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RESEARCH**

*APPLICATION NUMBER:*

**204654Orig1s000**

**MEDICAL REVIEW(S)**

**CLINICAL REVIEW**

Application Type	NDA
Application Number(s)	204654
Priority or Standard	Standard
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Division / Office	DBRUP/ODE III
Reviewer Name(s)	Daniel Davis, MD
Review Completion Date	June 28, 2013
Established Name	norethindrone acetate/ethinyl estradiol (EE) chewable tablets, ethinyl estradiol tablets and ferrous fumarate (FF) tablets
(Proposed) Trade Name	to be determined
Therapeutic Class	Hormonal contraception
Applicant	Warner Chilcott Company, LLC
Formulation(s)	Chewable tablet; tablet
Dosing Regimen	1 active chewable tablet for 24 days; 1 EE tablet for 2 days; 1 iron tablet for 2 days
Indication(s)	Prevention of pregnancy
Intended Population(s)	Women of reproductive age

## Table of Contents

<b>1</b>	<b>RECOMMENDATIONS/RISK BENEFIT ASSESSMENT .....</b>	<b>5</b>
1.1	Recommendation on Regulatory Action .....	5
1.2	Risk Benefit Assessment.....	5
1.3	Recommendations for Postmarket Risk Evaluation and Mitigation Strategies ...	5
1.4	Recommendations for Postmarket Requirements and Commitments .....	5
<b>2</b>	<b>INTRODUCTION AND REGULATORY BACKGROUND .....</b>	<b>6</b>
2.1	Product Information .....	6
2.2	Tables of Currently Available Treatments for Proposed Indications .....	6
2.3	Availability of Proposed Active Ingredient in the United States .....	7
2.4	Important Safety Issues with Consideration to Related Drugs.....	7
2.5	Summary of Presubmission Regulatory Activity Related to Submission .....	8
2.6	Other Relevant Background Information .....	8
<b>3</b>	<b>ETHICS AND GOOD CLINICAL PRACTICES.....</b>	<b>8</b>
3.1	Submission Quality and Integrity .....	8
3.2	Compliance with Good Clinical Practices .....	9
3.3	Financial Disclosures.....	9
<b>4</b>	<b>SIGNIFICANT EFFICACY/SAFETY ISSUES RELATED TO OTHER REVIEW DISCIPLINES .....</b>	<b>9</b>
4.1	Chemistry Manufacturing and Controls .....	9
4.2	Clinical Microbiology.....	9
4.3	Preclinical Pharmacology/Toxicology .....	10
4.4	Clinical Pharmacology .....	10
4.4.1	Mechanism of Action.....	10
4.4.2	Pharmacodynamics.....	10
4.4.3	Pharmacokinetics.....	10
<b>5</b>	<b>SOURCES OF CLINICAL DATA.....</b>	<b>11</b>
5.1	Tables of Studies/Clinical Trials .....	11
5.2	Review Strategy .....	11
5.3	Discussion of Individual Studies/Clinical Trials.....	11
5.3.1	Bioavailability and Food Effect Study PR-12111 .....	11
5.3.2	Oral Irritation Study PR-10007 (Report RR-01708).....	13
<b>6</b>	<b>REVIEW OF EFFICACY .....</b>	<b>18</b>
	Efficacy Summary .....	18
6.1	Indication .....	19
6.1.1	Methods .....	19
<b>7</b>	<b>REVIEW OF SAFETY.....</b>	<b>19</b>
	Safety Summary .....	19
7.1	Methods.....	19

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7.1.1	Studies/Clinical Trials Used to Evaluate Safety .....	19
7.1.2	Categorization of Adverse Events .....	20
7.1.3	Pooling of Data Across Studies to Estimate and Compare Incidence .....	20
7.2	Adequacy of Safety Assessments .....	21
7.2.1	Overall Exposure at Doses/Durations and Demographics .....	21
7.2.2	Explorations for Dose Response.....	21
7.2.3	Special Animal and/or In Vitro Testing .....	21
7.2.4	Routine Clinical Testing .....	21
7.2.5	Metabolic, Clearance, and Interaction Workup .....	21
7.2.6	Evaluation for Potential Adverse Events for Similar Drugs in Drug Class ..	21
7.3	Major Safety Results .....	21
7.3.1	Deaths.....	21
7.3.2	Nonfatal Serious Adverse Events .....	22
7.3.3	Dropouts and/or Discontinuations .....	22
7.4	Supportive Safety Results .....	22
7.4.1	Common Adverse Events .....	22
7.4.2	Laboratory Findings .....	23
7.4.3	Vital Signs .....	23
7.4.4	Electrocardiograms (ECGs) .....	23
7.4.5	Special Safety Studies/Clinical Trials .....	23
7.4.6	Immunogenicity .....	23
7.5	Other Safety Explorations.....	23
7.5.1	Dose Dependency for Adverse Events .....	23
7.5.2	Time Dependency for Adverse Events.....	23
7.5.3	Drug-Demographic Interactions .....	23
7.5.4	Drug-Disease Interactions.....	24
7.5.5	Drug-Drug Interactions.....	24
7.6	Additional Safety Evaluations .....	24
7.6.1	Human Carcinogenicity .....	24
7.6.2	Human Reproduction and Pregnancy Data.....	24
7.6.3	Pediatrics and Assessment of Effects on Growth .....	24
7.6.4	Overdose, Drug Abuse Potential, Withdrawal and Rebound.....	24
7.7	Additional Submissions / Safety Issues .....	24
7.7.1	4-Month Safety Update and Annual Report .....	24
<b>8</b>	<b>POSTMARKET EXPERIENCE.....</b>	<b>25</b>
<b>9</b>	<b>APPENDICES .....</b>	<b>25</b>
9.1	Literature Review/References .....	25
9.2	Labeling Recommendations .....	25
9.3	Advisory Committee Meeting.....	26

## Table of Tables

Table 1: Summary of Relevant Clinical Studies .....	11
Table 2: Visit Schedule for Study 10007 .....	15
Table 3: Demographics in Study 10007 .....	16
Table 4: Number (%) of Subjects with Gingival Irritation and Inflammation.....	17
Table 5: Common Adverse Events in Study 10007 (N = 56) .....	18

## List of Abbreviations and Definitions

AE	Adverse event
BMI	Body mass index
CI	Confidence interval
CHC	Combination hormonal contraceptive
COC	Combination oral contraceptive
DBRUP	Division of Bone, Reproductive and Urologic Products
EE	Ethinyl estradiol
FDA	Food and Drug Administration
FF	Ferrous fumarate
GCP	Good clinical practice
NETA	Norethindrone acetate
NDA	New Drug Application
NE	Norethindrone
OC	Oral contraceptive
ODE III	Office of Drug Evaluation III
OSI	Office of Scientific Investigation
PI	Pearl Index
SAE	Serious adverse event
VTE	Venous thromboembolism

## **1 Recommendations/Risk Benefit Assessment**

### **1.1 Recommendation on Regulatory Action**

From a clinical perspective, this reviewer recommends approval of NETA/EE chewable tablets containing norethindrone acetate (NETA) 1.0 mg and ethinyl estradiol (EE) 10 mcg for the Applicant's proposed indication of "for use by women to prevent pregnancy." The new product will be marketed as a 28-day regimen.

### **1.2 Risk Benefit Assessment**

The risk benefit profile for NETA and EE has been well established for many years and the current product contains the same amount and types of active hormones as Lo Loestrin Fe, approved on 10-21-10 under NDA 22-501.

The Pearl Index (PI) 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 PI calculation. A total of 1,270 subjects took the study medication over 12,482 completed 28-day cycles and 28 pregnancies occurred. The PI 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 supported the efficacy in preventing pregnancy.

### **1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies**

No special phase 4 postmarketing studies or risk management steps are recommended. The long-term safety of NETA and EE combination products (including Loestrin 24 Fe and Loestrin 21 products) has been well established over the past 30 years. There is no reason to expect a different safety profile for this new chewable formulation that has been shown to be bioequivalent to the marketed Lo Loestrin Fe oral tablets.

### **1.4 Recommendations for Postmarket Requirements and Commitments**

None are recommended.

## 2 Introduction and Regulatory Background

### 2.1 Product Information

The Applicant is seeking approval of a chewable combination oral contraceptive (COC) with the same dosage and regimen as found in the approved product Lo Loestrin Fe. The approved product contains the active hormones NETA (1.0 mg) and EE (10 mcg). Following 24 days of active hormone use (chewed and swallowed with 240 mL water), the patient then takes 2 days of EE 10 mcg tablets (swallowed) and 2 days of ferrous fumarate (75 mg) tablets (swallowed).

#### Reviewer's comment:

In this review, the study drug will be referred to either (b) (4) 1/10 chewable tablet (the name during development) or NETA/EE (the established name, as an acceptable tradename has not yet been submitted) and the currently marketed product will be referred to as Lo Loestrin Fe. The main benefit for chewable COCs is ease of use for patients who have a difficulty swallowing tablets.

### 2.2 Tables of Currently Available Treatments for Proposed Indications

Contraceptive methods for females include:

- Barrier methods (condom, diaphragm, cervical cap)
- COCs
- Progestin-only oral contraceptives
- Intrauterine devices (levonorgestrel-containing and copper-containing)
- Injectable contraceptives
- Contraceptive implants
- Contraceptive vaginal rings
- Surgical sterilization (tubal ligation, intratubal obstructive devices)

Over the past 40 years there have been several FDA-approved COCs containing norethindrone (NE) or NETA and EE on the US market. Many are now generic versions of the original products. For example, Loestrin FE 1.5/30 containing 1.5 mg NETA and 0.030 mg EE was approved in April 1973. Ovcon-50, containing 1 mg NETA and 0.050 mg EE, was approved under NDA 17-576 on August 28, 1975. Ovcon-35 (0.4 mg NETA and 0.035 mg EE tablets) was approved under NDA 17-716 by the FDA on March 29, 1976.

For the combination of EE and NETA, the Applicant has the following approved products:

- Loestrin FE 1.5/30 (EE = 0.03 mg / NETA = 1.5 mg x 21 days, then 7 days placebo ferrous fumarate) (NDA 17-355 approved 4-30-73)
- Loestrin FE 1/20 (EE = 0.02 mg / NETA = 1.0 mg x 21 days, then 7 days placebo ferrous fumarate) (NDA 17-354 approved 4-30-73)

- Loestrin 21 1.5/30 (EE = 0.03 mg / NETA = 1.5 mg. x 21 days, then 7 days placebo) (NDA 17-875 approved 10-1-76)
- Loestrin 21 1/20 (EE = 0.02 mg / NETA = 1.0 mg x 21 days, then 7 days placebo) (NDA 17-876)
- Estrostep 21/Fe (EE = 0.02 mg / NETA = 1.0 mg x 5 days, EE = 0.03 mg / NETA = 1.0 mg x 7 days, EE = 0.035 mg / NETA = 1.0 mg x 9 days, then 7 days placebo ferrous fumarate) (NDA 20-130 approved 10-09-96 and NDA 21-276)
- Loestrin 24 FE (EE = 0.02 mg / NETA = 1.0 mg x 24 days and 4 days placebo ferrous fumarate) (NDA 21-871 approved 2-17-06)
- Lo Loestrin FE (EE = 0.01 mg / NETA = 1.0 mg x 24 days, then 2 days of EE 0.01 mg, then 2 days of placebo ferrous fumarate) (NDA 22-501 approved 10-21-10)
- Minastrin 24 Fe soft gel capsules (EE = 0.02 mg / NETA = 1.0 mg x 24 days and 4 days placebo ferrous fumarate) (NDA 204426 approved 4-19-13)
- Chewable Tablets (EE = 0.02 mg / NETA = 1.0 mg x 24 days and 4 days placebo ferrous fumarate) (NDA 203667 approved 5-8-13)

### 2.3 Availability of Proposed Active Ingredient in the United States

NETA and EE are readily available and have been since 1968. COCs including the aforementioned products are produced by a number of different manufacturers. Most of these products are currently available as generics, except for the ones approved in the past 2-3 years.

### 2.4 Important Safety Issues with Consideration to Related Drugs

COCs as a general class have a number of safety issues that have been well-recognized since their introduction in the 1960s. The following adverse events represent the major concerns described in contraceptive labeling:

- Vascular events, which may be fatal, including:
  - Deep venous thrombosis (DVT), pulmonary embolism (PE), other venous thromboses
  - Myocardial infarction (especially in women >35 years who smoke)
  - Cerebrovascular accidents (CVA): Strokes (both ischemic and hemorrhagic types have been reported)
- Hepatic adenomas, hepatic (b) (4) cholestasis
- Blood pressure increase
- Gallbladder disease
- Headaches
- Irregular uterine bleeding, amenorrhea, oligomenorrhea
- Nausea

- Breast tenderness
- Mood changes
- Hypertriglyceridemia

## 2.5 Summary of Presubmission Regulatory Activity Related to Submission

There were no presubmission regulatory activities specific to this NDA. Based on prior experience and similar submissions to the Division (NDA 21-490, Ovcon chewable tablet, approved on November 14, 2003; (b) (4); NDA 203667, (b) (4) 24 Fe chewable tablet, approved on May 8, 2013), the Applicant was aware of the studies needed for approval of a different formulation of an approved COC. The Division recommended to the Applicant at a previous meeting concerning a (b) (4) that an oral irritation study would be required. There was also discussion relating to (b) (4)

## 2.6 Other Relevant Background Information

The proposed regimen, and consequently the exposure to NETA and EE, is the same as the approved regimen for Warner Chilcott's Lo Loestrin 24 Fe (NETA and EE tablets USP and ferrous fumarate tablets) which received approval as an oral contraceptive on October 21, 2010 under NDA 022501. The application contains results of Study PR-12111 (Report RR-04612), which show that (b) (4) 1/10 chewable tablets are bioequivalent to Lo Loestrin Fe tablets and can be taken without regard to meals.

The same 10 mcg EE tablets, referred to in this NDA as WC3016 EE10 tablets, that are used in Lo Loestrin Fe will be used for the administration of 10 mcg EE over two days (Days 25-26) and swallowed (not chewed). This is reflected in the proposed container labeling and proposed labeling text. Although the application provides results of Study PR-12011 (Report RR-04512) which compared the bioavailability of (b) (4) EE10 chewable tablets chewed to WC3016 EE10 tablets swallowed, it should be noted that the EE10 chewable tablets are not proposed for the to-be-marketed product. Results of Study PR-12011 are included by the Sponsor only in order to provide complete safety information for this NDA submission.

## 3 Ethics and Good Clinical Practices

### 3.1 Submission Quality and Integrity

There are no issues concerning the quality and integrity of the submission and the studies submitted with this NDA. The Office of Scientific Investigations (OSI) made inspections of the clinical and bioanalytical study sites for the clinical pharmacology studies and found no significant deficiencies.

### 3.2 Compliance with Good Clinical Practices

The submission quality and compliance of the clinical study 10007 (oral irritability) appears acceptable. The clinical pharmacology studies were in compliance with Good Clinical Practices (GPC) and appropriate consent forms were signed.

### 3.3 Financial Disclosures

All investigators who participated in Studies PR-12011, PR-12111 and PR-10007 certified to not having a financial interest. In addition, all investigators who participated in Studies PR-14106 and PR-14206 previously conducted in support of NDA 22-501 for Lo Loestrin Fe also certified to not having a financial interest. Therefore, there are no financial disclosures that need reviewing.

## 4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

### 4.1 Chemistry Manufacturing and Controls

The (b) (4) 1/10 chewable tablet formulation was based on the approved formulation for Lo Loestrin Fe 1 mg NETA/10 mcg EE tablets (referred to in the NDA as **WC3016 1/10 tablets** or by its formulation **WC3016-21C tablets**); a flavor and sweetener were added to (b) (4) 1/10 chewable tablets. The WC3016 EE10 tablets are identical to the marketed Lo Loestrin Fe 10 mcg EE tablets. The drug product is provided in a (b) (4) blister pack. The chewable combination tablets are contained in the first 24 wells of the blister pack, while the nonchewable EE tablets are contained in blister wells 25-26 and the inert, nonchewable FF tablets are in blister wells 27-28. The blister packaging is the same as used in the approved product under NDA 22501.

The FDA chemist Gene Holbert, PhD reviewed the data and concluded on 6-18-13 from the ONDQA perspective that:

“The applicant of this NDA has provided sufficient CMC information to assure the identity, strength, purity, and quality of the drug product.”

In his review he did note that:

- The Office of Compliance has **not** issued an overall “**Acceptable**” recommendation for the facilities involved in the NDA as of the date of this review.
- Labels/labeling issues have **not** yet been resolved.

### 4.2 Clinical Microbiology

There is no clinical microbiology report because it is not required for this oral tablet.

### 4.3 Preclinical Pharmacology/Toxicology

The preclinical review was done by Krishan Raheja, PhD, and completed on 4-19-13. Both NETA and EE are synthetic hormones that are widely used as components of both COCs and hormone replacement therapy. Also, the daily doses of NETA and EE proposed in the present application are found in currently approved COCs. The inactive ingredients used in the 24 active tablets, EE tablets, and in the ferrous fumarate tablets are compendial or Generally Recognized as Safe (GRAS) and are listed in the FDA's Inactive Ingredients Database. Dr. Raheja concludes: "Pharmacology/Toxicology recommends approval of (b) (4) under NDA 204654 for the indication of prevention of pregnancy."

#### **Reviewer's comment:**

**I concur with Dr. Raheja's recommendation.**

### 4.4 Clinical Pharmacology

Li Li, Ph.D. had the following recommendation in her primary review dated June 20, 2013:

"The Office of Clinical Pharmacology/Division of Clinical Pharmacology 3 (OCP/DCP3) finds NDA 204654 acceptable provided that agreement is reached between the Sponsor and the Division regarding the language in the package insert".

#### 4.4.1 Mechanism of Action

COCs lower the risk of becoming pregnant primarily by suppressing ovulation. Other possible mechanisms may include cervical mucus changes that inhibit sperm penetration and endometrial changes that reduce the likelihood of implantation.

#### 4.4.2 Pharmacodynamics

No specific pharmacodynamic studies were conducted for this NDA submission.

#### 4.4.3 Pharmacokinetics

In Study PR-12111 it was shown that the to-be-marketed chewable tablets are bioequivalent to the active combination Lo Loestrin Fe tablets.

#### **Reviewer's comment:**

**On 6-20-13, the clinical pharmacology review was completed by Li Li, PhD. Her recommendation follows:**

**"The Office of Clinical Pharmacology (OCP)/Division of Clinical Pharmacology 3 (DCP-3) has reviewed NDA 204426 submitted on June 21, 2012, September 11, 2012, and September 27, 2012. The overall Clinical Pharmacology information submitted to support this NDA is acceptable provided that a satisfactory agreement is reached regarding the labeling language."**

I concur with her recommendation.

## 5 Sources of Clinical Data

### 5.1 Tables of Studies/Clinical Trials

Only two clinical studies are relevant to the approval of this NDA submission. Study PR-12111 evaluated the bioavailability and food effect of the chewable (b) (4) tablet and the reference tablet WC3016 containing the combination of NETA and EE. The oral safety study (PR-10007) assessed the potential for oral irritation when tablets containing a higher dose of 1 mg NETA and 20 mcg EE are chewed daily for 24 days.

**Table 1: Summary of Relevant Clinical Studies**

Study	Objective	Design	Enrolled/ Completed	Clinical comment
PR-12111	Bioavailability and food effect	3-way cross-over; single dose single center	42/40	Studied only the NETA/EE chewable tablet
PR-10007	Oral irritation and safety	Open-label, single center	56/52	Studied higher dose NETA/EE

Source: modified from Sponsor's Tabular Listing of All Clinical Studies.

### 5.2 Review Strategy

Because this NDA is a request to approve a different formulation of an approved COC product, the primary requirement is to demonstrate bioequivalence to the reference drug. Most important for the approval are the clinical pharmacology and CMC reviews. All disciplines will review the label to make sure it is complete and accurate.

The clinical review will assess following:

- Oral irritability study
- Safety findings from the clinical pharmacology studies
- 4-month safety update
- Postmarketing safety review and Annual Report for Lo Loestrin Fe

### 5.3 Discussion of Individual Studies/Clinical Trials

#### 5.3.1 Bioavailability and Food Effect Study PR-12111

The chewable tablet formulation has added mint flavor and sweetener with a corresponding reduction in the amount of mannitol. There is one clinical pharmacology study that is critical to the approval of this NDA application. Study PR-12111 (Report

RR-04612) was conducted to compare (b) (4) 1/10 chewable tablets to approved and marketed WC3016 1/10 tablets and to assess the effect of food on the bioavailability of NETA and EE from the 1/10 chewable tablets in healthy female volunteers (median age 35; range 20–45 years). This single-center, randomized, balanced, single-dose, 3-treatment, 3-period, 6-sequence, crossover, comparative bioavailability/food effect study was conducted under medical supervision. Subjects were randomly assigned to receive one of the following 3 treatments in each of 3 treatment periods:

- Treatment A: WC3016 1/10 tablet orally administered under fasted conditions
- Treatment B: (b) (4) 1/10 chewable tablet orally administered under fasted conditions
- Treatment C: (b) (4) 1/10 chewable tablet orally administered with food

All tablets were administered with about 240 mL ambient-temperature water. Treatment periods were separated by at least 7 days. Forty-two (42) subjects were dosed, 40 subjects completed all 3 treatment periods, and 38 were evaluable for pharmacokinetic analysis.

WC3016 1/10 tablets and (b) (4) 1/10 chewable tablets were generally well-tolerated. The chewable tablets were demonstrated to be bioequivalent to WC3016 1/10 tablets (Lo Loestrin Fe).

When (b) (4) 1/10 chewable tablets were administered with food, the rate of NETA and EE absorption was decreased and  $C_{max}$  values were decreased by 46% for NETA and 41% for EE. However, the AUC values for the extent of NETA and EE absorption were not significantly different. The Sponsor concluded that the food effect is not clinically significant and that the 1/10 chewable tablets can be chewed and swallowed or swallowed whole.

**Reviewer's comment:**

**It should be noted that the clinical pharmacology team did not agree that the dosing instructions for the WC3016 tablet can allow an option that the tablet could also be swallowed whole. The bioavailability study specifically did not test the chewable tablet swallowed whole. The approved label will state that the 24 chewable blue tablets should be chewed, swallowed, and then followed immediately by a full glass (8 ounces) of water. This was the same procedure that was used in the study.**

**For a detailed analysis of this studies regarding study design and clinical results, see the Clinical Pharmacology review by Li Li, PhD.**

**There were no safety issues seen with this study which involved 42 subjects taking only 3 single tablets separated by at least 7 days.**

For this pivotal BE study, a formal consult to the Office of Scientific Investigations (OSI) was made on 1-18-13 for inspections of the clinical and bioanalytical study sites. There were no significant objectionable issues identified in the clinical site of the BE study and Form FDA-483 was not issued. Following inspection on the analytical site in (b) (4)

(b) (4) Form FDA-483 was issued on 4-19-13 based on the following observation: “Not all aspects of study conduct were documented. For example: failure to maintain documentation for individual QC sets used during sample processing.”

A written response from (b) (4) to the inspectional findings was received on May 14, 2013. Dr. Adrindam Dasgupta’s OSI consult review, dated 5-30-13 in DARRTS, states the following conclusion:

*Following review and evaluation of the Form FDA-483 observation and response from the analytical site, in my opinion, the clinical and analytical data generated for study PR-12111 were not affected by the cited deficiency. I recommend that the data for clinical and analytical portion of study PR-12111 be accepted for further agency review.*

**Reviewer’s comment:**

**On 6-4-13, Dr. Dasgupta clarified that the “data be accepted for further agency review” meant the data was acceptable for further review by the clinical reviewer (medical officer) and clinical pharmacology reviewer. The OSI review found the data from the clinical and bioanalytical sites to be acceptable.**

Discussion of the safety data from this study is included in the review of pooled safety data in Section 7.3.

### 5.3.2 Oral Irritation Study PR-10007 (Report RR-01708)

**Reviewer’s comment:**

**In order to support the oral safety of (b) (4) 1/10 chewable tablets when chewed, the NDA submission contains the results of Study PR-10007 (Report RR-01708), which assessed the potential for oral irritation when tablets containing 1 mg NETA and the higher dose of 20 mcg EE are chewed and then swallowed for 24 consecutive days. The review in this Section 5.3.2 was done by Jerry Willett, MD as part of the NDA 203667 clinical review for a new chewable formulation of (b) (4) 24 Fe. Dr. Willett’s review focuses on the clinical safety analysis and safety results in this section.**

#### 5.3.2.1 Title

“A Clinical Study to Evaluate the Safety of Loestrin Oral Contraceptive Following Daily Use by Human Female Subjects”

#### 5.3.2.2 Study Objective

The objective of the study was to determine the irritation potential of an oral contraceptive tablet following daily use of the active formulations for 24 days.

#### 5.3.2.3 Study Design

This was an open-label, uncontrolled, single-center study to determine the irritation

potential of the active formulation of an oral contraceptive when chewed daily for 24 days. Subjects were given an oral soft-tissue examination at each visit (Days 3, 8, 24 and 28). This examination consisted of examination pre-dose and 30 minutes after dosing.

#### 5.3.2.4 Inclusion Criteria

- Were females 18 to 45 years of age;
- Were in good general health and had a negative urine pregnancy test at Baseline;
- Were willing to switch to the study product during the course of the study if they were currently using oral, intravaginal, or transdermal combination contraceptives;
- Were willing to use a non-hormonal (e.g., barrier) method of contraception during the period of the clinical study, to be continued for 1 month after stopping use of the experimental medication
- Could read, understand, and sign an informed consent agreement.

#### 5.3.2.5 Exclusion Criteria

- Were currently 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 who were currently on oral, intravaginal or transdermal COC were switched directly to study medication
- Were postmenopausal or perimenopausal (experiencing hot flashes, new menstrual irregularities, etc.);
- Had any visible disease of the oral mucosa (i.e., a score of greater than “1” on the oral soft-tissue examination), which, in the opinion of the investigative personnel, would have interfered with the evaluation;
- Had any finding on the Screening pelvic examination or other clinical evaluations which, in the opinion of the investigator, would have placed the subject at undue risk or otherwise interfered with the interpretation of study results;
- Had a known sensitivity to oral contraceptives;
- Were age 35 or older and smoked;
- Had a contraindication for the use of oral contraceptives (e.g., history of thrombophlebitis or thromboembolic disorders, known or suspected clotting disorders, cerebral vascular or coronary artery disease, known or suspected carcinoma of the breast, known or suspected estrogen-dependent neoplasia, genital bleeding of unknown cause, or a history of benign or malignant liver tumor or liver disorders);
- Had dentures, which, in the opinion of the investigative personnel, would have resulted in reduced oral contact with the investigative drug;
- Had participated in another clinical trial within 1 month prior to Screening, or received an investigational drug within the last 3 months prior to Screening.

Subjects who participated in an oral contraceptive clinical trial, using FDA approved active ingredients, were to be enrolled 2 cycles after completing the preceding study;

- Were receiving systemic or topical drugs or medication which, in the opinion of the investigative personnel, would have interfered with the study results; and/or
- Were females who were pregnant, planning to become pregnant during the study, or were breastfeeding.

### 5.3.2.6 Visit Schedule

The visit schedule is shown in Table 2.

**Table 2: Visit Schedule for Study 10007**

	SCR	Treatment Period					FV
		Day 1		D3	D8	D24	D28
		BLPD	PD30				
Informed consent	X						
Medical history	X						
Entry criteria	X						
Urine pregnancy test		X					X
Pelvic examination	X						
Oral soft-tissue exam	X	X	X	X	X	X	X
Blood pressure/pulse	X	X		X	X	X	X
Product dispensed		X					
Prior or concomitant meds	X	X		X	X	X	X
Adverse events		X	X	X	X	X	X

SCR = screening; BLPD = baseline pre-dose; PD30 = 30 minutes post-dose; D = day; FV = final visit

**Source: Report for Study 10007; page 19 of 498.**

### 5.3.2.7 Oral Soft-Tissue Examination

Oral soft-tissue examinations were performed at Screening, Baseline/Day 1 (pre-dose and 30 minutes after dosing), Day 3, Day 8, Day 24, and Day 28. The oral health investigator evaluated the intra-oral soft tissues for inflammation/irritation, abrasions, and/or infection, and recorded the results on an Oral Soft-Tissue Clinical Examination Form. The condition of the lips, buccal mucosa, labial mucosa, sublingual mucosa, attached gingivae, tongue, hard/soft palate, uvula, and oropharynx were rated as normal or abnormal. Any abnormalities were described, and the examiner indicated whether the abnormality was attributable to the study product. Irritation/inflammation of each area was scored using the following scale:

- 0 = Normal
- 1 = Erythema plus slight edema
- 2 = Moderate erythema and/or edema (i.e., beginning of tissue breakdown or slough)
- 3 = Severe irritation/inflammation (i.e., definite blistering, ulceration, or epithelial slough)

Abrasions reported by the subject or observed by the oral health investigator were also noted as present or absent. Traumatic abrasions as a result of normal everyday chewing, i.e., traumatic abrasions on the labial and buccal mucosa and tongue, were not identified as irritation and were not reported as adverse events. Traumatic abrasions that were deemed clinically significant as a result of chewing the product were reported as adverse events. The locations of the abrasion(s) (i.e., lips, buccal mucosa, labial mucosa, sublingual mucosa, attached gingivae, tongue, hard/soft palate, uvula, and/or oropharynx) were specified and the severity of each abrasion was scored using the following scale:

- 0 = None
- 1 = Mild
- 2 = Moderate
- 3 = Severe

#### 5.3.2.8 Subject Disposition

Of 56 subjects enrolled, 4 discontinued (2 with voluntary withdrawal not related to an adverse event and 2 lost to follow-up). The number of subjects who completed was 52 (92.9%).

#### 5.3.2.9 Demographics

**Table 3: Demographics in Study 10007**

	Subject Data
Age (years)	
Mean (standard deviation)	34.4 (7.8)
Range	19-45
Race origin – N (%)	
Asian	3 (5.4%)
African-American	7 (12.5%)
Caucasian	46 (82.1%)
Ethnic origin – N (%)	
Hispanic or Latina	13 (23.2%)
Non Hispanic or Latina	43 (76.8%)

**Source: Report for Study 10007; page 27 of 498**

#### 5.3.3.10 Efficacy

There were no efficacy determinations in this study.

#### 5.3.2.11 Safety – Extent of Exposure

Of the 52 subjects who completed the study, 7 subjects did not dose as instructed. Four subjects discontinued the study early and therefore received less than the 24-day course of treatment; 2 subjects discontinued after 15 days, 1 after 8 days, and 1 after 6

days from the Baseline (Day 1) Visit. For Subject 55, the tablet count at the end of the Day 24 Visit did not correspond to the diary recording. Subject stated she dosed 23 tablets although the pill-pack had 19 tablets missing. Subject should have dosed an additional 4 tablets.

#### 5.3.2.12 Irritation and Inflammation

For most of the oral regions there was no evidence of any irritation or inflammation throughout the study (lips, buccal mucosa, labial mucosa, sublingual mucosa, tongue, hard/soft palate). The area affected most by irritation and inflammation was the gingivae. However, this was present only as erythema plus slight edema (Score of 1) at Screening and diminished thereafter (see Table 4) to zero. There was one subject with uvular irritation/inflammation at Day 8. There were two instances of irritation/inflammation of the oropharynx (one at Day 3 and the other at Day 8).

**Table 4: Number (%) of Subjects with Gingival Irritation and Inflammation**

Time Period (N)	n (%)	Clinical Comment
Screening (56)	8 (14.3%)	All were scored as 1
Baseline pre-dose (56)	6 (10.7%)	All were scored as 1
30 minutes post dose (56)	6 (10.7%)	All were scored as 1
Day 3 (53)	5 (9.4%)	All were scored as 1
Day 8 (53)	1 (1.9%)	Scored as 1
Day 24 (52)	1 (1.9%)	Scored as 1
Day 28 (53)	0	All subjects were normal

Source: Report for Study 10007; page 28 of 498

**Medical Officer's Comment:**

***The only oral site with notable irritation/inflammation was that of the gingivae and this area actually improved during the study. This reviewer concurs with the applicant that none of the irritation/inflammation findings were clinically significant in regard to the chewable tablets.***

#### 5.3.2.13 Abrasion

There were no subjects with abrasion at any of the oral regions identified in the previous section.

#### 5.3.2.14 Serious Adverse Events (SAEs) and Adverse Events Leading to Discontinuation

There were no deaths, SAEs or adverse events leading to discontinuation.

### 5.3.2.15 Common Adverse Events

There were 13 adverse events reported for 12 subjects. Common adverse events are shown in Table 5.

**Table 5: Common Adverse Events in Study 10007 (N = 56)**

Adverse Event	n (%)
Nasopharyngitis	2 (3.6%)
Laryngeal pain	2 (3.6%)
Influenza	2 (3.6%)
Tooth fracture	2 (3.6%)
Cough	1 (1.8%)
Pharyngitis streptococcal	1 (1.8%)
Tachycardia	1 (1.8%)
Abdominal pain	1 (1.8%)
Heart rate increased	1 (1.8%)

Source: Report for Study 10007; page 69 of 498.

**Medical Officer's Comment:**

***The tooth fractures were not related to the study drug product. Subject 22 broke her tooth while eating a piece of candy. Subject 48 chipped her porcelain crown while eating an orange. The only adverse event in the table that may be potentially related to COCs is that of abdominal pain.***

### 5.3.2.16 Vital Signs

There were no changes of clinical significance during the study

## 6 Review of Efficacy

### Efficacy Summary

The efficacy of the approved reference drug product Lo Loestrin Fe is well-established. Because the chewable tablet has been shown to be bioequivalent to the approved and marketed Lo Loestrin Fe, it is reasonable to assume that the efficacy of the new formulation with new formulation using the exact same dosing regimen will have acceptable efficacy. The Division did not require a separate clinical trial for efficacy and one was not done.

In the Lo Loestrin Fe clinical study, the Pearl Index (PI) was derived from the Pregnancy Intent to Treat cohort (PITT), which consisted of the subset of all treated women ages 18-35 (N=1,270) who were evaluated at least once for pregnancy after beginning the study medication and took the study medication for over 12,480 evaluable completed 28-day cycles. 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. The PI was 2.92 (1.94, 4.21). In support of the product's effectiveness, the life-table analysis was calculated to be 2.71 (1.86, 3.95).

Whether the compliance will be better with this new formulation remains to be shown, but the contraceptive effectiveness should be the same as the approved Lo Loestrin Fe oral tablet, assuming that the new formulation, NETA/EE, is taken as directed.

## 6.1 Indication

NETA/EE is indicated for the prevention of pregnancy [REDACTED] (b) (4)

### 6.1.1 Methods

A clinical trial for contraceptive efficacy was not required for this NDA application.

Efficacy is based on the 10-21-10 approval for NDA 22-501, the original [REDACTED] (b) (4)

[REDACTED] (b) (4) Summary details are stated in the Efficacy Summary above.

## 7 Review of Safety

### Safety Summary

As demonstrated by the pharmacology studies in this NDA submission, the WC3016 chewable tablets are bioequivalent to the marketed Lo Loestrin Fe tablets. Therefore, the systemic safety and efficacy profile of the WC3016 chewable product is presumed to be equivalent to that of the approved reference drug product.

The overall nature and frequency of adverse events seen were consistent with what would be expected in subjects receiving orally administered NETA and EE. No serious adverse events were noted in the submitted studies. The study drug WC3016 chewable tablets were well-tolerated.

Although the number of women exposed to the new chewable formulation for this product was very small, COCs containing NETA and EE have been marketed since 1973. Extensive systemic safety data is available for the specific combination of NETA 0.4 mg and EE 0.035 mg and for several products with higher amounts of NETA (0.5 to 1.0 mg) and the same, lower or higher amounts of EE (0.010 to 0.050 mg). **The subject exposure to the new chewable formulation is adequate under these circumstances.**

### 7.1 Methods

#### 7.1.1 Studies/Clinical Trials Used to Evaluate Safety

The key sections from the NDA 204654 application regarding safety were found in:

- Clinical Overview
- Summary of Clinical Safety

- Study Reports for PR-10007, PR-12111 and PR-14206
- 4-month safety update submitted 1-23-13
- Annual Report for NDA 22501 Lo Loestrin Fe submitted 12-19-12
- Postmarketing safety reports submitted to FDA for Lo Loestrin Fe

### 7.1.2 Categorization of Adverse Events

Two clinical pharmacology studies (12111 and 14206) were used to assess safety for the proposed formulation. A total of 60 women were exposed to the new chewable tablet formulation of NETA/EE tablets in the two studies.

In Bioavailability Study PR-12111, mild adverse events were reported: most common were headache, nausea, vomiting and dizziness. There were no serious adverse events or deaths and the single-dose WC3016 1/10 fasted treatment, (b) (4) 1/10 fasted treatment, and (b) (4) 1/10 fed treatment were generally well-tolerated. Vital signs were stable.

PK Study PR-14206 characterized the plasma NETA and EE PK profiles and SHBG following WC3016 administration for one cycle. All 18 of the enrolled subjects completed the study and received one WC3016 1/10 tablet per day under fasted conditions on Days 1 - 24 and a single WC3016 EE10 tablet per day under fasted conditions on Days 25 – 26. Nine (50%) of the 18 subjects reported a total of 13 adverse events (AEs) over the course of the study, none of which was severe, serious, or unexpected. The most commonly reported AEs were menstrual cramps (3 events in 3 subjects) and headache (2 events in 2 subjects). No subjects were withdrawn due to AE. The Investigator judged 4 AEs to be possibly related to study treatment and the others to be unlikely related to the study treatment. Clinical laboratory values, physical exams, and VSs were within normal limits.

#### **Reviewer's comment:**

**Standard methods were used for the evaluation of adverse events and no unexpected events were observed. Study PR-14206 was not comparative and not required for the approval of this NDA.**

### 7.1.3 Pooling of Data Across Studies to Estimate and Compare Incidence

This was not done and would not be meaningful because of the small number of subjects and the very limited exposure to the study drug in the short clinical pharmacology trials.

## 7.2 Adequacy of Safety Assessments

### 7.2.1 Overall Exposure at Doses/Durations and Demographics

The overall exposure is adequate because of the extensive use of the same product marketed as an oral tablet that is swallowed intact and very similar COC products marketed over the past 45 years.

### 7.2.2 Explorations for Dose Response

None were performed or required.

### 7.2.3 Special Animal and/or In Vitro Testing

None were performed or required.

### 7.2.4 Routine Clinical Testing

All that was critical for this NDA submission was the bioavailability (bioequivalence) study that was performed according to GCP (Good Clinical Practice) guidelines. There were no clinically significant safety findings in the two studies that were reviewed for this NDA approval. The other 3 studies that were submitted were not reviewed in detail because they were not relevant.

### 7.2.5 Metabolic, Clearance, and Interaction Workup

None were performed or required.

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

The most important adverse events when considering the safety of COCs are those of venous thromboembolic and arterial thrombotic events (VTEs and ATEs). There were no VTEs or ATEs in the submitted studies for this application. Common adverse events identified in some of the submitted studies to this application that might be related to the COC class of drugs include nausea, headache, dizziness, and abdominal cramps.

## 7.3 Major Safety Results

### 7.3.1 Deaths

There were no deaths in the studies submitted with this NDA.

### 7.3.2 Nonfatal Serious Adverse Events

There were no SAEs in the studies submitted with this NDA application. The studies (PK, bioavailability, food effect, and oral irritation) were not of sufficient size or duration to expect to see any SAEs or have meaningful data about the incidence of less serious or common adverse events.

#### **Reviewer's comment:**

**I concur with the Applicant's conclusion that: "The overall nature and frequency of AEs seen in the studies were consistent with what would be expected in subjects receiving orally administered NETA and EE. No serious AEs were noted. (b) (4) tablets administered with food or fasted were generally well tolerated."**

### 7.3.3 Dropouts and/or Discontinuations

Dropouts and discontinuations from Study 12111 were for minor reasons: a positive urine drug screen (she was not treated), failure to return, and one subject with headache and vomiting judged to be mild and possibly related to study treatment.

## 7.4 Supportive Safety Results

The Applicant submitted the following documents as supportive safety results:

1. The 120-day safety update [Safety Information Amendment] was submitted to the NDA on 1-23-13. No new significant information is reported that may reasonably affect the statement of Contraindications, Warnings and Precautions, and Adverse Reactions in the proposed labeling.
2. The most recent annual report for NDA 22501 (Lo Loestrin Fe) was submitted on 12-19-12.
3. NDA 204426 cross-references Warner Chilcott's NDA 21871 for Loestrin 24 Fe in support of the safety and efficacy of NETA and EE.
4. NDA submission Section 5.4 contains the submitted literature references.

#### **Reviewer's comment:**

**The above documents were reviewed and show no new significant safety signals or concerns for Lo Loestrin Fe or the other COC products containing NETA and EE. There is no current marketing of the chewable (b) (4) tablet anywhere in the world. If approved, this will be the first approval of this dosage as a chewable tablet.**

### 7.4.1 Common Adverse Events

These are expected to be the same for the chewable tablet as the reference drug. Therefore, the final approved label will mirror the Lo Loestrin Fe label.

#### 7.4.2 Laboratory Findings

No out-of-range laboratory values were classified as AEs or deemed to be clinically significantly abnormal.

**Reviewer's comment:**

**I agree with the Applicant's conclusion that there were no clinically significant abnormal lab values.**

#### 7.4.3 Vital Signs

Results from all physical and vital sign measurements were judged to be within normal limits or not clinically significant.

#### 7.4.4 Electrocardiograms (ECGs)

Not applicable for this submission.

#### 7.4.5 Special Safety Studies/Clinical Trials

The only special safety study was that of an irritation study for a similar, but higher dose, chewable NETA/EE product. There was no evidence of any safety concerns for the oral cavity based on Study PR-10007, which is reviewed in Section 5.3.2 of this document by Jerry Willett, MD (clinical reviewer in DBRUP).

#### 7.4.6 Immunogenicity

There are no issues or data on this topic.

### 7.5 Other Safety Explorations

**Reviewer's comment:**

**There were no other safety explorations to note in the NDA review.**

#### 7.5.1 Dose Dependency for Adverse Events

This section is not applicable.

#### 7.5.2 Time Dependency for Adverse Events

This section is not applicable.

#### 7.5.3 Drug-Demographic Interactions

There were none.

#### 7.5.4 Drug-Disease Interactions

There were none.

#### 7.5.5 Drug-Drug Interactions

There were no specific DDI studies or data presented with this NDA.

### 7.6 Additional Safety Evaluations

#### Reviewer's comment:

**There were no other safety explorations to note in the NDA review.**

#### 7.6.1 Human Carcinogenicity

No new or special data were submitted. Class labeling for CHCs has a short section on this topic.

#### 7.6.2 Human Reproduction and Pregnancy Data

See the class label section of the final label for this product. No new data are presented.

#### 7.6.3 Pediatrics and Assessment of Effects on Growth

None was required or performed.

#### 7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound

See Section 8 for overdose information in the approved Lo Loestrin Fe product. The drug abuse potential for COCs in general is very low. Overdose could lead to severe nausea and vomiting. The primary withdrawal effect is physiologic withdrawal bleeding.

### 7.7 Additional Submissions / Safety Issues

#### 7.7.1 4-Month Safety Update and Annual Report

The 120 Day Safety Update was submitted on 1-23-13. The Sponsor reported that no new significant information was reported that would reasonably affect the statement of Contraindications, Warnings and Precautions, and Adverse Reactions in the proposed labeling.

NDA 204654 cross-referenced Warner Chilcott's NDA 022501 for Lo Loestrin Fe in support of the safety and efficacy of NETA and EE in the prevention of pregnancy. The most recent annual report submitted to NDA 022501 covered the reporting period through October 2012 and contained a review of the nonclinical and clinical literature.

**Reviewer's comment:**

**There were no nonclinical or clinical studies being conducted with the chewable product at the time of submission of this application. No clinical or nonclinical studies have been subsequently started.**

**No new safety findings from the medical literature were reported by the Applicant or identified by this reviewer for COCs containing NETA/EE.**

## **8 Postmarket Experience**

There has been extensive postmarketing experience with the same COC product (Lo Loestrin Fe) since its approval in October 2010 and with various combinations of NETA/EE since 1973 (40 years ago). The FDAAA Section 915 Review for Lo Loestrin Fe was completed on September 10, 2012. It noted reports of VTEs (an expected labeled event). An action item in the 915 Review is that "The prescribing information for Lo Loestrin Fe should be updated to specify that [REDACTED] (b) (4)

[REDACTED] (b) (4)

**Reviewer's comment:**

**There have not been any recent new postmarketing safety concerns related to the combination of NETA or EE for contraception. The proposed product is not approved for any market, so there is no postmarketing experience with [REDACTED] (b) (4). The postmarketing experience with [REDACTED] (b) (4) will be noted in the label.**

## **9 Appendices**

### **9.1 Literature Review/References**

Review of the medical literature for NETA/EE combination hormonal contraceptives shows a well-established safety and efficacy profile. There are no new major issues with this combination of norethindrone acetate and ethinyl estradiol when used by women of reproductive age for the prevention of pregnancy.

### **9.2 Labeling Recommendations**

The Applicant's initial requested trade name for the product was [REDACTED] (b) (4). This name was found unacceptable by DMEPA, primarily because of name confusion resulting in possible medication errors with other currently marketed products. Pending completion of labeling negotiations, there are no further labeling recommendations. The new PLR format is used for the label and closely mirrors the labels for [REDACTED] (b) (4) 24 Fe chewable tablet (NDA 203667), [REDACTED] (b) (4) 24 Fe soft gel capsule (NDA 204426), and especially Lo Loestrin Fe (NDA 22501, the reference drug).

The proposed label was or will be reviewed by the following groups:

- DMEPA- Division of Medication Error Prevention and Analysis- Alison Park and Manizheh Siahpoushan
- OPDP - Carrie Newcomer
- CMC - Gene Holbert
- Clinical - DBRUP- Daniel Davis and Lisa Soule
- Clinical Pharmacology- Li Li and Myong-Jin Kim
- Pharmacology/Toxicology - Krishan Raheja
- SEALD - Abimbola Adebawale

**Reviewer's comment:**

**There were no major labeling issues except the finding that the name FemLo was unacceptable. Use of the PLR format will be helpful for both the healthcare provider who prescribes the product as well as the consumer who will use of product.**

### **9.3 Advisory Committee Meeting**

There was no need for an Advisory Committee meeting for this bioequivalent product.

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
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/s/  
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DANIEL DAVIS  
07/05/2013

LISA M SOULE  
07/05/2013

I concur with Dr. Davis' conclusions and recommendation for approval of NDA 204-654

## CLINICAL FILING CHECKLIST FOR A NEW NDA/BLA

**NDA Number: 204654**

**Applicant: Warner  
Chilcott**

**Stamp Date: Sept  
28, 2012**

**Drug Name: norethindrone acetate/ethinyl  
estradiol/ferrous fumarate chewable tablet**

**NDA Type: Standard**

	Content Parameter	Yes	No	NA	Comment
<b>FORMAT/ORGANIZATION/LEGIBILITY</b>					
1.	Identify the general format that has been used for this application, e.g. electronic CTD.	X			The submission is an e-CTD.
2.	On its face, is the clinical section of the application organized in a manner to allow substantive review to begin?	X			
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			
<b>LABELING</b>					
7.	Has the applicant submitted draft labeling in electronic format consistent with 21 CFR 201.56 <sup>1</sup> and 201.57 (or 21 CFR Subpart C for OTC products), current divisional and Center policies, and the design of the development package?	X			
<b>SUMMARIES</b>					
8.	Has the applicant submitted all the required discipline summaries (i.e., Module 2 summaries)?	X			
9.	Has the applicant submitted the integrated summary of safety (ISS)?			X	There is no need for an ISS for the NDA.
10.	Has the applicant submitted the integrated summary of efficacy (ISE)?			X	There is no need for an ISE for the NDA.
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?	b1			Reference is NDA 022501, Lo Loestrin® 24 Fe
<b>DOSE</b>					
13.	If needed, has the sponsor made an appropriate attempt to determine the correct dosage and schedule for this product (i.e., appropriately designed dose-ranging studies)? Study Numbers: See response to # 14.			X	The dose is the same as with the approved reference drug: Lo Loestrin 24 Fe
<b>EFFICACY</b>					
14.	On its face, do there appear to be the requisite number of adequate and well-controlled studies in the application? Pivotal Study #1 PR-12111 Indication: Bioequivalence Pivotal Study #2 PR-141060 for food effect for EE.  Safety Study 10007 for oral irritation over 24 days.	X			Demonstration of bioequivalence will be sufficient evidence of efficacy.

<sup>1</sup> [http://www.access.gpo.gov/nara/cfr/waisidx\\_01/21cfr201\\_01.html](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
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	
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	
<b>SAFETY</b>					
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 arrhythmogenic 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		Adequate information is available in Annual Reports.
21.	For chronically administered drugs, have an adequate number of patients (based on ICH guidelines for exposure <sup>2</sup> ) been exposed at the dose (or dose range) believed to be efficacious?			X	Not needed because this is only a change in dosage form of an approved drug.
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 <sup>3</sup> used for mapping investigator verbatim terms to preferred terms?			X	
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	The complete study reports contain sufficient safety data.
<b>OTHER STUDIES</b>					
26.	Has the applicant submitted all special studies/data requested by the Division during the pre-submission discussions with the sponsor?			X	Bioequivalence and food effect reports are submitted.
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	

<sup>2</sup> 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.

<sup>3</sup> 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 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
<b>PEDIATRIC USE</b>					
28.	Has the applicant submitted the pediatric assessment, or provided documentation for a waiver and/or deferral?	X			A full waiver is requested.
<b>ABUSE LIABILITY</b>					
29.	If relevant, has the applicant submitted information to assess the abuse liability of the product?			X	
<b>FOREIGN STUDIES</b>					
30.	Has the applicant submitted a rationale for assuming the applicability of foreign data in the submission to the U.S. population?			X	
<b>DATASETS</b>					
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	No efficacy data are needed for this NDA.
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			
<b>CASE REPORT FORMS</b>					
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	
<b>FINANCIAL DISCLOSURE</b>					
38.	Has the applicant submitted the required Financial Disclosure information?	X			
<b>GOOD CLINICAL PRACTICE</b>					
39.	Is there a statement of Good Clinical Practice; that all clinical studies were conducted under the supervision of an IRB and with adequate informed consent procedures?	X			See the study reports.
<b>CONCLUSION</b>					
40.	From a clinical perspective, is this application fileable? If not, please state why.	X			

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter. **There are none.**

Daniel Davis, MD

11-1-12

Reviewing Medical Officer

Date

Lisa Soule, MD

11-6-12

Clinical Team Leader

Date

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
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/s/  
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DANIEL DAVIS  
11/28/2012

LISA M SOULE  
11/28/2012

I concur with Dr. Davis that NDA 204-654 is fileable.