CENTER FOR DRUG EVALUATION AND RESEARCH

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."*

Dr. Soule stated the following in her updated CDTL review, signed on October 20, 2010, of the Applicant's complete response:

> "*I recommend approval of this Complete Response submission, because all deficiencies have been satisfactorily addressed*."

Division Director's Comment

- *I concur with the recommendations of both Drs. Orleans and Soule that Lo Loestrin be approved for the indication of use by women to prevent pregnancy.*

3. CMC

Original Submission

The primary Chemistry Reviewer, Yubing Tang PhD, made the following recommendations in her primary CMC Review signed on January 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 is not recommended for "Approval" until the final "Acceptable" recommendation is made by the Office of Compliance."*

On January 19, 2010, the Office of Compliance issued an overall rating of "Withhold" approval as described earlier in Section 1 of this Review; consequently, Dr. Tang made the following recommendation in an Addendum (signed on January 25, 2010) to her primary review:

> *"... from a CMC perspective, this NDA is recommended not to approve in its present form until all the facilities involved are fully in compliance with cGMP requirements to assure the identity, strength, purity, and quality of the drug product."*

Complete Response

In their complete response, the Applicant stated that the FDA's Division of Manufacturing and Product Quality had notified the drug substance manufacturer ((b) (4) (b) (4)) that previously noted deficiencies had been addressed. In addition, the Applicant stated that they were withdrawing one of the 2 duplicate analytical laboratories (the laboratory that was not prepared for inspection by the FDA during the first review cycle). The Applicant further stated in their complete response that "… Warner Chilcott considers all product quality deficiencies mentioned in the Division's Complete Response letter to have been completely resolved."

On May 26, 2010, an overall "Acceptable" recommendation was issued by the Office of Compliance for all facilities involved in the manufacturing and testing of Lo Loestrin.

Dr. Tang subsequently made the following recommendation in her Review signed on September 16, 2010:

> "*This NDA provided adequate information on the raw material controls, manufacturing process, specifications, and container/closure system. It also provided sufficient stability data to assure identity, strength, purity and quality of the drug product during the*

expiration dating period. Labels have required information. The Office of Compliance has issued the overall "Acceptable" recommendation for all manufacturing and testing facilities."

"Therefore, from the CMC perspective, this NDA is recommended for approval."

Division Director's Comment

- *I concur with Dr. Tang's overall assessments and recommendation.*

4. NONCLINICAL PHARMACOLOGY/TOXICOLOGY

Original Submission

The active ingredients of this product, NA and EE, have been marketed in a number of products for more than 35 years. The Applicant did not provide any new nonclinical pharmacology/toxicology data in the current NDA, but did reference their approved NDA (21-871) for Loestrin 24. The primary Toxicology Reviewer, Krishan Raheja DVM/PhD, made the following recommendations in his review signed on June 16, 2009:

Recommendations on approvability: *Pharmacology/toxicology data support approval of NDA 22-501 for* (b) (4) *[Lo Loestrin] for contraception*.

Recommendations for nonclinical studies: *All pharmacology/toxicology data were reviewed under the sponsor's approved NDA 21-871 for Loestrin® 24 Fe (norethindrone acetate and ethinyl estradiol tablets, USP, and ferrous fumarate tablets) for the contraception indication*.

Recommendations on labeling: *As required, the Labeling is in accordance with PLR and provided in SPL format.*

Complete Response

Dr. Raheja made the following statement in his Review signed on September 20, 2010:

"*The new resubmitted label for Lo Loestrin Fe is acceptable from the P/T perspective*."

Division Director's Comment

- *I concur with the recommendations of Dr. Raheja that the pharmacology/toxicology data support approval.*

5. CLINICAL PHARMACOLOGY/BIOPHARMACEUTICS

Original Submission

Three clinical pharmacology Phase 1 studies were conducted in support of this NDA. These studies were conducted to assess (1) the pharmacokinetics of NA and EE after a single dose and at steady state after once daily administration of Lo Loestrin for 24 days, (2) the relative bioavailability of NA and EE when dosed as Lo Loestrin tablets or as a hydroalcoholic solution of NA and EE, and (3) the effect of food on the bioavailability of NA and EE following administration of Lo Loestrin tablets.

Norethindrone acetate is deacetylated to norethindrone (NE) after oral administration. Norethindrone acetate and EE are absorbed from Lo Loestrin Fe, with maximum plasma concentrations of NE and EE generally occurring 1 to 2 hours postdose. Both are subject to

first-pass metabolism after oral dosing, resulting in an absolute bioavailability of approximately 64% for NA and 55% for EE.

The studies evaluating food effect showed that dosing under fed conditions reduced the Cmax for EE by about 23%, while Cmax for NA was unchanged. There was no effect of food on the AUC for EE, while the AUC for NA increased by about 24%. Because the clinical trial permitted dosing without regard to meals, instructions in labeling will also permit dosing without regard to meals.

Dr. Apparaju stated the following in her review signed on November 20, 2009:

> *"NDA 22-501 is acceptable from a Clinical Pharmacology perspective, provided an agreement can be reached with the sponsor pertaining to labeling language."*

Complete Response

During the current review cycle, additional labeling changes were conveyed to the Applicant. All were accepted by the Applicant. In her Clinical Pharmacology Review that she signed on October 7, 2010, Dr. Apparaju made the following recommendation:

> "*NDA 22-501 is acceptable from a Clinical Pharmacology perspective*."

Dr. Apparaju did not recommend any Phase 4 commitments.

Division Director's Comment

- *I concur with Dr. Apparaju's conclusion that the Clinical Pharmacology data and related labeling support approval.*

6. CLINICAL MICROBIOLOGY

The Applicant originally did not propose any microbial limits testing for the final tablets. Dr. Pawar, Microbiology Reviewer, expressed concern that the manufacturing process did not address the possibility of contamination by adventitious pathogens during manufacturing. The Applicant subsequently agreed to the product testing requested by Dr. Pawar. In a second review, signed on December 23, 2009, Dr. Pawar stated that the Applicant's response was acceptable, and he made the following recommendation on approvability:

> *"The amended original NDA is recommended for approval*."

Division Director's Comment

- *The Applicant's complete response was not re-reviewed by Microbiology because there were no microbiology deficiencies at the completion of the first review cycle.*
- *I concur with Dr. Pawar's recommendation of approval.*

7. CLINICAL/STATISTICAL-EFFICACY

The following efficacy data summarized in Section 7 is based primarily on the information contained in the Applicant's original NDA submission of March 2009.

7.1 Overview of Primary Phase 3 Clinical Trial and Subject Demographics

The Applicant conducted a single, multicenter, open-label, non-comparative, 12 month (thirteen 28-day treatment cycles), Phase 3 clinical trial (PR-05806) in which 1,660 women

received at least one dose of Lo Loestrin. Subjects were enrolled at 68 US sites. The modified intent-to-treat (MITT) population consisted of 1,582 women who received at least one dose of Lo Loestrin and who were evaluated for pregnancy at least once after beginning study medication. Subjects in the MITT were 18.0-45.9 years of age (mean [SD] age = 28.6 [6.9] years), and 1,270 of the subjects were ≤ 35 years of age. The inclusion and exclusion criteria were, in general, consistent with those of other clinical trials for oral contraceptives. As in many trials, women with a body mass index (BMI) > 35 kg/m^2 were to be excluded. The mean (SD) weight of the MITT subjects was 150.1 (29.3) pounds (range: 89-260). The racial distribution of the subjects who received at least one dose of study drug was 74.9% Caucasian, 11.8% African-American, 9.8% Hispanic, 1.3% Asian, and 2.2% other.

Division Director's Comments

- *The racial distribution of the population appears fairly representative of the general US population.*
- *Although the Protocol for Study PR-05806 excluded women with a BMI of >35 kg/m^2, the mean weight of subjects in the MITT population (150.1 pounds) was only 9 pounds less than that (i.e., 159 pounds) in the primary efficacy and safety study for another approved combination oral contraceptive that did not have any weight limit or BMI restrictions. Nevertheless, because women with a BMI >35 kg/m^2 were not studied in the Phase 3 clinical trial, this should be reflected in product labeling for Lo Loestrin.*

7.2 Study Populations and Subject Disposition

A total of 1,683 subjects were enrolled in Study PR-05806. Of these, 1,660 women took at least one dose of study drug. This constituted the safety population. A total of 692 women (42%) from the population who took at least one dose of Lo Loestrin discontinued prematurely for the reasons listed in Table 1.

Table 1 Study Populations, Subject Disposition, and Reasons for Premature Discontinuation (Study PR-05806)

Population/Disposition/Reason	Total
Total subjects enrolled	1,683
Total subjects treated [A]	1,660 (100%)
MITT population [B]	1,582 (95.3%)
PITT population [C]	1,270 (76.2%)
Completed the study	968 (58.3%)
Prematurely discontinued from the study	692 (41.7%)
• Lost to follow-up	227 (13.7)
• Adverse event	177 (10.7%)[D]
• Withdrawal of consent	147 (8.9%)
• Other	96 (5.8%)
• Lack of efficacy (pregnancy)	25 (1.5%)
• Protocol violation	20 (1.2%)
• Death	0

[A] Defined as all subjects who received at least one dose of study drug. This is the safety population.
[B] Modified Intent to Treat population. Defined as all subjects who received at least one dose of study drug and were evaluated for pregnancy at least once after beginning study medication.
[C] Pregnancy Intent to Treat population. Defined as the subgroup of the MITT population who were 18-35 years of age at enrollment.
[D] Includes 5 subjects in which the adverse event occurred prior to starting treatment with study drug.
Source: Table 6 from the primary Clinical Review signed on January 8, 2010.

Division Director's Comments

- *A premature discontinuation rate of 41.7% for a one year Phase 3 contraceptive clinical trial is similar to that reported for other recently reviewed one year Phase 3 contraceptive clinical trials.*
- *A discontinuation rate of 10.7% due to adverse events also is similar to that for other recently reviewed one year Phase 3 contraceptive clinical trials.*

7.3 Efficacy Findings

7.3.1 Primary Assessment of Efficacy (On-Treatment Pregnancies)

The primary efficacy analysis in this and other contraceptive trials is the Pearl Index, which is computed as:

$$\text{Pearl Index} = \frac{\text{(number of “on-treatment” pregnancies) x 13 cycles/year}}{\text{(total number of completed 28-day treatment cycles)*}} \times 100$$

* Only cycles in which no back-up contraceptive methods were used are included

The primary analysis population was the pregnancy intent-to-treat (PITT) population, defined as all subjects who received at least one dose of study drug, were evaluated for pregnancy at least once after beginning study drug, and were between the ages of 18-35 years at entry. All treatment cycles during which any backup method of birth control was used, including condoms, were excluded from the efficacy analysis unless the subject conceived during the

cycle. All pregnancies conceived after the onset of treatment with study drug or within 7 days after a subject's last tablet of study drug were included in the calculation of the Pearl Index.

Division Director's Comment

- *The Division's recent thinking on the window in which conceptions are counted as treatment failures is that pregnancies conceived within 7 days after the last pill taken (whether active or placebo pill) are to be counted. This allows for inaccuracy in ultrasound dating of pregnancies, but acknowledges that contraceptive protection is not expected to be maintained beyond the last tablet in a 28-day treatment cycle.*

7.3.2 Primary Efficacy Findings

The PITT population, comprised of 1,270 women aged 18-35 years, contributed a total of 12,482 treatment cycles during which no backup contraception was used. The Applicant initially identified 24 pregnancies for which the conception date was considered to be on-treatment. The primary Clinical Reviewer, however, identified 4 additional pregnancies that he believed were on-treatment pregnancies, for a total of 28 on-treatment pregnancies. These pregnancies included (1) 2 pregnancies in subjects who were 35 years of age at study entry but 36 years of age at the time of conception, (2) one pregnancy for which the estimated day of conception was 9 days after the onset of treatment, and (3) one pregnancy for which the documentation consisted solely of the subject's reporting to the Principle Investigator at her study site that she had had a positive urine pregnancy test 6 days after her last dose of study drug.

Division Director's Comment

- *Inclusion in the efficacy analysis of the single pregnancy that was based solely upon the subject's report of a positive pregnancy test without any further documentation could be questioned. Exclusion of this one subject would not have a significant effect on the assessment of the efficacy of Lo Loestrin as it would only reduce the Pearl Index from 2.92 to 2.81.*

7.3.3 Primary Efficacy Analysis

The Pearl Index values (and associated 95% confidence intervals) based on 28 on-treatment pregnancies in both the MITT (subjects of all ages) and the PITT population (subjects $\leq$ 35 years of age at enrollment) are listed in Table 2. Based on 28 on-treatment pregnancies and a total of 12,484 completed 28-day cycles of treatment for subjects $\leq$ 35 years of age during which no backup contraception was used (PITT population), the Pearl Index was calculated by the FDA statistician to be 2.92 (95% Confidence Interval [CI]: 1.94, 4.21).

Table 2 Pearl Index Values Based on Completed Treatment Cycles in which No Back-Up Contraception Was Used in the MITT and PITT Populations (Study PR-05806) *

Population	Total Number of Subjects	Number of Cycles Without Use of Back-up Birth Control	Number of On-treatment Pregnancies	**Pearl Index**	95% Confidence Interval
MITT **	1,555	15,591	28	**2.33**	(1.55, 3.37)
PITT ***	1,270	12,482	28	**2.92**	(1.94, 4.21)

* Analyses performed by FDA statistician and based on DRUP's determination of 28 on-treatment pregnancies.
** MITT: subjects of all ages
*** PITT: subjects ≤ 35 years of age at enrollment
Source: Table 3 of the FDA Statistical Review signed on December 28, 2009.

Division Director's Comment

- *No pregnancies were reported in the population of women who were > 35 years of age at enrollment. The Pearl Index was 2.33 (95% CI: 1.55, 3.37) in the MITT population, which included women of all ages (and is more representative of the population that is likely to use Lo Loestrin should the product be approved).*

Life table calculations also are commonly used as supportive assessments of contraceptive efficacy; these methods provide cumulative rates of pregnancy. The FDA statistician provided a life table estimate based on the 28 on-treatment pregnancies. The statistician excluded from the analyses only those cycles in which back-up contraception was used, rather than censoring a subject as soon as she used back-up contraception. The results of these analyses in the MITT and PITT populations are provided in Table 3.

Table 3 Life Table Analysis of the Cumulative Failure Rates after Thirteen 28-Day Cycles of Treatment *

Population	Number of On-treatment Pregnancies	Cumulative Pregnancy Rate	95% Confidence Interval
MITT **	28	2.17%	(1.49%, 3.17%)
PITT ***	28	2.71%	(1.86%, 3.95%)

* Analyses performed by FDA statistician and based on DRUP's determination of 28 on-treatment pregnancies.
** MITT: subjects of all ages
*** PITT: subjects ≤ 35 years of age at enrollment
Source: Table 4 of the FDA Statistical Review signed on December 28, 2009.

Division Director's Comment

- *Results from the life table analysis showed a cumulative one year pregnancy rate of 2.71% (95% CI: 1.86%, 3.95%) in the PITT population and were supportive of the estimate of the risk of pregnancy based on the Pearl Index (2.92).*

7.3.4 Statistician's Conclusion regarding Primary Efficacy Findings

The primary statistical reviewer, Kate Dwyer PhD, made the following statement in the conclusion of her original statistical review signed on December 28, 2009:

> *"From a statistical perspective, the study results support the efficacy of WC3016 [Lo Loestrin], a low dose oral contraceptive consisting of a new dose and new regimen of the combination of norethindrone acetate (NA) and ethinyl estradiol (EE), in the prevention of pregnancy."*

In her review, signed on October 18, 2010, of the Applicant's complete response, Dr. Dwyer stated:

> "*The efficacy (using Pearl Index) result in the label was evaluated and verified by this reviewer in the original statistical review of this NDA. Since no additional efficacy data was included in this resubmission, this reviewer agrees with the final version of the label*."

7.4 Overall Assessment of Efficacy

The Pearl Index for Lo Loestrin, calculated by the FDA statistician, was 2.92 pregnancies per 100 women-years of use (95% CI: 1.94, 4.21), based on 28 on-treatment pregnancies in subjects ≤ 35 years of age. This Pearl Index 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 which was approved in October 2008).

The primary Clinical Review (Dr. Orleans) did not express any concern in his original review or his review of the Applicant's complete response regarding the demonstrated efficacy of Lo Loestrin. He stated the following in his original review signed on January 8, 2010:

> *"The PI of 2.916 (1.938, 4.213) per 100 women-years of use for this product is slightly higher than previously approved combination OCs. However, it is problematic to make valid, cross-study, comparisons of Pearl Indices. The Pearl Indices for clinical trials vary considerably, even for the same formulation, depending on the studies from which data are obtained. ... Nevertheless, in my opinion, a PI of 2.92 is acceptable to support the efficacy of WC3016 [Lo Loestrin]."*

The issue of what constitutes an acceptable upper limit for the Pearl Index for oral contraceptives was discussed by a group of contraceptive experts at a meeting of the Advisory Committee for Reproductive Health Drugs (ACRHD) in January 2007. The Committee Members were asked if there was a specific Pearl Index above which they believed an oral contraceptive should not be approved. The Committee Members declined to recommend a specific value. In the Final Summary Minutes of the 2-day meeting, Dr. Charles Lockwood, who was the acting Chairperson of the meeting, made the following statement:

> "*However, the committee was unanimous in its desire to make clear that arbitrary limits be avoided in order to promote the widest range of new contraceptive products being developed and brought to the market. ... Most abstained from giving an exact point estimate or upper confidence interval. The key point to emphasize is that you have to provide all the information to the clinician and the patient in an easily understood format*

in labeling and then let them make the final decision on which product is most appropriate for the patient (i.e., caveat emptor)."

Division Director's Summary Comments

- *The Applicant has submitted an acceptable clinical trial database supporting the efficacy of this low-dose combination oral contraceptive for use by women to prevent pregnancy. The Pearl Index for Lo Loestrin was 2.92 pregnancies per 100 women-years of use (95% CI: 1.94, 4.21) in subjects ≤ 35 years of age. This Pearl Index value, as stated earlier, is slightly higher than that of any combination oral contraceptive approved by DRUP to date. For women who desire to use a combination oral contraceptive with a very low dose of estrogen (10 µg), Lo Loestrin will give them the choice of balancing the potential for a slight increase in the risk of an unplanned pregnancy against the potential, but yet unproven, safety benefit of lower daily exposure to estrogen.*
- *In summary, I have concluded that the demonstrated efficacy of Lo Loestrin, in conjunction with labeling that clearly presents the Pearl Index for the product, is adequate to support approval of Lo Loestrin. This conclusion also is consistent with the recommendation of the ACRHD in January 2007 regarding acceptable efficacy for an oral contraceptive product.*

8. SAFETY

The primary Clinical Reviewer has provided a thorough discussion and review of the safety findings for Lo Loestrin based on the data provided in the original submission of NDA 022501. The Clinical Team Leader also thoroughly reviewed the safety data in the original submission. Neither Medical Officer identified any safety issues in their original reviews or their reviews of the Applicant's complete response that would suggest that the overall safety profile for Lo Loestrin tablets would be less acceptable than that for other currently approved combination oral contraceptives. The following review of safety is focused mainly on items of greatest potential concern, and is not comprehensive, because of (1) the thorough and independent safety reviews by both the primary Clinical Reviewer and the Clinical Team Leader and (2) their assessments that the overall safety profile of Lo Loestrin does not raise any new safety concerns, beyond those normally associated with a combination oral contraceptive.

8.1 Safety Database and Subject Exposure to Study Drug

A total of 1,660 women took at least one dose of Lo Loestrin (identified as the Safety population), and 968 subjects (58.3%) completed the one year clinical trial. Mean drug exposure per subject in the safety population was 272.4 days and 9.93 cycles. The total exposure to study drug in the safety population slightly exceeded 15,600 x 28-day treatment cycles. The overall disposition of study subjects and reasons for early discontinuation are summarized in Table 1.

Another 66 healthy female adult subjects received single or multiple oral doses of either Lo Loestrin tablets or a hydroalcoholic solution containing one or both active ingredients in 3 uncontrolled Phase 1 bioavailability and pharmacokinetic studies.

Division Director's Comment

- *The size of the safety database is acceptable for the proposed product. For a new contraceptive product that is based on a previously approved progestin (e.g., NA) and estrogen (e.g., EE), DRUP generally requires a minimum database that includes (1) the equivalent of 10,000 x 28-day cycles of treatment and (2) 200 subjects completing one year of treatment. Both of these criteria were exceeded in Study PR-05806.*

8.2 Deaths and Other Serious Adverse Events

There were no deaths in any of the clinical trials. There were no serious adverse events (SAEs) in the three Phase 1 trials. Fifteen (15) of the 1,660 safety subjects (0.9%) in Phase 3 Study PR-05806 experienced a total of 18 SAEs, which are listed in Table 4. The SAEs in 12 of the 15 subjects were assessed as unlikely to be related to treatment with Lo Loestrin by both the primary Clinical Reviewer and the Clinical Team Leader. Three of the SAEs (deep vein thrombosis of left leg, ovarian vein thrombosis, and cholecystitis) were assessed as probably related (Clinical Team Leader) or possibly related (primary Clinical Reviewer) to treatment. Four of the SAEs (deep vein thrombosis of left leg, ovarian cyst, ovarian vein thrombosis, and transverse sigmoid sinus stenosis) resulted in discontinuation of the subject from the trial.

Table 4 Serious Adverse Events (SAEs) in Study PR05806

Subject No.	SAE (Preferred Term)	FDA Reviewer's Assessment of Likely Relationship to Study Drug [A]
004-005 [B]	Deep vein thrombosis of left leg	Probable[C] / Possible[D]
006-010	Appendicitis	Unlikely
018-015	Hyperemesis gravidarum	Unlikely
031-045	Appendicitis	Unlikely
033-004 [B]	Ovarian cyst (dermoid tumor)	Unlikely
035-004 [B]	Ovarian vein thrombosis	Probable[C] / Possible[D]
035-006	Cholecystitis	Probable[C] / Possible[D]
036-063	Pneumonia	Unlikely
040-001	Food poisoning	Unlikely
043-004 [B]	Transverse sigmoid sinus stenosis	Unlikely
045-096	Sepsis, dehydration, hypokalemia, pharyngitis	Unlikely
052-047	Appendicitis	Unlikely
052-055	Abdominal pain	Unlikely
056-031	Therapeutic procedure (elective hysterectomy and bladder sling)	Unlikely
066-032	Radius fracture	Unlikely

[A] Reviewers were the primary Clinical Review and the Clinical Team Leader. In instances where they disagreed, both assessments are provided.
[B] Subject discontinued from the clinical trial because of the SAE.
[C] Clinical Team Leader assessment
[D] Primary Clinical Reviewer assessment
Source; Modified from Table 12 of the CDTL Review signed on January 25, 2010.

Division Director's Comments

- *Subject 004-005 developed a deep vein thrombosis (DVT) of the left popliteal and superficial femoral veins approximately 23 days following arthroscopic surgery on her left knee. She had not discontinued Lo Loestrin prior to surgery. The subject's risk factors for DVT included obesity, smoking, arthroscopic surgery and oral contraceptive use. The subject's continuing use of Lo Loestrin, in spite of the surgical procedure, likely contributed to the development of her DVT.*
- *Ovarian vein thrombosis is an uncommon event and most commonly associated with postpartum endometritis. I concur with the assessment of the primary Clinical Reviewer that the use of Lo Loestrin may possibly be associated with this event.*
- *The total number of subjects with SAEs (15/1660 [0.9%]) and the specific SAEs in this trial of one-year duration do not raise any concerns about the overall safety profile of Lo Loestrin above those of combination oral contraceptives in general.*

8.3 Discontinuations for Adverse Events

A total of 172 subjects (10.4%) discontinued from Study PR05806 prematurely because of a treatment-emergent adverse event (AE). Five additional subjects discontinued because of an adverse event prior to starting study drug. Table 5 lists the most common AEs that led to a subject's discontinuation from the clinical trial. Events that occurred in only a single subject are shown only if they were clinically notable. The most frequent AEs resulting in a subject's discontinuation were those usually associated with combination oral contraceptives, including metrorrhagia (n=46), irregular menstruation (n=12), headache (n=10), mood swings (n=9), weight fluctuation (n=9), amenorrhea (n=8), acne (n=6), and migraine (n=5).

None of the 66 subjects in the three Phase 1 studies discontinued prematurely due to an AE.

Table 5 Most Common Adverse Events and Notable Adverse Events Leading to Subject Discontinuation from Study PR05806

Adverse Event (Preferred Term)	Number of Subjects with Event
Metrorrhagia	46
Irregular menstruation	12
Headache	10
Mood swings	9
Weight fluctuation	9
Amenorrhea	8
Acne	6
Migraine	5
Anxiety	4
Depression	4
Dysmenorrhea	4
Hypertension	4
Menorrhagia	4
Transient ischemic attack	1 (Subject 001-046)
Vaginal hemorrhage	1 (Subject 001-073)
SAEs	
Deep vein thrombosis	1 (Subject 004-005)
Ovarian vein thrombosis	1 (Subject 035-004)
Transverse sinus stenosis	1 (Subject 043-004)
Ovarian Cyst	1 (Subject 033-004)

Source: Modified from Table 23 of the primary Clinical Review signed on January 8, 2010.

Division Director's Comments

- *Subject 001-046 experienced left-sided numbness and difficulty speaking for about 10 minutes after* (b) (6) *on Lo Loestrin. She presented to the Emergency Department the next day, by which time all symptoms had resolved. She underwent a head CT, which was negative, as were all other tests. The investigator considered this to be a transient ischemic attack, possibly related to study drug.*
- *Subject 001-073 enrolled in the study with a baseline hematocrit of 39%, and experienced persistent unscheduled bleeding over 2 of her 3 months of treatment. Her end-of-study hematocrit remained at 39%.*
- *Subject 043-004 underwent endovascular stenting of her right transverse sigmoid sinus; the postoperative diagnosis was right transverse sigmoid sinus stenosis.*
- *Subjects 004-005 and 035-004 are discussed under SAEs (Section 8.2).*
- *The types of adverse events associated with discontinuation from Study PR 05806 and the numbers of subjects reporting them are consistent with those observed in prior one-year clinical trials for oral contraceptives.*
- *As would be expected in a clinical trial of a combination oral contraceptive, adverse events related to abnormal uterine bleeding were the most common cause of subject discontinuations. Bleeding patterns in Phase 3 study PR-05806 are described further in Section 8.4.*

- *The percentage of subjects who withdrew because of an adverse event (10.4%) was not excessive for a one year contraceptive clinical trial.*

8.4 Uterine Bleeding Patterns

Subjects completed a daily paper diary that recorded the occurrence and intensity of uterine bleeding. Light bleeding that required no use of sanitary protection (aside from panty liners) was classified as spotting. Spotting/bleeding was characterized as "withdrawal bleeding/spotting" (hereafter called "scheduled bleeding/spotting") if it started (1) after the last day of active treatment (defined by the Applicant to include the EE-only treatment days) and before starting the next treatment cycle or (2) within 4 days before the last day of active treatment and continuing through at least the first day after the end of active treatment. All other bleeding/spotting episodes were considered to be "intracyclic bleeding/spotting" by the Applicant (hereafter referred to as "unscheduled bleeding/spotting"). Unscheduled spotting/bleeding is likely to be more troublesome to subjects because it is unpredictable.

8.4.1 Unscheduled Bleeding/Spotting

Table 6 summarizes the (1) incidence and percentage of subjects with unscheduled bleeding/spotting and (2) number of days of unscheduled bleeding/spotting per each 28-day treatment cycle. A total of 1,257 women (85.9%) experienced unscheduled bleeding and/or spotting at some time during Cycles 2-13. The incidence of unscheduled bleeding and/or spotting was highest during Cycle 3 (53%) and lowest at Cycle 13 (36%). The mean number of days of unscheduled bleeding/spotting during a 28-day cycle ranged from 1.81-3.21 days.

Table 6 Incidence and Percentage of Subjects with Unscheduled Bleeding/Spotting and Number of Days of Unscheduled Bleeding/Spotting per Each 28-Day Cycle

Treatment Cycle	Incidence (n/N) and (%) of Subjects with Unscheduled Bleeding/Spotting	Number of Days of Bleeding/Spotting		
		Mean (SD)	Median	Range
Cycles 2-13	1257/1463 (85.9)	2.63 (2.95)		
Cycle 1	704/1514 (46.5)	2.65 (3.97)	0	0, 25
Cycle 2	762/1447 (52.7)	3.21 (4.15)	2	0, 23
Cycle 3	725/1391 (52.1)	2.79 (3.79)	0	0, 25
Cycle 4	603/1312 (46.0)	2.44 (3.60)	0	0, 25
Cycle 5	554/1254 (44.2)	2.25 (3.37)	0	0, 23
Cycle 6	483/1194 (40.5)	2.00 (3.12)	0	0, 20
Cycle 7	508/1164 (43.6)	2.28 (3.46)	0	0, 20
Cycle 8	431/1117 (38.6)	1.82 (3.02)	0	0, 26
Cycle 9	426/1077 (39.6)	1.93 (3.16)	0	0, 23
Cycle 10	394/1035 (38.1)	1.86 (3.16)	0	0, 24
Cycle 11	396/996 (39.8)	1.87 (3.04)	0	0, 22
Cycle 12	379/977 (38.8)	1.82 (2.98)	0	0, 21
Cycle 13	344/945 (36.4)	1.81 (3.01)	0	0, 19

Source: Modified from Tables 12 and 13 of the primary Clinical Review signed on January 8, 2010.

Division Director's Comments

- *Unscheduled bleeding/spotting appeared to decrease gradually over the first 6 months of use. It is possible, however, that subjects with more frequent unscheduled bleeding/spotting withdrew early from the study.*
- *The median number of days of unscheduled bleeding/spotting for all treatment cycles (except Cycle 2) was 0 days, indicating that at least 50% of subjects did not experience any unscheduled bleeding/spotting in each cycle other than Cycle 2.*

8.4.2 Scheduled Bleeding/Spotting

Table 7 summarizes the incidence and percentage of subjects with scheduled bleeding/spotting and number of days of scheduled bleeding/spotting per each 28-day treatment cycle. Fewer than 50% of subjects had scheduled (withdrawal) bleeding/spotting in any individual 28-day treatment cycle. The percentage of subjects with scheduled bleeding/spotting decreased from 43.3% in Cycle 1 to 22.4% in Cycle 13.

Table 7 Incidence and Percentage of Subjects with Scheduled Bleeding/Spotting and Number of Days of Scheduled Bleeding/Spotting per Each 28-day Cycle

Treatment Cycle	Incidence (n/N) and (%) of Subjects with Scheduled Bleeding/Spotting	Number of Days of Bleeding/Spotting		
		Mean (SD)	Median	Range
Cycles 2-13	1037/1463 (70.9)	-		
Cycle 1	655/1514 (43.3)	1.76 (2.48)	0	0, 12
Cycle 2	503/1447 (34.8)	1.36 (2.25)	0	0, 10
Cycle 3	479/1391 (34.4)	1.39 (2.31)	0	0, 10
Cycle 4	384/1312 (29.3)	1.18 (2.19)	0	0, 10
Cycle 5	372/1254 (29.7)	1.09 (1.99)	0	0, 10
Cycle 6	299/1194 (25.0)	1.00 (2.02)	0	0, 10
Cycle 7	311/1164 (26.7)	0.98 (1.96)	0	0, 10
Cycle 8	284/1117 (25.4)	0.98 (1.97)	0	0, 10
Cycle 9	273/1077 (25.3)	1.01 (2.02)	0	0, 10
Cycle 10	250/1035 (24.2)	0.94 (1.93)	0	0, 10
Cycle 11	257/996 (25.8)	0.93 (1.83)	0	0, 10
Cycle 12	223/977 (22.8)	0.87 (1.89)	0	0, 10
Cycle 13	212/945 (22.4)	1.55 (3.29)	0	0, 10

Source: Modified from Table 15 of the primary Clinical Review signed on January 8, 2010, and from Tables 10 and 11 of CDTL Review signed January 25, 2010.

Division Director's Comments

- *Fewer than 50% of subjects had scheduled (withdrawal) bleeding/spotting in any individual 28-day treatment cycle. After Cycle 6, approximately 75% of subjects in a given treatment cycle did not have scheduled bleeding.*
- *Women who wish to have light or no menstrual periods and are willing to accept a slightly greater risk of pregnancy than that associated with higher dosage combination oral contraceptives may prefer Lo Loestrin over other 28-day cyclic products. Women*

who use this product, however, may experience somewhat greater unscheduled bleeding compared to higher dosage products.

- *Amenorrhea (no scheduled or unscheduled bleeding/spotting) also was fairly common in a given treatment cycle and tended to increase over the 13-cycle treatment period. The incidence of amenorrhea during each of Cycles 1 to 3 was approximately 30% and increased to 49.1% in Cycle 13. Nine subjects discontinued the trial because of amenorrhea.*

8.4.3 Bleeding-related Adverse Events

According to the review of the Clinical Team Leader, 82 subjects (4.9%) reported bleeding-related AEs (metrorrhagia [3.4%], irregular menstruation [0.8%], menorrhagia [0.5%], vaginal hemorrhage [0.2%], and dysfunctional uterine bleeding [0.1%]).

A total of 63 subjects (3.8%) discontinued from the clinical trial because of bleeding-related adverse events (metrorrhagia, irregular menstruation, menorrhagia, or vaginal hemorrhage). Comparison of baseline and end-of-study hemoglobin and hematocrit values revealed no pattern of decreased hematologic indices associated with bleeding. Only 4 subjects had hemoglobin values < 12 g/dL at the end-of-study, and all 4 had values < 12 g/dL at baseline.

8.5 Safety Update

A Safety Update was included in the Applicant's complete response. The Applicant reported that (1) there were no safety data that had not been previously reported in the original NDA and (2) there were no new or ongoing studies with Lo Loestrin.

8.6 Overall Assessment of Safety

Among the safety issues of greatest concern are those related to venous thromboembolic events such as DVTs or pulmonary emboli. In the clinical development program for Lo Loestrin, one subject developed a DVT of the left popliteal and superficial femoral veins approximately 23 days following arthroscopic surgery on her left knee. She had not discontinued Lo Loestrin prior to surgery. Additional risk factors for a DVT in this subject included obesity and smoking. Another subject developed an ovarian vein thrombosis, an uncommon event that is most commonly associated with postpartum endometritis. Neither of these adverse events raises a concern that treatment with Lo Loestrin is associated with a risk of thromboembolism, above that associated with the use of other combination oral contraceptives. Lo Loestrin is not marketed in any country, so there are no postmarketing data on its safety. Nevertheless, there is an extensive safety database with higher dose combinations of NA and EE, the active components in Lo Loestrin. No concerns have been raised by recent annual reports or periodic safety update reports for these higher dose products.

The uterine bleeding pattern associated with the use of Lo Loestrin is acceptable. Women who wish to have light or no menstrual periods may prefer Lo Loestrin over other 28-day cyclic combination oral contraceptives. Women who use this product, however, may experience somewhat greater unscheduled bleeding compared to higher dosage products.

The primary Clinical Reviewer (Dr. Orleans) made the following statements regarding his assessment of the safety findings in Study PR-05806:

"The Applicant believes that the reduction of the estrogen dose in WC3016 [Lo Loestrin] may reduce the risks associated with the estrogen component of combination oral contraceptives and considers this a potential benefit for this product. The primary clinical trial, however, did not utilize an approved low dose oral contraceptive as a comparator drug, so a lower incidence of estrogen-related side effects could not be demonstrated. ... The primary clinical trial did demonstrate, however, that the safety profile of WC3016 was acceptable. 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."

"... The results of the phase 3 clinical trial did not indicate any safety concerns beyond those commonly attributed to OCs. WC3016 has been demonstrated to be a safe oral contraceptive when taken over 13 cycles."

Division Director's Summary Comment

- *The overall safety profile for Lo Loestrin, based on the data provided in the Application, appears to be comparable to that for other combination oral contraceptives currently approved for marketing in the US. The safety data from Study PR-05806, the primary source of safety data in the Application, do not raise any new safety concerns regarding Lo Loestrin beyond those that are known to be associated with the use of combination oral contraceptives. The most commonly reported adverse events, as well as the frequency and types of adverse events leading to premature subject discontinuation from Study PR-05806, are similar to those reported for other combination oral contraceptives in Phase 3 clinical trials.*

9. ADVISORY COMMITTEE MEETING

This Application was not presented to an Advisory Committee (AC) because DRUP did not believe that AC guidance was needed to make a regulatory decision concerning the approvability of the Application. In January 2007, the Advisory Committee for Reproductive Health Drugs (ACRHD) discussed efficacy and safety issues related to oral contraceptive products. Among the areas of focus, was an extensive discussion of acceptable efficacy for oral contraceptive products and labeling. The recommendations from the January 2007 meeting have been fully considered in (1) the review of this Application and (2) my decision regarding the approvability of Lo Loestrin.

10. PEDIATRICS

(b) (4). The Pediatric Review Committee (PeRC) PREA Subcommittee reviewed the request on November 4, 2009. The Committee granted a partial waiver for pre-menarcheal children because they are not at risk for pregnancy. The Committee also concurred with the recommendation of DRUP that the remainder of the PREA requirement for pediatric studies has been fulfilled by extrapolation from data in women ≥ 18 years of age. Clinical experience with a wide variety of oral hormonal contraceptives supports DRUP's expectation that the efficacy and safety of Lo Loestrin in postmenarcheal adolescents, like that of other previously approved oral contraceptives, will not differ from that in women ≥ 18 years of age.

11. OTHER RELEVANT REGULATORY ISSUES

Site inspections by the Division of Scientific Investigations were not requested by the primary clinical review team because (1) NA and EE combination contraceptives are well characterized after decades of use and (2) no clinical sites appeared to be outliers in terms of adverse event reporting, pregnancies, or dropouts.

The Applicant submitted financial disclosure information for all 68 investigators; only a single investigator ((b) (6)) reported a financial interest. (b) (6) enrolled only (b) (6) representing (b) (6) of the total study population. Dr. Orleans reviewed the data from (b) (4) site and noted (b) (6) minor protocol violations, (b) (6), and (b) (6) SAEs or AEs leading to premature termination. He concluded that there was no evidence of investigator bias.

12. LABELING

The Division of Medication Errors Prevention and Analysis (DMEPA) determined that the name "Lo Loestrin Fe" was acceptable during the first review cycle. DMEPA again determined the name was acceptable during the current review cycle.

The Lo Loestrin Fe label was submitted in the format prescribed by the Physician Labeling Rule (PLR). Consultative reviews were provided by the Division of Drug Marketing, Advertising and Communication (DDMAC), Division of Risk Management (DRISK), and the Study Endpoints and Label Development (SEALD) team. Their comments were incorporated into the label as appropriate.

To-be-approved physician and patient labeling for Lo Loestrin Fe follows for the most part PLR class labeling for other recently approved combination oral contraceptives. Among labeling components that are either unique to this label or not found in all labels for combination oral contraceptives are the following:

- Because the clinical development program did not enroll women with a BMI > 35 kg/m^2, the Indication and Usage section includes the following statement:

  "The efficacy of Lo Loestrin Fe in women with a body mass index of > 35 kg/m^2 has not been evaluated."

- To better inform healthcare providers of the Pearl Index for Lo Loestrin Fe, the statement in the Clinical Studies section of labeling regarding the efficacy findings in the clinical development program has been bolded and reads as follow:

  "**The pregnancy rate (Pearl Index [PI]) in women 18 to 35 years of age was 2.92 pregnancies per 100 women-years of use (95% confidence interval 1.94 – 4.21)**, based on 28 pregnancies that occurred after the onset of treatment and extending through the 7 days following the last dose of Lo Loestrin Fe."

Agreement on final labeling was reached on October 19, 2010.

13. DECISION/ACTION/RISK BENEFIT ASSESSMENT

13.1 Regulatory Action

The Applicant has satisfactorily addressed all deficiencies listed in the Complete Response letter issued on January 26, 2010. All primary Reviewers have now recommended that Lo Loestrin Fe be approved. The Applicant has provided sufficient information for me to conclude that Lo Loestrin Fe would be a safe and effective combination oral contraceptive when used in accordance with to-be-approved product labeling. Therefore, Lo Loestrin Fe will be approved for "use by women to prevent pregnancy."

13.2 Risk/Benefit Assessment

Safety considerations. The overall safety profile for Lo Loestrin Fe, based on the data obtained in Study PR-05806, appears to be comparable to that for other combination oral contraceptives approved for marketing in the US. These safety data do not raise any safety concerns regarding Lo Loestrin Fe beyond those that are known to be associated with the use of combination oral contraceptives. The uterine bleeding pattern associated with the use of Lo Loestrin Fe is acceptable. Women who wish to have light or no scheduled menstrual periods may prefer Lo Loestrin. Women who use this product, however, may experience somewhat greater unscheduled bleeding compared to higher dosage products. Lo Loestrin Fe is not currently marketed in any country, so there are no postmarketing data on its safety. Nevertheless, there is an extensive safety database with higher dose combinations of NA and EE, the active components in Lo Loestrin Fe. No safety concerns have been raised by recent annual reports or periodic safety update reports for these higher dose products.

Efficacy considerations. The Applicant has submitted an acceptable clinical trial database supporting the efficacy of Lo Loestrin Fe. The Pearl Index, calculated by the FDA statistician, was 2.92 pregnancies per 100 women-years of use (95% CI: 1.94, 4.21), based on 28 on-treatment pregnancies in subjects ≤ 35 years of age. Treatment cycles during which subjects used back-up contraception were excluded from the calculation. This Pearl Index is slightly higher than that of any combination oral contraceptive previously approved by DRUP. 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). For the reasons presented earlier in Section 7.4, I have concluded that the demonstrated efficacy of Lo Loestrin Fe is adequate to support approval.

Overall Risk/Benefit Assessment. The overall risk/benefit profile for Lo Loestrin Fe is acceptable for a combination oral contraceptive. Lo Loestrin Fe combination tablets contain a lower dose of ethinyl estradiol (10 µg) than other combination oral contraceptives currently approved in the US. Women using Lo Loestrin Fe will receive approximately 40% less ethinyl estradiol over a 28-day treatment cycle than women using an oral contraceptive containing 20 µg of ethinyl estradiol in each combination tablet. For women who desire to use a combination oral contraceptive with a very low daily dose of estrogen (i.e., 10 µg), Lo Loestrin Fe will give them the choice of balancing the potential for a slight increase in the risk of an unplanned pregnancy against the potential, but yet unproven, safety benefit of lower daily exposure to estrogen. Product labeling will clearly provide the Pearl Index and the population studied in the primary clinical trial so that prescribers and potential users will be

aware that (1) the Pearl Index is slightly higher than that of other approved combination oral contraceptives and (2) the efficacy of Lo Loestrin Fe has not been evaluated in women with a BMI > 35 kg/m^2.

13.3 Recommendation for Postmarketing Risk Evaluation and Mitigation Strategies (REMS)

None.

13.4 Recommendation for other Postmarketing Requirements and Commitments

No postmarketing risk management activities beyond routine pharmacovigilance monitoring and standard postmarketing periodic safety reporting are indicated.

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

/s/

SCOTT E MONROE
10/21/2010