CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

203667Orig1s000

SUMMARY REVIEW

Cross-Discipline Team Leader Review

Date	May 8, 2013
From	Christina Chang, MD, MPH
Subject	Cross-Discipline Team Leader Review
NDA #	NDA 203-667
Applicant	Warner Chilcott
Date of Submission	July 9, 2012
PDUFA Goal Date	May 9, 2013
Proprietary Name / Established (USAN) names	None proposed; Norethindrone acetate (NA)/ethinyl estradiol (EE), and ferrous (Fe) fumarate
Dosage forms / Strength	Chewable tablet supplied in a 28-day blister pack, containing: 24 active, chewable tablets each containing 1 mg NA/0.02 mg EE 4 placebo, (b) (4) tablets each containing 75 mg Fe fumarate
Proposed Indication(s)	Prevention of Pregnancy
Recommended:	**Approval**

1. Introduction

This is a summary review of a new drug application (NDA) that provides for a chewable tablet formulation of a combination oral contraceptive (COC) for the prevention of pregnancy. The applicant seeks marketing approval for this monophasic, 28-day OC regimen, which consists of one chewable tablet, containing 1 mg norethindrone acetate (NA) and 0.02 mg ethinyl estradiol (EE), taken daily for 24 days followed by one ferrous fumarate (Fe, placebo) tablet taken daily for four days. This chewable tablet product offers an alternative oral dosage form to COC users who may have difficulty swallowing whole tablets.

2. Background

Norethindrone acetate (NA) is a nor-testosterone derivative and ethinyl estradiol (EE) is a synthetic estrogen. Both active ingredients have been used in COC and hormone therapy products for decades. COC products prevent pregnancy primarily by suppressing ovulation and secondarily by altering the cervical mucus (rendering it less penetrable to sperm) and the endometrium (making it less favorable for implantation).

In this NDA, the Applicant seeks to demonstrate acceptable bioequivalence between the approved tablet formulation (Loestrin 24 Fe, NDA 21-871) and the proposed chewable tablet formulation to allow bridging of FDA's findings of safety and efficacy from Loestrin 24 Fe tablet to the new chewable tablet to support the regulatory approval. Loestrin 24 Fe tablet is a COC approved in 2006 for the prevention of pregnancy. The 28-day regimen of Loestrin 24 Fe consists of 24 daily doses of active oral tablets, each containing 1 mg NA/0.02 mg EE, followed by 4 placebo oral tablets, each containing of 75 mg Fe fumarate.

3. CMC/Device

The drug product consists of 24 white chewable tablets, each containing 1 mg NA and 0.02 mg EE, as well as 4 brown placebo tablets, each containing 75 mg Fe fumarate. The tablets are packaged in blister cards, which list the order in which the capsules are to be taken by the patient.

In his review dated April 3, 2013, the primary CMC reviewer (Dr. Raymond Frankewich) concludes that with the exception of tablet debossing and insignificant manufacturing changes, the proposed drug product is identical to approved Loestrin 24 Fe. Dr. Frankewich states that the proposed NA/EE tablet "is the same formulation as Loestrin 24 Fe tablets…The only difference in the tablet proposed in this NDA are the markings." As a result, Dr. Frankewich concludes that a review of biopharmaceutics was not necessary because "the proposed dissolution test and acceptance criteria are the same as the approved product" (Loestrin 24 Fe tablet). With respect to the inactive Fe fumarate tablets, Dr. Frankewich notes that the proposed new formulation differs slightly from the existing Fe fumarate tablet in Loestrin 24 Fe, with the addition of a sweetener and a flavoring component. Dr. Frankewich notes that

neither of these excipients are considered novel. Dr. Frankewich has also reviewed the stability data and determined that the proposed shelf life of 24 months is acceptable.

In an addendum dated May 8, 2013, Dr. Frankewich states that the Office of Compliance has given an overall "Acceptable" recommendation for all the facilities involved in the manufacture and test of the drug substance and drug product.

The CMC review team thus recommends approval for the NDA from a CMC perspective in this May 8, 2013 addendum.

CDTL comment: There are no outstanding CMC issues.

4. Nonclinical Pharmacology/Toxicology

No new nonclinical data were submitted with this NDA. The primary pharmacology/toxicology reviewer (Dr. Krishan Raheja) notes that all excipients in this proposed product have been qualified and that the inactive ingredients are in quantities "below the maximum concentration outlined in FDA's Inactive Ingredients Database." In a review dated March 1, 2013, the pharmacology/toxicology review team recommends approval for this NDA from their perspective.

CDTL comment: There are no outstanding pharmacology/toxicology issues.

5. Clinical Pharmacology/Biopharmaceutics

The Applicant submitted one clinical pharmacology study, PR-08507, to support this application. The primary clinical pharmacology reviewer (Dr. LaiMing Lee) summarized the key findings from this study in her review dated April 9, 2013.

Study PR-08507: This pivotal BE study is a randomized, single-dose, two-way crossover bioequivalence study comparing the proposed product (chewed then swallowed with 8 oz. of water) to Loestrin 24 Fe (swallowed whole) in 35 healthy, nonsmoking, premenopausal females. Given that the to-be-marketed product is essential identical to Loestrin 24 Fe, the aim of Study PR-08507 was to evaluate comparative bioavailability of NA and EE following oral administration of Loestrin tablets when swallowed compared to when chewed prior to swallowing.

Following oral administration of a single dose NA/EE chewable tablet, the mean time to maximum plasma concentrations of NA and EE were reached at 1.03 (standard deviation, SD 0.67 to 2.50) hours and 1.33 (SD 1.00 to 2.50) hours, respectively. For both NA and EE, the geometric mean ratios (the proposed product to Loestrin 24 Fe) were near unity for C_{max}, AUC_{0-t}, and AUC_{0-inf}. For both NA and EE, the 90% confidence intervals for C_{max}, AUC_{0-t}, and AUC_{0-inf} are shown to be within the BE acceptance criteria of 80.00 – 125.00%. The PK parameters from Study PR-08507 are shown in Table 1 (NA) and Table 2 (EE) below.

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Table 1. Summary of BE Analysis of NA PK Parameters Following A Single Dose of the Proposed Product (Chewable NA/EE Tablet) or a Loestrin 24 Fe Tablet (Reference)

Parameter	Geometric Mean		Geometric Mean Ratio (proposed product/reference)	90% CI
	Proposed Chewable Tablet	Reference		
$AUC_{0\text{-tldc}}$ (pg·hr/mL)	44710	43530	1.03	97.9 – 107.3
$AUC_{0\text{-inf}}$ (pg·hr/mL)	45350	45020	1.02	97.3 – 106.9
C_{max} (pg/mL)	9620	9250	1.04	95.9 – 112.2

Proposed Product: chewable tablet (1 mg NA/0.02 mg EE)
Reference: Loestrin 24 Fe tablet (1 mg NA/0.02 mg EE)
Study PR-08507 (N = 35)
Source: Clinical Pharmacology primary review (April 9, 2013), adapted from second table on page 14.

Table 2. Summary of BE Analysis of EE PK Parameters Following a Single Dose of the Proposed Product (Chewable NA/EE Tablet) or a Loestrin 24 Fe Tablet (Reference)

Parameter	Geometric Mean		Geometric Mean Ratio (proposed product/reference)	90% CI
	Proposed Chewable Tablet	Reference		
$AUC_{0\text{-tldc}}$ (pg·hr/mL)	645.0	633.6	1.02	97.6 – 106.0
$AUC_{0\text{-inf}}$ (pg·hr/mL)	703.8	739.1	0.97	91.5 – 103.5
C_{max} (pg/mL)	82.5	79.7	1.04	98.9 – 108.4

Proposed Product: chewable tablet (1 mg NA/0.02 mg EE)
Reference: Loestrin 24 Fe tablet (1 mg NA/0.02 mg EE)
Study PR-08507 (N = 35)
Source: Clinical Pharmacology primary review (April 9, 2013), adapted from second table on page 15.

Dr. Lee concludes that bioequivalence between the proposed NA/EE chewable tablets and the approved Loestrin 24 Fe tablets has been established. The clinical pharmacology review team finds "this NDA acceptable from a clinical pharmacology perspective."

CDTL comment: There are no outstanding clinical pharmacology issues. Results from this pivotal BE study demonstrate that the proposed product is pharmaceutically equivalent to Loestrin 24 Fe. Establishment of bioequivalence between the chewable tablet and Loestrin 24 Fe allows a regulatory conclusion of therapeutic equivalence.

6. Clinical Microbiology

A clinical microbiology review was not necessary for this NDA.

7. Clinical/Statistical- Efficacy

The primary statistical reviewer (Dr. Sonia Castillo) notes that efficacy of the proposed product is bridged to the Agency's findings of efficacy for Loestrin 24 Fe based on the establishment of bioequivalence between the two products. In a memo dated December 13, 2012, Dr. Castillo states that "There are no new efficacy issues to address in this application, so no statistical review of efficacy is necessary."

CDTL comment: There are no outstanding statistical issues.

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8. Safety

The safety profiles of norethindrone and ethinyl estradiol, the two drug substances in this COC, have been well characterized in women of reproductive age with decades of U.S. and ex-U.S. marketing experience. Safety issues related to COCs, particularly vascular events (such as thromboembolism and stroke), hepatic events (such as adenomas and cholestasis), and migraine headaches, are long-recognized and already included in all COC labels. Loestrin 24 Fe, the referenced drug for this proposed product, has been marketed since 2006 without triggering new safety concerns.

In this NDA, the Applicant submitted two studies to support safety, which were evaluated by the primary reviewer for clinical safety (Dr. Gerald Willett). Study PR-08507 is the pivotal BE study; Study PR-1007 is a supportive safety study to assess the oral irritation potential of this proposed formulation. A total of 95 women were exposed to the proposed formulation in the two studies. Dr. Willett noted that there were no deaths, serious adverse events, or discontinuations due to adverse events in either study. The nature and proportions of adverse events reported in these studies were consistent with current COC labeling and did not raise any new safety concerns. Other safety assessments, including vital signs, laboratory evaluations, and ECG measurements, were also reassuring.

Dr. Willett also reviewed supplementary safety information, which include the 4-month safety update and applicant's postmarketing pharmacovigilance data for Loestrin 24 Fe from February, 2006 through October, 2012. He states that "the types of drug-related adverse events and relative proportions are similar to other COC postmarketing reports."

Dr. Willett recommends an approval action for this NDA without any postmarketing requirements or risk management strategies.

CDTL comment: COC products containing NA/EE (in same or higher concentrations) have been extensively marketed worldwide; the safety profiles of these products are well documented. I concur with Dr. Willett that, from the clinical perspective, there are no outstanding issues precluding the approval of this application.

9. Advisory Committee Meeting

No Advisory Committee was held to discuss this application as expert advice was not needed.

10. Pediatrics

Neither Loestrin 24 Fe tablet nor the proposed chewable tablet has been evaluated in post-menarchal adolescents under the age of 18. The Applicant requested a full waiver for the required pediatric studies. The Division agreed with the Applicant's rationale that efficacy and safety of the proposed chewable tablet product in post-menarchal adolescents are expected to be the same as that established in women aged 18 to 35 years.

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In an electronic mail to the Division dated February 4, 2013, the Pediatric Review Committee (PeRC) conveyed their agreement with the Division's assessment, thereby granting the Applicant a full pediatric waiver.

11. Other Relevant Regulatory Issues

No Good Clinical Practice (GCP)-related irregularities are noted in the two studies (PR-08507 or PR-10007) submitted to support this application. In addition, the Applicant has certified to not having any financial arrangement with any investigators involved in either study whereby the value of compensation to the investigator could affect the outcome of the study.

During the audit of the bioanalytical site for the pivotal BE study (PR-08507), the Office of Scientific Investigation (OSI) identified issues with samples from four subjects. OSI recommended that data from two subjects be excluded from pharmacokinetic calculations and the data from two other subjects be recalculated. On February 19, 2013, the Applicant submitted an amended dataset and study report. The amended study report provides updated pharmacokinetic data, which were recalculated according to OSI's recommendations. Data from this amended study report formed the basis of the approval recommendation from the clinical pharmacology review team.

12. Labeling

No proprietary name has been proposed by the Applicant. Therefore, a trade name review customarily conducted by the Division of Medication Error Prevention and Analysis (DMEPA) in the Office of Surveillance and Epidemiology (OSE) is not necessary.

Submitted label and labeling for the proposed chewable tablet included the following components:

- Trade and professional sample blister card
- Trade and professional sample carton
- Package Insert (PI)
- Patient Package Insert (PPI)

The Applicant's proposed labeling is in the PLR format, and its content is based on the content of current labeling of Loestrin 24 Fe. Each discipline in the review team examined their respective sections of the labeling. DMEPA, the Office of Prescription Drug Promotion (OPDP), and the Study Endpoint and Labeling Development Team (SEALD) also provided a comprehensive review of the submitted materials.

Recommendations from all review disciplines related to labeling were communicated to the Applicant. Final labeling was agreed upon on May 6, 2013.

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13. Recommendations/Risk Benefit Assessment

13.1 Recommended Regulatory Action

I concur with the clinical, clinical pharmacology, CMC, and pharmacology/toxicology review teams that the proposed product **should be approved** for the prevention of pregnancy in women of reproductive age.

13.2 Risk/Benefit Assessment

By providing a new method of use, the proposed product will expand the therapeutic options for women who cannot or will not swallow a whole COC tablet but wish to use a COC with an iron supplementation for prevention of pregnancy. Results of the pivotal BE study demonstrated that pharmaceutical bioequivalence between the proposed product and Loestrin 24 Fe has been established. This finding ensures therapeutic equivalence between these two products and allows a clinical bridge of the Agency's findings of efficacy and safety between the two products.

The safety of combination oral contraceptive products containing norethindrone and ethinyl estradiol in various doses and regimens (including Loestrin 24 Fe, the referenced product) is well-established in the intended population. The safety data from the clinical pharmacology studies submitted in this application do not raise any new concerns.

I conclude that the proposed product, when used in accordance with approved product labeling, can be a safe and effective oral contraceptive product. The benefit-risk evaluation favors the approval of this new product.

13.3 Recommendations for Postmarketing Requirements and Commitments

None.

13.4 Recommendations for Postmarketing Risk Evaluation and Management Strategies

None.

13.5 Recommended Comments to the Applicant

None.

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

/s/

CHRISTINA Y CHANG
05/08/2013

AUDREY L GASSMAN
05/08/2013
I concur with the CDTL's review and approval recommendation