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APPLICATION NUMBER:

022501Orig1s000

MEDICAL REVIEW(S)

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 (b) (4) (b) (4)

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*

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