and is administered in the same regimen as Femcon Fe. Another Warner Chilcott chewable product, BE to Loestrin 24 Fe, was approved under NDA 203-667 in May 2013 and has not yet been marketed. A capsule bioequivalent to Loestrin 24 Fe was also approved, under NDA 204-426, in April 2013 and has not yet been marketed.

2.2 REGULATORY HISTORY

Because the Applicant had experience developing chewable formulations of approved COC products, it understood the Division's requirements for approval of such a formulation (e.g., conduct of an oral irritation study) and did not request advice during the development program for this product.

2.3 PRIMARY MEDICAL REVIEWER'S RECOMMENDATION FOR APPROVABILITY

The primary reviewer, Dr. Daniel Davis, stated in his review dated July 5, 2013:

> *From a clinical perspective, this reviewer recommends approval of NETA/EE chewable tablets containing norethindrone ACETATE (NETA) 1 mg and ethinyl estradiol (EE) 10 mcg for the Applicant's s proposed indication of "for use by women to prevent pregnancy." The new product will be marketed as a 28-day regimen.*
>
> **Team Leader Comment:**
> **I concur with Dr. Davis' recommendation.**

Dr. Davis did not recommend any postmarketing risk evaluation and mitigation strategies or postmarketing requirements/commitments.

3. CMC/Device

3.1 CMC

A USP monograph about the combination of the drug substances (EE and NETA) has been published. Information about each drug substance from its respective manufacturer is contained in drug master files (DMFs), which have been reviewed several times and determined to be adequate. The primary Chemistry Reviewer, Gene Holbert, Ph.D., noted that the formulation of the chewable combination tablets (b) (4)) is based on the previously approved formulation in NDA 22-501, with the difference being that the current tablet is chewable. The formulations are identical except for (b) (4) Dissolution

data confirm that the release of NETA and EE are similar for both formulations. The EE-alone and FF tablets are identical to those approved in NDA 22-501.

Dr. Holbert found the analytic methods to be appropriately validated. Expiry of 12 months was proposed by the Applicant based on six month data for the combination tablets at the long-term and intermediate conditions and extrapolation of the long-term data; this was acceptable. The expiry will be amended as results of ongoing stability testing become available.

Dr. Holbert provided labeling recommendations that were conveyed to the Applicant; carton and container labeling were acceptable. Five manufacturing and testing sites were found acceptable on profile and one based on district recommendation. One drug substance manufacturer (b) (4) was scheduled for inspection and one had been inspected but no recommendation made at the time of his review.

At the time of Dr. Holbert's review, labeling negotiations had not been completed and the overall recommendation by the Office of Compliance was pending; therefore, he made the following recommendations in his review dated June 18, 2013:

> *The applicant has provided sufficient information to assure the identity, strength, purity, and quality of the drug product.*
>
> *The Office of Compliance has **not** issued made an overall "**Acceptable**" recommendation for the facilities involved in the NDA as of the date of this review.*
>
> *Labels/labeling issues have **not** yet been resolved.*
>
> *Therefore, from the ONDQA perspective, this NDA is **not** recommended for approval per 21 CFR 314.125(b)(1), (13) until the issues delineated above are satisfactorily resolved.*

No post-marketing commitments or risk management strategies were recommended.

Following submission of acceptable labeling, Dr. Holbert submitted an addendum to his review on July 23, 2013, noting that CMC-related labeling issues had been resolved and carton/container labeling was acceptable. The Office of Compliance issues an overall "Acceptable" recommendation on July 9, 2013. He made the following recommendation:

> *This NDA is now recommended for **Approval** from the ONDQA perspective with an expiration dating period of 12 months.*

4. Nonclinical Pharmacology/Toxicology

The Applicant did not conduct any preclinical studies for this NDA, but referenced the NDA for its existing Lo Loestrin Fe product (22-501) to fulfill the requirements for nonclinical evaluation. The active ingredients are the same as those in the NDA 22-501, while the inactive ingredients are either compendial or Generally Recognized as Safe and are at or below the quantities listed in the FDA Inactive Ingredient Database for a chewable or oral tablet.

The primary Toxicology Reviewer, Krishan Raheja, D.V.M., Ph.D., made the following recommendations in his NDA review dated April 19, 2013:

Recommendations on approvability: Pharmacology/Toxicology recommends approved of (b) (4) *under NDA 204654 for the indication of prevention of pregnancy.*

Additional Non Clinical Recommendations: None

Recommendations on labeling: Sponsor has provided drug label in PLR format which is acceptable from the Pharmacology/Toxicology perspective.

5. Clinical Pharmacology/Pharmacometrics

5.1 Clinical Pharmacology

The Applicant submitted a bioequivalence (BE) study, Study PR-12111 to demonstrate that the chewable combination tablets in this NDA (known as (b) (4) 1/10 tablets) are bioequivalent to the combination tablets taken by swallowing with water in the approved product Lo Loestrin Fe. The EE-alone and FF tablets are identical to those used in Lo Loestrin so no demonstration of bioequivalence was needed for those tablets. Study PR-12111 also evaluated the effect of food on the bioavailability of NETA and EE from the (b) (4) 1/10 tablets.

The primary Clinical Pharmacology Reviewer, Li Li, Ph.D., concluded that the NETA and EE exposure with (b) (4) 1/10 tablets was bioequivalent to that obtained with the combination tablets from Lo Loestrin Fe. The 90% confidence intervals for the test:reference ratio for Cmax, AUC0-t and AUC 0-inf were within the 80-125% limit for both NETA and EE when both drugs were administered under fasting conditions. When the bioavailability of (b) (4) 1/10 tablets were compared for fasting and fed conditions (a high fat meal), the fed condition reduced the rate (Tmax), but not the extent of NETA and EE absorption. However, (b) (4) 1/10 tablets administered under fed conditions remained bioequivalent to Lo Loestrin Fe tablets (fasting).

No new drug interaction studies were conducted, nor were studies done to evaluate the impact of renal or hepatic impairment. Information from Lo Loestrin Fe labeling will be provided in the labeling for this chewable product.

Dr. Li stated the following in her review dated June 20, 2013:

The Office of Clinical Pharmacology/Division of Clinical Pharmacology 3 (OCP/DCP3) finds NDA 204654 acceptable provided that agreement is reached between the Sponsor and the Division regarding the language in the package insert..

Dr. Li did not recommend any phase 4 requirements or commitments.

Following submission of acceptable labeling, Dr. Li submitted an addendum to her review on July 24, 2013, noting that labeling issues had been resolved and the final labeling was acceptable. She made the following recommendation:

The Division of Clinical Pharmacology-3, Office of Clinical Pharmacology finds the NDA 204654 acceptable .

6. Clinical Microbiology

No clinical microbiology consult was requested for this oral tablet product.

7. Clinical/Statistical – Efficacy

No new efficacy data was submitted in this NDA; findings of efficacy for NDA 22-501 were bridged through the demonstration of bioequivalence of this chewable combination tablet to the non-chewable tablet in that NDA. The approval of NDA 22-501 was based on a single 13-cycle open label clinical trial that enrolled over 1,600 women and demonstrated a Pearl Index of 2.92 (95% confidence interval [CI] of 1.9-4.2). While this Pearl Index was higher than that for any previously approved COC, the 95% CI were within the range of other approved products. This trial excluded women with a body mass index (BMI) above 35 kg/m^2, and due to concerns about the already-high Pearl Index coupled with lack of data on efficacy in obese women, the Division determined that labeling should include a statement that safety and efficacy in women with BMI > 35 have not been determined.

Team Leader Comment:
The labeling for this chewable tablet should also contain the BMI statements found in Lo Loestrin Fe.

Xin Fang, Ph.D., the statistical reviewer, noted that no new efficacy data were provided in the current NDA and therefore, no statistical review was needed.

8. Safety

The safety database is based on results from Study PR-12111, the pivotal BE study that enrolled 42 healthy volunteers in a three-period, single dose cross-over design, and Study PR-10007, the oral irritation study that enrolled 56 women for a 24-day treatment period.

Team Leader Comment:
Given the safety database for NDA 22-501, the extent of exposure in this NDA is acceptable.

Deaths

There were no deaths in the clinical development program.

Serious Adverse Events

There were no serious adverse events in either study.

AEs leading to Discontinuation

A single subject in Study PR-12111 withdrew due to a mild headache and mild vomiting within the first two hours after dosing with (b) (4) with food. There were no AEs leading to discontinuation in Study PR-10007.

Common AEs

In Study PR-12111, 15 subjects who received the chewable tablet reported AEs (14.6% of those who received the tablet under fasted conditions and 21.4% who received it under fed conditions. Headache was the only AE that occurred in more than one subject.

In Study PR-10007, 21.4% of subjects reported a non-oral-soft-tissue AE (oral irritation is discussed in Section 8.1. AEs were typically respiratory infectious conditions; potential ARs included two cases of tooth fracture and one of tachycardia. The tooth fractures were unrelated to study drug; one occurred while eating chewy candy and one subject chipped a crown while eating an orange two days after dosing had been completed. The case of

tachycardia occurred after dosing had been completed and responded to oxygen; a work-up in the Emergency Department was negative.

Laboratory Testing and Vital Signs

There were no signals of concern in either study.

8.1 ORAL IRRITATION STUDY

Study PR-10007 was conducted using chewable tablets consisting of NETA 1 mg/EE 20 µg administered for 24 days, and was reviewed under NDA 203-667 by Dr. Gerald Willett. Because this study was conducted using a higher dose tablet, it was determined that it would also provide relevant oral safety data for this NDA.

Oral soft tissue examinations were multiple times during the treatment period, and subjects were scored for irritation/inflammation and for abrasions. Dr. Willet noted that the only site with notable inflammation (albeit scored only as erythema plus slight edema, the lowest non-0 score) was the gingiva, and these findings actually improved from screening. There were no oral abrasions reported. Dr. Willett concluded that there were no clinically significant safety findings in this study.

8.2 POSTMARKETING SAFETY FINDINGS

The current chewable product has not been approved for marketing anywhere in the world, so there are no postmarketing safety data on this product. However, safety information has been submitted regularly on the related Lo Loestrin Fe product, and this was reviewed. A 915 review was conducted in September 2012 and noted reports of VTEs (four pulmonary emboli and two deep vein thromboses). Although the risk of VTE is described in COC class labeling, because this product (like Lo Loestrin Fe) contains a particularly low dose of EE, which might be perceived as safer than higher-dose COCs, these reports should be noted in the Adverse Reactions section of labeling.

8.3 SAFETY UPDATE

A 120-day Safety Update was submitted on January 23, 2013, and consisted of updated Lo Loestrin Fe postmarketing safety data. There were no new or ongoing studies with the chewable tablet. No new safety findings or concerns were identified by the Applicant.

Team Leader Comment:

I concur that there is no new safety concern based on the Safety Update.

8.4 OVERALL ASSESSMENT OF SAFETY FINDINGS

The reference swallowed product, Lo Loestrin Fe, has been approved since late 2010, and no new or unexpected safety signals have been identified in postmarketing surveillance or in the 915 review done last fall. There is no reason to anticipate a different safety profile for this chewable version. The limited clinical trials submitted in support of this NDA did not reveal any safety concerns, and the oral irritation study did not demonstrate any adverse findings of concern.

9. Advisory Committee Meeting

An Advisory Committee meeting was not requested for this application, as it does not utilize a novel combination of contraceptive hormones or dose regimen, and it is not the first chewable COC marketed.

10. Pediatrics

The Applicant requested a full waiver of the requirement for pediatric studies. However, the change to a chewable formulation did not trigger PREA; therefore, no pediatric studies were required for this application.

11. Other Relevant Regulatory Issues

The Applicant certified that it did not use any debarred investigators. The Applicant certified that none of the investigators in Studies PR-12111 or PR-10007 had any financial disclosures.

The Office of Scientific Investigation (OSI) inspected the clinical and analytic sites for Study PR-12111. The inspection at the clinical site revealed no deficiencies and no Form FDA-483 was issued. Following the inspection at the analytical site in (b) (4) a Form FDA-483 was issued, and a written response was provided by the facility. The observation of concern was that the site failed to maintain documentation for individual quality control sets (i.e., identity of the spiking solutions used in pre-study qualification runs). The OSI inspector noted that evaluation of quality control stability and accuracy was also made during the actual study and confirmed the results obtained during the pre-study qualification.

Arindam Dasgupta, Ph.D. from OSI made the following overall assessment and general recommendations in his review dated May 30, 2013:

> *Following review and evaluation of the Form FDA-483 observation and response from the analytical site, in my opinion, the clinical and analytical data generated for Study PR-12111 were not affected by the cited deficiency. I recommend that the data for clinical and analytical portion of Study PR-12111 be accepted for further agency review.*

12. Labeling

The Applicant submitted the proposed proprietary name (b) (4) which was found to be unacceptable by the Division of Medication Error Prevention and Analysis (DMEPA). On June 27, 2013, the Applicant requested review of the proprietary name Lo Minastrin Fe, and this was found acceptable by DMEPA.

Final carton and container labeling was submitted on July 16, 2013 and was found acceptable by the DMEPA and CMC reviewers. The label was submitted in the format prescribed by the Physician Labeling Rule (PLR), and was revised in accord with current class labeling for COCs. Input from DMEPA, the Study Endpoints and Labeling Development (SEALD) team and the Office of Prescription Drug Promotion (OPDP) was incorporated in labeling revisions. Agreement on labeling was reached with the Applicant on July 24, 2013.

13. Recommendations/Risk Benefit Assessment

13.1 Recommended Regulatory Action

I recommend that this NDA receive an Approval action.

13.2 Risk Benefit Assessment

By demonstrating bioequivalence with the approved COC Lo Loestrin Fe, the Applicant has successfully bridged the current proposed chewable formulation to the previous findings of safety and efficacy for Lo Loestrin Fe. The safety profile in the two studies conducted in support of this NDA does not reveal any new or unexpected safety signals. The overall risk/benefit profile is acceptable.

13.3 Recommendation for Postmarketing Risk Management Activities

None

13.4 Recommendation for other Postmarketing Study Requirements and Commitments

None

13.5 Recommended Comments to Applicant

None

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/s/

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07/24/2013

AUDREY L GASSMAN
07/24/2013