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APPLICATION NUMBER:

204426Orig1s000

SUMMARY REVIEW

Cross-Discipline Team Leader Review

Date	April 19, 2013
From	Christina Chang, M.D., M.P.H.
Subject	Cross-Discipline Team Leader Review
NDA #	NDA 204-426
Applicant	Warner Chilcott
Date of Submission	June 21, 2012
PDUFA Goal Date	April 21, 2013
Proprietary Name / Established (USAN) names	MINASTRIN 24 FE Norethindrone acetate (NA)/ethinyl estradiol (EE), and ferrous (Fe) fumarate
Dosage forms / Strength	Oral Capsules supplied in a 28-day blister pack, containing: 24 active capsules each containing 1 mg NA/0.02 mg EE 4 placebo capsules each containing 75 mg Fe fumarate
Proposed Indication(s)	Prevention of Pregnancy
Recommended Regulatory Action:	**Approval**

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1. Introduction

This is a summary review of a new drug application (NDA) that provides for a new dosage form of combination oral contraceptive (COCs) for the prevention of pregnancy. The Applicant seeks marketing approval for this 28-day COC regimen, which consists of one capsule, containing 1 mg norethindrone acetate (NA) and 20 mcg ethinyl estradiol (EE), taken daily for 24 days followed by one ferrous fumarate (Fe, placebo) capsule taken daily for four days. If approved, this product would be the first COC marketed as a capsule.[1]

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).

Loestrin 24 Fe is a COC approved in 2006 for the prevention of pregnancy under NDA 21-871. 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. In this NDA, the Applicant seeks to demonstrate acceptable bioequivalence between the approved tablet formulation (Loestrin 24 Fe) and the proposed capsule formulation (Minastrin 24 Fe) to bridge FDA's findings of safety and efficacy of the oral tablet to the capsule formulation to support the regulatory approval for Minastrin 24 Fe.

3. CMC/Device

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

The CMC review team has determined that the application contains sufficient CMC information to assure the identity, strength, purity, and quality of the drug product. The primary CMC reviewer (Dr. Yichun Sun) states that the Drug Master Files containing detailed CMC information related to the composition, manufacture process, and in-process controls of both the active and placebo capsules are adequate.

The Applicant amended this NDA on February 11, 2013, to include information on photostability of the product. Exposure to ultraviolet light and visible light resulted in significant degradation in the NA component in the active capsule (b) (4) . In contrast, the EE component was photo-stable. In response to this finding and to ensure product protection from light exposure, the Applicant modified the packaging to include an additional cardboard carton. The labeling was also amended to instruct patients to store the product in a (b) (4) wallet for enhanced protection from

[1] A search of combination oral contraceptive products listed in Drugs@FDA by this medical officer (accessed on February 5, 2012) revealed no approved capsule formulations.

light when not using the product. Dr. Sun reviewed the photostability information as well as the labeling modification and found both to be acceptable. Dr. Sun determined that the proposed expiration dating period of 18 months for the drug product is supported by the stability data provided.

In an addendum dated April 19, 2013, Dr. Sun 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 April 19, 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 there are no novel excipients in the capsule formulation and that the inactive ingredients are in quantities that are below the maximum potency specified in FDA's Inactive Ingredient Database. The pharmacology/toxicology team recommends approval for this NDA from their perspective in a review dated November 23, 2012.

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

5. Clinical Pharmacology/Biopharmaceutics

The Applicant submitted two clinical pharmacology studies to support approval of Minastrin 24 Fe: (1) the pivotal bioequivalence (BE) study PR-00810 using Loestrin 24 Fe tablet as reference and (2) the food effect study PR-06011. The bioanalytical methods used in these studies comply with FDA's *Bioanalytical Method Validation Guidance*. Key findings from these two studies are summarized below:

Study PR-00810: This pivotal BE study was a two-way crossover study in 38 healthy, non-smoking, premenopausal females who received a single-dose tablet (Loestrin 24 Fe) or capsule (Minastrin 24 Fe) administration in a sequential manner under fasting condition. For Minastrin 24 Fe, mean time to maximum concentrations of NA and EE were reached at 1.1 (standard deviation 0.7 to 4.0) hours and 2.0 (SD 1.0 to 4.0) hours, respectively.

The primary clinical pharmacology reviewer (Dr. Chongwoo Yu) concludes that pharmacokinetic bioequivalence between Minastrin 24 Fe capsule and the approved Loestrin 24 Fe tablet was established. For both NA and EE, the 90% confidence intervals (CI) were within the acceptable BE limits of 80.00% to 125.00% for AUC_{tldc}, AUC_{inf}, and C_{max}, as shown in
Table 1 (NA) and Table 2 (EE) below.

Table 1. Summary of BE Analysis of NA PK Parameters Following a Single Dose of a Minastrin 24 Fe Capsule (Proposed product) or a Loestrin 24 Fe Tablet (Reference)

Parameter	Geometric Mean		LSM Ratio x 100 (Test/Reference)	90% CI
	Test	Reference		
$AUC_{0\text{-}tldc}$ (pg·hr/mL)	38711	42500	91.1	87.4-94.9
AUC_{inf} (pg·hr/mL)	39399	43128	91.4	87.6-95.3
C_{max} (pg/mL)	8588	8014	107.2	100.0-114.9

Test: One MINASTRIN 24 Fe capsule (1 mg NA/20 µg EE; Formulation: WC3042-05)
Reference: One Loestrin® 24 Fe tablet (1 mg NA/20 µg EE; Formulation: WC2061)
LSM: Least-square means
Study 00810; N = 38
Source: Clinical Pharmacology primary review (January 10, 2013), adapted from Table 8.

Table 2. Summary of BE Analysis of EE PK Parameters Following a Single Dose of a Minastrin 24 Fe Capsule (Proposed product) or a Loestrin 24 Fe Tablet (Reference)

Parameter	Geometric Mean		LSM Ratio x 100 (Test/Reference)	90% CI
	Test	Reference		
$AUC_{0\text{-}tldc}$ (pg·hr/mL)	503.2	520.5	96.7	92.1-101.6
AUC_{inf} (pg·hr/mL)[a]	576.7	580.4	99.4	94.2-104.8
C_{max} (pg/mL)	59.1	64.5	91.7	86.8-97.0

Test: One MINASTRIN 24 Fe capsule (1 mg NA/20 µg EE; Formulation: WC3042-05)
Reference: One Loestrin® 24 Fe tablet (1 mg NA/20 µg EE; Formulation: WC2061)
LSM: Least-square means
[a] N=32 as a terminal phase rate constant could not be determined for 4 subjects who received the Test treatment and 2 subjects who received the Reference treatment
Source: Clinical Pharmacology primary review (January 10, 2013), adapted from Table 9.

Study PR-06011: This food effect study was a randomized, two-treatment crossover, bioavailability study in 24 healthy, premenopausal females. Dr. Yu states that "When Minastrin 24 Fe capsules were administered with a high fat and high calorie meal, the median T_{max} values were delayed by 2 hours and 1.5 hours for NA and EE, respectively, and C_{max} values were decreased 35% and 34% for NA and EE, respectively." Dr. Yu notes, however, that "food intake did not affect the AUCs of NA and EE as the 90% CIs were within the BE limits of 80.00-125.00%." Dr. Yu concludes that, although the rate of NA and EE absorption was affected by administration with food, the overall extent of NA and EE absorption was not affected. Noting that the efficacy of Loestrin 24 Fe (the reference product) was demonstrated without regard of food intake,[2] Dr. Yu does not recommend new dosing directions based on food intake.

The Applicant did not conduct any distribution, metabolism, or excretion studies, as these pharmacokinetic parameters of NA and EE are expected to be the same as Loestrin 24 Fe. The Applicant also did not conduct any drug-drug interaction studies, drug-disease interaction studies (i.e., in patients with renal or hepatic impairment), or pediatric studies with Minastrin 24 Fe capsule.

The clinical pharmacology team recommends approval from a clinical pharmacology perspective in a review dated January 10, 2013. The team did not recommend any postmarketing requirements or commitments for this application.

[2] The phase 3 study, PR-03903, submitted to NDA 21-871 for Loestrin 24 Fe, was conducted without regard to food intake. The current Loestrin 24 Fe label, under the Dosage and Administration section, states that "Loestrin 24 Fe may be administered without regard to meals."

The biopharmaceutics review team (Dr. Elsbeth Chikhale) determined that applicant's proposed dissolution methodology and dissolution acceptance criteria are acceptable and recommends approval of the NDA from a biopharmaceutics perspective in a review dated March 6, 2013.

CDTL comment: The pivotal BE study was conducted in accordance to the Bioavailability and Bioequivalence Guidance (March 2003). The study results show that Minastrin 24 Fe is pharmaceutically equivalent to Loestrin 24 Fe. This demonstration of bioequivalence allows a regulatory conclusion of therapeutic equivalence.

There are no outstanding clinical pharmacology or biopharmaceutic issues.

6. Clinical Microbiology

A clinical microbiology review was not necessary for this NDA.

7. Clinical/Statistical- Efficacy

The primary statistical reviewer (Dr. Kate Dwyer) notes that efficacy of Minastrin 24 Fe 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 November 27, 2012, Dr. Dwyer concludes that "There was no new clinical efficacy data submitted in support of this submission. Therefore, no statistical review is necessary."

CDTL comment: There are no outstanding statistical issues.

8. Safety

Combination oral contraceptives (COCs) containing NA and EE have been marketed since 1976. The safety profiles of these two drug substances in reproductive aged women for prevention of pregnancy have been well characterized. The safety of Minastrin 24 Fe is bridged to the Agency's findings of safety for Loestrin 24 Fe by establishing bioequivalence between the two products.

Safety assessment of the two clinical pharmacology studies included in this application was conducted by the primary clinical reviewer (Dr. Daniel Davis). Dr. Davis reviewed safety data from a total of 66 women exposed to Minastrin 24 Fe in the two single-dose crossover studies. There were no deaths, nonfatal serious adverse events, or discontinuation due to adverse events. Only mild adverse events were reported; the most common events were nausea, headache, acne, venipuncture reactions, and abdominal pain. Other safety assessments, including vital signs, laboratory evaluations, and ECGs measurements, did not raise new safety concerns.

Dr. Davis concludes that the "overall nature and frequency of adverse events seen were consistent with what would be expected in subjects receiving orally administered norethindrone acetate (NA) and ethinyl estradiol (EE)." He recommends an approval action

for this application. He does not consider any postmarketing requirement, postmarketing commitment, or risk evaluation and mitigation strategies (REMS) to be necessary.

CDTL comment: Approved COC products containing NA/EE (in same or higher concentrations) have been extensively marketed in the US and worldwide for decades; safety profiles with these products are well documented. I concur with Dr. Davis' conclusion 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 required.

10. Pediatrics

Neither Loestrin 24 Fe tablet nor Minastrin 24 Fe capsule 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 Minastrin 24 Fe in post-menarchal adolescents are expected to be the same as that established in women aged 18 to 35 years.

The Pediatric Review Committee (PeRC) granted a full pediatric waiver for Minastrin 24 Fe on February 20, 2013.

11. Other Relevant Regulatory Issues

The Office of Scientific Investigations (OSI)/Division of Bioequivalence and GLP Compliance conducted an audit of the pivotal bioequivalence study (Study PR-00810); both clinical and bioanalytical study sites associated Study PR-00810 were inspected. Per the December 11, 2012, OSI memo (Dr. Michael Skelly), OSI concluded that there were no data integrity issues relating to the pharmacokinetic data from Study PR-00810.

12. Labeling

The proposed proprietary name – Minastrin 24 Fe – received conditional approval from the Division of Medication Error Prevention and Analysis (DMEPA) in the Office of Surveillance and Epidemiology on December 13, 2012. In a review dated February 25, 2013, DMEPA issued a final approval action for this name.

Submitted label and labeling for Minastrin 24 Fe included the following elements:

- 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 Loestrin 24 Fe (which is in a non-PLR format). 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 (including DMEPA, OPDP, and SEALD) related to labeling were communicated to the Applicant. Final labeling was agreed upon on April 16, 2013.

13. Recommendations/Risk Benefit Assessment

13.1 Recommended Regulatory Action

I concur with the Clinical, Clinical Pharmacology, Pharmacology/Toxicology, CMC, and Statistical review teams that Minastrin 24 Fe **should be approved** for the prevention of pregnancy in reproductive age women.

13.2 Risk/Benefit Assessment

Minastrin 24 Fe, as a new dosage form, will expand the therapeutic options for women who wish to use a COC capsule with an iron supplementation for prevention of pregnancy. Results of the pivotal BE study demonstrated that pharmaceutical bioequivalence between Minastrin 24 Fe capsule and the approved Loestrin 24 Fe tablet has been established for an orally administered product. This finding ensures therapeutic equivalence between these two products and allows a clinical bridge of the Agency's findings of efficacy and safety between Loestrin 24 Fe and Minastrin 24 Fe.

The safety of combination oral contraceptive products containing norethindrone and ethinyl estradiol in various doses and regimens (including Loestrin 24 Fe) is well-established in the intended population. More recently, ferrous fumarate has been added to several COC regimens, without evidence that this substance compromises the safety of COCs. The safety data from the clinical pharmacology studies submitted in this application do not raise any new concerns.

I conclude that Minastrin 24 Fe, 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 Minastrin 24 Fe.

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.

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/s/

CHRISTINA Y CHANG
04/19/2013

AUDREY L GASSMAN
04/19/2013
I concur with the recommendation in this review