CLINICAL REVIEW

Application Type	NDA
Application Number(s)	22-501 (Class 2 Resubmission)
Priority or Standard	Standard
Submit Date(s)	April 20, 2010
Received Date(s)	April 21, 2010
PDUFA Goal Date	October 21, 2010
Division / Office	Reproductive and Urologic Products/Office of New Drugs
Reviewer Name(s)	Ronald J. Orleans, M.D.
Review Completion Date	October 4, 2010
Established Name	Norethindrone acetate/ethinyl estradiol; ethinyl estradiol; ferrous fumarate
(Proposed) Trade Name	Lo Loestrin Fe
Therapeutic Class	Oral Contraceptive
Applicant	Warner Chilcott Company, Inc.
Formulation(s)	Twenty-four days of norethindrone acetate 1 mg/ethinyl estradiol 10 mcg tablets followed by two days of ethinyl estradiol 10 mg tablets followed by two days of ferrous fumarate tablets
Dosing Regimen	One tablet daily
Indication(s)	Prevention of Pregnancy
Intended Population(s)	Women of reproductive age at risk for pregnancy who desire contraception

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1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

In the original review of NDA 22-501, approval of Lo Loestrin Fe for prevention of pregnancy was recommended from the clinical perspective, based on Warner Chilcott (the Applicant) having demonstrated an acceptable Pearl Index and an acceptable safety profile for this product.

However, from a CMC perspective, this NDA was not recommended for "Approval" until the manufacturing facility and the control testing laboratory used to support the Application were in full compliance with cGMP requirements to assure the identity, strength, purity, and quality of the drug product. Therefore, the Applicant was sent a "Complete Response" letter.

This class 2 resubmission documents the Applicant's response to the complete response letter. The present submission contained no new efficacy or safety data. Therefore, from the clinical perspective, this Reviewer again recommends approval.

1.2 Risk Benefit Assessment

The Pearl Index for Lo Loestrin Fe was derived from the Pregnancy Intent to Treat Population (PITT), which consisted of all women ages 18-35 who completed at least one full cycle of therapy (N=1,270). All 28-day cycles in which subjects used additional back-up methods of birth control (including condoms) and all incomplete 28-day cycles (except those in which conception occurred) were excluded from the denominator used in the Pearl Index calculation. A total of 1,270 subjects took the study medication over 12,482 completed 28-day cycles. Twenty-eight (28) on-drug conceptions occurred during this clinical trial.

Based on the 28 pregnancies that occurred over 12,482 completed cycles, the Pearl Index was calculated by the FDA Statistician to be **2.92 (95% CI 1.94, 4.21)**. The life-table pregnancy rate was calculated to be 2.71 (95% CI 1.86, 3.95). The Pearl Index and the life-table analysis computations are comparable to those of other approved low dose oral contraceptive products and support the efficacy of Lo Loestrin Fe in preventing pregnancy.

The primary clinical trial also demonstrated that the safety profile of Lo Loestrin Fe was acceptable. No deaths occurred during the trial. The number of early withdrawals, and the frequency and type of adverse events leading to withdrawals, were comparable to other low dose combined oral contraceptives and did not raise any new or unexpected safety concerns.

In the Medical Reviewer's opinion, the original Application demonstrated that Lo Loestrin Fe was a safe and effective oral contraceptive and approval based on the clinical trial data was recommended.

1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies

No postmarketing risk evaluation and mitigation strategies were recommended.

1.4 Recommendations for Postmarket Requirements and Commitments

Standard post-marketing surveillance was recommended. No specific risk management steps were recommended.

2 Introduction and Regulatory Background

2.1 Product Information

Lo Loestrin Fe is a low dose oral contraceptive (OC) consisting of a new regimen of the combination of norethindrone acetate (NA) and ethinyl estradiol (EE). A tablet containing 10 mcg of EE in combination with 1 mg of NA is taken for 24 days, followed by a tablet containing 10 mcg of EE taken for 2 days, followed by a tablet containing ferrous fumarate 75 mg taken for 2 days. The proposed indication is for the prevention of pregnancy in women who elect to use oral contraceptives as a method of contraception.

2.2 Tables of Currently Available Treatments for Proposed Indications

Table 1 Combination 28-Day Oral Contraceptives Containing EE/NA

NDA/ANDA	Proprietary Name	Approval Date	EE Strength (mg)	NA Strength (mg)	Marketing Status
NDA 20-130	Estrostep 21	1996	0.02, 0.03, 0.035	1, 1, 1	Discontinued*
NDA 20-130	Estrostep Fe	1999	0.02, 0.03, 0.035	1, 1, 1	Prescription
NDA 17-875	Loestrin 21 1.5/30	1976	0.03	1.5	Prescription
NDA 17-876	Loestrin 21 1/20	1976	0.02	1.0	Prescription
NDA 17-355	Loestrin Fe 1.5/30	1973	0.03	1.5	Prescription
NDA 17-354	Loestrin Fe 1/20	1973	0.02	1	Prescription
NDA 21-871	Loestrin 24 Fe	2006	0.02	1.0	Prescription
NDA 16-749	Norlestrin 21 1/50	Prior to 1982	0.05	1.0	Discontinued*
NDA 16-852	Norlestrin 21 2.5/50	Prior to 1982	0.05	2.5	Discontinued*

NDA/ANDA	Proprietary Name	Approval Date	EE Strength (mg)	NA Strength (mg)	Marketing Status
NDA 16-723	Norlestrin 28 1/50	Prior to 1982	0.05	1.0	Discontinued*
NDA 16-766	Norlestrin Fe 1/50	Prior to 1982	0.05	1.0	Discontinued*
NDA 16-854	Norlestrin Fe 2.5/50	Prior to 1982	0.05	2.5	Discontinued*
ANDA 76381	Junel 1.5/30	2003	0.30	1.5	Prescription
ANDA 76380	Junel 1/20	2003	0.20	1.0	Prescription
ANDA 76064	Junel Fe 1.5/30	2003	0.30	1.5	Prescription
ANDA 76081	Junel Fe 1/20	2003	0.20	1.0	Prescription
ANDA 75647	Microgestin 1/20 Microgestin Fe 1/20	2001	0.20	1.0	Prescription
ANDA 75548	Microgestin 1.5/30 Microgestin Fe 1.5/30	2001	0.03	1.5	Prescription
ANDA 76405	Tri-Legest 21	2007	0.02, 0.03, 0.035	1, 1, 1	Prescription
ANDA 76105	Tri-Legest Fe	2007	0.02, 0.03, 0.035	1, 1, 1	Prescription
ANDA 77075	NA and EE and Fe	2005	0.3	1.5	Prescription
ANDA 77077	NA and EE and Fe	2005	0.2	1.0	Prescription
ANDA 78267	NA and EE and Fe	2009	0.2	1.0	Prescription

Source: Medical Reviewer compilation from http://www.accessdata.fda.gov/scripts/cder/drugsatfda/
*Federal Register determination that product was not discontinued or withdrawn for safety or efficacy reasons.

2.3 Availability of Proposed Active Ingredient in the United States

The active ingredients for this drug product, EE and NA, have been used in OC products for almost four decades. There is an extensive body of knowledge relating to the safety of both active ingredients in the doses proposed.

2.4 Important Safety Issues with Consideration to Related Drugs

The most significant adverse events are the potential thomboembolic and cardiovascular complications. Serious adverse events have decreased with reduction in daily doses of EE and progestins.

2.5 Summary of Presubmission Regulatory Activity Related to Submission

See the Medical Officer's Review, dated 1/9/09, of the original NDA submission.

2.6 Other Relevant Background Information

NDA 22-501 was received by FDA on March 26, 2009. The original PDUFA goal date was 1/26/2010. From a clinical perspective, the Application was recommended for approval based on the submitted safety and efficacy data from the primary phase 3 clinical trial, PR-05806.

However, from a CMC perspective, this NDA was not recommended for "Approval" until the manufacturing facility and the control testing laboratory used to support the Application were in full compliance with cGMP requirements to assure the identity, strength, purity, and quality of the drug product. Therefore, the Division determined that the Application could not be approved in its present form. On 1/26/10, a "Complete Response "letter was sent to the Applicant. For further details, see Section 4.1, Chemistry Manufacturing and Controls.

3 Ethics and Good Clinical Practices

Not applicable, as no new clinical or nonclinical data were submitted.

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Chemistry Manufacturing and Controls

The primary Chemistry reviewer, Yubing Tang PhD, made the following recommendations in her initial primary review signed on 1/8/2010:

> "This NDA has provided sufficient CMC information to assure the identity, strength, purity, and quality of the drug product. Labels have adequate information as required. However, the overall "Acceptable" recommendation has not been made by the Office of Compliance as of this review."

Therefore, from a CMC perspective, this NDA was not recommended for "Approval" until all the facilities involved were fully in compliance with cGMP requirements to assure the identity, strength, purity, and quality of the drug product. The NDA could not

be approved until the issues cited by the Office of Compliance were resolved and an "Acceptable" recommendation was made by the Office of Compliance.

During inspections of a drug substance manufacturing facility and a control testing laboratory used to support this application, the Office of Compliance field investigators conveyed deficiencies to the representatives of the respective facilities. These deficiencies were not resolved. Satisfactory resolution of these deficiencies was required before the NDA can be approved.

On 1/19/2010, the Office of Compliance issued an overall rating of "Withhold" approval. The recommendation by the Office of Compliance was based on:
(1) the failure of the contract manufacturer, (b) (4) of the drug substances (NA and EE) to adhere to current GMPs and
(2) a secondary contract drug substance testing site not being ready to conduct testing for the Applicant's product.

On 1/21/2010, the Applicant submitted by e-mail a proposal to address the deficiencies. The proposal included:
(1) Withdrawal of (b) (4) as a supplier of the drug substances and withdrawal of (b) (4) as a testing site,
(2) Listing only (b) (4) as the sole supplier of the drug substance for Lo Loestrin, and
(3) Using presently available stability data from a single batch of drug product that had been manufactured using (b) (4) drug substance.

The Applicant was informed that prior to approval of NDA 22-501, data from 3 batches of drug product manufactured with (b) (4) drug substance would need to be submitted and reviewed by the Agency if (b) (4) were to be the sole supplier of drug substance for Lo Loestrin Fe.

A "Complete Response" letter was therefore sent to the Applicant on 1/26/2010. This letter detailed several drug substance manufacturing deficiencies.

Warner Chilcott provided a complete response to the deficiencies noted in the Complete Response letter and resubmitted NDA 22-501 on 4/20/2010. In the submission, the Applicant stated that:

(1) (b) (4) has received correspondence that deficiencies cited in the 8/5/2009 (b) (4) facility have been addressed.
(2) (b) (4) is being withdrawn from NDA 22-501 and that all analytical testing of drug substances will be performed by (b) (4)

The CMC Reviewer, Yubing Tang, Ph.D. stated in her review of 9/16/2010 that "Now, the Office of Compliance has made the overall "Acceptable" recommendation. Therefore, from the CMC perspective, this NDA is recommended for approval."

5 Sources of Clinical Data

Not applicable, as the resubmission of NDA 22-501 contained no new clinical data.

5.2 Review Strategy

The complete, class 2 response to the 1/26/2010 action letter was received on 4/21/2010. This submission was reviewed.

5.3 Discussion of Individual Studies/Clinical Trials

No new studies or clinical trials were submitted.

6 Review of Efficacy

Efficacy Summary

Based on the 28 pregnancies that occurred over 12,482 completed cycles, the Pearl Index was calculated by the FDA Statistician to be **2.92 (95% CI 1.94, 4.21)**. The life-table pregnancy rate was calculated to be 2.71 (95% CI 1.86, 3.95).

6.1 Indication

The indication for Lo Loestrin Fe is for the prevention of pregnancy in women who elect to use oral contraceptives as a method of contraception. The Applicant submitted data from one primary phase 3 clinical trial report (Report # RR-03108) in support of this indication. Details of the medical review of the primary clinical trial can be found in the review by Dr. Ronald J. Orleans, dated 1/9/2010. No new studies or clinical trials were included in the recent submission.

7 Review of Safety

Safety Summary

The published literature concerning OCs clearly identifies the risks associated with the use of OCs. The most serious of these risks include arterial and venous thrombosis. However, the risk of serious morbidity or mortality is small in healthy women without underlying risk factors and is exceeded by the risks of pregnancy.

A full safety review of the clinical data submitted in the first review cycle is described in the review by Dr. Ronald J. Orleans, dated 1/9/2010. There were no deaths during the clinical development of Lo Loestrin Fe. The results of the phase 3 clinical trial did not indicate any safety concerns beyond those commonly attributed to OCs. Lo Loestrin Fe has been demonstrated to be a safe oral contraceptive when taken over 13 cycles.

7.1 Methods

A Safety Update was enclosed with the submission. There were no new nonclinical or clinical studies conducted or initiated at the time of the submission.

7.7 Additional Submissions / Safety Issues

NDA 22-501 was resubmitted for review on 4/20/2010 (SDN-20). A Safety Update was enclosed with the submission. There were no nonclinical or clinical studies conducted or initiated at the time of the submission.

A recent review of the clinical and non clinical literature was conducted by the Applicant through January 31, 2010, which did not identify new significant safety information.

There is extensive postmarketing experience with the 28-day combination OC formulations containing EE 20 mcg /NA 1mg. No worrisome safety signals have emerged from this extensive postmarketing experience.

8 Postmarket Experience

Lo Loestrin Fe tablets are not marketed outside the United States.

9 Appendices

9.2 Labeling Recommendations

Labeling negotiations are currently in progress. Clinical issues under discussion include revising the label for consistency with recently approved combination oral contraceptive PLR labels, defining and standardizing the terms used to describe the bleeding profile and adding some clarification to the DOSAGE AND ADMINISTRATION section.

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

/s/

RONALD J ORLEANS
10/12/2010

LISA M SOULE
10/12/2010
I concur with Dr. Orleans' recommendation that NDA 22-501 be approved for the prevention of pregnancy in women.