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APPLICATION NUMBER:

022501Orig1s000

SUMMARY REVIEW

Summary Review for Regulatory Action

Date	October 21, 2010
From	Scott Monroe, MD
Subject	Division Director Summary Review
NDA	NDA 022501
Applicant Name	Warner Chilcott Company, LLC
Date of Submission	April 20, 2010 (Class 2 resubmission)
PDUFA Goal Date	October 21, 2010
Proprietary Name	Lo Loestrin Fe
Established (USAN) Name	Norethindrone acetate (NA) and ethinyl estradiol (EE) tablets/EE tablets/ferrous fumarate (Fe) tablets
Dosage Forms/Strengths	Oral Tablet: 1 mg NA+10 µg EE tablet x 24 days, 10 µg EE tablet x 2 days, 75 mg Fe tablet x 2 days
Proposed Indication(s)	Use by women to prevent pregnancy
Proposed Regimen	See "Dosage Forms/Strengths"
Action	***Approve (see Section 13.1)***

Material Reviewed/Consulted OND Action Package, including:	**Names of Discipline Reviewers**
Medical Officer Review	Ronald Orleans MD (primary Clinical Reviewer)
Statistical Review	Kate Dwyer PhD/Mahboob Sobhan PhD
Pharmacology/Toxicology Review	Krishan Raheja DVM/PhD/Lynnda Reid PhD
CMC Review/OBP Review	Yubing Tang PhD/Moo-Jhong Rhee PhD
Microbiology Review	Vinayak Pawar PhD
Clinical Pharmacology Review	Sandhya Apparaju PhD/Myong-Jin Kim PharmD
DDMAC	Janice Maniwang PharmD/Carrie Newcomer PharmD
DSI	Not requested
CDTL Review	Lisa Soule MD (also Clinical Team Leader)
OSE/DMEPA	Tara Turner PharmD/Zachary Oleszczuk PharmD/Denise Toyer PharmD
OSE/DRISK	Robin Duer MBA, RN/LaShawn Griffiths, MSHS-PH, RN/Mary Willy PhD

OND=Office of New Drugs
CMC=Chemistry, Manufacturing and Control
DDMAC=Division of Drug Marketing, Advertising, and Communication
DSI=Division of Scientific Investigations
CDTL=Cross Discipline Team Leader
OSE= Office of Surveillance and Epidemiology
DMEPA=Division of Medication Errors Prevention and Analysis
DRISK=Division of Risk Management

DIVISION DIRECTOR SUMMARY REVIEW

1. INTRODUCTION

The objective of NDA 022501 is to obtain marketing approval for Lo Loestrin Fe (norethindrone acetate [NA] and ethinyl estradiol [EE] tablets/EE tablets/ferrous fumarate [Fe] tablets), a combination oral contraceptive. Lo Loestrin Fe (hereafter also referred to as Lo Loestrin) is a new dosage strength (lower dose of EE) and a new dosing regimen oral contraceptive in the "family" of Loestrin oral contraceptives that the Applicant currently markets in the US. The dosing regimen for Lo Loestrin is a 24/2/2 28-day regimen in which (1) a daily tablet containing 1 mg NA+10 µg EE is taken for 24 days, (2) a daily tablet containing 10 µg EE is taken for 2 days, and (3) a daily tablet containing 75 mg Fe is taken for 2 days. The lowest dosage combination oral contraceptive currently marketed by the Applicant contains 1 mg NA+20 µg EE in each active tablet. The Applicant believes (1) that the lower dose of EE in the proposed product (10 µg EE instead of 20 µg EE) might reduce the risk of thromboembolic adverse events associated with the use of estrogen-containing contraceptive products and (2) that 24 days of active treatment (instead of 21 days) followed by 2 days of EE alone might improve the bleeding profile with respect to both withdrawal (scheduled) and intracyclic (unscheduled) bleeding. Currently, the lowest dose of EE in the estrogen plus progestin tablet of any approved combination oral contraceptive in the US is 20 µg of EE. Lo Loestrin is not currently approved for marketing in any country.

NDA 022501 was originally submitted in March 2009. The Application was not approved during the original review cycle because 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 manufacturer ((b) (4)) of the drug substances (NA and EE) to adhere to current Good Manufacturing Practices (cGMPs) and (2) a secondary contract drug substance testing site not being ready to conduct testing for the Applicant's product. On January 26, 2010, a Complete Response letter was issued by the Division of Reproductive and Urologic Products (DRUP).

On April 20, 2010, Warner Chilcott submitted their complete response to the deficiencies listed in the Division's letter of January 2010. The Submission addressed the 2 chemistry, manufacturing and control (CMC) deficiencies and included updated product labeling and a safety update.

During the original review of this Application, the only significant issue bearing on the approvability of NDA 022501, other than the issues identified by the Office of Compliance, was the efficacy of Lo Loestrin based on the Pearl Index. The Pearl Index for Lo Loestrin was 2.92 pregnancies per 100 women-years of use in the single Phase 3 trial conducted by the Applicant. This value is slightly higher than that of any combination oral contraceptive approved by DRUP to date. The highest Pearl Index for a currently approved combination oral contraceptive in the US, based on the Phase 3 clinical trial that supported marketing approval, is 2.74 pregnancies per 100 women-years of use (Lo Seasonique approved in October 2008). No safety issues that would preclude approval of Lo Loestrin were identified during the original review of NDA 022501. The Applicant's complete response did not include any new clinical data. All reviewers, including both the primary Clinical Reviewer

(Dr. Orleans) and the Clinical Team Leader (Dr. Soule), have recommended that NDA 022501 for Lo Loestrin be approved. I concur with their recommendations. The basis for my concurrence is provided later in this Memorandum (see Section 7.4 and Section 13.2).

2. BACKGROUND

2.1 Description of the Product

Lo Loestrin is a low dose combination oral contraceptive consisting of a new lower dosage of EE (i.e., 10 µg) and a new dosing regimen (i.e., 24/2/2) for the "family" of Loestrin combination oral contraceptives. A 28-day dosing cycle of Lo Loestrin consists of a daily tablet containing 1 mg NA and 10 µg EE for 24 days, followed by a daily tablet containing 10 µg EE for 2 days, and followed by a daily tablet containing 75 mg ferrous fumarate for 2 days.

Norethindrone is one of the 2 progestins that were used in the first combination oral contraceptives to be approved for marketing in the US. Norethindrone and norethindrone acetate, along with levonorgestrel, are considered by some clinicians to be among the progestins that are associated with the lowest risk of venous thromboembolic adverse events. According to the primary Clinical Review, combination oral contraceptive products containing EE and NA (1) have been marketed in the US in various formulations since 1973 and (2) more than 20 such products are currently available in the US. Ethinyl estradiol is the estrogen in virtually every combination oral contraceptive product currently marketed in the US.

2.2 Regulatory History

The development program for Lo Loestrin was conducted under IND 73,510 that was opened in 2006. The Applicant was advised by DRUP that a single clinical study would be adequate to support an NDA as long as the trial (1) provided at least 10,000 x 28-day evaluable treatment cycles and (2) included data from at least 200 women, aged 18-35 years, who took the study drug for at least one year (thirteen 28-day treatment cycles). The Applicant's single Phase 3 clinical trial provided the requested number of treatment cycles.

2.3 Clinical Content of NDA

Original submission: The primary support for the efficacy and safety of Lo Loestrin is based on the Applicant's single, multicenter, open-label, non-comparative Phase 3 clinical trial (Study PR-05806) that treated 1,660 women for up to one year. The Applicant's NDA submission also included Final Study Reports from three Phase 1 pharmacokinetic studies. Summary data from a Phase 1 pharmacodynamic study to assess the capacity of (1 mg NA plus 5 µg EE) tablets to inhibit ovulation also were provided.

Complete Response: The Applicant's complete response addressed the 2 chemistry, manufacturing and control (CMC) deficiencies and included updated product labeling and a safety update.

2.4 Recommendations of Primary Clinical Reviewer and Cross-Discipline Team Leader regarding Approvability

The primary Clinical Reviewer, Ronald Orleans MD, stated the following in his review of the original submission that he signed on January 8, 2010:

> *"Approval of WC3016 [Lo Loestrin] for prevention of pregnancy is recommended based on Warner Chilcott (the Applicant) having demonstrated an acceptable Pearl Index and an acceptable safety profile for this product.*"
>
> *"In this Reviewer's opinion, the Applicant has clearly demonstrated that WC3016 is a safe and effective oral contraceptive and approval is recommended with labeling that clearly shows the pregnancy rates reported in the primary clinical trial.*"
>
> *"Epidemiologic evaluations of oral contraceptives and vascular disease have indicated that minimizing exposure to estrogen and progestin reduces the risk for both arterial and venous thrombotic events. WC3016, with its reduced ethinyl estradiol dosage, may be especially useful in subsets of woman who are at increased risk for these thrombotic complications (e.g., women over 40, obese women, smokers), yet who still desire combined oral contraception."*

Dr. Orleans stated the following in his primary Clinical Review, signed on October 12, 2010, of the Applicant's complete response:

> *"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."*
>
> *"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*."

The Cross Disciple Team Leader (CDTL) Lisa Soule MD, who also was the Clinical Team Leader, stated the following in her review of the original submission that she signed on January 25, 2010:

> *"I agree with Dr. Orleans that the submitted clinical trial demonstrates an acceptable safety profile for Lo Loestrin Fe, and the pregnancy rate is clearly lower than what would be expected in the absence of contraception. There may be a population of women who desire the lowest possible dose of EE, and are willing to accept the risk of a higher pregnancy rate. For these reasons, from a clinical perspective, I concur with Dr. Orleans' recommendation for approval. However, it will be critical that labeling clearly describe the Pearl Index and the population studied so that prescribers and potential users will be aware of the risk of pregnancy when using this product, and the fact that the product was not studied in a population broadly representative of the target population with respect to weight."*
>
> *"Although the clinical evidence of safety and efficacy is acceptable to support approval, the NDA is not approvable from a CMC perspective. At the present time, based on the Withhold recommendation by the Office of Compliance with respect to facilities inspections, I recommend that a Complete Response action be taken."*

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