CENTER FOR DRUG EVALUATION AND RESEARCH

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*

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 (b) (4) Warning Letter for its (b) (4) 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.

Summary Review for Regulatory Action

Date	January 26, 2010
From	Scott Monroe, MD
Subject	Division Director Summary Review
NDA	NDA 22-501
Applicant Name	Warner Chilcott Company, Inc
Date of Submission	March 26, 2009
PDUFA Goal Date	January 26, 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	***Complete Response (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/Kellie Taylor PharmD/Carol Holquist RPh
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
OSE= Office of Surveillance and Epidemiology
DMEPA=Division of Medication Errors Prevention and Analysis
DSI=Division of Scientific Investigations
DRISK=Division of Risk Management
CDTL=Cross Discipline Team Leader

DIVISION DIRECTOR SUMMARY REVIEW

1. INTRODUCTION

The objective of NDA 22-501 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 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, which the Applicant currently markets in the U.S. 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 U.S. is 20 µg of EE. Lo Loestrin is not currently approved for marketing in any country.

The only significant issues that could affect the approvability of NDA 22-501, which were identified during the review of the Application, were (1) the Office of Compliance issuing on January 19, 2010, an overall rating of "Withhold" approval and (2) the demonstrated efficacy of Lo Loestrin based on the Pearl Index. The recommendation by the Office of Compliance was based on (1) the failure of the manufacturer ([redacted] (b) (4) (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.

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 the Division of Reproductive and Urologic Products (DRUP) to date. The highest Pearl Index for a currently approved combination oral contraceptive in the U.S., 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). No safety issues that would preclude approval of Lo Loestrin were identified during the review of NDA 22-501. Both the primary Clinical Reviewer (Dr. Orleans) and the Clinical Team Leader (Dr. Soule) recommended that, from a clinical perspective, 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). Because of the overall rating of "Withhold" from the Office of Compliance, however, a Complete Response letter will be issued for NDA 22-501 during the present review cycle.

2. BACKGROUND

2.1 Description of the Product

Lo Loestrin is a low dose combination oral contraceptive consisting of a new 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 of NA and 10 µg EE for 24 days, followed by a daily tablet containing 10 µg of EE for 2 days, 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 U.S. Norethindrone and norethindrone acetate, along with levonorgestrel, are considered by some clinicians to be 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 U.S. in various formulations since 1973 and (2) more than 20 such products are currently available in the U.S. Ethinyl estradiol is the estrogen in virtually every combination oral contraceptive product currently marketed in the U.S.

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 (13 x 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

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.

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 that was signed 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."*

The Cross Disciple Team Leader (CDTL, who was also the Clinical Team Leader), Lisa Soule MD, stated the following in her review signed 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."*

Division Director's Comment

- *I concur with the overall recommendations of both Drs. Orleans and Soule and believe that Lo Loestrin should be approved after (1) resolution of the CMC issues identified by the Office of Compliance and (2) agreement on acceptable labeling is reached.*

3. CMC

The primary Chemistry reviewer, Yubing Tang PhD, made the following recommendations in her primary 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, the recommendation by the Office of Compliance was based on (1) the failure of the contract manufacturer ([redacted] (b) (4) [redacted] (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.

In an Addendum (signed on January 25, 2010) to her primary review, Dr. Tang made the following recommendation:

> *"Therefore, 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."*

Dr. Tang did not recommend any Phase 4 commitments.

Division Director's Comments

- *I concur with the assessment/recommendation made by Dr. Tang that from a CMC perspective, this NDA should not be approved until the issues cited by the Office of Compliance are satisfactorily resolved.*
- *On January 20, 2010, the Applicant was notified in a teleconference that the Office of Compliance had issued an overall rating of "Withhold" approval because of deficiencies that were identified during an inspection of the* [redacted] (b) (4) *drug substance manufacturing facility and a control testing laboratory. Later on January 20, 2010, the Applicant submitted by e-mail a proposal to address the deficiencies. The proposal included*
  1. *Withdrawal of* [redacted] (b) (4) *as a supplier of the drug substances and withdrawal of* [redacted] (b) (4) *as a testing site,*
  2. *Listing only* [redacted] (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* [redacted] (b) (4) *drug substance.*

  The Applicant also proposed to manufacturer 2 additional batches of drug product using [redacted] (b) (4) *drug substance. They also stated in their communication that they would not launch Lo Loestrin until they had submitted 3-month stability data from these 2 additional batches to the Agency. The Applicant further stated that they believed that this approach was consistent with advice that they had received concerning another of their products* [redacted] (b) (4)

  The Applicant was notified in a teleconference on January 22, 2010, that the advice provided for resolution of the deficiency for [redacted] (b) (4) *would not resolve the deficiency identified for Lo Loestrin. The issues regarding the deficiency for NDA 22-501 were not identical to those for* [redacted] (b) (4) *The Applicant was informed that prior to approval of NDA 22-501 data from 3 batches of drug product manufactured with* [redacted] (b) (4) *drug substance would need to be submitted and reviewed by the Agency if* [redacted] (b) (4) *were to be the sole supplier of drug substance for Lo Loestrin.*

4. NONCLINICAL PHARMACOLOGY/TOXICOLOGY

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* [redacted] (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.*

Division Director's Comment

- *I concur with the conclusions and recommendations of Dr. Raheja.*

5. CLINICAL PHARMACOLOGY/BIOPHARMACEUTICS

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.

The studies evaluating food effect showed that dosing under fed conditions reduced the Cmax for EE by about 23%, while that for NA was unchanged. There was no effect of food on the AUC for EE, while that for NA increased by about 24%. The clinical trial, however, was conducted without regard to meals, so dosing instructions without respect to meals were acceptable to the Clinical Pharmacology Reviewer, Sandhya Apparaju PhD.

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."*

Dr. Apparaju did not recommend any Phase 4 commitments.

Division Director's Comment

- *I concur with Dr. Apparaju's conclusion and recommendation that the Clinical Pharmacology data are acceptable to support approval of Lo Loestrin.*

6. CLINICAL MICROBIOLOGY

In the Applicant's original submission, no microbial limits testing was to be performed on the final tablets. Dr. Pawar expressed concern in his primary Product Quality Microbiology Review that the manufacturing process did not address the possibility of contamination by adventitious pathogens during manufacturing. He recommended that product specifications include the revised USP <111>, <61> and <62> requirements at batch release and at the stability endpoint.

Dr. Pawar made the following recommendation in his primary Product Quality Microbiology Review that he signed on November 14, 2009:

> *"This submission is approvable pending resolution of the deficiency listed in Product Quality Microbiology Assessment Section 3 of this review*."

In a submission dated December 17, 2009, the Applicant 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

- *I concur with the recommendation of Dr. Pawar regarding the microbiology aspect of the drug product.*

7. CLINICAL/STATISTICAL-EFFICACY

7.1 Overview of Primary Phase 3 Clinical Trial and Subject Demographics

The Applicant conducted a single, multicenter, open-label, non-comparative, 12-month (13 x 28-day) treatment period, Phase 3 clinical trial (PR-05806) in which 1,660 women received at least one dose of Lo Loestrin. Subjects were enrolled at 68 U.S. sites. Subjects who received at least one dose of Lo Loestrin and were evaluated for pregnancy at least once after beginning study medication (the Modified Intent to Treat [MITT] population) consisted of 1,582 women who were 18.0-45.9 years of age (mean [SD] age = 28.6 [6.9] years). In the MITT population, 1,295 subjects (81.9%) were ≤ 35 years of age and 287 (18.1%) 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 were to be excluded. The mean (±SD) weight of the subjects in the MITT population 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 1.7% other.

Division Director's Comments

- *The racial distribution of the population appears fairly representative of the general U.S. population.*
- *Although the Protocol for Study PR-05806 excluded women with a BMI of greater than 35, 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 recently approved combination oral contraceptive that did not have any weight limit or BMI restrictions. However, because women with a BMI of greater than 35 were not studied in the current NDA, 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:

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

* 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, with exclusion of any cycles in which an alternate birth control method (BCM) was used (also referred to as the PITT, non-BCM population). 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 non-BCM population comprised 1,270 women aged 18-35 years, who contributed a total of 12,482 non-BCM cycles that also excluded condom use. The Applicant initially identified 24 pregnancies for which the conception date was considered to be on-treatment. The FDA's 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 only 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 Comments

- *The primary Clinical Reviewer identified 28 pregnancies that he considered to be "on-treatment pregnancies." These consisted of (1) 24 pregnancies for which he considered conception to have occurred while the subject was actively taking study drug, (2) two pregnancies with estimated conception dates within 7 days after the subject's last dose of study drug, and (3) two pregnancies for which the relationships of the date of conception to that of the last dose of study drug were uncertain.*
- *Inclusion of the single pregnancy, which was based only on the subject's report of a positive pregnancy test without any further documentation, in the efficacy analysis could be questioned. Exclusion of this one subject, however, 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 non-BCM population (subjects of all ages) and the PITT non-BCM population (subjects ≤ 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 ≤ 35 years of age during which no backup contraception was used (PITT non-BCM 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 non-BCM **	1,555	15,591	28	**2.33**	(1.55, 3.37)
PITT non-BCM ***	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 non-BCM: subjects of all ages
*** PITT non-BCM: 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. In the MITT non-BCM 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), the Pearl Index was 2.33 (95% CI: 1.55, 3.37).*

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 non-BCM and PITT non-BCM populations are provided in Table 3.

Table 3 Life Table Analysis of the Cumulative Failure Rates after 13 x 28-Day Cycles of Treatment *

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

* Analyses performed by FDA statistician and based on DRUP's determination of 28 on-treatment pregnancies.
** MITT non-BCM: subjects of all ages
*** PITT non-BCM: 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 non-BCM 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 statistical review:

> *"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."*

7.4 Overall Assessment of Efficacy

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, 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 U.S., 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). For the reasons that follow, I have concluded that the demonstrated efficacy of Lo Loestrin is adequate to support approval of the product when it is used in accordance with appropriate product labeling.

Division Director's Comments

The primary Clinical Review (Dr. Orleans) did not express any concern in his review regarding the demonstrated efficacy of Lo Loestrin. He states the following:

> *"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]."*

I concur with Dr. Orleans' assessment.

The Clinical Team Leader (Dr. Soule) expressed concern about the Pearl Index for Lo Loestrin, but also concluded that the demonstrated efficacy, based on the Pearl Index, is acceptable to support approval. She stated the following in her CDTL review:

> "*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 …*"

I concur with Dr. Soule's assessment.

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).*"

I concur with the summary statement by Dr. Lockwood.

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 NDA 22-501. The Clinical Team Leader also thoroughly reviewed the safety data. Neither Medical Officer identified any safety issues 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 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 these 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 PR05806 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. The percentage of subjects with unscheduled bleeding/spotting (approximately 50%) and the mean number of days of unscheduled bleeding/spotting (ranging from 2.65-3.21 days) were highest during the first 3 months of treatment and tended to decrease over time.

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 with the duration of treatment, although it is possible that subjects with more frequent spotting/bleeding withdrew early from the study.*
- *The median number of days of 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

- *The mean number of days of scheduled bleeding/spotting in each cycle was low and ranged from 0.87 days (Cycle 12) to 1.76 days (Cycle 1). 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 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 during the course of the study. 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 had had values < 12 g/dL at baseline.

8.5 Overall Assessment of Safety

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 U.S. 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.

Among the safety issues of greatest concern are those related to venous thromboembolic events such as DVTs or pulmonary emboli. In the present Application, 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 an increased 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. However, 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. In addition, the trial was not large enough to demonstrate a reduction in the serious risks associated with estrogen/progestin drug products, such as deep vein thrombosis or myocardial infarction, as these are rare events. 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."

"There were no deaths during the clinical development of WC3016. The deep vein thrombosis in the phase 3 clinical trial occurred in an obese patient who smoked 10 cigarettes/day and who was 3 weeks post arthroscopic knee surgery. 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."

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) DRUP's decision regarding the approvability and labeling of Lo Loestrin.

10. PEDIATRICS

(b) (4) The Pediatric Review Committee (PeRC) granted a partial waiver for pre-menarcheal children because they are not at risk for pregnancy. The remainder of the PREA requirement for pediatric studies has been fulfilled by extrapolation. 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 adult women.

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) (6) 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. The Applicant also reported that no investigators utilized in the study were debarred under Section 306 (a) and (b) of the Federal Food, Drug, and Cosmetic Act.

12. LABELING

The proprietary name initially proposed by the Applicant, [redacted] (b) (4) was unacceptable to the Division of Medication Errors Prevention and Analysis (DMEPA). The Applicant then proposed the name "Lo Loestrin Fe" which DMEPA found acceptable.

The Lo Loestrin Fe label was submitted in the format prescribed by the Physician Labeling Rule (PLR). Agreement on final labeling was not reached during the current review cycle.

13. DECISION/ACTION/RISK BENEFIT ASSESSMENT

13.1 Regulatory Action

The Applicant has provided sufficient information for me to conclude that Lo Loestrin would be a safe and effective combination oral contraceptive when used in accordance with appropriate product labeling. The Office of Compliance, however, has issued an overall rating of "Withhold" approval for this Application because they identified deficiencies at a drug substance manufacturing facility and a control testing laboratory used to support this Application. Therefore, a Complete Response letter will be issued for this NDA. Eventual approval of this Application will require satisfactory resolution of the deficiencies identified by the Office of Compliance and agreement on acceptable product labeling.

13.2 Risk/Benefit Assessment

Safety considerations. The overall safety profile for Lo Loestrin, 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 U.S. These safety data do not raise any safety concerns regarding Lo Loestrin 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 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. Lo Loestrin is not marketed in any country, so there are no postmarketing data on its safety. However, 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.

Efficacy considerations. The Applicant has submitted an acceptable clinical trial database supporting the efficacy of Lo Loestrin. 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 approved by DRUP to date. The highest Pearl Index for a currently approved combination oral contraceptive in the U.S., 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). For the reasons presented earlier in Section 7.4, I have concluded that the demonstrated efficacy of Lo Loestrin is adequate to support approval of the product when Lo Loestrin would be used in accordance with appropriate product labeling.

Overall Risk/Benefit Assessment. The overall risk/benefit profile for Lo Loestrin is acceptable for a combination oral contraceptive. Lo Loestrin, if approved, will contain the lowest daily dose of ethinyl estradiol (10 µg) of any combination oral contraceptive approved in the U.S. Women using Lo Loestrin will receive 40% less ethinyl estradiol over a 28-day treatment cycle than those taking the lowest currently approved combination oral contraceptive. Although women taking Lo Loestrin may be exposed to a slightly greater risk of pregnancy based on the Pearl Index of 2.92, their exposure to ethinyl estradiol will be lower than with any other currently approved product. For women who desire to take a combination oral contraceptive with a low dose of estrogen, Lo Loestrin will give them the choice of balancing a potential increased risk of pregnancy against the potential, but yet unproven, safety benefit of a lower daily exposure to estrogen. Should this product eventually be approved, labeling will clearly describe the Pearl Index and the population studied in the primary clinical trial so that prescribers and potential users will be aware (1) of the potential risk of pregnancy when using this product and (2) that the product was not studied in women with a BMI ≥ 35.

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

None.

13.4 Recommendation for other Postmarketing Requirements and Commitments

None.

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22501	ORIG-1	WARNER CHILCOTT CO INC	(b) (4)

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
01/26/2010

Cross-Discipline Team Leader Review

Date	January 25, 2010
From	Lisa M. Soule, M.D.
Subject	Cross-Discipline Team Leader Review
NDA/BLA #	22-501
Applicant	Warner Chilcott, LLC
Date of Submission	March 26, 2009
PDUFA Goal Date	January 26, 2010
Proprietary Name / Established (USAN) names	Lo Loestrin Fe Norethindrone acetate (NA)/Ethinyl estradiol (EE) tablets and ferrous fumarate tablets
Dosage forms / Strength	Tablets; 1 mg NA and 10 µg EE x 24 days, 10 µg EE x 2 days and 75 mg ferrous fumarate x 2 days
Proposed Indication(s)	Prevention of pregnancy
Recommended:	***Complete Response (based on CMC deficiency related to Office of Compliance "Withhold" recommendation)***

1. Introduction

This NDA seeks marketing approval for a new dose and new dose regimen of norethindrone acetate (NA) and ethinyl estradiol (EE), steroid hormones commonly used in combined oral contraceptives. The Applicant proposes a 24/2/2 day regimen, in which women take a combination pill containing 1 mg NA and 10 µg EE (lower than any EE dose currently marketed) for the first 24 days of the cycle, followed by a 10 µg EE tablet taken for two days, followed by a ferrous fumarate (Fe) tablet taken for two days. The indication sought is prevention of pregnancy. The Applicant anticipates that the lower dose of EE might mitigate concerns about the thromboembolic risk associated with contraceptive hormones, while the use of 24 days of active treatment followed by two days of EE alone might improve the bleeding profile with respect to both withdrawal (scheduled) and intracyclic (unscheduled) bleeding.

The proposed proprietary name "Lo Loestrin Fe" has been found acceptable by the Division of Medication Error Prevention and Analysis (DMEPA), and is therefore used in this review. The initial proposed name was "[redacted] (b) (4);" although this was found unacceptable by DMEPA, the name is referenced in some of the discipline reviews cited herein. The product was called WC3016 during the clinical trial, and this name is used by Dr. Orleans in his primary medical review.

The Applicant submitted one pivotal safety and efficacy trial, which was an open label, single arm, multicenter, 13-cycle trial. The trial enrolled over 1,600 women to meet the Division's exposure requirements for a new contraceptive regimen, allowing for a substantial discontinuation rate. The primary efficacy endpoint, the Pearl Index in women aged ≤ 35 years and based on cycles in which no other methods of birth control were used, showed a

higher risk of pregnancy, 2.92 per 100 women-years, than any hormonal contraceptive approved by the Division of Reproductive and Urologic Drugs (DRUP) to date. However, the confidence interval around this point estimate was narrower, and the upper bound was lower than that for other approved products which conducted smaller and/or shorter clinical trials. The highest Pearl Index for a currently approved oral contraceptive is that for Lo Seasonique (Pearl Index of 2.74), which was approved in October 2008.

The bleeding profile of Lo Loestrin is acceptable. The mean number of days of unscheduled bleeding/spotting actually surpasses the mean number of days of withdrawal bleeding/spotting at each cycle, which may be considered a drawback by users. The overall profile of unscheduled bleeding/spotting appears similar to that seen in other, recently reviewed low EE COCs. It is unclear what relative contributions the very low EE dose and the extended dosing of EE make to the overall profile. However, it appears that a 10 µg EE dose when administered for 26 days of a 28 day cycle results in an acceptable bleeding profile.

The major issues addressed in this review involve the acceptability of the Pearl Index and the generalizability of the efficacy results, given the restrictions the Applicant placed on trial entry with respect to body mass index (BMI). These two concerns will be appropriately addressed in labeling in the next review cycle.

2. Background

2.1 DESCRIPTION OF PRODUCT

Lo Loestrin Fe is a combination oral contraceptive (COC) containing 10 µg of EE and 1 mg of NA, to be taken in the 24/2/2 regimen over a 28 day cycle for the prevention of pregnancy, as described in the preceding section. The combination tablets are taken for the first 24 days of the cycle, then tablets containing only 10 µg of EE are taken for two days. The final two days of the cycle, tablets containing 75 mg ferrous fumarate are taken. The ferrous fumarate is not considered to serve any therapeutic purpose; it is essentially placebo. Dose selection was supported by a phase 2 ovulation inhibition study conducted using continuous administration of 5 µg of EE and 1 mg of NA compared to 20 µg of EE and 1 mg of NA over 21 days in 60 women over age 40 who showed no signs of estrogen deficiency. The ovulation rate in the lower dose, continuous administration arm was about 10%, compared to 24% in the higher dose, 21-day administration.

The combination of these specific hormones has been approved since 1968, albeit in much higher doses. The Applicant has a "family" of Loestrin products using the same hormones in doses ranging from 1 mg NE/20 µg EE to 1.5 mg NE/30 µg EE, with approvals dating back to 1973. The newest product, approved in 2006, (Loestrin 24 Fe) utilizes a 24/4 regimen, with 24 days of 1 mg NE/20 µg EE, followed by four days of ferrous fumarate. No safety or efficacy concerns have been raised over the long history of use of these products.

Other products (i.e., Mircette, Seasonique, Lo Seasonique) have included five to seven days of 10 µg EE following the combination tablets. The additional EE has been hypothesized to improve the bleeding profile of the products, but this has not been conclusively demonstrated.

2.2 REGULATORY HISTORY

The development program for Lo Loestrin Fe was conducted under IND 73,510, which was opened in 2006. A scheduled pre-IND teleconference to be held in August 2006 was cancelled after the Applicant received preliminary responses from the Division of Reproductive and Urologic Products (DRUP). In these responses, the Division advised that:

- A single clinical study would be adequate as long as it provided at least 10,000 evaluable cycles and at least 200 women aged 18-35 who took the study drug for at least on year (13 cycles)
- The efficacy analysis should be based on the Pearl Index in the population of women aged 35 or less, and based on all at-risk cycles in which no other method of birth control was used. The 95% confidence interval around the point estimate of the Pearl Index and a life table analysis of the risk of pregnancy was also requested.

The phase 3 protocol was reviewed and a few comments were conveyed to the Applicant in January 2007. The advice concerning the primary efficacy analysis was reiterated.

In lieu of a preNDA meeting, the Applicant submitted information regarding the content of the forthcoming NDA. The Division provided comments in March 2009 on labeling and NDA format from the Office of Business Process and Support and from the statistical reviewer regarding data elements requested for the efficacy dataset.

2.3 PRIMARY MEDICAL REVIEWER'S RECOMMENDATION FOR APPROVABILITY

The primary reviewer, Dr. Ronald Orleans, stated in his review, dated January 9, 2010:

> *Approval of WC3016 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.*
>
> **Team Leader Comment**
>
> **I find the Pearl Index for this product, which approached 3, to be of concern because it would constitute the highest Pearl Index for a product approved by DRUP to date. However, the regulatory grounds for refusing to approve an application (CFR 414.125) do not include concerns with respect to efficacy relative to other approved products.**
>
> **The Division has never set an absolute standard for what constitutes an acceptable Pearl Index, or upper bound of the 95% confidence interval around the point estimate of the Pearl Index. However, there is general consensus that an upper bound above 5 would likely be unacceptable. This product falls below that value, so I cannot state that the efficacy for this product is not acceptable.**
>
> **I am particularly concerned about the efficacy of this product when used by subgroups of women who were excluded from the clinical trial; specifically, obese women with a BMI above 35 mg/m^2. This concern will be addressed in labeling.**
>
> **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. For these reasons, 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.

3. CMC/Device

The primary Chemistry reviewer, Yubing Tang, Ph.D., made the following recommendations in her review dated 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.*

She submitted an addendum to her original review, which was dated January 22, 2010, with the following recommendation:

> *CMC Review #1 was completed on 08-JAN-2010 with all CMC issues resolved except for the absence of an overall "Acceptable" recommendation from the Office of Compliance.*
>
> *Now the Office of Compliance has issued an overall rating of "Withhold" on 19-JAN-2010 (see attached EES summary report).*
>
> *Therefore, 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.*

Dr. Tang did not recommend any phase 4 commitments.

3.1 Facilities review/inspection

The Office of Compliance issued a "Withhold" recommendation on January 19, 2010. One drug substance manufacturing site is under a Warning letter. The Applicant has sent in a response that is currently under review by the Office of Compliance, and a reinspection of the site is planned but has not yet been scheduled. A second facility, a drug product testing site, is not yet ready for inspection.

3.2 Other notable issues (resolved or outstanding)

The need for USP microbial limits tests was conveyed to the Applicant, and is further discussed in Section 6. The Applicant agreed to the specification "the product meets the requirements of USP <61>, <62>, and <111), if tested" as requested by the microbiology reviewer, Dr. Pawar.

The originally proposed acceptance criteria for related substances were found not to be justified by the release data and stability results; proposed acceptance criteria were believed by Dr. Tang to be too broad. Specifications were revised to the satisfaction of Dr. Tang following discussion with the Applicant.

A 24-month expiry was granted based on stability data.

4. Nonclinical Pharmacology/Toxicology

The active ingredients of this product, EE and NA, have been marketed in a number of products for many years. All nonclinical studies were referenced to the Applicant's approved NDA (21-871) for Loestrin 24. The primary Toxicology reviewer, Krishan Raheja, D.V.M., Ph.D., made the following recommendations in his review dated June 22, 2009:

> ***Recommendations on approvability**: Pharmacology/toxicology data support approval of NDA 22-501 for* (b) (4) *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 require, the Labeling is in accordance with PLR and provided in SPL format.*
>
> **Team Leader Comment**
>
> **At the Division's request, the Applicant submitted a revised label that included Section 13, as required under PLR requirements. This revision was acceptable to Dr. Raheja.**

5. Clinical Pharmacology/Biopharmaceutics

The clinical development program included three phase 1 studies in addition to the phase 3 trial. The phase 1 studies included a bioavailability study of multiple doses of Lo Loestrin Fe, a relative bioavailability study of EE and NA from administration of Lo Loestrin Fe tablets in the fasted and fed states as compared to an EE/NA solution, and a relative bioavailability study of EE from administration of an EE 10 µg tablet in the fasted and fed states as compared to an EE solution. The studies evaluating food effect showed that dosing under fed conditions reduced the EE Cmax by about 23%, while that for NA was unchanged. The AUC for EE was unchanged, while that for NA increased by about 24%. However, the clinical trial was conducted without regard to meals, so dosing instructions without respect to meals were acceptable to the Clinical Pharmacology reviewer, Sandhya Apparaju, Ph.D.

No specific drug-drug interaction studies were conducted; however, interactions of specific drugs with combined oral contraceptives generally are included in class labeling for combined hormonal contraceptives. Dr. Apparaju made extensive revisions to the Clinical Pharmacology sections of the label, and these were conveyed to the Applicant.

Dr. Apparaju stated the following in her review dated November 27, 2009:

> *NDA 22-501 is acceptable from a Clinical Pharmacology perspective, provided an agreement can be reached with the sponsor pertaining to labeling language.*
>
> **Team Leader Comment**
>
> **Labeling agreement was not reached in this review cycle; however, there were no other outstanding issues from a Clinical Pharmacology perspective.**

No phase 4 commitments were recommended.

6. Clinical Microbiology

The Product Quality Microbiology reviewer, Vinayak Pawar, Ph.D., noted that USP microbial limits testing is performed on excipients, and that the Applicant claims that excipients and NA are used unchanged, which ensures absence of pathogens in the final product. The Applicant also claims that manufacture of the EE (b) (4) uses (b) (4) (b) (4). However, no microbial limits testing is performed on the drug product tablets. Dr. Pawar states that the compendial excipients used may be conducive to microorganism proliferation, and that the three month stability data on the Fe tablets showed an increase in moisture content, which can also facilitate microbial growth. He expressed concern that the manufacturing process does not address the possibility of contamination by adventitious pathogens during manufacturing. He recommended that product specifications include the revised USP <111>, <61> and <62> requirements at batch release and at stability endpoint. Batch release criteria should identify the specific manufacturing process tests and criteria used for assessment of the finished product as microbiologically suitable for release. The tests should include

- Microbial limits data for critical raw materials
- Microbiological environmental monitoring data for critical processing steps
- In-process control parameters that may affect product quality microbiology

Dr. Pawar recommended in his review dated November 25, 2009:

> *This submission is approvable pending resolution of the deficiency listed in Product Quality Microbiology Assessment Section 3 of this review.*

In a submission dated December 17, 2009, the Applicant agreed to the specification "the product meets the requirements of USP <61>, <62>, and <111), if tested" as requested by the microbiology reviewer, Dr. Pawar. In a second review dated December 23, 2009, Dr. Pawar determined that the Applicant's response was acceptable, and made the following recommendation on approvability:

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

No phase 4 commitments were recommended.

7. Clinical/Statistical - Efficacy

7.1 OVERVIEW OF CLINICAL PROGRAM

Clinical data submitted in this NDA include one pivotal phase 3 safety and efficacy trial, Study PR-05806, and three phase 1 bioavailability and pharmacokinetic (PK) studies. Study PR-05806 enrolled 1,683 subjects out of 2,235 screened. Twenty-three subjects did not start study medication. Subjects were enrolled at 68 US sites. The trial provided efficacy data based on 12,482 cycles and safety data based on 16,483 cycles. Almost 1,000 women completed 13 cycles of treatment.

> **Team Leader Comment**
>
> **The phase 3 trial met the Division's requirements regarding cycles of exposure and number of women completing 13 cycles of treatment.**

Entry criteria are detailed in Dr. Orleans' review, but primary criteria for eligibility were those

usually utilized in hormonal contraceptive trials. However, the inclusion criteria also required a body mass index (BMI) of ≤ 35 kg/m^2.

Team Leader Comments

- **The Division has discouraged restricting enrollment in hormonal contraception trials on the basis of weight or BMI. There are both safety and efficacy concerns regarding the use of hormonal contraception by obese women. Obese women may achieve lower serum hormone concentrations, which could pose a particular concern with respect to efficacy for a lower dose product like Lo Loestrin Fe. Conversely, obesity is a risk factor for venous thromboembolism (VTE), a major safety issue with hormonal contraceptives. Theoretically, a lower EE dose product might have a lower risk of VTE, although no data exist on a 10 μg EE product aside from that provided in this NDA submission. Safety and efficacy data obtained in obese women would be of great interest.**
- **At the time the protocol was reviewed, no comment was provided discouraging the Applicant from the BMI exclusion. However, I believe it is important that labeling disclose the fact that safety and efficacy was not studied in heavier women. I recommend the inclusion in the Clinical Trials section of the label of a statement:**

  Women with body mass index (BMI) greater than 35 kg/m^2 were excluded from the study.
- **I would also favor additional labeling in the Indications section of the package insert and in the patient labeling stating that the effectiveness of Lo Loestrin Fe in women with a BMI above 35 kg/m^2 has not been studied.**

Trial instructions included dosing without regard to meals, but recommended dosing at the same time each day. A Day 1 start was used (i.e., subjects switching from another COC began taking Lo Loestrin Fe on the day they would have resumed use of their previous product, and new users began on the first day of their period). Subjects who did not adhere to the dosing regimen and missed a period were discontinued from further dosing until pregnancy had been ruled out. Adherent subjects who missed a period were instructed to take a home pregnancy test. Subjects who missed two consecutive active pills in Week 1 or 2 were instructed to take the missed pills over two days and use backup contraception until they had taken seven consecutive active pills. Subjects who missed two or more consecutive active pills in Week 3 or 4 were instructed to take start a new pack immediately and use backup contraception until they had taken seven consecutive active pills.

7.2 DEMOGRAPHICS

Table 1 shows the demographics of the modified Intent to Treat (MITT) population in Study PR-05806, which is 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.

Table 1 Study PR-05806 – Demographics and Baseline Characteristics (MITT)

Parameter	N=1582
Age (years)	
Mean ± SD	28.6 (6.9)
Range	18.0, 45.9
Age cohorts, n (%)	
18-35 years	1295 (81.9)
>35 years	287 (18.1)
Ethnic origin, n (%)	
Asian	21 (1.3)
Black	186 (11.8)
Caucasian	1185 (74.9)
Hispanic	155 (9.8)
Native American	8 (0.5)
Other	27 (1.7)
User Status, n (%)	
Switcher	775 (49.0)
New User	807 (51.0)
Current smoker, n (%)	
Yes	235 (14.9)
No	1347 (85.1)
Height (inches)	
Mean ± SD	64.7 (2.7)
Range	55.8, 75.0
Weight (pounds)	
Mean ± SD	150.1 (29.3)
Range	89.0, 260.0

Source: Summary of Clinical Efficacy, Table 3; page 11

Team Leader Comments

- **The racial distribution of the population appears fairly representative of the general population.**
- **The mean weight is about 14 lbs. lower than seen in a recent comparable COC trial that did not restrict entry on the basis of BMI or weight.**
- **The Applicant uses a very broad definition of "new user," including women who had not been using a COC immediately before enrollment. Thus, even a prior user with a long history of COC use, who had been off her prior product for as few as four weeks was considered a new user. While new users are usually expected to have higher pregnancy and AE rates, I would not necessarily hold this expectation for the "new users" in this trial.**

7.3 DISPOSITION OF SUBJECTS

A total of 2,235 women were screened for the study, with 1,683 enrolled. 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 All Treated population (all women who took at least one dose of Lo Loestrin Fe) discontinued prematurely for the reasons described in Table 2.

Table 2 Study PR-05086 – Subject Disposition (All-Treated Population)

Disposition / Reason	Total
Screened	2,235
Screening failures	552
All Treated population (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%)
• Withdrawal of consent	147 (8.9%)
• Other	96 (5.8%)
• Lack of efficacy (pregnancy)	25 (1.5%)
• Protocol violation	20 (1.2%)
Study medication never administered	23

a = Defined as all subjects who received at least one dose of study drug
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 at enrollment
Source: Summary of Clinical Efficacy, Table 2; page 10

Team Leader Comment

The rate of premature discontinuation is typical of that seen for contraceptive trials, as is the distribution of reasons for premature discontinuation.

7.4 EFFICACY FINDINGS

7.4.1 Assessment of Efficacy

The primary endpoint was the Pearl Index, calculated as

$$\text{Pearl Index} = \frac{100 \times \text{number of pregnancies} \times 13 \text{ cycles/year}}{\text{Number of 28-day cycles of treatment*}}$$

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

The 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, with exclusion of any cycles in which an alternate method of birth control was used (also known as the PITT, non-BCM population).

Team Leader Comment

The PITT population is the appropriate one for evaluation of the primary endpoint (Pearl Index), and cycles in which other contraception (including condoms) was used were appropriately excluded.

Pregnancies conceived on drug or within 14 days after the last pill (whether EE/NA, or EE only) were included in calculation of the Pearl Index. The Applicant initially excluded pregnancies conceived in the first 13 days on study drug or in women who were 36 at

conception; however, the Division did not allow these exclusions, which are not typically used in contraceptive trials.

> **Team Leader Comment**
>
> **The Division's recent thinking on the window in which conceptions are counted 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 "placebo" week in a typical 21/7 regimen. However, at the time this study was discussed with the Division, the Division was recommending a 14-day window. For this reason, the Applicant initially reported all pregnancies conceived in the 14-day window; however, following the Division's subsequent advice, the Applicant and the FDA statistician reported pregnancies conceived within the 7-day window. For this particular application, where no pregnancies occurred in the window of 7-14 days after last active tablet, the Pearl Index calculations did not change based on the revision of the conception window.**

Life table methods are also commonly used to assess contraceptive efficacy; these provide cumulative rates of pregnancy at the end of the study, and at the end of each preceding cycle. Life tables do not typically exclude individual cycles for a given subject, such as a cycle in which an alternate method of birth control was used, so they are not directly comparable to the Pearl Index based on the PITT, non-BCM population.

7.4.1.1 Primary Efficacy Analysis

The PITT population comprised 1,270 women aged 18-35 years, who contributed a total of 12,482 non-BCM cycles that also excluded condom use (the Applicant counted four more cycles than did the DRUP statistician). The Applicant initially determined that a total of 41 pregnancies occurred in subjects in the trial, with 24 occurring on-treatment in women <36 years of age. However, after communication from the Division regarding the appropriate conception window and the unacceptability of censoring subjects once they turned 36, the Applicant agreed with the Division's count of 27 on-treatment pregnancies, and provided recalculations based on this number. Subsequently, the primary reviewer determined that one additional pregnancy should be counted (Subject # 25-017); the Applicant concurred but did not recompute the Pearl Index or life table estimate. Twenty-four women became pregnant on treatment, two additional women became pregnant within seven days after discontinuing treatment, and two had missing data regarding either date of last pill intake or date of conception, but were conservatively included in the Pearl Index calculation.

Table 3 Timing of Conception

Timing of conception	N	Comment
Prior to starting treatment	9	
On treatment	**24**	Applicant only considers 8 on-treatment, with 1 > 14 days and 1 unverified
≤ 7 days after last E+P pill	**2**	**# 22-041 (7 days)** **# 60-007 (3 days)**
Unknown last E+P intake	**1**	**# 21-024**
Unknown conception date	**1**	**# 25-017**
> 7 to ≤ 14 days after last E+P pill	0	
> 14 days after last E+P pill	4	Occurred 15-18 days after last dose

Bold = Pregnancies counted in computing the Pearl Index

Team Leader Comment

There were four subjects on which the Applicant and the medical reviewers initially disagreed:

- **Subjects 001-104 and 017-022 were age 35 upon enrollment, but 36 at the time of conception. The Sponsor initially excluded them from the PITT population. Per the Division's conventions, Pearl Indices are based on women aged 18 to 35 years at enrollment, regardless of age at the time of conception.**
- **Subject 28-055 conceived nine days after starting study drug;** (b) (4)
- **Subject 025-017 was considered by the Applicant to have insufficient documentation of pregnancy; however, review of her records by Dr. Orleans revealed that she had reported a positive urine pregnancy test on 12/28/07, six days after her last dose of study drug. Although examinations by her private Ob-Gyn on 2/1/08 and at her final study visit on 2/4/08 revealed no evidence of pregnancy, and she had negative pregnancy testing on 2/4, the investigator indicated in the subject's Case Report Form that she was a "suspected pregnancy." The Applicant ultimately agreed with the Division that she should be counted as an on-treatment pregnancy.**

The Applicant was further asked to indicate which pregnancies were associated with missed pills; in a submission dated December 3, 2009, the Applicant indicated that only three of the 28 pregnancies occurred in a cycle in which pills had been missed or early in a following cycle. Review of the submitted data showed that one subject had discrepancies between her pill packs (which indicated complete pill intake) and her diary (which indicated missed pills). For the other two subjects, they had clearly missed at least three consecutive pills before conceiving.

Team Leader Comment

It appears that at least 25 of the 28 pregnancies occurred in the face of "perfect use."

Pearl Index

The Applicant provided revised PITT, non-BCM data, including the initial 27 pregnancies determined by the Division to have occurred on treatment. The statistical reviewer, Kate Dwyer, Ph.D., reviewed the Applicant's revised data and recalculated the Pearl Index including the final pregnancy counted by the primary reviewer (see Table 4). The "gold

standard analysis" relied upon by the Division is the PITT, non-BCM, which gives a Pearl Index of 2.92 (95% confidence interval [CI] 1.94 – 4.21).

Table 4 Pearl Index Calculation of Treatment Failure Rates using 7-Day after Last Pill Conception Rule, in the PITT, non-BCM Population

	Population	N	Number of On-Treatment Pregnancies	Number of Cycles	Pearl Index	95% Confidence Interval
Sponsor	MITT	1,555	27	15,595	2.25	(1.48, 3.27)
	PITT	1,270	27	12,486	2.81	(1.85, 4.09)
Reviewer	MITT	1,555	28	15,591	2.33	(1.55, 3.37)
	PITT	1,270	28	12,482	2.92	(1.94, 4.21)

Source: Table 3, Statistical review by Kate Dwyer, dated December 28, 2009

Team Leader Comment

Based on clinical trial data submitted in support of NDAs for OCs, this Pearl Index exceeds that of any approved combination OC in the U.S.

Life Table Analysis

The Applicant provided a twelve-month life table estimate of the pregnancy rate based upon the 27 pregnancies initially identified by DRUP and on the PITT cohort. The FDA statistician provided a life table estimate based on the 28 pregnancies ultimately agreed upon by the Applicant. Dr. Dwyer excluded only those cycles in which back-up contraception was used, rather than censoring a subject as soon as she used back-up contraception.

Table 5 Life Table Estimates of Treatment Failure Rates - Patients 18-35 Years of Age with at Least One Complete Cycle of Treatment (PITT)

		PITT Population	
Cycle	**# of Pregnancies**	**Cumulative Pregnancy Rate %**	**95% Confidence Interval**
1	3	0.00	-
2	4	0.24	0.08 - 0.74
3	2	0.57	0.27 - 1.19
4	2	0.74	0.39 - 1.42
5	4	0.92	0.51 - 1.66
6	2	1.31	0.79 - 2.16
7	1	1.51	0.94 - 2.42
8	4	1.62	1.02 - 2.56
9	1	2.07	1.36 - 3.13
10	1	2.18	1.45 - 3.28
11	2	2.31	1.54 - 3.43
12	1	2.56	1.74 - 3.76
13	1	2.71	1.86 - 3.95
Total	28		

Source: Prepared by FDA Statistical Reviewer, Kate Dwyer, Ph.D.

Team Leader Comment

The life table estimate is reasonably close to the Pearl Index, and, like the Pearl Index, is higher than that reported for other approved oral contraceptives.

Effect of Weight on Efficacy

Based on the review of a previous low-dose COC that showed a disproportionate distribution of pregnancies in heavier subjects, the Applicant was asked to stratify pregnancies by weight and BMI. Using deciles based on either weight or BMI, 50% of pregnancies occurred in the lower five deciles and 50% in the top five deciles. The FDA statistician computed stratified Pearl Indices by subject weight and BMI. These calculations show a numerically higher Pearl Index in women of higher weight and BMI, but the confidence intervals overlapped, suggesting that this was not a significant difference (see Table 6 and Table 7).

Table 6 Pearl Indices Based on Body Mass Index at Screening

BMI	N	Number of On-Treatment Pregnancies	Number of Cycles	Pearl Index	95% Confidence Interval
< 24	624	12	6,065	2.57	(1.33, 4.49)
≥ 24	646	16	6,417	3.04	(1.86, 5.26)
Total	1,270	28	12,482	2.92	(1.94, 4.21)

Source: FDA Statistician; table from Dr. Orleans' primary medical review, dated January 9, 2010, Table 17

Table 7 Pearl Indices Based on Weight at Screening

Weight	N	Number of On-Treatment Pregnancies	Number of Cycles	Pearl Index	95% Confidence Interval
< 144	623	12	6,102	2.56	(1.32, 4.46)
≥ 144	647	16	6,380	3.26	(1.86, 5.29)
Total	1,270	28	12,482	2.92	(1.94, 4.21)

Source: FDA Statistician; table from Dr. Orleans' primary medical review, dated January 9, 2010, Table 18

Team Leader Comment

I do not believe the data show a significant impact of higher weight or BMI on efficacy for Lo Loestrin Fe. However, given that the study population was truncated at a BMI of 35, it is possible that the pregnancy rate in heavier women in the general population could be statistically significantly higher than that in less heavy women.

Statistician's Conclusion

The statistical reviewer, Kate Dwyer, Ph.D., essentially confirmed the Applicant's primary efficacy findings, although the Applicant did not update its calculations with the final agreed-upon pregnancy.

Subgroup analyses were performed on the basis of weight, BMI and ethnic origin (Caucasian, Black, Hispanic, Others). The weight and BMI analyses have been described previously. Dr. Dwyer noted that the Pearl Indices appeared to vary substantially by ethnicity (Caucasian 2.07, Black 2.96, Hispanic 8.13 and Other 5.51); however the estimates were based on fewer than 140 subjects and < 1400 cycles for all subgroups except Caucasians.

Dr. Dwyer made the following recommendation in her review of December 28, 2009:

> *From a statistical perspective, the study results support the efficacy of WC3016, 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.*

7.4.1.2 Secondary Efficacy Analysis

Subjects completed a daily paper diary that recorded occurrence and intensity of bleeding or spotting. The following bleeding intensity definitions were used:

- None: no vaginal bleeding
- Light: less than the subject's normal menses
- Normal: like the subject's normal menses
- Heavy: more than the subject's normal menses

Light bleeding that required no use of sanitary protection (aside from panty liners) was classified as spotting.

Bleeding/spotting was characterized as withdrawal (herein referred to as "scheduled") if it started after the last day of active treatment (defined by the Applicant to include the EE-only days) and before starting the next treatment cycle, or if it started within four days before the last day of active treatment and continued through at least the first day after the end of active treatment. All other bleeding/spotting episodes were considered "intracyclic" by the Applicant (herein referred to as "unscheduled").

The Applicant provided the following bleeding data (see Table 8 through Table 11). The Applicant also reported that 49% of women became amenorrheic by Cycle 13.

Table 8 Days with Unscheduled Bleeding per 28-Day Cycle

Cycle	N	Mean (SD)	Minimum	Median	Maximum
1	1514	2.0 (3.49)	0	0	25
2	1447	2.5 (3.67)	0	0	22
3	1391	2.3 (3.51)	0	0	25
4	1312	2.0 (3.19)	0	0	22
5	1254	1.8 (2.96)	0	0	23
6	1194	1.6 (2.72)	0	0	19
7	1164	1.8 (2.98)	0	0	19
8	1117	1.5 (2.65)	0	0	20
9	1077	1.6 (2.66)	0	0	17
10	1035	1.5 (2.84)	0	0	24
11	996	1.5 (2.60)	0	0	20
12	977	1.5 (2.68)	0	0	20
13	945	1.5 (2.61)	0	0	19

Source: Based on Applicant submission dated October 16, 2009

Table 9 Days with Unscheduled Spotting per 28-Day Cycle

Cycle	N	Mean (SD)	Minimum	Median	Maximum
1	1514	0.7 (1.75)	0	0	21
2	1447	0.7 (1.86)	0	0	19
3	1391	0.5 (1.47)	0	0	17
4	1312	0.5 (1.66)	0	0	24
5	1254	0.4 (1.47)	0	0	17
6	1194	0.4 (1.46)	0	0	18
7	1164	0.5 (1.74)	0	0	19
8	1117	0.3 (1.21)	0	0	18
9	1077	0.4 (1.55)	0	0	23
10	1035	0.3 (1.22)	0	0	17
11	996	0.3 (1.44)	0	0	17
12	977	0.3 (1.27)	0	0	15
13	945	0.3 (1/43)	0	0	17

Source: Based on Applicant submission dated October 16, 2009

Team Leader Comments

- **Unscheduled bleeding and spotting tends to be heavier during the initial cycles of use, stabilizing by about Cycle 6. On average, subjects experienced about three days of unscheduled bleeding or spotting in Cycles 1-3, and about two days of unscheduled bleeding/spotting in Cycles 4-13. However, using medians, at least 50% of users will experience no unscheduled bleeding/spotting.**
- **Compared to other recently reviewed low-dose COCs (Cette, with 20 µg EE in a 21/7 regimen and Lo Seasonique with 20 µg EE in an 84/7 regimen), Lo Loestrin Fe appears to have a similar pattern of unscheduled bleeding/spotting days.**

Table 10 Days with Scheduled Bleeding per 28-Day Cycle

Cycle	N	Mean (SD)	Minimum	Median	Maximum
1	1514	1.5 (2.28)	0	0	12
2	1447	1.1 (2.03)	0	0	10
3	1391	1.2 (2.09)	0	0	10
4	1312	1.0 (1.94)	0	0	10
5	1254	0.9 (1.81)	0	0	10
6	1194	0.8 (1.76)	0	0	10
7	1164	0.8 (1.71)	0	0	10
8	1117	0.9 (1.82)	0	0	10
9	1077	0.9 (1.81)	0	0	10
10	1035	0.8 (1.65)	0	0	10
11	996	0.8 (1.64)	0	0	10
12	977	0.7 (1.66)	0	0	10
13	945	1.3 (3.05)	0	0	10

Source: Based on Applicant submission dated October 21, 2009

Table 11 Days with Scheduled Spotting per 28-Day Cycle

Cycle	N	Mean (SD)	Minimum	Median	Maximum
1	1514	0.2 (0.89)	0	0	10
2	1447	0.2 (0.92)	0	0	10
3	1391	0.2 (0.94)	0	0	10
4	1312	0.2 (0.88)	0	0	10
5	1254	0.2 (0.71)	0	0	10
6	1194	0.2 (0.86)	0	0	10
7	1164	0.2 (0.87)	0	0	10
8	1117	0.1 (0.54)	0	0	6
9	1077	0.2 (0.73)	0	0	8
10	1035	0.2 (0.87)	0	0	10
11	996	0.1 (0.65)	0	0	8
12	977	0.2 (0.76)	0	0	10
13	945	0.2 (1.32)	0	0	10

Source: Based on Applicant submission dated October 21, 2009

Team Leader Comments

- **The mean number of days of scheduled bleeding was low, 1.5 days at the first cycle, and tended to decrease over time, with < 1 day per cycle from Cycle 5 until Cycle 12.**
- **The number of scheduled spotting days was also very low.**
- **The mean number of days of scheduled bleeding or spotting never exceeded two in any cycle.**

The frequency of adverse events and discontinuations due to bleeding was also evaluated. Eighty-two 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%). As discussed in Section 8.1, 63 subjects (3.8%) discontinued due to bleeding-related adverse events (metrorrhagia, irregular menstruation, menorrhagia or vaginal hemorrhage).

Team Leader Comment

The bleeding profile of Lo Loestrin Fe is acceptable. The short withdrawal bleeding/spotting duration is likely to appeal to users. However, this is offset by the inconvenience of having several days of unexpected, unscheduled bleeding/spotting in each cycle.

7.4.2 Overall Assessment of Efficacy

The single clinical trial included sufficient cycles of exposure to meet the Division's requirements for a new contraceptive regimen using well established contraceptive hormones. This product, which would provide the lowest dose of EE in any approved combination product, also demonstrates a higher Pearl Index than any approved COC. Although I am concerned by the Pearl Index of 2.92 for this product, the regulatory grounds for refusing to approve an application (CFR 414.125) do not include concerns with respect to efficacy relative to other approved products. The Division has never set an absolute standard for what constitutes an acceptable Pearl Index, or upper bound of the 95% confidence interval around the point estimate of the Pearl Index. However, there is general consensus that an upper bound

above 5 would likely be unacceptable. This product falls below that value, so I cannot state that the efficacy for this product is unacceptable.

However, I am particularly concerned about the efficacy of this product in subgroups of women who were excluded from the clinical trial; specifically, obese women with a BMI above 35 kg/m^2. This concern will be addressed in labeling.

The bleeding profile of Lo Loestrin Fe is acceptable. The mean number of days of unscheduled bleeding/spotting actually surpasses the mean number of days of withdrawal bleeding/spotting at each cycle. The overall profile of unscheduled bleeding/spotting appears similar to that seen in other, recently reviewed low EE COCs. Those products differed from Lo Loestrin in multiple ways: dose regimen, dose (20 µg EE), and progestin, so it is unclear what relative contributions the very low EE dose and the extended dosing of EE make to the overall profile. However, it appears that a 10 µg EE dose administered for 26 days of a 28 day cycle results in an acceptable bleeding profile.

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.

8. Safety

This review of the safety of Lo Loestrin Fe is primarily based on data from Study PR-05806, supplemented by safety data from the three phase 1 trials.

The safety population in Study PR-05806 included 1,660 women who took at least one dose of Lo Loestrin Fe, or 98.6% of all enrolled subjects. The three phase 1 studies included 66 women exposed to Lo Loestrin Fe. Safety data on women completing one year of treatment was available for 968 subjects.

Safety evaluations included vital signs and laboratory monitoring, pregnancy testing and adverse event reporting.

8.1 Deaths and Serious Adverse Events

There were no deaths in the clinical trial, or in any of the three PK studies. There were no serious adverse events (SAE) in phase 1; 15 subjects in Study PR-05806 experienced a total of 18 SAEs, which are detailed in Table 12. Four of these resulted in discontinuation of the subject from the trial.

Table 12 SAEs in Study PR-05806

Subject No.	SAE(s) Preferred Term	Reviewer's Assessment of Causality
004-005*	Deep vein thrombosis	Probable
006-010	Appendicitis	Unlikely
018-015	Hyperemesis gravidarum	Unlikely
031-045	Appendicitis	Unlikely
033-004*	Ovarian cyst (dermoid tumor)	Unlikely
035-004*	Ovarian vein thrombosis	Probable
035-006	Cholecystitis	Probable
036-063	Pneumonia	Unlikely
040-001	Food poisoning	Unlikely
043-004*	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

*Discontinued for SAE
Source: Summary of Clinical Safety, pp 31-34

Team Leader Comments

- **Subject 004-005 developed a deep vein thrombosis (DVT) 23 days following arthroscopic surgery on the ipsilateral leg. She had not discontinued Lo Loestrin Fe prior to surgery. Additional risk factors for DVT included smoking and obesity (222 lbs), and arthroscopic surgery is a strong risk factor for DVT in itself. Nonetheless, I believe this is a drug-related SAE, although not one that I find unexpected.**
- **Subject 035-004 presented to the emergency department after (b) (6) on Lo Loestrin Fe complaining of abdominal pain and was treated for "an ovarian cyst." She returned (b) (6) days later with worsening pain. (b) (6) days following the second visit she was called to return to the hospital due to a "blood clot on the right ovary" noted on the CT scan from the second visit. She was admitted and started on Lovenox. The patient informed the investigators that the hospital physicians did not believe the thrombus was related to her use of OCs.**

  A Pubmed search revealed two articles pertaining to non-puerperal ovarian vein thrombosis[1,2] (OVT). The first article details a case of OVT that followed treatment for pelvic inflammatory disease (PID) but was unassociated with recent pregnancy or hereditary hypercoagulopathies. No mention of the patient's contraceptive status is mentioned. Following the patient's leaving the hospital against medical advice, while inadequately anticoagulated, she represented with a pulmonary embolus that was determined to originate from the OVT. The second case report describes a patient who had discontinued her oral contraceptive (unspecified) two months prior to diagnosis with OVT. The

[1] Heavrin, BS and Wrenn K. Ovarian vein thrombosis: a rare cause of abdominal pain outside the peripartum period. J Emerg Med 2008, 34: 67-9

[2] Murphy, C and Tarsa, T. Idiopathic ovarian vein thrombosis: a rare cause of abdominal pain. Am J Emerg Med 2006, 24: 636-7

authors state that at least four weeks of abstinence from estrogens/progestins is needed to reverse potentially hemostatic changes that occur during COC use.

In summary, while I can find no reports of OVT associated with COC use, I do not find reason to exclude a contribution of Lo Loestrin Fe to the occurrence of the OVT in this study subject.

- **For Subject 035-006, there appeared to be no prior history of cholecystitis or cholelithiasis. She became symptomatic after almost seven months on study drug. She underwent cholecystectomy and a second procedure to remove additional gallstones from her biliary ducts. Cholecystitis is a known and labeled risk associated with OCs.**
- **Subject 043-004 underwent endovascular stenting of her right transverse sigmoid sinus; the postop diagnosis was right transverse sigmoid sinus stenosis, which had been documented preoperatively by venogram. I do not believe this is attributable to Lo Loestrin Fe use.**
- **Subject 052-055 was discontinued from the study for pregnancy, and was hospitalized at 34 weeks of pregnancy for abdominal pain. No cause was determined. It was determined that she conceived prior to starting study drug.**

A total of 172 subjects (10.4%) discontinued the trial due to adverse events (AEs) in Study PR-05806; five additional subjects discontinued prior to taking study drug. Table 13 displays the common AEs that led to withdrawal; events occurring in only a single subject are shown only if they are notable.

Table 13 Common and Notable Adverse Events Leading to Discontinuation in Study PR-05806

Adverse Event Preferred Term	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: Based on Table 23, primary medical review by Dr. Orleans, dated January 9, 2010

Team Leader Comments

- **Subject 001-046 experienced left-sided numbness and difficulty speaking for about 10 minutes after (b) (6) on Lo Loestrin Fe. 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. She was discharged from the Emergency Department on low dose aspirin and instructed to discontinue study drug. The investigator considered this to be a transient ischemic attack, possibly related to study drug. I agree, and consider that this is likely related to study drug.

- **Subject 001-073 enrolled in the study with a baseline hematocrit of 39, and experienced persistent unscheduled bleeding over two of her three months of enrollment. Her end of study hematocrit remained at 39.**
- **Subjects 004-005, 035-004, 043-004 and 033-004 are discussed under SAEs or listed in** Table 12**.**

None of the 66 phase 1 subjects discontinued prematurely due to AEs.

8.2 Other Adverse Events

The Applicant provided a table of common adverse events, defined as those occurring in at least 2% of the safety population; see Table 14.

Table 14 Most Commonly Reported (≥2%) Treatment-Emergent AEs in Study PR-05806

AE Preferred Term	Number (%) of Subjects
Headache	116 (7.0)
Upper respiratory tract infection	103 (6.2)
Sinusitis	86 (5.2)
Nasopharyngitis	85 (5.1)
Nausea	80 (4.8)
Dysmenorrhoea	73 (4.4)
Urinary tract infection	65 (3.9)
Vaginitis bacterial	64 (3.9)
Human papilloma virus	62 (3.7)
Weight fluctuation	59 (3.6)
Breast tenderness	58 (3.5)
Metrorrhagia	56 (3.4)
Acne	55 (3.3)
Abnormal Pap smear	50 (3.0)
Fungal infection	44 (2.7)
Abdominal pain	42 (2.5)
Influenza	40 (2.4)
Vomiting	40 (2.4)
Pharyngitis streptococcal	39 (2.3)
Vulvovaginal mycotic infection	38 (2.3)
Bronchitis	36 (2.2)
Anxiety	35 (2.1)
Depression	33 (2.0)

Source: Table 24, primary medical review by Dr. Orleans, dated January 9, 2010

Team Leader Comment

AEs that are likely to be drug-related include headaches, nausea, weight changes, breast tenderness and bleeding irregularities. Incidence of these events is not markedly different from other approved OCs.

The Division requested that the Applicant provide shift tables of hemoglobin and hematocrit, as well as hematologic indices for subjects who withdrew due to bleeding-related adverse events. The shift table for hemoglobin showed that only 14 of 1249 subjects (1.1%) who had

normal values at baseline shifted to low values at the end of the study (no subjects had high values at baseline). For hematocrit, only 9 of 1283 subjects (0.7%) who had normal values at baseline shifted to low values at the end of the study (no subjects had high values at baseline). For each parameter, the proportion of subjects who shifted from low baseline to normal at end-of-study was greater than those who shifted downward.

A total of 63 subjects withdrew due to bleeding-related AEs. Comparison of baseline and end-of-study hemoglobin and hematocrit revealed no pattern of decreased hematologic indices associated with bleeding. Only four subjects had hemoglobin < 12 g/dl at end-of-study, and all had been < 12 g/dl at baseline as well, although three showed a decrease ranging from -0.1 to -0.8 g/dl.

Data on other laboratory parameters and vital signs data are discussed in Dr. Orleans' review, and did not provide any signal of concern.

8.3 Postmarketing Safety Findings

Lo Loestrin Fe is not marketed in any country, so there are no postmarketing data on its safety. However, there is an extensive safety database with higher dose combinations of EE/NA. No concerns have been raised by recent annual reports or periodic safety update reports for these higher dose products.

8.4 Safety Update

The Applicant submitted a safety update on July 23, 2009, which indicated that no studies were ongoing. No new safety issues were identified.

8.5 Overall Assessment of Safety Findings

Lo Loestrin Fe does not appear to present an unusual or concerning safety profile. The rate and types of SAEs are typical of those observed in COC trials, as are the rates and reasons for premature discontinuations attributable to AEs. While Dr. Orleans notes that epidemiologic studies show a decreased risk of VTEs with lower exposure to estrogen and progestin, and that Lo Loestrin Fe may "be especially useful in subsets of women who are at increased risk for these thrombotic complications," I am unconvinced that this is true. In this trial of 1,660 women, there were three events (one DVT, one OVT and one transient ischemic attack [TIA]) that I consider to represent VTEs or possible arterial thromboembolic events (in the case of the TIA). This would translate to a rate of 18/10,000 women-years, which is certainly not lower than that described for higher EE dose COCs. On the other hand, I do not believe Lo Loestrin Fe poses a risk beyond that associated with other COCs. The DVT clearly occurred when the product was continued in contradiction to trial instructions and COC labeling directions (discontinue prior to surgery associated with VTE risk).

The only other SAE likely related to drug use was cholecystitis, which is a well-recognized and labeled risk associated with COC use. The frequency and nature of common AEs is similar to that seen in COCs generally. Again, I do not find that the lower EE dose of Lo Loestrin Fe distinguishes it from other COCs in terms of AE profile. In light of the drug's protection against pregnancy, a condition with serious health and social impact upon women, I believe the safety profile is acceptable.

9. Advisory Committee Meeting

The Division determined that an Advisory Committee was not needed to review this application. The combination of hormones used in this product is already approved for the prevention of pregnancy, and this application raised no new safety concerns.

10. Pediatrics

(b) (4) As recommended by DRUP, the Pediatric Review Committee (PeRC) granted a partial waiver for ages 0 to 11 years (i.e., premenarcheal patients), because there is no risk of pregnancy in this population. The remainder of the PREA requirement has been fulfilled by extrapolation from studies on adult women. DRUP's long experience with a variety of hormonal contraceptives has supported the expectation that efficacy and safety results in postmenarcheal adolescents do not differ from those in adult women.

11. Other Relevant Regulatory Issues

The Applicant submitted financial disclosure information for all 68 investigators, only a single one of whom reported a financial interest. (b) (6) enrolled only (b) (6) subjects, representing (b) (6) of the total study population. The Applicant also reported that no investigators utilized in the study were debarred under Section 306 (a) and (b) of the Federal Food, Drug and Cosmetic Act.

Dr. Orleans reviewed the data from (b) (6) 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. Site inspections by the Division of Scientific Investigation (DSI) were not requested for this or any of the study sites, based on the fact that this is a well characterized drug combination and that no sites appeared unusual in terms of adverse event reporting, pregnancies or dropouts.

12. Labeling

The proprietary name initially proposed by the Applicant, "(b) (4)," was unacceptable to DMEPA. The Applicant then proposed the name "Lo Loestrin Fe;" DMEPA found this acceptable on January 21, 2010.

The Lo Loestrin Fe label was submitted in the format prescribed by the Physician Labeling Rule (PLR). DRUP's review of this label was informed by the internal updated draft Guidance for oral contraceptive (OC) labeling, as well as by the first approved OC label in PLR format. Consultative reviews were provided by the Division of Drug Marketing, Advertising and Communication (DDMAC) and the Division of Risk Management (DRISK), and their comments were incorporated into the label as appropriate.

The major issues addressed in labeling negotiations with the Applicant included:

- Changes inherent in moving from the previous OC labeling format (used by the Applicant in the remainder of their "Loestrin" product line) to PLR format.

- Indicating that heavier women were not studied in the clinical trial and that the efficacy of Lo Loestrin Fe in women with a BMI above 35 kg/m2 has not been determined.
- Discussion of only a "Day 1 start," as this was the method used exclusively in the clinical trial. The option of a (b) (4) proposed by the Applicant was removed from the label.

Agreement with the Applicant on labeling was not reached during this review cycle.

13. Recommendations/Risk Benefit Assessment

13.1 Recommended Regulatory Action

The Pearl Index for Lo Loestrin Fe would represent the highest Pearl Index for a hormonal contraceptive product approved by DRUP. The upper bound of the confidence interval around the Pearl Index, however, is exceeded by that for Seasonale, and possibly for other approved products (confidence intervals have not always been included in labeling). Although I am concerned by the Pearl Index approaching 3 for this product, the regulatory grounds for refusing to approve an application (CFR 414.125) do not include relative lack of efficacy.

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.

13.2 Risk Benefit Assessment

As noted above, the Pearl Index for Lo Loestrin Fe would represent the highest for a product ever approved by DRUP. However, I cannot state that the point estimate is unacceptable, and the upper bound of the confidence limit has been exceeded by at least one other approved product (albeit likely because that product submitted a small and short clinical trial). Nonetheless, there may be women who wish to use the lowest possible dose of EE and are willing to accept a possibly greater risk of pregnancy.

The bleeding profile of Lo Loestrin is acceptable. The mean number of days of unscheduled bleeding/spotting actually surpasses the mean number of days of withdrawal bleeding/spotting at each cycle, and this may be seen as a drawback by users. The overall profile of unscheduled bleeding/spotting appears similar to that seen in other, recently reviewed low EE COCs.

Lo Loestrin Fe does not appear to present an unusual or concerning safety profile. The rate and types of SAEs are typical of those observed in COC trials, as are the rates and reasons for premature discontinuations attributable to AEs. I do not agree with Dr. Orleans that Lo Loestrin Fe may be of value to women with an increased risk of VTE, as the risk demonstrated in this trial is certainly not lower than that described for higher EE dose COCs. On the other hand, I do not believe Lo Loestrin Fe poses a risk beyond that associated with other COCs. The frequency and nature of common AEs is similar to that seen in COCs generally.

While I do not find that the lower EE dose of Lo Loestrin Fe distinguishes it from other COCs in terms of the AE profile, given the drug's protection against pregnancy, I believe the safety profile is acceptable.

13.3 Recommendation for Postmarketing Risk Evaluation and Management Strategies

No postmarketing risk management activities beyond labeling are recommended.

13.4 Recommendation for Other Postmarketing Requirements and Commitments

No postmarketing studies are recommended.

13.5 Recommended Comments to Applicant

None

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22501	ORIG-1	WARNER CHILCOTT CO INC	(b) (4)

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

/s/

LISA M SOULE
01/25/2010

SCOTT E MONROE
01/26/2010
I concur with Dr. Soule's overall conclusions and her recommendation.

CLINICAL REVIEW

Application Type	NDA
Application Number(s)	22-501
Priority or Standard	Standard
Submit Date(s)	March 26, 2009
Received Date(s)	March 26, 2009
PDUFA Goal Date	January 26, 2010
Division / Office	Reproductive and Urologic Products/Office of New Drugs
Reviewer Name(s)	Ronald J. Orleans, M.D.
Review Completion Date	January 7, 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

Approval of WC3016 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.

1.2 Risk Benefit Assessment

The Pearl Index for WC3016 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 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 WC3016 in preventing pregnancy.

The Applicant believes that the reduction of the estrogen dose in WC3016 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. In addition, the trial was not large enough to demonstrate a reduction in the serious risks associated with estrogen/progestin drug products, such as deep vein thrombosis or myocardial infarction, as these are rare events. 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.

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.

1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies

None

1.4 Recommendations for Postmarket Requirements and Commitments

Standard post-marketing surveillance is recommended to further monitor the efficacy and safety of WC3016. No specific risk management steps are recommended.

2 Introduction and Regulatory Background

2.1 Product Information

WC3016 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. In the submission, the Applicant refers to this new oral contraceptive product as WC3016 and initially proposed the trade name of (b) . The proposed indication is for the prevention of pregnancy in women (b) (4) .

<u>Medical Reviewer's Comments</u>

- *The Applicant's proposed drug product will be referred to as WC3016 throughout this review.*
- *The Applicant believes that extending the active treatment from 21 to 24 days and decreasing the drug-free interval to 2 days can decrease withdrawal bleeding such that overall bleeding will be reduced with this product.*

- *The ferrous fumarate tablets are present to facilitate ease of drug administration via a 28-day regimen; the ferrous fumarate tablets do not serve a therapeutic purpose.*
- *During the course of the review, the proposed proprietary name, (b) (4) was found unacceptable by the Division of Medication Error Prevention and Analysis (DMEPA) because it did not provide adequate distinction from other combination products in the Loestrin product line. See Section 5.2, Review Strategy.*

2.2 Tables of Currently Available Treatments for Proposed Indications

There are currently approximately 24 approved OC products containing EE/NA available in the US. Over the last two decades there has been a gradual decrease in both the estrogen and the progestin content in these formulations, which has led to a reduction in both side effects and cardiovascular complications. Most current EE/NA OCs contain 20 to 35 mcg of EE and 1 to 1.5 mg of NA.

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 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/ANDA	Proprietary Name	Approval Date	EE Strength (mg)	NA Strength (mg)	Marketing Status
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.

Medical Reviewer's Comments

- *Combination 28-day OC products containing EE and NA have been marketed in the US in various formulations since 1973. EE doses have decreased from 150 mcg to 20 mcg without a significant decrease in effectiveness. Since 1988, EE doses greater than 50 mcg have not been sold in the US. NA doses have also decreased over time. Initially as high as 10 mg, NA doses are now 100-150 mcg.*
- *WC3016 contains 10 mcg of EE, which is half the dose of EE used in currently, approved OCs. The dose of NA is comparable to many approved OCs.*

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.

Medical Reviewer's Comments

- *The efficacy profile for a combination OC containing EE 10 mcg instead of 20 or 30 mcg has not previously been thoroughly studied in phase 3 clinical trials.*
- *Based on the long history of EE/NA oral contraceptives, no major safety concerns with this new low dose formulation are anticipated.*

2.4 Important Issues with Consideration to Related Drugs

Important issues with OCs revolve around contraceptive efficacy and adverse events. Efficacy and safety have been well categorized for this pharmacologic class as a whole since its initiation in the 1960s. The most significant adverse events are thomboembolic and cardiovascular. Serious adverse events have decreased with reduction in daily doses of EE and progestins.

Medical Reviewer's Comments

- *The WC3016 regimen employs a lower dose of EE and the same dose of NA found in currently approved COCs. The Applicant states that the risk of ovulation with this regimen remains low because the EE is continued for 26 days and the dose of NA is not reduced. Should ovulation occur with regular drug intake, the Applicant believes that the NA will provide additional protection from pregnancy during midcycle through progestin-mediated mechanisms such as thickening of the cervical mucus.*
- *The decrease in the EE component of the pill to 10 mcg may be associated with fewer venous and arterial thrombotic events. VTE is such a rare event in young reproductive-age women (4-5 per 100,000), however, that this is difficult to demonstrate in a prospective, randomized clinical trial.*
- *This Reviewer is not aware of any data from well-controlled, comparative, randomized, clinical trials that detect possible differences in contraceptive effectiveness between 20 and 35 mcg EE formulations, but a decrease in effectiveness is theoretically possible, especially in obese women or if the OC is not taken consistently (same time each and every day).*

2.5 Summary of Presubmission Regulatory Activity Related to Submission

A pre-IND 73,510 meeting with the Applicant was held on 8/11/ 2006 to determine the adequacy of the proposed application, including the planned statistical analysis. At that

time, the Division agreed that one clinical trial would be adequate, providing it contained (1) at least 10,000 evaluable cycles in women who are heterosexually active and not using other contraceptive methods and (2) at least 200 women, aged 18-35, who take the study drug for at least one year (13 cycles). In addition, the Division agreed with the Applicant's proposed statistical analysis plan for the efficacy assessment of this product.

The Applicant submitted IND 73,510 on September 9, 2006. The Division reviewed the submitted phase 3 protocol and included the following comments:

- The primary efficacy analysis should be based on the Pearl Index (PI) in the group of women 35 years of age or less, based on all at-risk cycles where no other method of birth control is used
- Exclusion criterion should state that injectable progestins should not be used within nine months prior to enrollment and known hypersensitivity to estrogens and/or progestins should be added to the exclusion criteria.

NDA 22-501 was received by CDER on March 26, 2009.

2.6 Other Relevant Background Information

Important regulatory actions in this country or in other countries do not indicate any areas of major concern regarding currently approved oral contraceptive products containing EE and NA.

3 Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity

This was a paper submission but the quality of the overall submission was adequate for review.

Medical Reviewer's Comment

- *A total of 68 investigational sites enrolled 1,683 subjects for the primary clinical trial (Protocol 05806). All sites were in the United States. The three sites with the highest number of enrolled subjects were Site 1 (114 subjects or 6.7% of enrolled subjects), Site 45 (99 subjects or 5.8% of enrolled subjects), and Site 22 (89 subjects or 5.2% of enrolled subjects). A review of the subject demographics regarding screen failures, adverse events and pregnancies did not indicate any specific reason to audit these sites. Therefore, this Reviewer did not request DSI inspections of these or other sites.*

3.2 Compliance with Good Clinical Practices

The Applicant states that this phase 3 trial was designed and conducted in accordance with the regulations pertaining to Good Clinical Practices, the Declaration of Helsinki, relevant International Conference on Harmonization (ICH) and Food and Drug Administration (FDA) guidelines, and applicable national regulations. Written informed consent was obtained from each subject prior to study participation.

3.3 Financial Disclosures

Only one Form FDA 3455 ("Disclosure: Financial Interests and Arrangements of Clinical Investigators") was submitted in the NDA. On this form, the Applicant identified (b) (6) as having received "significant payments" from Warner Chilcott, LCC.

Medical Reviewer's Comments

- (b) (6) (b) (6) *which comprised only* (b) (6) *of the 1683 subjects enrolled in the primary trial.* (b) (6) *subjects were enrolled in the study prior to the final Pap smear results being received at the site but these subjects were not excluded from the per protocol population.* (b) (6) *was reported from this site. There were* (b) (6) *serious adverse or adverse events leading to study discontinuation reported.*
- *A general review of these and other data submitted from Study* (b) (6) *did not provide evidence of investigator bias.*

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Chemistry Manufacturing and Controls

The NDA submission contains chemistry, manufacturing and controls information on WC3016 NA/EE tablets, WC3016 EE 10 mg tablets and the ferrous fumarate tablets. Information on NA and EE was found in the manufacturers' Drug Master Files (DMFs) for which authorization letters from the DMF holders were provided in the Application. The active ingredients of WC3016 are obtained from (b) (4) (b) (4). The inactive components of WC3016 tablets are listed in FDA's Inactive Ingredient Database. The study drug was prepared by Warner Chilcott Company, Fajardo, Puerto Rico. Three batches (80416, 80037, and 80277) of study drug were used. The composition and manufacturing processes of the to-be-marketed formulation will be identical to that of the clinical study formulation.

Medical Reviewer's Comments

- *The CMC Reviewer had some initial concerns about inconsistency regarding the description of the ferrous fumarate tablets and asked the Applicant for further clarification. In addition, the CMC Reviewer believed that the impurity specifications were not justified by the release data and stability results and requested revised acceptance criteria from the Applicant.*
- *One drug substance site is under a Warning Letter. The Applicant has sent in a response to the letter that is currently under review in the Office of Compliance. A reinspection of this site is planned but has not as yet been scheduled. The second manufacturing site is a contract testing laboratory that is not ready to perform testing for this NDA.*
- *The above CMC issue regarding the manufacturing of the drug product has not as yet been fully resolved.*

4.2 Clinical Microbiology

The Applicant originally proposed that no microbial test for the tablets was necessary stating that USP microbial limits testing are performed on the excipients and this ensures absence of pathogens in the formulation.

Medical Reviewer's Comments

- *The CMC Reviewer had concerns that the WC3016 ferrous fumarate tablets picked up moisture during storage and questioned whether this moisture would facilitate microbial growth. There was also concern that the compendial excipients in the drug product may also be conducive to the proliferation of microorganisms. For these reasons, a consult was requested from the Office of New Drug Microbiology Staff.*
- *The microbial reviewer agreed that the moisture and excipients in the drug product are a high risk for microbial contamination and concluded that the application is deficient pending microbial limits data and microbiological environmental monitoring data.*
- *At the time of this review, the Applicant has agreed to the Microbial Limits Testing and updating the specifications for residual solvents. The microbial reviewer found this acceptable and recommends approval of this NDA.*

4.3 Preclinical Pharmacology/Toxicology

A review of the nonclinical pharmacology and toxicology information was not included in the Application as the Applicant believed the nonclinical safety of the active and inactive ingredients in WC3016 is well established and the quantity of each of these ingredients is found in similar or higher amounts in previously approved oral tablets. The Application made reference to Warner Chilcott's NDA 21-871 for Loestrin® 24 Fe (norethindrone acetate and ethinyl estradiol tablets, USP and ferrous fumarate tablets)

in support of the nonclinical safety of NA and EE. Loestrin® 24 Fe is an approved oral contraceptive containing NA 1 mg and EE 20 mcg.

Medical Reviewer's Comment

- *The Pharm/Tox Reviewer stated in his review that there were no nonclinical safety issues relevant to the clinical use of this product and recommended approval of this NDA.*

4.4 Clinical Pharmacology

The Applicant has conducted three phase 1 bioavailability and pharmacokinetic studies in support of this NDA.

Protocol PR-14006 was conducted to characterize NA and EE bioavailability following the single-dose administration of the NA 1 mg/EE 10 mcg found in the WC3016 combination tablet. This tablet was ingested under fasted or fed conditions or dissolved/suspended in a hydroalcoholic solution. This was a 2-day study in 24 healthy female subjects.

Protocol PR-14106 studied the single-dose administration of the WC3016 EE 10 mcg tablets under fasted or fed conditions or dissolved in a hydroalcoholic solution. This was a 2-day study in 24 healthy female subjects.

Protocol PR-14206 characterized the plasma pharmacokinetic profiles of EE and NA and SHBG concentrations during the 24 days of WC3016 NA/EE and 2 days of WC3016 EE 10 mcg administration. Eighteen subjects were dosed; all 18 completed, and data from 15 subjects was evaluable for pharmacokinetic analysis.

4.4.1 Mechanism of Action

Oral contraceptive formulations containing EE and NA prevent ovulation by inhibiting gonadotropin secretion via an effect on both pituitary and hypothalamic centers. The progestational agent (NA) in the pill primarily suppresses luteinizing hormone secretion thus preventing ovulation while the estrogen component (EE) suppresses follicle stimulating hormone secretion preventing the emergence of a dominant follicle. Therefore, both the NA and EE significantly contribute to the contraceptive efficacy.

Medical Reviewer's Comment

- *The Applicant believes that even if the low EE 10 mcg dosage does not reliably inhibit follicular growth, the NA component would prevent the LH surge necessary for ovulation and sufficiently thicken the cervical mucus.*

4.4.2 Pharmacodynamics

The Applicant based the expectation of efficacy for WC3016 on data obtained from a phase 1 pharmacodynamic trial (Protocol PR-08903). This was a single center, open-label trial to evaluate the effects on ovarian activity of EE 5 mcg/NA 1 mg administered continuously compared to EE 20 mcg/NA 1 mg administered for 21 days out of 28. After a pretreatment cycle to determine that each subject was ovulatory, 60 women over 40 years of age who were having regular periods and who had no symptoms of estrogen deficiency were randomized to receive treatment for three 28-day cycles. Follicle size was assessed 3x/week by sonography. In addition, serum estradiol, serum progesterone, LH and FSH levels and cervical mucus were also evaluated.

Table 2 Effcacy Results, Protocol PR-08903

Treatment Group	Number of Subjects	Number of Cycles	Number (%) of Subjects with Ovulations	Number (%) of Ovulations
NA 1/EE 5 (28 days)	31	90	3 (9.7%)	5 (6.7%)
NA 1/EE 20 (21 days)	29	81	7 (24.1%)	9 (11.1%)

Source: Clinical Overview Page 6, Table 3, Data on File with Applicant.

Medical Reviewer's Comments

- *At the time of this review, the final report for this study had not yet been submitted by the Applicant.*
- *Based on the data collected from this small study, the Applicant believes that EE doses lower than 10 mcg/day could be sufficient in a combination OC.*
- *Although the dose of EE is reduced to 10 mcg in WC3016, the Applicant postulated that the risk of ovulation will remain low because it is continued for 26 days. In addition, the dose of NA is not reduced so that, should ovulation occur, additional protection will be provided through progesterone-mediated mechanisms such as LH surge prevention and cervical mucus thickening.*

4.4.3 Pharmacokinetics

NA is rapidly deacetylated to norethindrone after oral administration, and the disposition of NA is indistinguishable from that of orally administered norethindrone. Both NA and EE are subject to first-pass metabolism after oral dosing, resulting in a bioavailability of approximately 64% for norethindrone and 55% for EE. EE and norethindrone exposure increased by factors of 1.6 and 2.5, respectively, following multiple-dose administration of WC3016 NA/EE tablets as compared to single-dose administration of WC3016 NA/EE tablets. Steady-state with respect to EE and norethindrone was reached by Day

5 and Day 13, respectively. Administration with food did not affect the rate of norethindrone absorption, but the extent of absorption was increased.

Medical Reviewer's Comment

- *The food effect is not clinically significant, so WC3016 may be administered without regard to meals.*

5 Sources of Clinical Data

This application includes clinical data from one phase 3 safety and contraceptive efficacy study (Protocol PR-05806). In agreement with Division guidance detailed in the pre-IND meeting minutes dated September 1, 2006, Protocol PR- 05806 assessed 15,596 total cycles of treatment. This included 968 subjects who completed the 13 month clinical trial.

5.1 Tables of Studies/Clinical Trials

The single phase 3 clinical trial, Study PR-05806, was an open-label, uncontrolled, multicenter study that enrolled 1683 heterosexually active women aged 18 to 45 years and at risk of becoming pregnant who were assigned to take WC3016 daily for thirteen 28-day cycles of treatment.

Table 3 Overview of Phase 3 Clinical Trial, PR-05806

Phase 3 Trial: PR-05806 (RR-03108)	Trial Design	Number of Subjects	Trial Duration	Study Drug
- First subject enrolled: 11/01/2006 - Last subject completed: 08/27/2008 - 68 sites	- Multicenter - Open-label - Single arm - Uncontrolled	- Subjects enrolled: N=1683 - All Treated subjects* (n=1660) - Modified intent-to-treat cohort (MITT)** (n=1582) - PITT subgroup 18-35 years of age (n=1295) - Completed the trial*** (n=968)	-Thirteen 28-day cycles of treatment	- WC3016: (NA 1 mg/EE 10 mcg oral tablets administered for 24 days followed by EE 10 mcg alone for 2 days followed by ferrous fumarate tablets for 2 days)

*All Treated subjects is defined as all subjects who took at least one dose of study medication.
**MITT population is defined as the subset of the All Treated population who were evaluated for pregnancy at least once after beginning study medication.
***Subset of MITT subjects who completed at least 360 days of treatment based on the diary reports.

5.2 Review Strategy

Review strategy involved a review of the 317-page Clinical Study Report (RR-03108.0) and proposed label. In addition, previous meeting minutes and agreements between the Division and Applicant were reviewed.

During the course of this review, numerous clinical information requests were made of the Applicant:

- The 74-Day Filing Letter of 6/8/09 notified the Applicant of the Division's definition of "on-drug" pregnancies and the definition of the Pregnancy Intent to Treat population upon which the Pearl Index calculations should be based. We also requested the Applicant to stratify all pregnancies included in the Pearl Index calculations by weight and BMI.
- The Applicant's submission dated 7/22/09 (SDN 5) recalculated the Pearl Index based on these definitions and provided the requested stratification of pregnancies based on weight and BMI.deciles.
- On 9/3/09, the Applicant was notified that the Pearl Index point estimate and confidence interval (based on the 28 pregnancies determined at this point in the review to have occurred "on-drug") was a significant concern. The Applicant was also asked to provide the mean, median, and range for the number of observed days of 1) intracyclic bleeding only, 2) intracyclic spotting only and 3) intracyclic bleeding/spotting combined, within each cycle. Also more data regarding hematologic indices were requested.
- The Applicant replied in letters dated 10/16/09 (SDN 8) and 10/20/09 (SDN 9) providing the requested bleeding/spotting and hematologic indices data.
- On 11/30/09, the Applicant was requested to provide information regarding how many of the 28 on-drug pregnancies occurred despite "perfect use" of the product and to provide data identifying which pills were missed during each subject's conception cycle.
- The Applicant submitted a response by email on 12/3/09 that provided the above information.

Medical Reviewer's Comment

- *The point estimate of the calculated PI for WC3016 is higher than the Pearl Indices of previously approved oral contraceptives. This higher PI will be weighed against the theoretical benefits of lowering the EE dosage to determine if the drug should be approved.*

The Principal Investigators and the study sites were reviewed for total enrollments, pregnancies, serious adverse events and drop-outs. There was collaboration with the FDA Statistician regarding the PI calculations.

Consultations from the Division of Medication Error Prevention and Analysis (DMEPA - tradename review), Division of Drug Marketing, Advertising, and Communications (DDMAC - package insert review), and Division of Risk Management (DRISK - patient package insert review) were requested and received. After a review of the investigative sites (principal investigators, enrollments, study drop-outs, pregnancies, and adverse events) the Division elected not to request DSI inspections of a specific site.

DMEPA

DMEPA objected to the name (b) (4) proposed by the Applicant, stating that "Our evaluation found that this product line extension may cause confusion given that (b) (4) Thus, the Division of Medication Error Prevention and Analysis (DMEPA) objects to the use of the proposed proprietary name, (b) (4), for this product."

Medical Reviewer's Comment

- *The Applicant was made aware of DMEPA's objection to the proposed tradename. The final product name has not as yet been finalized but the Applicant, in a submission to OSE dated 11/30/2009, has proposed the tradename name "Lo Loestrin Fe."*

DDMAC

DDMAC reviewed the label materials for WC3016. On 12/10/2009, they issued a "Pre-Decisional Agency Memo" containing comments regarding the proposed product labeling.

Medical Reviewer's Comment

- *DDMAC's comments were reviewed and several were incorporated into the proposed label.*

DRISK

DRISK comments on the patient labeling are pending, and will be conveyed to the Applicant as appropriate.

5.3 Discussion of Individual Studies/Clinical Trials

Primary Phase 3 Clinical Trial, PR-05806

Clinical Trial Design
This was a single phase 3, open-label, uncontrolled, multicenter clinical trial entitled "An Open-Label Study of the Safety and Efficacy of a New Low Dose Oral Contraceptive Containing Norethindrone Acetate and Ethinyl Estradiol." A total of 1,683 heterosexually active women, ages 18-45, were enrolled. Treatment was administered for 13 28-day cycles. The primary objective of the trial was to assess the efficacy of WC3016 in the prevention of pregnancy. The secondary objectives were to assess the incidence of intracyclic (unscheduled) bleeding as well as the safety and tolerability of WC3016. No comparator oral contraceptive was used in this trial.

The following populations were studied in this clinical trial:

- The All Qualified population included all subjects qualified to receive treatment in the trial (N=1,683).
- The safety analysis in this trial was based on the All Treated population, which consisted of all subjects who received at least one dose of therapy (N=1,660).
- The Modified Intent to Treat (MITT) population was defined as the subset of women in the All Treated population who were evaluated for pregnancy, whether positive or negative, at least once after beginning the study medication (N=1,582). A total of 27 women in this population had no cycles evaluable for pregnancy because they used additional contraceptive methods. Therefore, there were a total of 1,555 subjects evaluable to determine drug efficacy.
- The Pregnancy Intent to Treat (PITT) population was defined as the subgroup of women in the MITT population aged 18-35 years at the time of study enrollment who did not use other methods of birth control during the clinical trial (N=1,270).
- The Completed Subjects population was defined as the subset of MITT subjects who completed at least 360 days of treatment based on the diary reports (N=968).

Clinical Trial Sites
A total of 68 investigational sites in the United States participated in this trial.

Inclusion Criteria:
1. Age ≥ 18 and ≤ 45 years of age;
2. Negative serum pregnancy test;
3. Regular cycles with a usual length of 21-35 days and a variability of +/– 3 days

(subjects who were recently post-partum or post-abortion were to have had at least 2 normal cycles);
4. Body mass index ≤ 35;
5. Willing to use the study drug as the only method of contraception;
6. Signed an informed consent.

Medical Reviewer's Comment

- *The Division discourages the use of a BMI restriction as an inclusion criterion in oral contraceptive trials since data on safety and contraceptive efficacy in heavier subjects is useful.*
- *The BMI restriction in the primary clinical trial will be noted in labeling.*

Exclusion Criteria

1. Were using hormonal contraception via the following routes and during the specified timeframes: progestational implants; progestin, estrogen or estrogen/progestational injectable drug therapy within 9 months; intrauterine within 3 months. Women currently on oral, intravaginal or transdermal combined steroid contraception could have been switched directly to study medication.
2. Were currently taking the herbal supplement St. John's Wort.
3. Had an abnormal Pap smear suggestive of low-grade squamous intraepithelial lesion (LGSIL) or worse. Enrollment of subjects with an interpretation of "atypical squamous cells but could not exclude high-grade squamous intraepithelial lesion (ASC-H)" was not allowed. However, enrollment of subjects with an interpretation of "atypical squamous cells of undetermined significance (ASC-US)" was permitted, if human papilloma virus (HPV) reflex test result was negative.
4. Were currently nursing.
5. Had an untreated chlamydia infection.
6. Had any disease or condition that could compromise the function of the body systems and/or could result in altered absorption, excessive accumulation, impaired metabolism, or altered excretion of the study medication.
7. Had known or suspected premalignant or malignant disease (excluding successfully treated skin cancers) or a history of steroid-dependent malignancy, including malignant melanoma.
8. Had severe systemic disease, which might have interfered with the conduct of the study or the interpretation of the results.
9. Had any abnormal findings or condition on the medical history, screening, physical / gynecological exam including abnormal baseline laboratory values that were considered clinically significant.

10. Had a history of manifestations of cardiovascular disease: myocardial infarction, coronary artery bypass graft surgery, percutaneous angioplasty, or more than 50% angiographic narrowing of a coronary artery.
11. Had congestive heart failure.
12. Had uncontrolled hypertension defined as a sitting systolic BP > 160 mmHg or a diastolic > 95 mmHg.
13. Had a history of stroke or transient ischemic attacks.
14. Had thombophlebitis or thomboembolic disorder or a history of these conditions or known or suspected genetic component.
15. Were undergoing treatment with anticoagulants (heparin or warfarin).
16. Had uncontrolled thyroid disorders.
17. Had a history during pregnancy of cholestatic jaundice, severe pruritus, or deterioration of otosclerosis.
18. Had insulin-dependent diabetes mellitus.
19. Had porphyria.
20. Had experienced an increased frequency or severity of headaches including migraines during previous estrogen therapy.
21. Had a history of drug addiction or alcohol abuse (within the last 2 years).
22. Currently suffered from depression or had a significant history of depression.
23. Had participated in another clinical trial within 1 month or had received an investigational drug within the last 3 months (90 days) prior to study entry. Subjects who had participated in an oral contraceptive clinical trial, using Food and Drug Administration (FDA) approved active ingredients, could be enrolled 2 months (60 days) after completing the preceding study.
24. Smoked > 15 cigarettes/day if > 35 years of age.
25. Were, in the opinion of the Investigator, unable to fully comply with the study
26. Had a known hypersensitivity to estrogen and/or progestins.

Clinical Trial Procedures

Potential subjects were assessed for their eligibility to enroll in the study at a pre-treatment screening visit. The subject returned for Visit 1A after all results of the screening tests were available. If the subject was eligible, and the urine and serum pregnancy tests, Pap smear, and HPV and Chlamydia tests all were negative, the subject was enrolled in the study and medication, home pregnancy test, and diary cards were dispensed.

Medical Reviewer's Comment

- *All subjects followed the same dosing regimen. They were advised to take the tablet at approximately the same time each day, with or without food.*

Subjects who were users of combination OCs ("switchers") immediately before enrolling in the study began taking the study drug on the same day that they would have resumed using the active formulation of the previous product. Subjects who were not using COCs began taking study drug on the first day of their menstrual period.

Each subject entered a daily record of her bleeding occurrences in a diary. If spotting occurred, the subject was to continue her medication. If unscheduled bleeding occurred which resembled menstruation, the subject was advised to discontinue medication and begin to take tablets from a new tablet dispenser on the next day. Persistent bleeding not controlled by this method prompted an examination.

Visits 2, 3, 4, 5, 6, and 7 took place at the ends of Cycles 1, 3, 5, 7, 9, and 11, respectively. Assessments performed at each study visit are found in Table 4. Pregnancy tests were performed at each study visit.

Visit 8 was the final study visit, which occurred at the end of cycle 13.

After completion of the treatment phase of the study, all subjects were followed to determine if any pregnancy had occurred in the immediate post-treatment period. At the Final Visit (Visit 8), all subjects were given a brief questionnaire to determine if they had a withdrawal bleed after cessation of treatment with study medication. Subjects who did not return the questionnaire within 2-4 weeks after the last day of study drug intake were contacted by telephone to determine if the subject experienced a withdrawal bleed. If the subject had not had a withdrawal bleed, she was asked to return to the study site for further evaluation to determine if she had become pregnant. The status of any on-going adverse events was also assessed at that time.

Subjects withdrawing from the study due to an adverse event were contacted by phone within one month of the termination visit if the adverse event was ongoing at the time of withdrawal from the study.

If a pregnancy was diagnosed during the course of the study, or in the immediate post-study period, the pregnancy was followed until completion and the condition of the fetus/baby was determined.

Subjects were withdrawn from the study if they lost the study drug or if use of the active study drug was interrupted by more than five consecutive days for any reason.

Medical Reviewer's Comment

- *Electronic diaries are generally recommended for oral contraceptive studies but are not required.*

Table 4 Study Schedule by Visit

Assessment	Screening	Qualification	Interim Visits	Final Visit[1]	Follow-up[2]
Visit[3]	1	1A	2, 3, 4, 5, 6, and 7	8	
Day	-14	1	28, 84, 140, 196, 252, and 308	364	378-392
Cycle			1, 3, 5, 7, 9, 11	13	
Informed consent	X				
History	X				
Physical/gyn exam	X			X	
Pap	X			X	
Chlamydia	X				
BP, heart rate	X			X	
Height, weight	X			X	
Pregnancy test	X[4]	X[4]	X	X[4]	
Chem. screen, hematology, urinalysis	X			X	
Qualification		X			
Medication, diary cards and home pregnancy kits dispensed		X	X		
Diary cards and medication returned			X	X	
Adverse events	X	X	X	X	
Concomitant medication	X	X	X	X	
Compliance assessment			X	X	
End of study evaluation				X	
Questionnaire follow-up					X

[1] If a subject was prematurely withdrawn from the trial, all evaluations under final visit 8 were performed at that visit.
[2] Subjects were contacted or seen within 2-4 weeks at end of treatment to determine if they had a withdrawal bleed or if ongoing AEs had resolved. If the subject did not have a withdrawal bleed, a pregnancy test was performed.
[3] Visits 2, 3, 4, 5, 6, and 7 occurred within a window of +/- 7 days.
[4] Serum and urine pregnancy tests were done at Visit 1 and 8; serum pregnancy test was repeated at Visit 1A if it was 3 weeks or more after the serum tests done at Visit 1; urine pregnancy test was be done at Visit 1A and all subsequent visits.

Protocol Amendments

There was one amendment to the original protocol. This Amendment was dated 1/31/07 and included the following changes:

- The plan for data analysis and the primary target variable was amended to specify that the primary efficacy analysis would be based on (1) the PI in the group of women 35 years of age or less based on all at risk cycles where no other method of birth control was used and (2) the PI for all subjects, regardless of age, based on all risk cycles where no other method of birth control was used.
- The overall study design and plan description was amended so that select sites would be permitted to enroll up to 80 subjects.
- The subject exclusion criteria were amended as follows:
    - Women who had used progestational implants; progestin, estrogen or estrogen/progestational injectable drug therapy within 9 months of the study initiation were excluded.
    - Women who had participated in a previous oral contraceptive clinical trial were permitted to enroll in the current study 2 months (60 days) after completing the preceding study.
    - Women with known hypersensitivity to estrogen and/or progestins were excluded.
- The specifications for the gynecological examination were changed to require the performance of an HPV panel if the transformation zone was not present in the Pap smear.
- The day of the Screening visit (Visit 1) was changed from Day -14 to Day "not Applicable," as the day was to be based on the subject's anticipated menstrual period.
- The window for the final study visit was increased so that Visit 8 could occur from Day 360 – Day 371.

6 Review of Efficacy

Summary-Prevention of Pregnancy

Efficacy was based on the ability of WC3016 to prevent pregnancy in a single phase 3 clinical trial submitted to the NDA. "On-drug" pregnancies were defined as those pregnancies for which conception occurred on or after the date of first taking the study drug and extending through the 7 days following the last dose of the study drug. Conceptions that occurred 8 days or more past the last dose of WC3016 were not considered as "on-drug" pregnancies.

The PI was derived from the Pregnancy Intent to Treat cohort (PITT), which consisted of the subset of all treated women ages 18-35 who were evaluated for pregnancy at least once after beginning the study medication (N=1,270). All 28-day cycles where additional back-up methods of birth control (including condoms) were used and all incomplete 28-day cycles (except those in which conception occurred) were excluded

from the denominator used in the PI calculation. The 1,270 subjects took the study medication over 12,482 completed 28-day cycles.

As determined by the Medical Reviewer, 28 on-drug pregnancies occurred in the PITT population during the study. Based on these 28 pregnancies, the PI for WC3016 was calculated by the FDA Statistician as 1300 X 28 pregnancies = 36,400 ÷ 12,482 woman-cycles = 2.916 (1.938, 4.213). In support of the product's effectiveness, the life-table analysis was calculated to be 2.71 (1.86, 3.95).

Medical Reviewer's Comments

- *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. The difference may be due to the lower EE content of this drug but may also be due to differences in trial methodology and demographic characteristics. Evaluation of the PI in this clinical trial would have been more meaningful had an approved comparator OC arm been utilized. Nevertheless, in my opinion, a PI of 2.92 is acceptable to support the efficacy of WC3016.*
- *Seasonale®, an extended-cycle combination OC containing EE 30 mcg/ levonorgestrel 150 mcg, was approved in 2003. The PI for Seasonale, as calculated by the FDA Statistician, is 1.98 (0.54, 5.03). Of note is that the upper bound of the 95% CI for Seasonale is higher than the upper bound of 4.21 calculated for WC3016.*
- *In this reviewer's opinion, the efficacy of WC3016 has been demonstrated even with an almost 50% reduction in the amount of estrogen compared to current low-dose OCs.*

Summary-Cycle Control

The incidence of unscheduled bleeding/spotting (B/S) decreased over the course of the study, from 52.7% in Cycle 2 to 36.4% in Cycle 13. The mean number of days per cycle of unscheduled B/S also decreased over the course of the study from 2.65 days during Cycle 1 and 3.21 days during Cycle 2 to 1.82 days during Cycle 13. The mean maximum intensity score for unscheduled B/S episodes remained fairly stable throughout the study between 1 and 2, that is, between light and normal bleeding intensity.

Amenorrhea was common and tended to increase during the course of the study. The incidence of withdrawal bleeding decreased over the course of the study, from 43.3% of subjects during Cycle 1 to 22.4% during Cycle 13.

When new users and switchers were compared, the incidence and the intensity of unscheduled B/S all tended to be higher in the new users than in the switchers. In general, the incidence of amenorrhea was higher in switchers than in new users.

Medical Reviewer's Comments

- *The most bothersome B/S for patients is the unexpected (unscheduled) type.*
- *The incidence of unscheduled B/S was common during the primary clinical trial, as 85.9% of subjects experienced an episode at least once during the trial. This B/S was described by subjects as between light and normal in intensity.*
- *Based on review of other products' trials, the lower EE 10 mcg dosage in WC3016 is accompanied by slightly more unscheduled B/S and a higher incidence of amenorrhea than is seen with higher dose OCs.*
- *In this Reviewer's opinion, the B/S profile of WC3016 is not clinically different from other low dose OC products despite an almost 50% reduction in the amount of estrogen compared to current low-dose OCs.*

6.1 Indication

The proposed indication for WC3016 is for the prevention of pregnancy in women who elect to use oral contraceptives as a method of contraception. The Applicant has submitted data from one primary phase 3 clinical trial report (Report # RR-03108) in support of this indication.

6.1.1 Methods

As noted in Table 4, pregnancy testing was performed frequently during this clinical trial. Serum and urine pregnancy tests were done at Visit 1 and 8. The serum pregnancy test was repeated at Visit 1A if it occurred 3 weeks or more after the serum test done at Visit 1. A urine pregnancy test was done at Visit 1A and all subsequent visits. Each subject also received a home pregnancy test which to be used if she missed a scheduled withdrawal bleed.

All suspected pregnancies that occurred during the trial were evaluated and documented to determine the estimated date of conception (EDC). The methods used to define the EDC and the actual results of these assessments, information about bleeding and drug intake (which were reconciled with diary data), information about concomitant medications (which were reconciled with information in the case report form [CRF]), and the final diagnosis were also recorded. Upon confirmation or exclusion of pregnancy, all required information was documented on the Suspected Pregnancy page of the CRF.

The EDC was determined from ultrasound (or by menses information in the subject diary if no ultrasound was performed). This information was compared to the start and stop dates (as noted in the subject diary) for study medication.

6.1.2 Demographics

Demographic and baseline characteristics are summarized for the MITT population in Table 5. In the MITT population, the mean age was 28.6 years, and 81.9% were between the ages of 18 and 35 years. The majority of subjects were Caucasian (74.9%), and 51.0% had not been using oral, intravaginal or transdermal contraception immediately prior to enrolling in this study (i.e., they were "New Users").

Table 5 Demographics (MITT Population)

Parameter	N=1,582
Age (years)	
Mean ± SD	28.6 (6.9)
Range	18.0, 45.9
Age cohorts, n (%)	
18-35 years	1,295 (81.9%)
>35 years	287 (18.1%)
Ethnic origin, n (%)	
Asian	21 (1.3%)
Black	186 (11.8%)
Caucasian	1,185 (74.9%)
Hispanic	155 (9.8%)
Native American	8 (0.5%)
Other	27 (1.7%)
User Status, n (%)	
Switcher	775 (49.0%)
New User	807 (51.0%)
Current smoker, n (%)	
Yes	235 (14.9%)
No	1,347 (85.1%)
Height (inches)	
Mean ± SD	64.7 (2.7)
Range	55.8, 75.0
Weight (pounds)	
Mean ± SD	150.1 (29.3)
Range	89.0, 260.0

SD : Standard Deviation
Source: Clinical Study Report

Medical Reviewer's Comments

- *The majority of subjects in this study (75%) were Caucasian. Approximately 10% of the subjects were of Hispanic origin. These ethnic demographics are similar to other oral contraceptive studies I have reviewed.*
- *51% of those enrolled were new users. New users were defined as subjects who had not been using oral, intravaginal or transdermal combination steroid contraception prior to enrollment in the trial. This percentage of new users is significantly higher than in other OC applications; however, this Applicant used a particularly strict definition of "new user" that may include women who have used hormonal contraception previously, but not immediately before enrollment. Truly new users will have higher pregnancy rates and higher rates of unscheduled B/S than switchers.*
- *Cross-trial comparisons of various oral contraceptive products are difficult to make because each study varies with regard to user characteristics. These characteristics include educational attainment, ethnicity, previous experience with the method, extent of method counseling, fecundity and frequency of sexual intercourse.*

6.1.3 Subject Disposition

The disposition of subjects enrolled in the phase 3 study is shown in Table 6. A total of 2,235 subjects were screened for the study and 1,683 were enrolled. Twenty-three enrolled subjects later returned all of the dispensed study medication unused. Therefore, a total of 1,660 enrolled subjects took at least one dose of study medication.

Clinical Trial Populations

The following populations were studied:

- The All Qualified population included all subjects qualified to receive treatment in the trial.
- The All Treated population consisted of all subjects who received therapy.
- The Modified Intent to Treat (MITT) population was defined as the subset of women in the All Treated Population who were evaluated for pregnancy, whether positive or negative, at least once after beginning the study medication.
- The Pregnancy Intent to Treat (PITT) population consisted of all subjects in the MITT population who were between 18-35 years of age at trial enrollment.
- The Completed Subjects population was defined as the subset of MITT subjects who completed at least 360 days of treatment based on the diary reports.

Subject Disposition
The disposition of subjects enrolled in this clinical trial is shown in Table 6.

Table 6 Subject Disposition

Parameter	N (%)
Screened subjects	2,235
All Qualified Population: Subjects enrolled	1,683
All Treated Population: Received drug	1,660 (100)
MITT Population: Evaluated for pregnancy	1,582 (95.3)
Completed subjects	968 (58.3)
Discontinued subjects:	692 (41.7)
Lost to follow-up	227 (13.7)
Adverse events	177 (10.7)
Withdrew consent	147 (8.9)
Other reasons	96 (5.8)
Pregnancy	28 (1.5)
Protocol violation	20 (1.2)
Death	0

Source: Adapted from Clinical Study Report (RR-03108), Page 44 and Pages 101-102.

Medical Reviewer's Comments

- *In the overall MITT population (N=1,582), 27 women had no cycles evaluable for pregnancy because they used alternative contraceptive methods in all cycles. A total of 28 "on-drug" pregnancies occurred in the remaining 1,555 evaluable subjects.*
- *The Pregnancy Intent to Treat population or the PITT cohort is defined as the women in the MITT population who were 18 to 35 years of age at enrollment.*
- *There was no Per-Protocol population defined in this study. Subjects were included in the Completed Subjects population regardless of their compliance to planned study procedures.*

Evaluable Subjects
For Pearl Index calculation purposes, a cycle was considered evaluable if at least 1 pill was taken and no other form of birth control was used. The evaluable subject populations are listed in Table 7 below.

Table 7 Evaluable Subject Populations

MITT Population	N	Evaluable Subjects
MITT ages 18-45	1,582*	1,555
MITT ages 18-35 (PITT)	1,295**	1,270
MITT ages 36-45	285***	285

* A total of 27 women in the MITT population had no cycles evaluable for pregnancy because they used alternative contraceptive methods in all cycles.
** A total of 25 women in the PITT did not have evaluable cycles for the reason stated above.
*** All cycles evaluable.
Source: Adapted from Clinical Study Report, Pages 101-102.

6.1.4 Analysis of Primary Endpoint

The primary efficacy endpoint in this study was the incidence of pregnancy in the group of women 35 years of age or less at enrollment based on all at-risk cycles where no other method of birth control was used (PITT population). The primary efficacy analysis was calculation of the Pearl Index, defined as the number of pregnancies per 100 women-years of exposure in women in the PITT cohort. The cumulative pregnancy rate on a cycle-by-cycle basis was also estimated using a life-table analysis.

The Pearl Index was computed as:

$$\text{Pearl Index} = \frac{1300 \times \text{number of pregnancies}}{\text{Number of woman-cycles of treatment*}}$$

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

<u>Medical Reviewer's Comments</u>

- *The Division defines the principal analysis cohort for pregnancy evaluation to be the PITT cohort or all women who were 18 to 35 years of age at the time of study enrollment who were evaluated for pregnancy.*
- *The Division defines "on-drug" pregnancies as all conceptions that occur from Day 1 (the initiation of taking study drug) to seven days after the final tablet (i.e., the second Fe tablet) in the pill pack is taken. If the pills are stopped prior to completing a 28-day pack, we define "on drug" pregnancies as all conceptions occurring from the first day that the study drug is taken to seven days after the final tablet is taken.*

In the original submission, the Applicant defined an "on-drug" pregnancy as a conception due to an ovulation presumed to have occurred while taking study drug, i.e., >13 days after starting or >14 days after stopping active pill intake (Day 26). They also censored subjects from the PI analysis if the subject was 36 years old at the time of conception. The Applicant's PI in the original submission based on 24 "on-drug" pregnancies was 2.554.

At the Filing Meeting of April 30, 2009, the Applicant's definition of "on-drug" pregnancies and the Applicant's policy of censoring subjects who were 35 years of age at enrollment but 36 years of age at conception were identified as review issues.

The following was communicated to the Applicant in the 74-Day letter of 6/8/09:

- "We do not agree with your definitions of the pregnancy intent-to-treat cohort (PITT) population and "on-drug pregnancies." We define the PITT cohort as including women aged 18 to less than 36 years <u>at the time of enrollment</u> in the clinical trial. The PITT cohort is the principal analysis cohort for pregnancy evaluation. Subjects in this group should not be censored on their 36th birthday in the pregnancy assessment. Therefore, the pregnancies occurring in Subject 01-104 and Subject 17-022 should be included in the pregnancy assessment."
- "We define on-drug pregnancies as all conceptions that occur from Day 1 (the initiation of taking study drug) to seven days after the final tablet (i.e., the second Fe tablet) in the pill pack is taken. If the pills are stopped prior to completing a 28-day pack, we define on drug pregnancies as all conceptions from Day 1 to seven days after the final tablet was taken. Thus, Subject 28-055 should be included in the pregnancy assessment."
- "Based on the above definitions of the PITT population and "on-drug pregnancies," you are requested to submit a recalculation of the Pearl Index and life table pregnancy rates."
- In addition, the Division also requested the following information:
    - Provide a stratification of all the pregnancies included in the Pearl Index calculations by weight and BMI deciles.
    - Provide the Case Report Form (CRF) for Subject 25-017, who was lost to follow-up but was described as a "possible pregnancy."
    - Clarify the meaning of the phrase "last active pill" in the subject narratives. It was unclear whether this meant the last combination pill or the last EE-alone pill.

The Applicant responded with the requested information in a submission (SDN 5) dated 7/23/09. In this submission:

- The Applicant recalculated the PI based on a total of 27 on-drug pregnancies in the PITT population. This PI recalculation included the three additional subjects (Subjects 01-104, 17-022 and 28-055) who met the Division's definition and were

reclassified as "on-drug" conceptions. The recalculated PI provided by the Applicant was 2.811.

- The Applicant clarified that the term "last active pill" mentioned in the pregnancy narratives refer to the last EE-alone (Day 26) pill if these were taken by the subject.
- Per the Division request, the Applicant provided stratification by weight and body mass index of all pregnancies included in the PI.
- The requested CRF for Subject 25-017 was also received.

Medical Reviewer's Comment

- *The CRF for Subject 25-017 was subsequently reviewed and this patient was also determined to have had an "on-drug" pregnancy, thus making the total number of "on-drug" pregnancies occurring in this clinical trial to be 28. Specifics regarding the pregnancy narrative of this subject can be found in the Efficacy section of this review.*

The Division's mid-cycle meeting for this Application was held on 8/27/09. The following clinical comments were included and communicated to the Applicant in a letter dated 9/3/09:

- Provide the CRF for Subject 011-010. This subject was included in Data Listing 16.2.14 on page 7352 of 22444 under Suspected Pregnancies, All Enrolled Subjects.
- Provide clarification regarding the discrepancy noted for Subject 043-004. Please verify that she had a stenosis rather than thrombosis of her sigmoid sinus.
- Provide, at a minimum, the mean, median, and range for the number of observed days of 1) intracyclic bleeding only, 2) intracyclic spotting only and 3) intracyclic bleeding/spotting combined, within each cycle. Provide the same data for withdrawal bleeding/spotting. Provide figures displaying the number of subjects on the y-axis and the number of days of (1) intracyclic bleeding only, (2) intracyclic spotting only, and (3) intracyclic bleeding/spotting combined on the x-axes for each cycle. (Refer to Mishell et al., Contraception 75: 11-15, 2007 for examples.)
- Provide the following information about hematologic indices:
    - Provide shift tables of hemoglobin and hematocrit laboratory values, classifying subjects as low, normal, or high at baseline and end of study.
    - Provide data on hematologic indices at baseline and end of study for subjects who withdrew due to bleeding-related adverse reactions.
- Clarify what instructions were given to subjects regarding condom use during the phase 3 clinical trial and verify that subjects who used condoms during this trial were not included in the MITT population.

The Applicant responded with the requested information in a submission (SDN 8) dated 10/16/09. In this submission:

- The Applicant submitted all the requested data including the CRF for Subject 011-010.
- The Applicant concurred that Subject 025-017 should have "been included in the on-treatment pregnancy group as noted by the Division reviewer."
- The Applicant clarified that Subject 043-004 had the symptoms of pseudotumor cerebri and a stenosis in the intracranial venous system at the junction of the sigmoid and transverse sinuses. She did not have a thrombosis of her sigmoid sinus.
- The Applicant confirmed that "Cycles in which subjects used a condom or alternative method of birth control for any reason were not counted in the calculation of the PI for the MITT population."

Medical Reviewer's Comment

- *A final total of 28 on-drug pregnancies have occurred during the primary clinical trial with WC-3016.*

Pregnancies during the Primary Clinical Trial

Twenty-three (23) subjects were found to be pregnant at screening so were not enrolled into the study. A total of 13 subjects were enrolled in the study whose pregnancies were not counted in the calculation of the Pearl Index:

- Nine (9) subjects became pregnant after enrollment but before the initiation of study drug.
- Four (4) subjects were found to be pregnant more than 7 days after taking the last dose of study drug.

During the clinical trial, there were a total of 32 reported pregnancies of which 28 were determined to be "on-drug."

Table 8 is a summary of all reported pregnancies which occurred during the clinical trial.

Table 8 Reported Pregnancies (N=32)

#	Site # Pt #	Age Weight (lbs)	User Type	Drug Start Date	Last Active Pill	Date of Positive Pregnancy Test	Conception Date	On/Off Drug Per Applicant	On/Off Drug Per Medical Reviewer
1	1-104	35 144	Switch	6/3/07	8/23/07	8/23/07	7/24/07 (Spont. Ab)	Off (Subject was 36 at the time of conception)	On (Subject was 35 at the time of enrollment)
2	2-033	24 142	Switch	4/15/07	12/12/07	12/13/07	11/22/07	On	On
3	13-018	23 144	New	5/1/07	7/20/07	7/20/07	6/30/07	On	On

#	Site # Pt #	Age Weight (lbs)	User Type	Drug Start Date	Last Active Pill	Date of Positive Pregnancy Test	Conception Date	On/Off Drug Per Applicant	On/Off Drug Per Medical Reviewer
4	17-022	35 108	Switch	8/14/07	4/16/08	4/16/08	3/14/08 (Missed Ab)	Off (Subject was 36 at the time of conception)	On (Subject was 35 at the time of enrollment)
5	18-015	25 131	New	4/2/07	8/28/07	Home Test positive? Date	8/15/07	On	On
6	18-020	23 149	Switch	6/6/07	3/16/08	3/19/08	2/20/08	On	On
7	21-001	19 119	New	11/28/06	1/18/07	1/19/07	12/7/06	On	On
8	21-024	21 121	New	3/26/07	Unknown	Unknown	7/16/07	On	On
9	21-038	22 165	New	5/13/07	10/1/07	10/2/07	9/12/07	On	On
10	22-041	32 146	New	3/10/07	3/4/08	Unknown	3/11/08	On	On
11	22-070	24 137	New	6/5/07	4/8/08	4/8/08	3/13/08	On	On
12	23-019	21 117	New	3/30/07	9/26/07	11/0/07	8/13/07	On	On
13	25-019	18 118	New	5/31/07	10/3/07	10/22/07	8/8/07	On	On
14	26-011	19 159	Switch	6/9/07	1/18/08	2/1/08	1/3/08	On	On
15	28-055	22 200	Switch	5/27/07	7/17/07	7/20/07	6/5/07	Off per Applicant's definition of "on-drug" pregnancy[1]	On per Division's definition[2]
16	36-009	20 113	New	1/12/07	12/26/07	1/2/08	12/1/07	On	On
17	37-012	27 168	New	2/26/07	1/4/08	1/24/08	12/28/07	On	On
18	38-012	35 196	New	6/8/07	9/3/07	10/11/07	8/18/07	On	On
19	38-018	23 196	New	8/2/07	2/7/08	2/28/08	1/1/08 to 1/8/08	On "Chemical pregnancy" per Applicant[3]	On
20	45-056	26 146	Switch	4/29/07	8/24/07	8/30/07	8/5/07	On	On
21	45-067	20 156	Switch	6/8/07	10/21/07	10/25/07	9/10/07	On	On
22	50-009	22 189	New	4/28/07	7/26/07	8/1/07	7/24/07	On	On
23	53-012	24 152	Switch	5/8/07	11/17/07	12/4/07	11/13/07	On "Chemical pregnancy" per Applicant[3]"	On
24	54-016	23 111	New	5/14/07	5/8/08	5/9/08	4/17/08	On	On

#	Site # Pt #	Age Weight (lbs)	User Type	Drug Start Date	Last Active Pill	Date of Positive Pregnancy Test	Conception Date	On/Off Drug Per Applicant	On/Off Drug Per Medical Reviewer
25	57-012	30 129	New	1/28/07	4/19/07	4/19/07	3/25/07	On "Chemical pregnancy" per Applicant[3]	On
26	60-007	24 157	New	12/19/06	5/20/07	5/30/07	5/23/07 (Ectopic)	On	On
27	64-004	22 170	Switch	3/18/07	6/14/07	6/19/07	5/22/07	On	On
28	25-017	22 128	New	6/2/07	12/22/07	12/28/07	Unknown	Off	On
29	7-003	36 133	New	12/24/06	12/25/07	3/4/08 (serum)	1/10/08 (Ectopic)	Off	Off-16 days after last dose
30	22-007	29 208	New	1/28/07	4/19/07	5/14/07 (serum)	5/4/07	Off	Off-15 days after last dose
31	22-068	19 122	Switch	4/27/07	9/25/07	10/24/07	10/11/07	Off	Off-16 days after last dose
32	39-010	28 153	Switch	12/31/06	12/26/07	1/26/08	1/14/08	Off	Off-18 days after last dose

[1] Applicant originally defined an "on-drug" pregnancy as any as conception which occurred after 14 days of starting WC3016. Subject 28-055 conceived 9 days after starting WC3016.
[2] Subject 28-055 conceived within the Division's definition of an "on-drug" pregnancy which is any conception occurring after the first dose of WC3016 is taken.
[3] Chemical pregnancies are defined as a positive serum pregnancy test result but an ultrasound examination which failed to document an intrauterine pregnancy.

Medical Reviewer's Comments

- *Each of the 28 pregnancies included in the calculation of efficacy resulted from an ovulation presumed to have occurred while the subjects were taking study drug (i.e., conception probably occurred within the timeframe between the ingestion of the first dose of WC3016 to 7 days after the last tablet was taken).*
- *The Applicant initially agreed that 26 of the subjects conceived during the trial; however, 2 subjects conceived after they turned 36 years of age. Because these subjects (Subjects 01-104 and 17-022) were 36 years of age when they conceived, they were "censored" by the Applicant and were not included in the Applicant's original PI calculation. However, this Reviewer defined these conceptions as being "on-drug."*
- *During the course of the review, 2 additional subjects (Subjects 25-017 and 28-055) were determined to have had "on-drug" pregnancies*
- *Subject 28-055 conceived within 14 days after initiating study medication. The Applicant did not include this subject as an "on-drug" pregnancy. This Reviewer considers this conception to be "on-drug" and is also included in the PI calculation.*

- *Subject 25-017 was screened on April 18, 2007 at the age of 22 with a screening weight of 128.4 lbs. She enrolled in the study on May 8, 2007 and began taking study drug on June 2, 2007. According to the subject narrative, her last active pill was reported on December 12, 2007 and her last bleeding episode was January 31, 2008 (Day 244). She had negative urine pregnancy tests at Study Visits 1, 1A, 2 (6/25/07), 3 (9/5/07), 4 (10/12/07), and 8 (2/4/08). On February 1, 2008, she saw her private ObGyn at which time she had a gynecologic examination and a normal pelvic sonogram with no evidence of an intrauterine gestational sac. On 1/29/2008, she contacted the study center and reported a positive urine pregnancy test done on 12/28/07. She also reported that her last dose of study medication was 12/22/07. At her final study visit on February 4, 2008, she refused the physical and pelvic examinations but urine and serum pregnancy test results were both negative. She did not complete the study for reasons specified as "other" (i.e., suspected pregnancy and was lost to follow up). The Applicant initially considered the documentation in this case to be insufficient to diagnose an on-drug pregnancy. A review of the subject's CRF revealed evidence that Subject 25-017 conceived during the clinical trial and may have had a spontaneous abortion. According to the Case Report Form, this subject took her last dose of study drug on 12/22/09. There is a note written by the Principal Investigator in the "Suspected Pregnancy" section of the CRF which states that the subject had a positive pregnancy test on 12/28/07, which would have been 6 days after her last dose. The Applicant agreed in the submission of 10/16/09 (SDN 8) that this pregnancy should be considered "on-drug." This subject is also included in the Pearl Index calculation.*
- *The final total of "on-drug" pregnancies used for the Pearl Index calculation in this clinical trial was 28.*

Pearl Index Calculations

In the PITT cohort of women 18 to 35 years of age (n=1270), 28 pregnancies occurred while using WC3016 in 12,482 at-risk cycles. The calculated PI for this population was 2.916 (1.938, 4.213).

In the subgroup of women aged 36 to 45 years in the MITT population (n=285), no pregnancies occurred while using WC3016 in 3,109 at-risk cycles.

In the overall MITT population (N=1,555), 28 women became pregnant during 15,591 at-risk cycles while using WC3016. According to calculations by the FDA statistician, the PI for all subjects aged 18-45 was 2.33 (1.55, 3.37).

Table 9 is a summary of both the Applicant's pregnancy outcomes based on 27 on-drug pregnancies and this Reviewer's pregnancy outcomes based on 28 on-drug pregnancies. The Medical Reviewer's calculations were done with the FDA Statistician.

Medical Reviewer's Comment

- *The Applicant has not submitted a recalculated PI based on the agreed 28 on-drug pregnancies.*

Table 9 Summary of Pregnancy Outcomes, PITT Cohort

PITT Cohort (18-35 Years)	Applicant	Medical Reviewer
Number of Subjects	1,270	1,270
Number of Pregnancies	27	28
Number of Women-Cycles of Treatment*	12,486	12,482
Pearl Index	2.81	2.92
95% Confidence Intervals	1.85, 4.09	1.94, 4.21

*The FDA Statistician could not confirm the Applicant's calculation regarding cycles of treatment.
Source: Medical Reviewer based on NDA 22-501, submissions of 7/22/09 (SDN 5) and 10/16/09 (SDN 8).

Medical Reviewer's Comments

- *Pearl index for the PITT cohort = 1300 X 28 pregnancies = 36,400 ÷ 12,482 woman-cycles = 2.916 (1.938, 4.213).*
- *The small discrepancy in the number of treatment cycles could not be reconciled by the FDA Statistician.*
- *There is no Division consensus as to the highest PI (or upper bound of the 95% CI) acceptable to be considered "effective" oral contraception.*
- *PI calculations in the various subpopulations of this study are discussed in Section 6.1.7.*
- *In the submission of 10/16/09 (SDN 8), the Applicant agreed that Subject 025-017 should have been included in the "on-drug" pregnancy group bringing the total of "on-drug" pregnancies to 28.*

Life-table Analysis

Life-table analysis is an estimate of the cumulative probability of a subject not becoming pregnant while receiving the study medication. The life-table analysis for subjects ages 18-35 is shown in Table 10 below.

Table 10 Summary of Pregnancy Outcomes, PITT Population

Cycle	Number of Pregnancies (N=28)	Cumulative Rate (%)	Cumulative Rate (95% CI)
1	1	0.00	-
2	5	0.24	0.08 - 0.74
3	3	0.57	0.27 - 1.19
4	2	0.74	0.39 - 1.42
5	4	0.92	0.51 - 1.66
6	2	1.31	0.79 - 2.16
7	1	1.51	0.94 - 2.42
8	4	1.62	1.02 - 2.56
9	0	2.07	1.36 - 3.13
10	2	2.18	1.45 - 3.28
11	1	2.31	1.54 – 3.43
12	2	2.56	1.74 - 3.76
13	1	2.71	1.86 - 3.95

Source: FDA Statistician

The life-table analysis for all subjects (ages 18-45) in the clinical trial is shown in Table 11 below.

Table 11 Summary of Pregnancy Outcomes, MITT Population

Cycle	Number of Pregnancies (N=28)	Cumulative Rate (%)	Cumulative Rate (95% CI)
1	1	0.00	-
2	5	0.20	0.06 - 0.61
3	3	0.47	0.22 - 0.98
4	2	0.61	0.32 - 1.16
5	4	0.75	0.42 - 1.36
6	2	1.06	0.64 - 1.75
7	1	1.22	0.76 - 1.96
8	4	1.31	0.83 - 2.07
9	0	1.66	1.10 - 2.52
10	2	1.76	1.17 - 2.64
11	1	1.85	1.24 - 2.76
12	2	2.06	1.40 - 3.02
13	1	2.17	1.49 - 3.17

Source: FDA Statistician

Medical Reviewer's Comments

- *The life-table analysis (cumulative pregnancy rate) in the PITT population for the trial was 2.71%.*
- *The greatest number of conceptions occurred during the second treatment cycle with the majority (17/28) occurring in the first 6 months of the trial.*

6.1.5 Analysis of Secondary Endpoints(s)

Cycle Control

A secondary objective of the phase 3 primary trial was to assess the incidence of intracyclic (unscheduled) bleeding and/or spotting (B/S). For this purpose, all subjects were to keep daily diaries recording the incidence and severity of bleeding. Only cycles which were evaluable for bleeding were included in the analysis. A cycle was evaluable for bleeding if the diary documented at least 14 days of pill use and the diary was scored for bleeding.

Bleeding data were analyzed for the MITT population (the subset of all treated subjects who were evaluated for pregnancy at least once after beginning the study medication) and the population of Completed Subjects (the subset of MITT subjects who completed at least 360 days of active treatment). The overall MITT population consisted of 1,582 subjects.

Bleeding Definitions:

- Withdrawal (scheduled) B/S episode:
  - The first bleeding episode starting after the last day of active drug intake during a treatment cycle (Day 26) and before the beginning of the next treatment cycle, or
  - A bleeding episode starting within 4 days before the last day of active drug intake during the treatment cycle and continuing past the last day of active drug intake in that cycle.
- Intracyclic (unscheduled) B/S episode: One or more days of bleeding or spotting, which could be consecutive or interrupted once or more than once by no more than one day without bleeding or spotting and was not withdrawal bleeding/spotting.
- The duration of a B/S episode was defined as the number of days from the first to the last day of the episode, inclusive, including single isolated bleed-free (spot-free) days.
- Spotting: Defined as light bleeding which did not require any sanitary protection including panty liners.
- Bleeding: Defined as any bleeding which required some type of sanitary protection.

Unscheduled Bleeding/Spotting

Unscheduled B/S was defined as any bleeding/spotting that was not considered withdrawal or scheduled bleeding. Unscheduled B/S was not uncommon in this study. One unscheduled B/S episode occurred at least once in 85.9% of the MITT population during Cycle 2 through Cycle 13. The incidence of unscheduled B/S is summarized in Table 12. Unscheduled B/S was highest (52.7%) during Cycle 2 and gradually decreased thereafter. The incidence fell below 40% at Cycle 8, and the lowest incidence (36.4%) occurred at Cycle 13.

Table 12 Incidence of Unscheduled B/S (N=1582)

Cycle(s)	Bleeding/Spotting	Bleeding	Spotting
	Incidence n/N (%)	Incidence n/N (%)	Incidence n/N (%)
Cycles 2-13	1257/1463 (85.9)	1186/1463 (81.1)	745/1463 (50.9)
Cycle 1	704/1514 (46.5)	575 (38.0)	341 (22.5)
Cycle 2	762/1447 (52.7)	685 (47.3)	296 (20.5)
Cycle 3	725/1391 (52.1)	636 (45.7)	269 (19.3)
Cycle 4	603/1312 (46.0)	527 (40.2)	208 (15.9)
Cycle 5	554/1254 (44.2)	485 (39.5)	188 (15.0)
Cycle 6	483/1194 (40.5)	418 (35.0)	166 (13.9)
Cycle 7	508/1164 (43.6)	442 (38.0)	168 (14.4)
Cycle 8	431/1117 (38.6)	385 (34.5)	133 (11.9)
Cycle 9	426/1077 (39.6)	376 (34.9)	142 (13.2)
Cycle 10	394/1035 (38.1)	349 (33.7)	139 (13.4)
Cycle 11	396/996 (39.8)	348 (34.9)	116 (11.6)
Cycle 12	379/977 (38.8)	345 (35.3)	115 (11.8)
Cycle 13	344/945 (36.4)	306 (32.4)	102 (10.8)

Source: Adapted from Clinical Study Report, Pages 67, 69.

Medical Reviewer's Comments

- *Cycle 1 represents a transition cycle for subjects switching pills or new users initiating pill use. In either case, some unscheduled B/S is not unexpected, especially in new users.*
- *The incidence of unscheduled B/S was greatest during the second cycle.*
- *At the end of the study, approximately 1/3 of subjects still experienced some unscheduled B/S.*
- *85.9% of subjects experienced an unscheduled B/S episode at some point during this trial. The incidence decreased over the course of the study from 52.7% in Cycle 2 to 36.4% in Cycle 13.*
- *The incidence of unscheduled B/S is somewhat higher than with other OC formulations.*
- *With the exception of Cycles 2 and 3, during each individual cycle, half of the women in this trial had no unscheduled bleeding and/or spotting.*

The mean and median number of days of unscheduled B/S is recorded in Table 13.

Table 13 Mean/Median/Range Days of Unscheduled B/S (N=1582)

Cycle(s) (N)	Bleeding/Spotting			Bleeding			Spotting		
	Mean (SD)	Median	Range	Mean (SD)	Median	Range	Mean (SD)	Median	Range
Cycles 2-13 (1257)	2.63 (2.95)	-	-	2.14 (2.67)	-	-	0.49 (1.10)	-	-
Cycle 1 (1514)	2.65 (3.97)	0	0, 25	1.99 (3.49)	0	0, 25	0.66 (1.75)	0	0, 21
Cycle 2 (1447)	3.21 (4.15)	2	0, 23	2.54 (3.67)	0	0, 22	0.67 (1.86)	0	0, 19
Cycle 3 (1391)	2.79 (3.79)	0	0, 25	2.29 (3.51)	0	0, 25	0.51 (1.47)	0	0, 17
Cycle 4 (1312)	2.44 (3.60)	0	0, 25	1.96 (3.19)	0	0, 22	0.48 (1.66)	0	0, 24
Cycle 5 (1254)	2.25 (3.37)	0	0, 23	1.83 (2.96)	0	0, 23	0.42 (1.47)	0	0, 17
Cycle 6 (1194)	2.00 (3.12)	0	0, 20	1.60 (2.72)	0	0, 19	0.40 (1.46)	0	0, 18
Cycle 7 (1164)	2.28 (3.46)	0	0, 20	1.83 (2.98)	0	0, 19	0.45 (1.74)	0	0, 19
Cycle 8 (1117)	1.82 (3.02)	0	0, 26	1.52 (2.65)	0	0, 20	0.29 (1.21)	0	0, 18
Cycle 9 (1077)	1.93 (3.16)	0	0, 23	1.55 (2.66)	0	0, 17	0.38 (1.55)	0	0, 23
Cycle 10 (1035)	1.86 (3.16)	0	0, 24	1.53 (2.84)	0	0, 24	0.33 (1.22)	0	0, 17
Cycle 11 (996)	1.87 (3.04)	0	0, 22	1.53 (2.60)	0	0, 20	0.34 (1.44)	0	0, 17
Cycle 12 (977)	1.82 (2.98)	0	0, 21	1.50 (2.58)	0	0, 20	0.32 (1.27)	0	0, 15
Cycle 13 (945)	1.81 (3.01)	0	0, 19	1.47 (2.61)	0	0, 19	0.34 (1.43)	0	0, 17

Source: Adapted from Clinical Study Report, Table 14.2.2.1.1, Pages 121-127 and Submission of 10/16/09 (SDN 8) Table CL4.

Medical Reviewer's Comments

- *The mean number of days per cycle of unscheduled B/S decreased during the study, from 3.21 days in Cycle 2 to 1.81 days in Cycle 13.*
- *With the exception of Cycle 2, unscheduled B/S averaged 2-3 days per cycle.*

Intensity of Unscheduled B/S

- Intensity was defined as the maximum intensity of the component IB/IS days.

- 0 = none (no bleeding or spotting)
- 1= light (less than associated with normal menstruation relative to the subject's experience)
- 2 = normal (like normal menstruation relative to the subject's experience)
- 3 = heavy (more than normal menstruation relative to the subject's experience)

An episode of unscheduled B/S was scored by the highest intensity of bleeding on any day during that episode. The mean maximum intensity score for unscheduled B/S episodes was 1.56 for Cycle 2 through Cycle 13 in the MITT population. Mean maximum intensity scores per cycle are summarized below.

Table 14 Maximum Intensity of Unscheduled B/S (N=1582)

Cycle(s)	Maximum Intensity Mean (SD)
Cycles 2-13	1.56 (0.55)
Cycle 1	1.55 (0.73)
Cycle 2	1.67 (0.73)
Cycle 3	1.58 (0.69)
Cycle 4	1.56 (0.67)
Cycle 5	1.60 (0.70)
Cycle 6	1.59 (0.69)
Cycle 7	1.62 (0.71)
Cycle 8	1.65 (0.72)
Cycle 9	1.64 (0.71)
Cycle 10	1.60 (0.71)
Cycle 11	1.63 (0.69)
Cycle 12	1.62 (0.71)
Cycle 13	1.67 (0.70)

Source: Adapted from Clinical Study Report, Page 78
SD: Standard Deviation

Medical Reviewer's Comments

- *The mean maximum intensity score for unscheduled B/S episodes remained fairly stable throughout the study between 1 and 2, i.e., between light and normal bleeding intensity. Scores ranged from 1.55 (Cycle 1) and 1.56 (Cycle 4) to a high value of 1.67 (Cycle 2 and Cycle 13).*
- *Data regarding the proportion of subjects who reported each level of intensity for unscheduled B/S was not provided by the Applicant.*
- *No comparator drug was used in this study. However, based on data from several approved 20 mcg OCs (Loestrin 1/20; Loestrin 24), the incidence and duration of unscheduled B/S is somewhat higher with this drug. However in my*

opinion, the difference is not clinically meaningful nor is it a safety issue. The bleeding profile of this drug can be addressed in labeling.

- *A total of 692 subjects discontinued the trial prior to its completion. Of these, 177 subjects (25.6%) withdrew due to an adverse event. Of the 177 subjects, 63 subjects withdrew because of a bleeding-related problem.*

Scheduled (Withdrawal) Bleeding

Scheduled bleeding was defined as the first bleeding episode starting after the last day of active drug intake during a treatment cycle and before the beginning of the next treatment cycle or a bleeding episode starting within 4 days of the last day of active drug intake during a treatment cycle and continuing past the last day of active drug intake in that cycle.

The incidence of withdrawal B/S decreased over the course of the trial, from 43.3% of subjects during Cycle 1 to 22.4% during Cycle 13.

Table 15 Incidence, Duration and Intensity of Scheduled B/S (N=1582)

Cycle(s)	Incidence n/N (%)	Mean Days (SD)	Median Intensity Score, Mean (SD)
Cycles 2-13	1037/1463 (70.9)	-	1.53 (0.59)
Cycle 1	655/1514 (43.3)	1.76 (2.48)	1.65 (0.68)
Cycle 2	503/1447 (34.8)	1.36 (2.25)	1.59 (0.68)
Cycle 3	479/1391 (34.4)	1.39 (2.31)	1.60 (0.68)
Cycle 4	384/1312 (29.3)	1.18 (2.19)	1.60 (0.66)
Cycle 5	372/1254 (29.7)	1.09 (1.99)	1.52 (0.62)
Cycle 6	299/1194 (25.0)	1.00 (2.02)	1.57 (0.67)
Cycle 7	311/1164 (26.7)	0.98 (1.96)	1.51 (0.64)
Cycle 8	284/1117 (25.4)	0.98 (1.97)	1.67 (0.69)
Cycle 9	273/1077 (25.3)	1.01 (2.02)	1.59 (0.66)
Cycle 10	250/1035 (24.2)	0.94 (1.93)	1.60 (0.68)
Cycle 11	257/996 (25.8))	0.93 (1.83)	1.57 (0.66)
Cycle 12	223/977 (22.8)	0.87 (1.89)	1.56 (0.66)
Cycle 13	212/945 (22.4)	1.55 (3.29)	1.51 (0.65)

Source: Adapted from CSR, Tables 14, 15, Pages 75, 76 and from Submission of 10/16/09 (SDN 8) Table CL4.

Medical Reviewer's Comment

- *The incidence of withdrawal bleeding/spotting decreased during the trial from 43.3% to 22.4%.*

Amenorrhea
A subject was considered to have amenorrhea for any interval if no bleeding or spotting (either scheduled or unscheduled) was reported during that interval. Amenorrhea was common and tended to increase during the course of the study. The incidence during Cycles 1 to 3 was approximately 30%-32%, and increased to 49.1% for Cycle 13.

Table 16 Incidence of Amenorrhea (N=1582)

Cycle(s)	Incidence n/N (%)
Cycles 2-13	126/1463 (8.6)
Cycle 1	478/1514 (31.6)
Cycle 2	444/1447 (30.7)
Cycle 3	420/1391 (30.2)
Cycle 4	496/1312 (37.8)
Cycle 5	479/1254 (38.2)
Cycle 6	512/1194 (42.9)
Cycle 7	480/1164 (41.2)
Cycle 8	497/1117 (44.5)
Cycle 9	468/1077 (43.5)
Cycle 10	475/1035 (45.9)
Cycle 11	429/996 (43.1)
Cycle 12	437/977 (44.7)
Cycle 13	464/945 (49.1)

Source: CSR Table 18 Page 80

Medical Reviewer's Comment

- *Amenorrhea was fairly common during the study.*
- *A total of 9 subjects discontinued the trial because of amenorrhea.*

6.1.6 Other Endpoints

No other efficacy endpoints were utilized in this trial.

6.1.7 Subpopulations

The FDA Statistician has calculated PIs for subgroups based on body mass index, weight at screening, and ethnic origin.

Table 17 Pearl Indices Based on Body Mass Index at Screening

BMI	N	Number of On-Treatment Pregnancies	Number of Cycles	Pearl Index	95% Confidence Interval
< 24	624	12	6,065	2.57	(1.33, 4.49)
≥ 24	646	16	6,417	3.04	(1.86, 5.26)
Total	1,270	28	12,482	2.92	(1.94, 4.21)

Source: FDA Statistician

Table 18 Pearl Indices Based on Weight at Screening

Weight	N	Number of On-Treatment Pregnancies	Number of Cycles	Pearl Index	95% Confidence Interval
< 144	623	12	6,102	2.56	(1.32, 4.46)
≥ 144	647	16	6,380	3.26	(1.86, 5.29)
Total	1,270	28	12,482	2.92	(1.94, 4.21)

Source: FDA Statistician

Medical Reviewer's Comment

- *It is unclear in the medical literature whether heavier women have overall higher failure rates when using oral contraceptives. Clinical trials such as this one have excluded women with high body weight; therefore, the effect of body weight on contraception has not been well studied. Efficacy in overweight women is still greater than that with barrier methods.*

Table 19 Pearl Indices Based on Ethnic Origin

Race	N	Number of On-Treatment Pregnancies	Number of Cycles	Pearl Index	95% Confidence Interval
Caucasian	948	15	9,414	2.07	(1.16, 3.41)
Black	139	3	1,316	2.96	(0.61, 8.64)
Hispanic	137	8	1,280	8.13	(3.51, 15.96)
Others	46	2	472	5.51	(0.67, 19.79)
Total	1270	28	12,482	2.92	(1.94, 4.21)

Source: FDA Statistician

Medical Reviewer's Comment

- *Twenty-nine percent (8 of the 28 "on-drug" pregnancies) occurred in the Hispanic population which comprised 9.8% (155 of the 1270 PITT subjects). The reason for the disproportionally high PI in this subgroup is not entirely clear.*

6.1.8 Analysis of Clinical Information Relevant to Dosing Recommendations

There is only one dosage regimen for this drug product.

6.1.9 Discussion of Persistence of Efficacy and/or Tolerance Effects

Persistence of efficacy and/or tolerance effects was not discussed in the submission. No persistent effects would be expected for this oral contraceptive product.

6.1.10 Additional Efficacy Issues/Analyses

There are no additional efficacy issues or analyses.

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.

There were no deaths during the clinical development of WC3016. The deep vein thrombosis that occurred in the phase 3 clinical trial occurred in an obese patient who smoked 10 cigarettes/day and who was 3 weeks post arthroscopic knee surgery. 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.

7.1 Methods

The data used by the Applicant to evaluate product safety included adverse events, physical and gynecological examinations, vital signs and laboratory results which were recorded on CRFs during the trials.

Medical Reviewer's Comment

- *The Applicants' methods to evaluate drug safety were appropriate and consistent with methods used in oral contraceptive trials.*

7.1.1 Studies/Clinical Trials Used to Evaluate Safety

There were three completed phase 1 studies (Study PR-14006, Study PR-14106, and Study PR-14206) submitted to the NDA. These studies enrolled a total of 66 healthy female subjects who were between the ages of 18 to 35 years. Median age across the phase 1 studies ranged between 25 and 28 years, and median body weights were between 60.7 and 62.2 kg.

Study PR-14006 (N=24): A single-center, randomized, balanced, single-dose, 3-treatment, 3-period, 6-sequence crossover study where oral doses of WC3016-1/10 tablet (EE 10 mcg/NA 1 mg) and a hydroalcoholic solution/suspension containing EE 10 mcg/NA 1 mg were administered. A total of 22 subjects completed all three treatment periods. A total of 23 AEs were reported in this study; all mild in intensity. The most commonly reported AE (16.7% of subjects) was menometrorrhagia. No subjects were withdrawn from treatment due to an AE.

Study PR-14106 (N=24): A single-center, randomized, balanced, single-dose, 3-treatment, 3-period, 6-sequence crossover study where oral doses of WC3016 10 tablet (EE 10 mcg) and a hydroalcoholic solution containing EE 10 mcg were administered. All 24 subjects completed the three treatment periods. A total of 16 AEs were reported; all mild in intensity. The most frequent AE was headache.

Study PR-14206 (N=18): A single-center, single-treatment, multiple-dose study where one WC3016-1/10 tablet (EE 10 mcg/NA 1 mg) was administered daily for 24 days and then one WC3016 EE 10 mcg was administered daily for 2 days. All 18 subjects completed the study. A total of 13 treatment-emergent AEs were reported in this study. The most commonly reported AEs were menstrual cramps and headache.

Medical Reviewer's Comments

- *Results from all physical examinations and vital sign measurements during the Phase 1 studies were judged by the investigators to be within normal limits and not clinically significant. Results from the screening ECG measurements were all considered normal.*
- *No subjects reported SAEs during the phase 1 bioavailability and pharmacokinetic studies.*

The majority of the safety data included in this submission was obtained from the open-label primary phase 3 clinical trial (Study PR-05806).

Study PR- 05806 (N= 1,683): The single phase 3 clinical trial assessed 15,596 total cycles of treatment. A total of 968 subjects completed the 13 month clinical trial. The health of each subject enrolled in the trial was assessed prior to treatment through medical, surgical, medication, and gynecological histories, physical and gynecological examinations, breast examinations, Pap smears, vital sign assessments (blood pressure, heart rate, and body weight), clinical laboratory tests (serum chemistry, hematology, and urinalysis), human papilloma virus (HPV) screen and Chlamydia test, and urine and serum pregnancy tests. Vital sign assessments and urine pregnancy tests were repeated at each interim study visit. Physical and gynecological examinations, breast examinations, Pap smears, vital sign assessments, clinical laboratory tests (serum chemistry, hematology, and urinalysis), and urine and serum pregnancy tests were repeated at the end of the study. Concomitant medication use was recorded at all visits.

Medical Reviewer's Comment

- *A summary of the demographic and baseline characteristics of the phase 3 study subjects can be found in Section 6.1.2 of this review.*

7.1.2 Categorization of Adverse Events

Adverse events occurring from the point of screening through the end of study were recorded.

Adverse events (AEs) were elicited by indirect questioning and spontaneous reporting. The date the AE began and ended or that the AE was ongoing, severity, relationship to the use of study drug, and action taken or outcome were recorded by the investigator in the subject's case report form (CRF). AEs were classified as mild, moderate or severe and also assessed for relationship to the study drug (unrelated, unlikely, possible, probable or definitely related to the study drug).

7.1.3 Pooling of Data across Studies/Clinical Trials to Estimate and Compare Incidence

There was only one phase 3 clinical trial submitted for review in this Application. Pooling of data from different studies/clinical trials was not done.

7.2 Adequacy of Safety Assessments

7.2.1 Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations

Drug Exposure in the Phase 3 Clinical Trial
The safety data is derived from the All Treated Population, which consisted of 1,660 subjects who received at least one dose of study drug during the clinical trial. The mean drug exposure in the All Treated population was 272.4 days and 9.93 cycles.

Table 20 Drug Exposure

	All Treated Population N=1660	**MITT Population N=1582**	**Completed Subjects N=968**
Mean Drug Exposure (Days)	272.4	273.8	355.8
Mean Drug Exposure (Cycles)	9.93	10.38	12.80

Source: CSR, Adapted from Table 14.14.1, Page 114

Medical Reviewer's Comment

- *The Division considers the Applicant's sample size and length of drug exposure to be adequate for the evaluation of the safety of this oral contraceptive product.*

7.2.2 Explorations for Dose Response

No explorations for dose response were performed, as only one dosage form was utilized in the phase 3 clinical trial.
The daily dose of EE in WC3016 is only 10 mcg and is given for 26 of the 28 days of the treatment cycle. This represents an almost 50% reduction in the total estrogen exposure from even the lowest doses of currently marketed OCs.

Demonstration of superior safety of lower estrogen doses in combination OCs is beyond the scope of a single trial, even a study of more than 1,600 women during 1 year of treatment such as the phase 3 clinical trial submitted in this application. However,

epidemiologic data have demonstrated a progressive reduction in the incidence of vascular adverse events that parallels the progressive reduction in hormone content, especially estrogen content, of OCs since their introduction.

7.2.3 Special Animal and/or In Vitro Testing

No special animal and/or in vitro testing was indicated or required.

7.2.4 Routine Clinical Testing

The routine clinical testing obtained in this NDA was adequate and typical for the evaluation of this combined oral contraceptive.

7.2.5 Metabolic, Clearance, and Interaction Workup

No special metabolic, clearance or interaction studies were performed for this NDA.

7.2.6 Evaluation for Potential Adverse Events for Similar Drugs in Drug Class

The evaluation for potential adverse events known to occur with oral contraceptives was adequate.

7.3 Major Safety Results

7.3.1 Deaths

No subject deaths occurred during the clinical trials (Studies PR-14006, PR-14106, PR-14206, and PR-05806) or within 30 days after study completion.

7.3.2 Nonfatal Serious Adverse Events

In the primary phase study (PR-05806), a total of 18 SAEs were reported in 15 subjects (0.9%). All but three of these SAEs were considered by the investigator to be not related or unlikely related to study treatment. Three subjects had SAEs considered probably related or possibly related to study treatment, including: (1) deep vein thrombosis (Subject 004-005), (2) ovarian vein thrombosis (Subject 035-004), and (3) cholecystitis (Subject 035-006).

Four subjects were discontinued for SAEs, including deep vein thrombosis (Subject 004-005), ovarian cyst (Subject 033-044), ovarian vein thrombosis (Subject 035-004), and transverse sinus stenosis (Subject 043-004).

Medical Reviewer's Comments

- *The relative risk of venous thomboembolism (VTE) is increased with OC use. Nevertheless, the rarity of VTE in women of reproductive age means that the absolute increase in risk remains small.*
- *A recent study on OCs and VTEs published in the British Medical Journal in August, 2009 (BMJ 2009;339:b2921) concluded that the risk of venous thrombosis clearly differed by type of progestogen and dose of estrogen. The risk of venous thrombosis decreased with duration of use and decreasing estrogen dose. These findings were also supported in a second study (BMJ 2009;339:b2890). For the same dose of estrogen and the same length of use, OCs containing levonorgestrel conferred a significantly lower risk of venous thrombosis than pills containing other types of progestins. An accompanying editorial in the BMJ pointed out that the absolute risk of having venous thomboembolism is low, even when taking the pill, and stated that the products of choice should be those containing either levonorgestrel or norethisterone,* ***"with as low dose of estrogen as possible."***

Table 21 Serious Adverse Events

Subject Number	SAE	Severity	Day of Onset	Applicant's Assessment of Relationship to Treatment	Outcome
004-005*	DVT of left leg	Severe	136	Possible	Recovered
006-010	Appendicitis	Severe	219	None	Recovered
018-015	Hyperemesis	Moderate	201	None	Recovered
031-045	Appendicitis	Severe	20	None	Unknown
033-004*	Ovarian cyst	Severe	242	Unlikely	Recovered
035-004*	Ovarian vein thrombosis	Severe	83	Probable	Recovered
035-006	Cholecystitis	Severe	204	Possible	Recovered
036-063	Pneumonia	Severe	222	None	Recovered
040-001	Food poisoning	Severe	76	None	Recovered
043-004*	Transverse sigmoid sinus stenosis	Severe	254	None	Recovered
045-096	Dehydration	Severe	364	None	Recovered
	Hypokalemia	Severe	364	None	Recovered
	Pharyngitis,	Severe	364	None	Recovered
	Sepsis due to pharyngitis	Severe	364	None	Recovered
052-047	Appendicitis	Moderate	185	None	Recovered
052-055***	Abdominal pain	Moderate	226	None	Recovered
056-031**	Therapeutic procedure (elective hysterectomy with sling)	Moderate	124	None	Recovered
066-032	Radius fracture	Moderate	351	None	Ongoing

Source: Adapted from CSR, Table 24, Page 88; Table 16.2.17.2; Page 317.
* Discontinued the study due to SAE
** Discontinued by the PI due to elective surgery
*** Discontinued by the PI due to pregnancy

Medical Reviewer's Comment

- *I agree with the Applicant's assessment of a possible relationship to treatment for Subjects 004-005, and 035-006. The relationship of the study drug to the case of ovarian vein thrombosis (Subject 035-004) is unclear.*

Case Synopses of Possible "Drug-Related" SAEs

Subject 004-005 (Deep vein thrombosis) was a 25-year-old woman who was started on study drug on 12/31/06. She was 5 ft. 10 in. tall, weighed 222 lbs. and smoked 10

cigarettes/day. On (b) (6), she underwent arthroscopic surgery on her left knee for loose cartilage. Postoperatively, on (b) (6), she was hospitalized for a deep vein thrombosis of the left popliteal and superficial femoral vein. She discontinued study drug. The investigator assessed the event as serious and possibly related. The subject was discontinued from the study (b) (6) and was discharged from the hospital on Coumadin. As of 6/26/07, the SAE had resolved. The subject's risk factors for DVT included obesity, smoking, arthroscopic surgery and oral contraceptive use. Her family history was negative for pulmonary embolism or clotting abnormalities.

Medical Reviewer's Comments

- *Subject 004-005 had several risk factors (obesity, smoking, arthroscopic surgery) for developing her DVT.*
- *This subject did not discontinue her study drug prior to her arthroscopic surgery.*
- *The use of oral contraceptives at the time of arthroscopic surgery has been observed to increase the risk of venous thomboembolism (Delis et al., Incidence, natural history and risk factors of deep vein thrombosis in elective knee surgery.Thromb Haemost 2001;86:817-21).*

Subject 033-004 (Ovarian cyst) was a 41-year-old woman who began taking study drug on 12/8/06. On (b) (6) she developed severe right sided pelvic pain which was treated with analgesics in the emergency department. Ultrasound on (b) (6) showed a dermoid tumor of the left ovary. The dermoid was removed on (b) (6) At the time of surgery, the right ovary was noted to be hemorrhagic and was also removed. The subject stopped study drug and was discontinued from the study on 8/10/07.

Medical Reviewer's Comment

- *It appears unlikely that this SAE was related to the study drug.*

Subject 035-004 (Ovarian vein thrombosis) was a 33-year-old woman who began taking study drug on 1/4/07. She was 5' 5" tall, weighed 162 lbs., and was a non-smoker. The subject went to the Emergency Department on (b) (6) with a complaint of abdominal pain and was given medication for an "ovarian cyst." She returned on (b) (6) with worse pain. On (b) (6), she received a call from the ER telling her to go to the hospital because the CT scan showed a "blood clot in the right ovary." She was hospitalized and placed on Lovenox. She was discharged on (b) (6) continuing the Lovenox at home. The Principal Investigator, in a memo to Warner Chilcott dated 4/24/07, stated the patient "mentioned that the doctors a (b) (6) hospital informed her that they did not believe that the clot in her right ovary was related to her use of oral contraceptives."

Medical Reviewer's Comment

- *Risk factors for ovarian vein thrombosis are not well known but the condition is usually associated with postpartum endometritis following vaginal delivery, abortion, or cesarean section and results from an ascending septic*

thombophlebitis. In nonpuerperal patients, hypercoagulable states may predispose to thrombosis but the role of oral contraceptives as an independent etiologic agent is not well defined in the literature.

Subject 035-006 (Cholecystitis) is 38-year-old woman who began taking study drug on 2/9/07. On (b) (6), she developed abdominal pain and went to an urgent care center. Initially treated with analgesics, she had an ultrasound on (b) (6) and was hospitalized for a cholecystectomy the next day. A follow-up procedure was performed on (b) (6) to remove additional gallstones from her biliary ducts and she was discharged on (b) (6). She remained in the study at the time, but discontinued study drug on 11/15/07.

Medical Reviewer's Comment

- *Oral contraceptive use may precipitate a symptomatic attack in women known to have gallstones. This is a known and labeled risk of OC use.*

7.3.3 Dropouts and/or Discontinuations

A total of 692 subjects (41.7%) in the All Treated Population of 1660 subjects discontinued this study prior to its conclusion. Of these, 177 subjects discontinued due to an AE; however five of these subjects discontinued prior to the start of treatment. Therefore, a total of 172 (10.4%) subjects in the All Treated Population discontinued the study as a result of a treatment-emergent AE.

Table 22 Subject Discontinuations (N=692)

Reasons for Discontinuation	n (% of 692 who withdrew)
Lost to follow-up	227 (32.8)
Adverse events	177 (25.6)
Withdrew consent	147 (21.2)
Other reasons	96 (13.9)
Pregnancy	25 (3.6)
Protocol violation	20 (2.8)

Source: CSR, Page 44 and Pages 101-102.

The most frequent AEs resulting in study 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).

Four subjects were discontinued for SAEs, including deep vein thrombosis (Subject 004-005), ovarian cyst (Subject 033-044), ovarian vein thrombosis (Subject 035-004), and transverse sinus stenosis (Subject 043-004).

Table 23 Subjects with AEs Leading to Discontinuation (N=1660)

Adverse Event Preferred Term	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: CSR, Adapted from Data Listing 16.2.17.2, Pages 319-349; Table 25, Page 89,
* Narratives below

Case Synopses

Subject 001-046 was a 39 year old woman who began taking study drug on 3/25/07. On 4/10/07, she experienced an episode of numbness on the left side of her body and difficulty speaking lasting about 10 minutes. On (b) (6) she went to the ER but by that time she had fully recovered. All laboratory tests in the ER, including a CT scan of the head, were negative. She was told to discontinue taking meds, which she did, and to start taking low dose aspirin. She was discharged from the ER and not admitted to acute inpatient care. The investigator considered the AE to be a transient ischemic attack, mild in severity, and possibly related to study drug. Study medication was discontinued. She subsequently did well without sequelae or morbidity.

Subject 001-073 was a 27 year old G0P0 who enrolled in the trial on 4/12/07. Her baseline hematocrit on enrollment was 39%. During the trial, she experienced persistent unscheduled bleeding from 5/11/07 to 7/27/07and discontinued the study 7/26/07. Her hematocrit at her final visit remained at 39%.

Subject 043-004 *was* a 23-year old woman who began taking study drug on 1/8/07. On (b) (6), she began to experience neck strain, headache and blurred vision. She was noted to have disconjugate gaze in her left eye and was hospitalized. After admission to the hospital, the subject underwent cerebral angiography and venography and transvenous stenting of the right transverse sigmoid sinus on (b) (6). Her initial and final diagnosis was pseudotumor cerebri and transverse sigmoid sinus stenosis. The investigator assessed the adverse event to be severe and unrelated to study drug. The investigator assessed the patient's final status as recovered. She was discontinued from the study.

Medical Reviewer's Comments

- *The number of early withdrawals, and the frequency and type of AEs leading to withdrawals, were comparable to other COCs and did not raise any new or unexpected safety concerns.*
- *Four subjects were discontinued for SAEs, including deep vein thrombosis (Subject 004-005), ovarian cyst (Subject 033-004), ovarian vein thrombosis (Subject 035-004), and transverse sigmoid sinus stenosis (Subject 043-004). These subject narratives have been previously discussed in Section 7.3.2.*
- *A total of 63 subjects withdrew from the trial because of a bleeding-related problem. The Division requested the Applicant to submit hemoglobin and hematocrit data for all these subjects. On 10/19/09, the Division received the requested data. In this group of subjects, changes in baseline and end of study hemoglobin and hematocrit values were not clinically significant. The lowest end of study hematocrit in this group was 33% in Subject 042-003. This represented a drop of 2% from her baseline hematocrit of 35%. The greatest decrease in hematocrit in this group was 5%, which occurred in Subject 45-024 ((43% to 38%). Decreases in hemoglobin through the study were likewise clinically insignificant.*

7.3.4 Significant Adverse Events

No additional significant adverse events were reported in the clinical trials.

7.3.5 Submission Specific Primary Safety Concerns

No additional submission specific primary safety concerns were reported.

7.4 Supportive Safety Results

7.4.1 Common Adverse Events

An AE was defined as treatment-emergent if its date of onset is Day 1 (first dose) or later. Treatment-emergent AEs were reported in 1,064 subjects (64.1%). Of these subjects, AEs considered by the investigator to be treatment-related were reported in 442 (26.6%).

Table 24 Most Commonly Reported (≥2%) Treatment-Emergent AEs, (N=1,660)

AE Preferred Term	Number (%) of Subjects
Headache	116 (7.0)
Upper respiratory tract infection	103 (6.2)
Sinusitis	86 (5.2)
Nasopharnygitis	85 (5.1)
Nausea	80 (4.8)
Dysmenorrhoea	73 (4.4)
Urinary tract infection	65 (3.9)
Vaginitis bacterial	64 (3.9)
Human papilloma virus	62 (3.7)
Weight fluctuation	59 (3.6)
Breast tenderness	58 (3.5)
Metrorrhagia	56 (3.4)
Acne	55 (3.3)
Abnormal Pap smear	50 (3.0)
Fungal infection	44 (2.7)
Abdominal pain	42 (2.5)
Influenza	40 (2.4)
Vomiting	40 (2.4)
Pharyngitis streptococcal	39 (2.3)
Vulvovaginal mycotic infection	38 (2.3)
Bronchitis	36 (2.2)
Anxiety	35 (2.1)
Depression	33 (2.0)

Source: CSR, Page 83, Table 20

Medical Reviewer's Comments

- *A total of 134 of the above AEs were classified as severe in intensity. These severe AEs were reported in 101 subjects (6.1%). The most commonly occurring severe AEs were migraine (11 subjects, 0.5%), headache (9 subjects, 0.5%), dysmenorrhea (6 subjects, 0.4%), and abdominal pain (6 subjects, 0.4%).*

- *A total of 172 subjects (10.4%) discontinued the trial due to a treatment-emergent AE (see Table 23).*
- *AEs classified as respiratory, thoracic and mediastinal disorders were the most frequently reported (23.1%). These included upper respiratory infections, sinusitis, and nasopharnygitis.*

Table 25 Most Commonly Reported Treatment-Related AEs, (N=1,660)

AE Preferred Term	Number (%) of Subjects
Number of subjects with at least one treatment-related AE	442 (26.6)
Headache	79 (4.8)
Metrorrhagia	54 (3.3)
Nausea	53 (3.2)
Breast tenderness	50 (3.0)
Weight Fluctuation	48 (4.8)
Dysmenorrhea	42 (2.5)
Acne	35 (2.1)
Mood swings	23 (1.4)
Migraine	14 (0.8)
Abdominal distension	13 (0.8)
Libido decreased	13 (0.8)
Depression	12 (0.7)

Source: CSR, Page 86, Table 23

Medical Reviewer's Comment

- *The above most common treatment-related AEs, as determined by the Applicant, are those generally associated with OC use.*

7.4.2 Laboratory Findings

Clinical laboratory tests were performed at the Screening Visit and at study completion and included the following:

- Serum Chemistry: Sodium, potassium, calcium, chloride, glucose, uric acid, creatinine, blood urea nitrogen, ALT, AST, total protein, albumin, cholesterol, triglycerides, alkaline phosphatase, gamma glutamyl transferase (GGT), lactate dehydrogenase (LDH), and inorganic phosphorus.
- Hematology: Hemoglobin, hematocrit, red blood cell count, platelets, white blood cell count and differential.
- Urinalysis: pH, ketones, protein, occult blood, and glucose.

During the phase 1 studies, no abnormal laboratory values were classified as AEs and none were deemed clinically significantly abnormal.

During the phase 3 study, a total of 161 abnormal laboratory test results in 67 subjects in the All Treated population were considered clinically significant by the investigator. Of these, 24 in 21 subjects were positive pregnancy tests. The remainder included mostly elevated cholesterol and triglycerides; and moderately elevated AST, ALT, and GGT. Slightly reduced hemoglobin and hematocrit were also common.

Medical Reviewer's Comments

- *A total of 46 subjects had abnormal laboratory tests unrelated to pregnancy testing. None of these subjects was withdrawn from the trial based on these tests.*
- *An abnormal laboratory test reported as an adverse event occurred in 50 of the 1,660 study subjects (3%).*

7.4.3 Vital Signs

No clinically significant mean changes in vital signs were noted during the course of the primary phase 3 study for the All Treated population. Nine subjects were discontinued because of weight gain and 4 subjects were discontinued for hypertension. Three subjects had an increase in blood pressure (one of which was considered as possibly related to study drug), and two subjects had an increase in heart rate (considered not related to study drug).

Six subjects had vital signs measurements reported as AEs:

- Three subjects with blood pressure increased (one of which was considered as possibly related to study drug)
- Two subjects with heart rate increased (considered not related to study drug)
- Two subjects with weight decreased (not related to study drug).

Table 26 Vital Signs, Mean Change from Baseline

	Baseline Mean	End of Treatment	Mean Change
Mean Systolic Blood Pressure (mmHg)	112.9	114.0	0.9
Mean Diastolic Blood Pressure (mmHg)	71.8	72.7	0.8
Heart Rate	72.5	74.4	1.9
Mean Weight Gain (lbs)	150.2	151.6	1.7

Source: Adapted from CSR, Table 26, Page 95 and Table 14.3.5, Page 280.

Medical Reviewer's Comments

- *There were no significant changes in vital signs (i.e., systolic and diastolic blood pressure, heart rate, or weight) over time.*
- *There were no clinically significant abnormalities in vital signs that occurred during the trial.*
- *Although treatment-emergent headache occurred in 7.0% of the subjects taking WC3016, there was no indication of unusual blood pressure elevations related to the use of this drug.*

7.4.4 Electrocardiograms (ECGs)

Electrocardiograms were not performed during the phase 3 clinical trial. No significant ECG changes were noted in the phase 1studies.

7.4.5 Special Safety Studies/Clinical Trials

No special safety studies were performed.

7.4.6 Immunogenicity

No immunogenicity studies were performed.

7.5 Other Safety Explorations

7.5.1 Dose Dependency for Adverse Events

Table 26 compares the annual exposures of EE and NA compared to other approved combination OCs.

Table 27 Total Annual Exposure to EE and NA

	Loestrin Fe 1/20	Loestrin Fe 1.5/30	Loestrin 24	WC3016
EE/NA tablet (mg)	0.02/1	0.03/1.5	0.02/1	0.01/1
EE/NA tablets/cycle	21	21	24	24
# of cycles/year	13	13	13	13
EE/NA tablets/year	273	273	312	312
EE alone tablets/cycle	0	0	0	2
EE alone tablet (mg)	0	0	0	0.01
EE alone/year (mg)	0	0	0	0.26
Total EE/year (mg)	5.46	8.19	6.24	3.38
Total NA/year (mg)	273	409.5	312	312

Source: Medical Reviewer

Medical Reviewer's Comments

- *WC3016 contains less EE then any previously approved combined OC.*
- *Minimizing exposure to estrogen and progestin reduces the risk of thrombotic events. For any particular estrogen/progestin combination, the recommended dosage regimen is that which contains the least amount of estrogen and progestin that is compatible with a low pregnancy rate and the medical needs of the individual patient.*

7.5.2 Time Dependency for Adverse Events

Exploration for time dependency of adverse events was not performed.

7.5.3 Drug-Demographic Interactions

This product is indicated for use only in women (b) (4) No other special populations were studied. There is no evidence in the current medical literature that the safety or efficacy of OCs is significantly affected by race or ethnicity.

Medical Reviewer's Comment

- *Twenty-nine percent (8 of the 28 "on-drug" pregnancies) occurred in the Hispanic population, which comprised 9.8% (155 / 1270) of the subjects in the PITT cohort. The reason for the disproportionally high PI in this subgroup is not entirely clear but is probably related to the low sample size rather than a true effect.*

7.5.4 Drug-Disease Interactions

No drug-disease interactions were studied.

7.5.5 Drug-Drug Interactions

No drug-drug interaction studies were performed for this NDA application. Class labeling for OCs includes a section on drug-drug interactions, which will be included in the WC3016 label.

Medical Reviewer's Comments

- *Both In vitro and in vivo studies have shown that estrogens are metabolized partially by cytochrome P450 3A4 (CYP3A4).*
- *Inducers of CYP3A4 may reduce plasma concentrations of estrogens, possibly resulting in a decrease in therapeutic effects and/or changes in the uterine bleeding profile.*
- *Inhibitors of CYP3A4 may increase plasma concentrations of estrogens, which may result in result in side effects.*

7.6 Additional Safety Evaluations

7.6.1 Human Carcinogenicity

No human carcinogenicity trials were indicated or performed. Class labeling for OCs discusses potential associations with malignancies (breast, cervix).

7.6.2 Human Reproduction and Pregnancy Data

No human reproduction or pregnancy data was required for this NDA. No fetal or maternal toxicity has been attributed to the NA/EE combination therapy found in oral contraceptives.

7.6.3 Pediatrics and Assessment of Effects on Growth

All applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

(b) (4)

Medical Reviewer's Comments

- *A partial waiver for premenarchal girls is recommended.*
- *The pediatric study requirement will be met by extrapolation from the trial data obtained on adult women in this development program, demonstrating that WC3016 is safe and effective.*
- *The Division's recommendations regarding the partial waiver for premenarchal girls and data extrapolation from adult to postpubertal females has been accepted by the Pediatric Review Committee (PeRC).*

7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound

There is no known withdrawal or abuse potential for NA/EE. The potential for either intentional or accidental overdose with WC3016 is viewed as unlikely, and probably would not cause serious effects even if it occurred.

7.7 Additional Submissions / Safety Issues

A Four-Month Safety Update was received on 7/23/09 (SDN-4). There were no new or ongoing nonclinical or clinical studies conducted at the time of the submission. Therefore, no new significant safety issues were identified.

8 Postmarket Experience

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.

9 Appendices

9.1 Literature Review/References

No literature review was performed.

9.2 Labeling Recommendations

The proposed label underwent revisions mainly to harmonize the label with the existing PLR label for oral contraceptives. Major clinical revisions were made in Section 4 CONTRAINDICATIONS, Section 5 WARNINGS AND PRECAUTIONS, Section 6 ADVERSE REACTIONS and in Section 17 PATIENT COUNSELING INFORMATION. Recommendations regarding these label changes have been communicated to the Applicant.

Medical Reviewer's Comments

- *Numerous suggestions regarding the label were made by DDMAC. Some of the traditional language of prior OC labels was revised in order to make the label less complex, more concise and more readable, An effort was made in several sections to refer to the product name instead of the generic term "birth control pills."*
- *The consultation requested from DRISK is still pending.*

9.3 Advisory Committee Meeting

This drug product was not an NME and did not raise any major safety concerns. No Advisory Committee meeting was indicated or held.

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22501	ORIG-1	WARNER CHILCOTT CO INC	(b) (4)

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
01/08/2010

LISA M SOULE
01/09/2010
I concur with Dr. Orleans' conclusion that, from a clinical perspective, NDA 22-501 can be approved.

CLINICAL FILING CHECKLIST FOR A NEW NDA/BLA

NDA Number: 22-501 **Applicant: Warner Chilcott** **Stamp Date: 03/26/2009**

Drug Name: (b) (4) **NDA Type: 505(b)(1) Standard Review** **PDUFA Goal Date: 01/26/2010**

	Content Parameter	Yes	No	NA	Comment
FORMAT/ORGANIZATION/LEGIBILITY					
1.	Identify the general format that has been used for this application, e.g. electronic CTD.	X			eCTD (not Global Summit Review enabled) and paper components (97 volumes)
2.	On its face, is the clinical section of the application organized in a manner to allow substantive review to begin?	X			Well organized.
3.	Is the clinical section of the application indexed (using a table of contents) and paginated in a manner to allow substantive review to begin?	X			
4.	For an electronic submission, is it possible to navigate the application in order to allow a substantive review to begin (*e.g.*, are the bookmarks adequate)?	X			
5.	Are all documents submitted in English, or are English translations provided when necessary?	X			
6.	On its face, is the clinical section of the application legible so that substantive review can begin?	X			
LABELING					
7.	Has the applicant submitted draft labeling in electronic format consistent with 21 CFR 201.56[1] and 201.57 (or 21 CFR Subpart C for OTC products), current divisional and Center policies, and the design of the development package?	X			Module 1.14
SUMMARIES					
8.	Has the applicant submitted all the required discipline summaries (*i.e.*, Module 2 summaries)?	X			Chemistry submitted but no non-clinical pharmacology and toxicology information provided. Reference to Warner Chilcott NDA 21-871 for Loestrin® 24 Fe
9.	Has the applicant submitted the integrated summary of safety (ISS)?		X		Only one phase 3 study included in the submission
10.	Has the applicant submitted the integrated summary of efficacy (ISE)?		X		Only one phase 3 study included in the submission
11.	Has the applicant submitted a benefit-risk analysis for the product?	X			
12.	Indicate if the Application is a 505(b)(1) or a 505(b)(2). If Application is a 505(b)(2) and if appropriate, what is the reference drug?			X	Application filed as a 505(b)(1)
DOSE					
13.	If needed, has the sponsor made an appropriate attempt to			X	Dose ranging studies

[1] http://www.access.gpo.gov/nara/cfr/waisidx_01/21cfr201_01.html

CLINICAL FILING CHECKLIST FOR A NEW NDA/BLA

	Content Parameter	Yes	No	NA	Comment
	determine the correct dosage and schedule for this product (*i.e.*, appropriately designed dose-ranging studies)? Study Number: Study Title: Sample Size: Arms: Location in submission:				are not necessary for this product.
EFFICACY					
14.	On its face, do there appear to be the requisite number of adequate and well-controlled studies in the application?	X			Pivotal Study: Protocol PR-05806 Indication: Prevention of pregnancy in women who elect to use oral contraceptives as a method of contraception
15.	Do all pivotal efficacy studies appear to be adequate and well-controlled within current divisional policies (or to the extent agreed to previously with the applicant by the Division) for approvability of this product based on proposed draft labeling?	X			
16.	Do the endpoints in the pivotal studies conform to previous Agency commitments/agreements? Indicate if there were not previous Agency agreements regarding primary/secondary endpoints.	X			Division commented on statistical analysis for the primary study endpoints on 11/08/2006.
17.	Has the application submitted a rationale for assuming the applicability of foreign data to U.S. population/practice of medicine in the submission?			X	
SAFETY					
18.	Has the applicant presented the safety data in a manner consistent with Center guidelines and/or in a manner previously requested by the Division?	X			
19.	Has the applicant submitted adequate information to assess the arythmogenic potential of the product (*e.g.*, QT interval studies, if needed)?			X	
20.	Has the applicant presented a safety assessment based on all current worldwide knowledge regarding this product?			X	
21.	For chronically administered drugs, have an adequate number of patients (based on ICH guidelines for exposure[2]) been exposed at the dose (or dose range) believed to be efficacious?	X			-At least 200 subjects completing 13 cycles -Minimum of 10,000 28-day cycles
22.	For drugs not chronically administered (intermittent or short course), have the requisite number of patients been exposed as requested by the Division?			X	
23.	Has the sponsor submitted the coding dictionary[3] used for mapping investigator verbatim terms to preferred terms?	X			MedDRA coding dictionary (Version

[2] For chronically administered drugs, the ICH guidelines recommend 1500 patients overall, 300-600 patients for six months, and 100 patients for one year. These exposures MUST occur at the dose or dose range believed to be efficacious.

[3] The "coding dictionary" consists of a list of all investigator verbatim terms and the preferred terms to which they were mapped. It is most helpful if this comes in as a SAS transport file so that it can be sorted

CLINICAL FILING CHECKLIST FOR A NEW NDA/BLA

	Content Parameter	Yes	No	NA	Comment
					11.0)
24.	Has the sponsor adequately evaluated the safety issues that are known to occur with the drugs in the class to which the new drug belongs?	X			
25.	Have narrative summaries been submitted for all deaths and adverse dropouts (and serious adverse events if requested by the Division)?	X			
OTHER STUDIES					
26.	Has the applicant submitted all special studies/data requested by the Division during the pre-submission discussions with the sponsor?			X	
27.	For Rx-to-OTC switch and direct-to-OTC applications, are the necessary consumer behavioral studies included (*e.g.*, label comprehension, self selection and/or actual use)?			X	
PEDIATRIC USE					
28.	Has the applicant submitted the pediatric assessment, or provided documentation for a waiver and/or deferral?	X			Module 1.9.1
ABUSE LIABILITY					
29.	If relevant, has the applicant submitted information to assess the abuse liability of the product?			X	
FOREIGN STUDIES					
30.	Has the applicant submitted a rationale for assuming the applicability of foreign data in the submission to the U.S. population?			X	Sites for the primary study are all in the US
DATASETS					
31.	Has the applicant submitted datasets in a format to allow reasonable review of the patient data?	X			
32.	Has the applicant submitted datasets in the format agreed to previously by the Division?	X			
33.	Are all datasets for pivotal efficacy studies available and complete for all indications requested?	X			
34.	Are all datasets to support the critical safety analyses available and complete?	X			
35.	For the major derived or composite endpoints, are all of the raw data needed to derive these endpoints included?	X			
CASE REPORT FORMS					
36.	Has the applicant submitted all required Case Report Forms in a legible format (deaths, serious adverse events, and adverse dropouts)?	X			
37.	Has the applicant submitted all additional Case Report Forms (beyond deaths, serious adverse events, and adverse drop-outs) as previously requested by the Division?	X			
FINANCIAL DISCLOSURE					
38.	Has the applicant submitted the required Financial Disclosure information?	X			Module 1.3.4.2
GOOD CLINICAL PRACTICE					
39.	Is there a statement of Good Clinical Practice; that all clinical studies were conducted under the supervision of an	X			Module 5.3.5.2

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as needed; however, if it is submitted as a PDF document, it should be submitted in both directions (verbatim -> preferred and preferred -> verbatim).

CLINICAL FILING CHECKLIST FOR A NEW NDA/BLA

	Content Parameter	Yes	No	NA	Comment
	IRB and with adequate informed consent procedures?				
CONCLUSION					
40.	From a clinical perspective, is this application fileable? If not, please state why.	X			From a clinical perspective, this application is fileable

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

Potential Review Issues:

- Recalculation of the Pearl Index based on the Division's definition of "on-drug pregnancies." The Division defines "on-drug pregnancies" as all conceptions occurring from Day 1 (the initiation of taking study drug) to 7 days after the conclusion of the final pill packet.

Ronald J. Orleans, M.D. April 30, 2009

Reviewing Medical Officer Date

Lisa M. Soule, M.D. May 5, 2009

Clinical Team Leader Date

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

/s/

Ronald Orleans
5/5/2009 04:06:42 PM
MEDICAL OFFICER

Lisa Soule
5/5/2009 04:46:31 PM
MEDICAL OFFICER