

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**204654Orig1s000**

**OTHER REVIEW(S)**

## SEALD Director Sign-Off Review of the End-of-Cycle Prescribing Information: Outstanding Format Deficiencies

Product Title	LO MINASTRIN FE (norethindrone acetate and ethinyl estradiol chewable tablets, ethinyl estradiol tablets and ferrous fumarate tablets), for oral use
Applicant	Warner Chilcott Company, LLC
Application/Supplement Number	NDA 204654
Type of Application	Original NDA
Indication(s)	For use by women to prevent pregnancy
Established Pharmacologic Class <sup>1</sup>	Estrogen/Progestin
Office/Division	ODE III/DRUP
Division Project Manager	Pamela Lucarelli
Date FDA Received Application	September 28, 2012
Goal Date	July 28, 2013
Date PI Received by SEALD	July 22, 2013
SEALD Review Date	July 23, 2013
SEALD Labeling Reviewer	Abimbola Adebawale
SEALD Division Director	Laurie Burke

PI = prescribing information

<sup>1</sup> The established pharmacologic class (EPC) that appears in the final draft PI.

This Study Endpoints and Labeling Development (SEALD) Director Sign-Off review of the end-of-cycle, draft prescribing information (PI) for critical format elements reveals **outstanding labeling format deficiencies that must be corrected** before the final PI is approved. After these outstanding labeling format deficiencies are corrected, the SEALD Director will have no objection to the approval of this PI.

The critical format elements include labeling regulation (21 CFR 201.56 and 201.57), labeling guidance, and best labeling practices (see list below). This review does not include every regulation or guidance that pertains to PI format.

Guide to the Selected Requirements of Prescribing Information (SRPI) Checklist: For each SRPI item, one of the following 3 response options is selected:

- **NO:** The PI **does not meet** the requirement for this item (**deficiency**).
- **YES:** The PI **meets** the requirement for this item (**not a deficiency**).
- **N/A (not applicable):** This item does not apply to the specific PI under review.

## Selected Requirements of Prescribing Information

### Highlights (HL)

#### GENERAL FORMAT

- YES** 1. Highlights (HL) must be in two-column format, with ½ inch margins on all sides and in a minimum of 8-point font.

**Comment:**

- YES** 2. The length of HL must be less than or equal to one-half page (the HL Boxed Warning does not count against the one-half page requirement) unless a waiver has been granted in a previous submission (i.e., the application being reviewed is an efficacy supplement).

**Instructions to complete this item:** If the length of the HL is less than or equal to one-half page then select “YES” in the drop-down menu because this item meets the requirement. However, if HL is longer than one-half page:

➤ **For the Filing Period (for RPMs)**

- *For efficacy supplements:* If a waiver was previously granted, select “YES” in the drop-down menu because this item meets the requirement.
- *For NDAs/BLAs and PLR conversions:* Select “NO” in the drop-down menu because this item does not meet the requirement (deficiency). The RPM notifies the Cross-Discipline Team Leader (CDTL) of the excessive HL length and the CDTL determines if this deficiency is included in the 74-day or advice letter to the applicant.

➤ **For the End-of Cycle Period (for SEALD reviewers)**

- The SEALD reviewer documents (based on information received from the RPM) that a waiver has been previously granted or will be granted by the review division in the approval letter.

**Comment:**

- YES** 3. All headings in HL must be presented in the center of a horizontal line, in UPPER-CASE letters and **bolded**.

**Comment:**

- NO** 4. White space must be present before each major heading in HL.

**Comment:** *Insert a white space before the Boxed Warning in Highlights.*

- NO** 5. Each summarized statement in HL must reference the section(s) or subsection(s) of the Full Prescribing Information (FPI) that contains more detailed information. The preferred format is the numerical identifier in parenthesis [e.g., (1.1)] at the end of each information summary (e.g. end of each bullet).

**Comment:** *The reference (i.e. 12.3) at the end of the information summary of the fifth bullet in the Dosage and Administration section in Highlights does not include the identifying number (2.1) that corresponds to the location of the information in the Dosage and Administration section of the FPI.*

- NO** 6. Section headings are presented in the following order in HL:

Section	Required/Optional
• <b>Highlights Heading</b>	Required
• <b>Highlights Limitation Statement</b>	Required
• <b>Product Title</b>	Required

## Selected Requirements of Prescribing Information

• <b>Initial U.S. Approval</b>	Required
• <b>Boxed Warning</b>	Required if a Boxed Warning is in the FPI
• <b>Recent Major Changes</b>	Required for only certain changes to PI*
• <b>Indications and Usage</b>	Required
• <b>Dosage and Administration</b>	Required
• <b>Dosage Forms and Strengths</b>	Required
• <b>Contraindications</b>	Required (if no contraindications must state “None.”)
• <b>Warnings and Precautions</b>	Not required by regulation, but should be present
• <b>Adverse Reactions</b>	Required
• <b>Drug Interactions</b>	Optional
• <b>Use in Specific Populations</b>	Optional
• <b>Patient Counseling Information Statement</b>	Required
• <b>Revision Date</b>	Required

\* RMC only applies to the Boxed Warning, Indications and Usage, Dosage and Administration, Contraindications, and Warnings and Precautions sections.

**Comment:** *The ninth section heading in Highlights should read as “Dosage Forms and Strengths” (as shown above) and not “Dosage Form and Strength” as currently written.*

**YES**

7. A horizontal line must separate HL and Table of Contents (TOC).

**Comment:**

### HIGHLIGHTS DETAILS

#### Highlights Heading

**NO**

8. At the beginning of HL, the following heading must be **bolded** and appear in all UPPER CASE letters: “**HIGHLIGHTS OF PRESCRIBING INFORMATION**”.

**Comment:** *The Highlights Heading is not at the beginning of the HL. Align the heading to the left so that it is at the beginning of the HL.*

#### Highlights Limitation Statement

**YES**

9. The **bolded** HL Limitation Statement must be on the line immediately beneath the HL heading and must state: “**These highlights do not include all the information needed to use (insert name of drug product in UPPER CASE) safely and effectively. See full prescribing information for (insert name of drug product in UPPER CASE).**”

**Comment:**

#### Product Title

**YES**

10. Product title in HL must be **bolded**.

**Comment:**

#### Initial U.S. Approval

**NO**

11. Initial U.S. Approval in HL must be placed immediately beneath the product title, **bolded**, and include the verbatim statement “**Initial U.S. Approval:**” followed by the **4-digit year**.

**Comment:** *Initial U.S. Approval in HL is not placed immediately beneath the product title. There is a white space between the two. Delete the space.*

#### Boxed Warning

**YES**

12. All text must be **bolded**.

## Selected Requirements of Prescribing Information

### Comment:

- YES** 13. Must have a centered heading in UPPER-CASE, containing the word “**WARNING**” (even if more than one Warning, the term, “**WARNING**” and not “**WARNINGS**” should be used) and other words to identify the subject of the Warning (e.g., “**WARNING: SERIOUS INFECTIONS**”).

### Comment:

- YES** 14. Must always have the verbatim statement “*See full prescribing information for complete boxed warning.*” in *italics* and centered immediately beneath the heading.

### Comment:

- YES** 15. Must be limited in length to 20 lines (this does not include the heading and statement “*See full prescribing information for complete boxed warning.*”)

### Comment:

- YES** 16. Use sentence case for summary (combination of uppercase and lowercase letters typical of that used in a sentence).

### Comment:

### Recent Major Changes (RMC)

- N/A** 17. Pertains to only the following five sections of the FPI: Boxed Warning, Indications and Usage, Dosage and Administration, Contraindications, and Warnings and Precautions.

### Comment:

- N/A** 18. Must be listed in the same order in HL as they appear in FPI.

### Comment:

- N/A** 19. Includes heading(s) and, if appropriate, subheading(s) of labeling section(s) affected by the recent major change, together with each section’s identifying number and date (month/year format) on which the change was incorporated in the PI (supplement approval date). For example, “Dosage and Administration, Coronary Stenting (2.2) --- 3/2012”.

### Comment:

- N/A** 20. Must list changes for at least one year after the supplement is approved and must be removed at the first printing subsequent to one year (e.g., no listing should be one year older than revision date).

### Comment:

### Indications and Usage

- YES** 21. If a product belongs to an established pharmacologic class, the following statement is required in the Indications and Usage section of HL: “(Product) is a (name of established pharmacologic class) indicated for (indication)”.

### Comment:

### Dosage Forms and Strengths

- YES** 22. For a product that has several dosage forms, bulleted subheadings (e.g., capsules, tablets,

## Selected Requirements of Prescribing Information

injection, suspension) or tabular presentations of information is used.

Comment:

### Contraindications

- YES** 23. All contraindications listed in the FPI must also be listed in HL or must include the statement “None” if no contraindications are known.

Comment:

- YES** 24. Each contraindication is bulleted when there is more than one contraindication.

Comment:

### Adverse Reactions

- YES** 25. For drug products other than vaccines, the verbatim **bolded** statement must be present: “**To report SUSPECTED ADVERSE REACTIONS, contact (insert name of manufacturer) at (insert manufacturer’s U.S. phone number) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch**”.

Comment:

### Patient Counseling Information Statement

- YES** 26. Must include one of the following three **bolded** verbatim statements (without quotation marks):

If a product **does not** have FDA-approved patient labeling:

- “**See 17 for PATIENT COUNSELING INFORMATION**”

If a product **has** FDA-approved patient labeling:

- “**See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.**”
- “**See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.**”

Comment:

### Revision Date

- YES** 27. **Bolded** revision date (i.e., “**Revised: MM/YYYY or Month Year**”) must be at the end of HL.

Comment:

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## Contents: Table of Contents (TOC)

### GENERAL FORMAT

- YES** 28. A horizontal line must separate TOC from the FPI.

Comment:

- YES** 29. The following **bolded** heading in all UPPER CASE letters must appear at the beginning of TOC: “**FULL PRESCRIBING INFORMATION: CONTENTS**”.

Comment:

## Selected Requirements of Prescribing Information

- NO** 30. The section headings and subheadings (including title of the Boxed Warning) in the TOC must match the headings and subheadings in the FPI.  
***Comment:** Subsection heading 2.1 in the TOC reads as “How to Take Lo Minastrin FE” but subsection heading 2.1 in the FPI reads as “How to Lo Minastrin FE.” The subsection heading in the TOC must match the FPI subsection heading.*
- YES** 31. The same title for the Boxed Warning that appears in the HL and FPI must also appear at the beginning of the TOC in UPPER-CASE letters and **bolded**.  
***Comment:***
- YES** 32. All section headings must be **bolded** and in UPPER CASE.  
***Comment:***
- YES** 33. All subsection headings must be indented, not bolded, and in title case.  
***Comment:***
- YES** 34. When a section or subsection is omitted, the numbering does not change.  
***Comment:***
- YES** 35. If a section or subsection from 201.56(d)(1) is omitted from the FPI and TOC, the heading “**FULL PRESCRIBING INFORMATION: CONTENTS**” must be followed by an asterisk and the following statement must appear at the end of TOC: “\*Sections or subsections omitted from the Full Prescribing Information are not listed.”  
***Comment:***

## Full Prescribing Information (FPI)

### GENERAL FORMAT

- YES** 36. The following heading must appear at the beginning of the FPI in UPPER CASE and **bolded**: “**FULL PRESCRIBING INFORMATION**”.  
***Comment:***
- YES** 37. All section and subsection headings and numbers must be **bolded**.  
***Comment:***
- YES** 38. The **bolded** section and subsection headings must be named and numbered in accordance with 21 CFR 201.56(d)(1) as noted below. If a section/subsection is omitted, the numbering does not change.

<b>Boxed Warning</b>
<b>1 INDICATIONS AND USAGE</b>
<b>2 DOSAGE AND ADMINISTRATION</b>
<b>3 DOSAGE FORMS AND STRENGTHS</b>
<b>4 CONTRAINDICATIONS</b>
<b>5 WARNINGS AND PRECAUTIONS</b>
<b>6 ADVERSE REACTIONS</b>
<b>7 DRUG INTERACTIONS</b>
<b>8 USE IN SPECIFIC POPULATIONS</b>
<b>8.1 Pregnancy</b>

## Selected Requirements of Prescribing Information

8.2 Labor and Delivery
8.3 Nursing Mothers
8.4 Pediatric Use
8.5 Geriatric Use
<b>9 DRUG ABUSE AND DEPENDENCE</b>
9.1 Controlled Substance
9.2 Abuse
9.3 Dependence
<b>10 OVERDOSAGE</b>
<b>11 DESCRIPTION</b>
<b>12 CLINICAL PHARMACOLOGY</b>
12.1 Mechanism of Action
12.2 Pharmacodynamics
12.3 Pharmacokinetics
12.4 Microbiology (by guidance)
12.5 Pharmacogenomics (by guidance)
<b>13 NONCLINICAL TOXICOLOGY</b>
13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
13.2 Animal Toxicology and/or Pharmacology
<b>14 CLINICAL STUDIES</b>
<b>15 REFERENCES</b>
<b>16 HOW SUPPLIED/STORAGE AND HANDLING</b>
<b>17 PATIENT COUNSELING INFORMATION</b>

**Comment:**

- YES** 39. FDA-approved patient labeling (e.g., Medication Guide, Patient Information, or Instructions for Use) must not be included as a subsection under Section 17 (Patient Counseling Information). All patient labeling must appear at the end of the PI upon approval.

**Comment:**

- YES** 40. The preferred presentation for cross-references in the FPI is the section heading (not subsection heading) followed by the numerical identifier in italics. For example, “[see Warnings and Precautions (5.2)]”.

**Comment:**

- N/A** 41. If RMCs are listed in HL, the corresponding new or modified text in the FPI sections or subsections must be marked with a vertical line on the left edge.

**Comment:**

### FULL PRESCRIBING INFORMATION DETAILS

#### Boxed Warning

- YES** 42. All text is **bolded**.

**Comment:**

- YES** 43. Must have a heading in UPPER-CASE, containing the word “**WARNING**” (even if more than one Warning, the term, “**WARNING**” and not “**WARNINGS**” should be used) and other words to identify the subject of the Warning (e.g., “**WARNING: SERIOUS INFECTIONS**”).

**Comment:**

## Selected Requirements of Prescribing Information

- YES** 44. Use sentence case (combination of uppercase and lowercase letters typical of that used in a sentence) for the information in the Boxed Warning.

**Comment:**

### Contraindications

- N/A** 45. If no Contraindications are known, this section must state “None”.

**Comment:**

### Adverse Reactions

- YES** 46. When clinical trials adverse reactions data is included (typically in the “Clinical Trials Experience” subsection of Adverse Reactions), the following verbatim statement or appropriate modification should precede the presentation of adverse reactions:

*“Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice.”*

**Comment:**

- YES** 47. When postmarketing adverse reaction data is included (typically in the “Postmarketing Experience” subsection of Adverse Reactions), the following verbatim statement or appropriate modification should precede the presentation of adverse reactions:

*“The following adverse reactions have been identified during post-approval use of (insert drug name). Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.”*

**Comment:**

### Patient Counseling Information

- YES** 48. Must reference any FDA-approved patient labeling, include the type of patient labeling, and use one of the following statements at the beginning of Section 17:

- “See FDA-approved patient labeling (Medication Guide)”
- “See FDA-approved patient labeling (Medication Guide and Instructions for Use)”
- “See FDA-approved patient labeling (Patient Information)”
- “See FDA-approved patient labeling (Instructions for Use)”
- “See FDA-approved patient labeling (Patient Information and Instructions for Use)”

**Comment:**

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/s/  
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ABIMBOLA O ADEBOWALE  
07/23/2013

LAURIE B BURKE  
07/23/2013

**FOOD AND DRUG ADMINISTRATION  
Center for Drug Evaluation and Research  
Office of Prescription Drug Promotion**

**\*\*\*Pre-decisional Agency Information\*\*\***

## Memorandum

**Date:** July 19, 2013

**To:** Pam Lucarelli  
Project Manager  
Division of Bone, Reproductive, and Urologic Products (DBRUP)

**From:** Carrie Newcomer, PharmD  
Regulatory Review Officer  
Office of Prescription Drug Promotion (OPDP)

**Subject: NDA: 204654**  
**Norethindrone acetate and ethinyl estradiol chewable tablets,  
ethinyl estradiol tablets and ferrous fumarate tablets**

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As requested in DBRUP's consult dated October 9, 2012, OPDP has reviewed the draft labeling (package insert [PI], patient package insert [PPI], and carton/container labeling) for the original NDA submission for norethindrone acetate and ethinyl estradiol chewable tablets, ethinyl estradiol tablets and ferrous fumarate tablets. OPDP's comments are based on the proposed, substantially complete, marked-up version of the draft PI and PPI provided to OPDP on July 15, 2013, via access to the DBRUP eRoom. OPDP's comments on the draft carton/container labeling are based on the draft labeling submitted by the applicant on July 16, 2013, and provided to OPDP on July 16, 2013, via email.

OPDP's comments on the PI and PPI are provided directly in the attached copy of the labeling.

OPDP does not have any comments on the carton/container labels.

Thank you for your consult. If you have any questions, please contact Carrie Newcomer at 6-1233, or [carrie.newcomer@fda.hhs.gov](mailto:carrie.newcomer@fda.hhs.gov).

33 Pages of Draft  
Labeling have been  
Withheld in Full as b4  
(CCI/TS) immediately<sup>1</sup>  
following this page

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/s/  
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CARRIE A NEWCOMER  
07/19/2013

**Department of Health and Human Services  
Public Health Service  
Food and Drug Administration  
Center for Drug Evaluation and Research  
Office of Surveillance and Epidemiology  
Office of Medication Error Prevention and Risk Management**

**Label, Labeling, and Packaging Memorandum**

Date: July 12, 2013

Reviewer: Manizheh Siahpoushan, PharmD  
Division of Medication Error Prevention and Analysis

Team Leader: James Schlick, RPh  
Division of Medication Error Prevention and Analysis

Drug Name and Strength: Lo Minastrin Fe  
(Norethindrone Acetate and Ethinyl Estradiol Acetate  
Chewable Tablets, Ethinyl Estradiol Tablets and Ferrous  
Fumarate Tablets)  
1 mg/10 mcg and 10 mcg

Application Type/Number: NDA 204654

Applicant: Warner Chilcott, LLC

OSE RCM #: 2013-1-1

**\*\*\* This document contains proprietary and confidential information that should not be released to the public.\*\*\***

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## **1 INTRODUCTION**

This memorandum evaluates the revised container labels and carton labeling for Lo Minastrin Fe (Norethindrone Acetate and Ethinyl Estradiol Chewable Tablets, Ethinyl Estradiol Tablets and Ferrous Fumarate Tablets) submitted on June 27, 2013 (see Appendix A). The Division of Medication Error Prevention and Analysis (DMEPA) initially reviewed the container labels and carton labeling in OSE Review 2013-1, dated May 21, 2013.

## **2 MATERIALS REVIEWED**

DMEPA evaluated the revised container labels and carton labeling submitted on June 27, 2013. We compared the revised labels and labeling against our recommendations in OSE Review 2013-1, dated May 21, 2013, to assess whether the revised labels and labeling address our concerns from a medication error perspective.

## **3 CONCLUSIONS AND RECOMMENDATIONS**

Our review of the revised container labels and carton labeling determined the Applicant has implemented all of our recommendations and we find the revisions acceptable. Therefore, we have no further recommendations.

If you have further questions or need clarifications, please contact OSE Project Manager, Marcus Cato, at 301-796-3903.

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/s/  
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MANIZHEH SIAHPOUSHAN  
07/12/2013

JAMES H SCHLICK  
07/12/2013

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES  
PUBLIC HEALTH SERVICE  
FOOD AND DRUG ADMINISTRATION  
CENTER FOR DRUG EVALUATION AND RESEARCH

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DATE: January 18, 2013

TO: Director, Investigation Branch  
Florida District Office  
555 Winderley Place, Suite 200  
Maitland, FL 32751

Chief, Medical Products and Tobacco Trip Planning  
Branch  
Division of Medical Products and Tobacco Inspections  
Office of Medical Products and Tobacco Operations

FROM: Sam H. Haidar, Ph.D., R.Ph.  
Chief, Bioequivalence Branch  
Division of Bioequivalence and GLP Compliance  
Office of Scientific Investigations

SUBJECT: FY 2013, **CDER High Priority User Fee NDA, Pre-Approval  
Data Validation Inspection**, Bioresearch Monitoring,  
Human Drugs, CP 7348.001

RE: NDA 204-654  
DRUG: Norethindrone Acetate and Ethinyl Estradiol  
Chewable Tablets, Ethinyl Estradiol Tablets,  
and Ferrous Fumarate Tablets  
SPONSOR: Warner Chilcott Company, LLC, USA

This memo requests that you arrange for inspections of the clinical and analytical portions of the following bioequivalence study. **Following identification of the FDA investigator, background materials will be forwarded directly. Please contact the DBGLPC point of contact (POC) for background materials. Please complete the inspections prior to April 12, 2013.**

**Do not identify the application, sponsor, study to be inspected, drug names, or the study investigator prior to the start of the inspections. The information will be provided to the sites at the inspection opening meetings. Please note that these inspections will be conducted under Bioresearch Monitoring Compliance Program CP 7348.001, and not under CP 7348.811 (Clinical Investigators).**

**At the completion of the inspections, please send a scanned copy of the completed sections B & C of this memo to Dr. Sam Haidar, and the DBGLPC POC listed at the end of this memo.**

**Study Number:** PR-12111

**Study Title:** "A study to assess the comparative bioavailability of norethindrone acetate and ethinyl estradiol from WC3016 tablets and WC3064 tablets and to assess the effect of food on bioavailability from WC3064 tablets in healthy female volunteers, Study PR-12111"

**Clinical Site:** Comprehensive Clinical Development  
3400 Enterprise Way  
Miramar, FL 33025  
Tel: 954-266-1000, Ext 1100  
Fax: 954-266-1012

**Investigator:** Maria Gutierrez, MD

**Please confirm documented informed consent for 100% of subjects enrolled at all the sites. Please audit the reports for at least 50% of the total subjects included for the conduct of study by site. The subject records in the NDA submission should be compared to the original documents at the sites. Include a description of your findings in the EIR.**

#### **SECTION B**

**RESERVE SAMPLES:** Because this bioequivalence study is subject to 21 CFR 320.38 and 320.63, the site conducting the study (i.e., each investigator site) is responsible for randomly selecting and retaining reserve samples from the shipments of drug product provided by the sponsor for subject dosing.

Please note that the final rule for "Retention of Bioavailability and Bioequivalence Testing Samples" (Federal Register, Vol. 58, No. 80, pp. 25918-25928, April 28, 1993) specifically addresses the requirements for bioequivalence studies

(<http://www.fda.gov/ScienceResearch/SpecialTopics/RunningClinicalTrials/ucm120265.htm>).

Please refer to CDER's "Guidance for Industry, Handling and Retention of BA and BE Testing Samples" (May 2004), which clarifies the requirements for reserve samples

(<http://www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM126836.pdf>).

Please follow the instructions below:

- Verify if reserve samples were retained according to regulations.
- If the reserve samples were stored at a third party site, please verify and collect an affidavit to confirm that the third party is independent from the sponsor, manufacturer, and packager, and that the sponsor was notified in writing of the location. In an event the reserve samples were not retained or are not adequate in quantity, please notify the POC immediately.
- Please obtain a written assurance from the clinical investigator or the responsible person at the clinical site that the reserve samples are representative of those used in the specific bioequivalence study, and that they were stored under conditions specified in accompanying records. Document the signed and dated assurance [21 CFR 320.38(d, e, g)] on the facility's letterhead, or Form FDA 463a, Affidavit.
- Samples of the test and reference products in their original containers should be collected and shipped to the Division of Pharmaceutical Analysis, St. Louis, MO, for screening, at the following address:

Benjamin Westenberger, Ph.D.  
Center for Drug Evaluation and Research  
Division of Pharmaceutical Analysis (DPA)  
Center for Drug Analysis (HFH-300)  
US Courthouse and Customhouse Bldg  
1114 Market Street, Room 1002  
St. Louis, MO 63101  
TEL: (314) 539-2135

### SECTION C

#### Data Audit Checklist:

- Primary pharmacodynamic endpoint data verifiable? \_\_\_\_\_
- Evidence of under-reporting of AEs identified? \_\_\_\_\_
- Other endpoint data verifiable? \_\_\_\_\_
- Evidence of inaccuracy in electronic data capture? \_\_\_\_\_
- Presence of 100% of signed and dated informed consent forms: \_\_\_\_\_
- Reports for the subjects audited: \_\_\_\_\_
- Number of subjects screened at the site: \_\_\_\_\_

- Number of subjects enrolled at the site:\_\_\_\_\_
- Number of subjects completing the study:\_\_\_\_\_
- Verify from source documents that evaluations related to the primary endpoint were accurately reported in case report forms:\_\_\_\_\_
- Confirm that clinical assessments were conducted in a consistent manner and in accordance with the protocol:\_\_\_\_\_
- Number of subject records reviewed during the inspection:\_\_\_\_\_
- SOPs were followed during study conduct:\_\_\_\_\_
- Examine correspondence files for any sponsor- or monitor-requested changes to study data or reports:\_\_\_\_\_
- Include a brief statement summarizing your findings (IRB approvals, study protocol and SOPs, protocol deviations, adverse events, concomitant medications, inclusion/exclusion criteria, adequacy of records, drug accountability documents and case report forms for dosing, whether the **randomization schedule was followed for dosing of subjects**, etc.)
- Other Comments:

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Collect relevant exhibits for all findings, including discussion items at closeout, as evidence of the findings.

**Analytical Site:**



**Contact:**

**Methodology:** Gas Chromatography - Mass Spectrometry

**Please confirm the following during the inspection:**

- All pertinent items related to the analytical method used for the measurement of ethinyl estradiol and norethindrone acetate concentrations in human plasma should be examined.
- The accuracy of the analytical data provided in the NDA submission by the applicant should be compared with the original documents at the site.

- The method validation and the actual assay of the subject plasma samples, the variability between and within runs, QC, demonstration of accuracy and precision in matrix using standards and QCs prepared from separate stocks, stability of subject samples covered by validated stability period.
- Use of freshly made calibrators and/or freshly made QCs for stability evaluations during pre-study method validation.
- At least one demonstration of precision and accuracy from QCs and calibrators prepared from separate stock solutions.
- Scrutinize the number of repeat assays of the subject plasma samples, and the reason for such repetitions, the SOP(s) for repeat assays and if relevant stability criteria like freeze thaw cycles sufficiently covered the stability of reanalyzed subject samples.

**Additional instructions to ORA Investigator:**

In addition to the compliance program elements, other study specific instructions may be provided by the DBGLPC POC prior to the inspection. Therefore, we request that the DBGLPC POC be contacted for further instructions before the inspection, and also regarding data anomalies or questions noted during review of study records. The ORA investigator should contact the DBGLPC POC for inspection-related questions or clarifications.

Please fax/email a copy of Form FDA 483 if issued, as soon as possible. If at close-out of the inspection, it appears that the violations may warrant an OAI classification, please notify the POC as soon as possible. At completion of inspection, please remind the inspected entity of the 15 business-day timeframe for submission of a written response to observations listed on Form FDA 483. Please forward written response as soon as you receive it to Dr. Sam H. Haidar and POC (Fax: 1-301-847-8748 or Email: [sam.haidar@fda.hhs.gov](mailto:sam.haidar@fda.hhs.gov)).

DBGLPC POC: Sripal R. Mada, Ph.D.  
[sripal.mada@fda.hhs.gov](mailto:sripal.mada@fda.hhs.gov)  
Tel: (301)-796-4112  
FAX: (301)-847-8748

DMPTI POC: Arindam Dasgupta, Ph.D.  
[arindam.dasgupta@fda.hhs.gov](mailto:arindam.dasgupta@fda.hhs.gov)  
Tel: (301)-796-3326  
FAX: (301)-847-8748

Page 6 - BIMO Assignment, NDA 204-654 Norethindrone Acetate and  
Ethinyl Estradiol Chewable Tablets, Ethinyl Estradiol  
Chewable Tablets, and Ferrous Fumarate Tablets

cc:

CDER OSI PM TRACK

OSI/DBGLPC/Haidar/Skelly/Mada/Dejernet

OND/DRUP/Mercier

OCP/DCP3/Li/Kim/Bashaw

HFR-SE250/Torres (BIMO) / Sinninger (DIB)

HFR-SE200/Singleton (DIB)

ORAHQ/OMPTO/DMPTI/BIMO/Arline/Turner/Alexis/Braswell/Johnson  
/Colon

Draft: SRM 1/18/2013

Edit: MFS 1/18/2013; SHH 1/18/2013

OSI file BE6415; O:\BE\assigns\bio204654.doc

ECMS: Cabinets/CDER\_OC/OSI/Division of Bioequivalence & Good  
Laboratory Practice Compliance/Electronic Archive/BEB

FACTS: 1488907

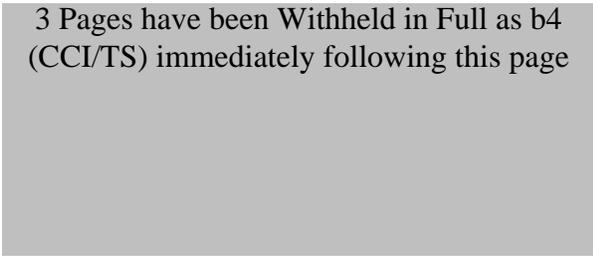
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/s/  
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SRIPAL R MADA  
01/18/2013

SAM H HAIDAR  
01/22/2013

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/s/  
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JENNIFER L MERCIER  
01/18/2013

**MEMORANDUM**

**DEPARTMENT OF HEALTH AND HUMAN SERVICES  
PUBLIC HEALTH SERVICE  
FOOD AND DRUG ADMINISTRATION  
CENTER FOR DRUG EVALUATION AND RESEARCH**

---

DATE: May 30, 2013

TO: Hylton V. Joffe, M.D.  
Director, Division of Bone, Reproductive and Urologic  
Products  
(DBRUP)

FROM: Arindam Dasgupta, Ph.D.  
Pharmacologist, Bioequivalence Branch  
Division of Bioequivalence and GLP Compliance  
Office of Scientific Investigations

THROUGH: Sam H. Haidar, Ph.D., R.Ph.  
Chief, Bioequivalence Branch  
Division of Bioequivalence and GLP Compliance  
Office of Scientific Investigations

William H. Taylor, Ph.D.  
Director  
Division of Bioequivalence and GLP Compliance  
Office of Scientific Investigations

SUBJECT: Review of EIR Covering NDA 204-654; Norethindrone  
Acetate and Ethinyl Estradiol Chewable Tablets,  
Ethinyl Estradiol Tablets, and Ferrous Fumarate  
Tablets sponsored by Warner Chilcott Company, LLC, USA

At the request of DBRUP, the Division of Bioequivalence and GLP Compliance (DBGLPC) conducted inspections of the clinical and analytical portions of the following bioequivalence study:

**Study Number:** PR-12111  
**Study Title:** "A study to assess the comparative bioavailability of norethindrone acetate and ethinyl estradiol from WC3016 tablets and WC3064 tablets and to assess effect of food on bioavailability from (b) (4) tablets in healthy female volunteers, Study PR-12111"

The clinical and analytical portions of the study were audited at Comprehensive Clinical Development, Inc., Miramar, Florida (3/27-4/03/2013 by ORA Investigator Collen M. Aspinwall) and

(b) (4) by  
ORA Investigator Erin L. McFiren and OSI/DBGLPC Scientist  
Arindam Dasgupta).

The audits included a thorough examination of facilities and  
equipment; examination of study PR-12111 records, including  
ations among Comprehensive Clinical Development,  
(b) (4) and the sponsor; and interviews  
nsive Clinical Development's and (b) (4) management  
and staff.

Following the inspection at the clinical site (Comprehensive  
Clinical Development, Miramar, Florida), no objectionable  
conditions were observed and Form FDA-483 wa  
lytical site (b) (4)  
(b) (4) Form FDA-483 was issued  
(Attachment 1). DBGLPC rece written response to the  
inspectional findings from (b) (4) on May 14, 2013. The Form  
FDA-483 observation, (b) (4) psonse (Attachment 2) and my  
evaluation of the observation follow.

**Analytical Site:** (b) (4)

1. **Not all aspects of study conduct were documented. For  
example:**
  - a) **Failure to maintain documentation for individual QC sets  
used during sample processing.**

During the audit of the source records of the study, we observed  
that the forms to record preparation of fresh Quality Control  
solutions used in pre-study qualifi  
information on the identity of the (b) (4)  
s did not allow us to ver (b) (4)  
were stored under conditions of demonstra  
The QC preparation forms also lacked information on  
volumes of QC samples that were prepared for use during study  
sample analyses.

In their response, (b) (4) acknowledged the observation and  
promised to change (b) (4) cumentation forms to capture full  
documentation of QC solution preparation.

**Assessment of Data Integrity:** While the documenta s  
incomplete for the pre-study qualification runs, (b) (4)  
processed study samples and QCs in comparison to  
prepared calibrators. This design allowed evaluation of QC

stability and accuracy during the actual study. Precision and accuracy data from the QC program confirmed the pre-study qualification results. In my opinion, the above observation is not likely to affect acceptability of study data.

**Conclusions:**

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.

Arindam Dasgupta, Ph.D.  
Bioequivalence Branch, DBGLPC, OSI

**Final Classifications:**

NAI: Comprehensive Clinical Development Inc., Miramar, Florida  
FEI 3006116374

VAI:

(b) (4)

cc:

CDER OSI PM TRACK

OSI/DBGLPC/Taylor/Haidar/Skelly/Dejernett/Dasgupta/CF

OND/ODEIII/DBRUP/Joffe/Mercier

OTS/OCP/DCPIII/Bashaw/Myong Jin Kim/Li Li

ORA/CE-FO/BLT-DO/BLT-IB/McFiren

Draft: AD 05/23/2013

Edit: MFS 5/23/13

OSI: BE6415; O:\Bioequiv\EIRCover\204654war.nor.eth.doc

ECMS: Cabinets/CDER OC/OSI/Division of Bioequivalence & Good  
Laboratory Practice Compliance/Electronic Archive/BEB

FACTS: 1488907

# Attachment 1

**DEPARTMENT OF HEALTH AND HUMAN SERVICES  
FOOD AND DRUG ADMINISTRATION**

**DISTRICT OFFICE ADDRESS AND PHONE NUMBER**

FDA, Center for Drug Evaluation and Research, Attn: Sam H. Haidar, R.Ph, Ph.D.  
DBGLPC, OSI, Office of Compliance, Bldg. 51, Room 5330  
10903 New Hampshire Ave  
Silver Spring, MD 20993 USA

Industry Information: [www.fda.gov/oc/industry](http://www.fda.gov/oc/industry)

**DATE(S) OF INSPECTION**

April 15-19, 2013

**FEI NUMBER**

(b) (4)

**NAME AND TITLE OF INDIVIDUAL TO WHOM REPORT IS ISSUED**

**TO:** Bernhard Schmid, Vice President, Bioanalytics & Biopharmaceutics

**FIRM NAME**

(b) (4)

**STREET ADDRESS**

(b) (4)

**CITY, STATE AND ZIP CODE**

(b) (4)

**TYPE OF ESTABLISHMENT INSPECTED**

Contract Research Organization

THIS DOCUMENT LISTS OBSERVATIONS MADE BY THE FDA REPRESENTATIVE(S) DURING THE INSPECTION OF YOUR FACILITY. THEY ARE INSPECTIONAL OBSERVATIONS; AND DO NOT REPRESENT A FINAL AGENCY DETERMINATION REGARDING YOUR COMPLIANCE. IF YOU HAVE AN OBJECTION REGARDING AN OBSERVATION, OR HAVE IMPLEMENTED, OR PLAN TO IMPLEMENT CORRECTIVE ACTION IN RESPONSE TO AN OBSERVATION, YOU MAY DISCUSS THE OBJECTION OR ACTION WITH THE FDA REPRESENTATIVE(S) DURING THE INSPECTION OR SUBMIT THIS INFORMATION TO FDA AT THE ADDRESS ABOVE. IF YOU HAVE ANY QUESTIONS, PLEASE CONTACT FDA AT THE PHONE NUMBER AND ADDRESS ABOVE.

DURING AN INSPECTION OF YOUR FIRM (I) (WE) OBSERVED:

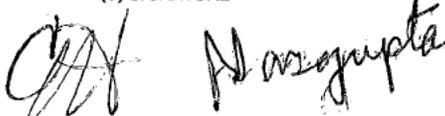
The following observations were made during an evaluation of study PR-12111, "A study to assess the comparative bioavailability of norethindrone acetate and ethinyl estradiol from WC3016 tablets and (b) (4) tablets, and to assess the effect of food on bioavailability from (b) (4) tablets in healthy female volunteers", and its associated method validation, conducted in support of NDA 204-654:

1. Not all aspects of study conduct were documented. For example:

a) Failure to maintain documentation for individual QC sets used during sample processing.

SEE  
REVERSE  
OF THIS  
PAGE

**EMPLOYEE(S) SIGNATURE**



**EMPLOYEE(S) NAME AND TITLE (Print or Type)**

Erin L. McFire, Investigator  
Arindam Dasgupta, Ph.D., Pharmacologist

**DATE ISSUED**

04/19/2013

# Attachment 2

3 Pages have been Withheld in Full  
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following this page

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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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ARINDAM DASGUPTA  
05/30/2013

SAM H HAIDAR  
05/30/2013

WILLIAM H TAYLOR  
05/30/2013

## RPM FILING REVIEW

(Including Memo of Filing Meeting)

**To be completed for all new NDAs, BLAs, and Efficacy Supplements [except SE8 (labeling change with clinical data) and SE9 (manufacturing change with clinical data)]**

Application Information		
NDA # 204654 BLA#	NDA Supplement #:S- BLA Supplement #	Efficacy Supplement Type SE-
Proprietary Name: (b) (4) Established/Proper Name: norethindrone acetate and ethinyl estradiol (b) (4) and ferrous fumarate		
Dosage Form: Tablet Strengths:		
Applicant: Warner Chilcott Agent for Applicant (if applicable):		
Date of Application: September 27, 2012 Date of Receipt: September 28, 2012 Date clock started after UN:		
PDUFA Goal Date: July 28, 2013	Action Goal Date (if different):	
Filing Date: November 27, 2012	Date of Filing Meeting: November 6, 2012	
Chemical Classification: (1,2,3 etc.) (original NDAs only)		
Proposed indication(s)/Proposed change(s): Prevention of Pregnancy		
Type of Original NDA: AND (if applicable) Type of NDA Supplement:	<input checked="" type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2) <input type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2)	
<i>If 505(b)(2): Draft the "505(b)(2) Assessment" review found at: <a href="http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/UCM027499">http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/UCM027499</a> and refer to Appendix A for further information.</i>		
Review Classification:	<input checked="" type="checkbox"/> Standard <input type="checkbox"/> Priority  <input type="checkbox"/> Tropical Disease Priority Review Voucher submitted	
<i>If the application includes a complete response to pediatric WR, review classification is Priority.</i>		
<i>If a tropical disease priority review voucher was submitted, review classification is Priority.</i>		
Resubmission after withdrawal? <input type="checkbox"/>	Resubmission after refuse to file? <input type="checkbox"/>	
Part 3 Combination Product? <input type="checkbox"/>	<input type="checkbox"/> Convenience kit/Co-package <input type="checkbox"/> Pre-filled drug delivery device/system (syringe, patch, etc.) <input type="checkbox"/> Pre-filled biologic delivery device/system (syringe, patch, etc.) <input type="checkbox"/> Device coated/impregnated/combined with drug <input type="checkbox"/> Device coated/impregnated/combined with biologic <input type="checkbox"/> Separate products requiring cross-labeling <input type="checkbox"/> Drug/Biologic <input type="checkbox"/> Possible combination based on cross-labeling of separate products <input type="checkbox"/> Other (drug/device/biological product)	
<i>If yes, contact the Office of Combination Products (OCP) and copy them on all Inter-Center consults</i>		

<input type="checkbox"/> Fast Track <input type="checkbox"/> Rolling Review <input type="checkbox"/> Orphan Designation  <input type="checkbox"/> Rx-to-OTC switch, Full <input type="checkbox"/> Rx-to-OTC switch, Partial <input type="checkbox"/> Direct-to-OTC  Other:	<input type="checkbox"/> PMC response <input type="checkbox"/> PMR response: <input type="checkbox"/> FDAAA [505(o)] <input type="checkbox"/> PREA deferred pediatric studies [21 CFR 314.55(b)/21 CFR 601.27(b)] <input type="checkbox"/> Accelerated approval confirmatory studies (21 CFR 314.510/21 CFR 601.41) <input type="checkbox"/> Animal rule postmarketing studies to verify clinical benefit and safety (21 CFR 314.610/21 CFR 601.42)			
Collaborative Review Division ( <i>if OTC product</i> ):				
List referenced IND Number(s):				
<b>Goal Dates/Product Names/Classification Properties</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
PDUFA and Action Goal dates correct in tracking system?  <i>If no, ask the document room staff to correct them immediately. These are the dates used for calculating inspection dates.</i>	X			
Are the proprietary, established/proper, and applicant names correct in tracking system?  <i>If no, ask the document room staff to make the corrections. Also, ask the document room staff to add the established/proper name to the supporting IND(s) if not already entered into tracking system.</i>	X			
Is the review priority (S or P) and all appropriate classifications/properties entered into tracking system (e.g., chemical classification, combination product classification, 505(b)(2), orphan drug)? <i>For NDAs/NDA supplements, check the New Application and New Supplement Notification Checklists for a list of all classifications/properties at: <a href="http://inside.fda.gov:9003/CDER/OfficeofBusinessProcessSupport/ucm163969.htm">http://inside.fda.gov:9003/CDER/OfficeofBusinessProcessSupport/ucm163969.htm</a></i>  <i>If no, ask the document room staff to make the appropriate entries.</i>	X			
<b>Application Integrity Policy</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Is the application affected by the Application Integrity Policy (AIP)? <i>Check the AIP list at: <a href="http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm">http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm</a></i>		X		
<b>If yes, explain in comment column.</b>				
<b>If affected by AIP, has OC/OMPQ been notified of the submission? If yes, date notified:</b>				
<b>User Fees</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Is Form 3397 (User Fee Cover Sheet) included with authorized signature?	X			

<p><u>User Fee Status</u></p> <p><i>If a user fee is required and it has not been paid (and it is not exempted or waived), the application is unacceptable for filing following a 5-day grace period. Review stops. Send Unacceptable for Filing (UN) letter and contact user fee staff.</i></p>	<p>Payment for this application:</p> <p>X Paid</p> <p><input type="checkbox"/> Exempt (orphan, government)</p> <p><input type="checkbox"/> Waived (e.g., small business, public health)</p> <p><input type="checkbox"/> Not required</p>																			
<p><i>If the firm is in arrears for other fees (regardless of whether a user fee has been paid for this application), the application is unacceptable for filing (5-day grace period does not apply). Review stops. Send UN letter and contact the user fee staff.</i></p>	<p>Payment of other user fees:</p> <p><input type="checkbox"/> Not in arrears</p> <p><input type="checkbox"/> In arrears</p>																			
<p><b>505(b)(2)</b> <b>(NDAs/NDA Efficacy Supplements only)</b></p>	<p><b>YES</b></p>	<p><b>NO</b></p>	<p><b>NA</b></p>	<p><b>Comment</b></p>																
<p>Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA?</p>																				
<p>Is the application for a duplicate of a listed drug whose only difference is that the extent to which the active ingredient(s) is absorbed or otherwise made available to the site of action is less than that of the reference listed drug (RLD)? [see 21 CFR 314.54(b)(1)].</p>																				
<p>Is the application for a duplicate of a listed drug whose only difference is that the rate at which the proposed product's active ingredient(s) is absorbed or made available to the site of action is unintentionally less than that of the listed drug [see 21 CFR 314.54(b)(2)]?</p> <p><i>If you answered yes to any of the above questions, the application may be refused for filing under 21 CFR 314.101(d)(9). Contact the 505(b)(2) review staff in the Immediate Office of New Drugs</i></p>																				
<p>Is there unexpired exclusivity on the active moiety (e.g., 5-year, 3-year, orphan, or pediatric exclusivity)?</p> <p><i>Check the Electronic Orange Book at:</i> <a href="http://www.accessdata.fda.gov/scripts/cder/ob/default.cfm">http://www.accessdata.fda.gov/scripts/cder/ob/default.cfm</a></p> <p><b>If yes, please list below:</b></p> <table border="1" data-bbox="203 1451 1349 1587"> <thead> <tr> <th data-bbox="203 1451 495 1486">Application No.</th> <th data-bbox="495 1451 773 1486">Drug Name</th> <th data-bbox="773 1451 1060 1486">Exclusivity Code</th> <th data-bbox="1060 1451 1349 1486">Exclusivity Expiration</th> </tr> </thead> <tbody> <tr> <td> </td> <td> </td> <td> </td> <td> </td> </tr> <tr> <td> </td> <td> </td> <td> </td> <td> </td> </tr> <tr> <td> </td> <td> </td> <td> </td> <td> </td> </tr> </tbody> </table>	Application No.	Drug Name	Exclusivity Code	Exclusivity Expiration																
Application No.	Drug Name	Exclusivity Code	Exclusivity Expiration																	
<p><i>If there is unexpired, 5-year exclusivity remaining on the active moiety for the proposed drug product, a 505(b)(2) application cannot be submitted until the period of exclusivity expires (unless the applicant provides paragraph IV patent certification; then an application can be submitted four years after the date of approval.) Pediatric exclusivity will extend both of the timeframes in this provision by 6 months. 21 CFR 314.108(b)(2). Unexpired, 3-year exclusivity will only block the approval, not the submission of a 505(b)(2) application.</i></p>																				
<p><b>Exclusivity</b></p>	<p><b>YES</b></p>	<p><b>NO</b></p>	<p><b>NA</b></p>	<p><b>Comment</b></p>																
<p>Does another product (same active moiety) have orphan exclusivity for the same indication? <i>Check the Orphan Drug Designations and Approvals list at:</i> <a href="http://www.accessdata.fda.gov/scripts/opdlisting/oopd/index.cfm">http://www.accessdata.fda.gov/scripts/opdlisting/oopd/index.cfm</a></p>		<p>X</p>																		

<p><b>If another product has orphan exclusivity</b>, is the product considered to be the same product according to the orphan drug definition of sameness [see 21 CFR 316.3(b)(13)]?</p> <p><i>If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy</i></p>				
<p>Has the applicant requested 5-year or 3-year Waxman-Hatch exclusivity? (<i>NDAs/NDA efficacy supplements only</i>)</p> <p><b>If yes, # years requested:</b></p> <p><i>Note: An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.</i></p>				
<p>Is the proposed product a single enantiomer of a racemic drug previously approved for a different therapeutic use (<i>NDAs only</i>)?</p>		X		
<p><b>If yes</b>, did the applicant: (a) elect to have the single enantiomer (contained as an active ingredient) not be considered the same active ingredient as that contained in an already approved racemic drug, and/or (b): request exclusivity pursuant to section 505(u) of the Act (per FDAAA Section 1113)?</p> <p><i>If yes, contact Mary Ann Holovac, Director of Drug Information, OGD/DLPS/LRB.</i></p>				

Format and Content				
<p><i>Do not check mixed submission if the only electronic component is the content of labeling (COL).</i></p>	<input type="checkbox"/> All paper (except for COL) <input checked="" type="checkbox"/> All electronic <input type="checkbox"/> Mixed (paper/electronic)			
	<input checked="" type="checkbox"/> CTD <input type="checkbox"/> Non-CTD <input type="checkbox"/> Mixed (CTD/non-CTD)			
<p><b>If mixed (paper/electronic) submission</b>, which parts of the application are submitted in electronic format?</p>				
Overall Format/Content	YES	NO	NA	Comment
<p><b>If electronic submission</b>, does it follow the eCTD guidance?<sup>1</sup>  <b>If not</b>, explain (e.g., waiver granted).</p>	X			
<p><b>Index:</b> Does the submission contain an accurate comprehensive index?</p>	X			
<p>Is the submission complete as required under 21 CFR 314.50 (<i>NDAs/NDA efficacy supplements</i>) or under 21 CFR 601.2 (<i>BLAs/BLA efficacy supplements</i>) including:</p>	X			

1

<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072349.pdf>

X legible X English (or translated into English) X pagination X navigable hyperlinks (electronic submissions only)				
<b>If no, explain.</b>				
<b>BLAs only:</b> Companion application received if a shared or divided manufacturing arrangement?				
<b>If yes, BLA #</b>				
<b>Applications in “the Program” (PDUFA V) (NME NDAs/Original BLAs)</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Was there an agreement for any minor application components to be submitted within 30 days after the original submission?				
<ul style="list-style-type: none"> <li>If yes, were all of them submitted on time?</li> </ul>				
Is a comprehensive and readily located list of all clinical sites included or referenced in the application?				
Is a comprehensive and readily located list of all manufacturing facilities included or referenced in the application?				
<b>Forms and Certifications</b>				
<i>Electronic forms and certifications with electronic signatures (scanned, digital, or electronic – similar to DARRTS, e.g., /s/) are acceptable. Otherwise, paper forms and certifications with hand-written signatures must be included. Forms include: user fee cover sheet (3397), application form (356h), patent information (3542a), financial disclosure (3454/3455), and clinical trials (3674); Certifications include: debarment certification, patent certification(s), field copy certification, and pediatric certification.</i>				
<b>Application Form</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Is form FDA 356h included with authorized signature per 21 CFR 314.50(a)?	X			
<i>If foreign applicant, a U.S. agent must sign the form [see 21 CFR 314.50(a)(5)].</i>				
Are all establishments and their registration numbers listed on the form/attached to the form?	X			
<b>Patent Information (NDAs/NDA efficacy supplements only)</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Is patent information submitted on form FDA 3542a per 21 CFR 314.53(c)?	X			
<b>Financial Disclosure</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Are financial disclosure forms FDA 3454 and/or 3455 included with authorized signature per 21 CFR 54.4(a)(1) and (3)?	X			

<p><i>Forms must be signed by the APPLICANT, not an Agent [see 21 CFR 54.2(g)].</i></p> <p><i>Note: Financial disclosure is required for bioequivalence studies that are the basis for approval.</i></p>				
<b>Clinical Trials Database</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
<p>Is form FDA 3674 included with authorized signature?</p> <p><i>If yes, ensure that the application is also coded with the supporting document category, "Form 3674."</i></p> <p><i>If no, ensure that language requesting submission of the form is included in the acknowledgement letter sent to the applicant</i></p>		X		
<b>Debarment Certification</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
<p>Is a correctly worded Debarment Certification included with authorized signature?</p> <p><i>Certification is not required for supplements if submitted in the original application; If foreign applicant, <b>both</b> the applicant and the U.S. Agent must sign the certification [per Guidance for Industry: Submitting Debarment Certifications].</i></p> <p><i>Note: Debarment Certification should use wording in FD&amp;C Act Section 306(k)(1) i.e., "[Name of applicant] hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application." Applicant may not use wording such as, "To the best of my knowledge..."</i></p>	X			
<b>Field Copy Certification (NDAs/NDA efficacy supplements only)</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
<p><b>For paper submissions only:</b> Is a Field Copy Certification (that it is a true copy of the CMC technical section) included?</p> <p><i>Field Copy Certification is not needed if there is no CMC technical section or if this is an electronic submission (the Field Office has access to the EDR)</i></p> <p><i>If maroon field copy jackets from foreign applicants are received, return them to CDR for delivery to the appropriate field office.</i></p>	X			
<b>Controlled Substance/Product with Abuse Potential</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
<p><u>For NMEs:</u> Is an Abuse Liability Assessment, including a proposal for scheduling, submitted per 21 CFR 314.50(d)(5)(vii)?</p> <p><i>If yes, date consult sent to the Controlled Substance Staff:</i></p> <p><u>For non-NMEs:</u> <i>Date of consult sent to Controlled Substance Staff:</i></p>			X	
<b>Pediatrics</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>

<b><u>PREA</u></b>			X	
Does the application trigger PREA?  <i>If yes, notify PeRC RPM (PeRC meeting is required)<sup>2</sup></i>  <i>Note: NDAs/BLAs/efficacy supplements for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration trigger PREA. All waiver &amp; deferral requests, pediatric plans, and pediatric assessment studies must be reviewed by PeRC prior to approval of the application/supplement.</i>				
<b>If the application triggers PREA</b> , are the required pediatric assessment studies or a full waiver of pediatric studies included?				
<b>If studies or full waiver not included</b> , is a request for full waiver of pediatric studies OR a request for partial waiver and/or deferral with a pediatric plan included?  <i>If no, request in 74-day letter</i>				
<b>If a request for full waiver/partial waiver/deferral is included</b> , does the application contain the certification(s) required by FDCA Section 505B(a)(3) and (4)?  <i>If no, request in 74-day letter</i>				
<b><u>BPCA</u> (NDAs/NDA efficacy supplements only):</b>  Is this submission a complete response to a pediatric Written Request?  <i>If yes, notify Pediatric Exclusivity Board RPM (pediatric exclusivity determination is required)<sup>3</sup></i>				
<b>Proprietary Name</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Is a proposed proprietary name submitted?  <i>If yes, ensure that the application is also coded with the supporting document category, "Proprietary Name/Request for Review."</i>		X		
<b>REMS</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Is a REMS submitted?  <i>If yes, send consult to OSE/DRISK and notify OC/OSI/DSC/PMSB via the CDER OSI RMP mailbox</i>		X		
<b>Prescription Labeling</b>	<input type="checkbox"/> <b>Not applicable</b>			
Check all types of labeling submitted.	<input checked="" type="checkbox"/> Package Insert (PI) <input checked="" type="checkbox"/> Patient Package Insert (PPI) <input type="checkbox"/> Instructions for Use (IFU) <input type="checkbox"/> Medication Guide (MedGuide) <input checked="" type="checkbox"/> Carton labels			

<sup>2</sup> <http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/PediatricandMaternalHealthStaff/ucm027829.htm>

<sup>3</sup> <http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/PediatricandMaternalHealthStaff/ucm027837.htm>

	<input checked="" type="checkbox"/> Immediate container labels <input type="checkbox"/> Diluent <input type="checkbox"/> Other (specify)			
	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Is Electronic Content of Labeling (COL) submitted in SPL format?  <i>If no, request applicant to submit SPL before the filing date.</i>	X			
Is the PI submitted in PLR format? <sup>4</sup>	X			
<b>If PI not submitted in PLR format</b> , was a waiver or deferral requested before the application was received or in the submission? <b>If requested before application was submitted</b> , what is the status of the request?  <i>If no waiver or deferral, request applicant to submit labeling in PLR format before the filing date.</i>				
All labeling (PI, PPI, MedGuide, IFU, carton and immediate container labels) consulted to OPDP?	X			
MedGuide, PPI, IFU (plus PI) consulted to OSE/DRISK? (send WORD version if available)	X			
Carton and immediate container labels, PI, PPI sent to OSE/DMEPA and appropriate CMC review office (OBP or ONDQA)?	X			
<b>OTC Labeling</b>	<b>X Not Applicable</b>			
Check all types of labeling submitted.	<input type="checkbox"/> Outer carton label <input type="checkbox"/> Immediate container label <input type="checkbox"/> Blister card <input type="checkbox"/> Blister backing label <input type="checkbox"/> Consumer Information Leaflet (CIL) <input type="checkbox"/> Physician sample <input type="checkbox"/> Consumer sample <input type="checkbox"/> Other (specify)			
	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Is electronic content of labeling (COL) submitted?  <i>If no, request in 74-day letter.</i>				
Are annotated specifications submitted for all stock keeping units (SKUs)?  <i>If no, request in 74-day letter.</i>				
If representative labeling is submitted, are all represented SKUs defined?  <i>If no, request in 74-day letter.</i>				

4

<http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/StudyEndpointsandLabelingDevelopmentTeam/ucm025576.htm>

All labeling/packaging, and current approved Rx PI (if switch) sent to OSE/DMEPA?				
<b>Other Consults</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Are additional consults needed? (e.g., IFU to CDRH; QT study report to QT Interdisciplinary Review Team)		X		
<i>If yes, specify consult(s) and date(s) sent:</i>				
<b>Meeting Minutes/SPAs</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
End-of Phase 2 meeting(s)? <b>Date(s):</b>		X		
<i>If yes, distribute minutes before filing meeting</i>				
Pre-NDA/Pre-BLA/Pre-Supplement meeting(s)? <b>Date(s):</b>		X		
<i>If yes, distribute minutes before filing meeting</i>				
Any Special Protocol Assessments (SPAs)? <b>Date(s):</b>		X		
<i>If yes, distribute letter and/or relevant minutes before filing meeting</i>				

ATTACHMENT

**MEMO OF FILING MEETING**

**DATE:** November 6, 2012

**NDA:** 204654

**PROPRIETARY NAME:**

**ESTABLISHED/PROPER NAME:** norethindrone acetate and ethinyl estradiol and ferrous fumarate (b) (4)

**DOSAGE FORM/STRENGTH:** (b) (4) and Tablets

**APPLICANT:** Warner Chilcott

**PROPOSED INDICATION(S):** Prevention of Pregnancy

**REVIEW TEAM:**

Discipline/Organization	Names		Present at filing meeting? (Y or N)
Regulatory Project Management	RPM:	Jennifer Mercier	
	CPMS/TL:	Jennifer Mercier	
Cross-Discipline Team Leader (CDTL)	Lisa Soule, M.D.		
Clinical	Reviewer:	Daniel Davis, M.D.	Y
	TL:	Lisa Soule, M.D.	Y
Social Scientist Review ( <i>for OTC products</i> )	Reviewer:		
	TL:		
OTC Labeling Review ( <i>for OTC products</i> )	Reviewer:		
	TL:		
Clinical Microbiology ( <i>for antimicrobial products</i> )	Reviewer:		
	TL:		

Clinical Pharmacology	Reviewer:	Li Li, Ph.D.	Y
	TL:	Myong Jin Kim, Ph.D.	Y
Biostatistics	Reviewer:	Xin Fang, Ph.D.	Y
	TL:	Mahboob Sobhan, Ph.D.	Y
Nonclinical (Pharmacology/Toxicology)	Reviewer:	Krishan Raheja, DVM	Y
	TL:	Alexander Jordan, Ph.D.	N
Statistics (carcinogenicity)	Reviewer:		
	TL:		
Immunogenicity (assay/assay validation) ( <i>for BLAs/BLA efficacy supplements</i> )	Reviewer:		
	TL:		
Product Quality (CMC)	Reviewer:	Gene Holbert, Ph.D.	Y
	TL:	Donna Christner, Ph.D.	Y
Quality Microbiology ( <i>for sterile products</i> )	Reviewer:		
	TL:		
CMC Labeling Review	Reviewer:		
	TL:		
Facility Review/Inspection	Reviewer:		
	TL:		
OSE/DMEPA (proprietary name)	Reviewer:	Manizheh Siahpoushan	Y
	TL:	Zachary Oleszczuk	Y
OSE/DRISK (REMS)	Reviewer:	Franklin Stephenson	Y
	TL:		
OC/OSI/DSC/PMSB (REMS)	Reviewer:		
	TL:		

Bioresearch Monitoring (OSI)	Reviewer:		
	TL:		
Controlled Substance Staff (CSS)	Reviewer:		
	TL:		
Other reviewers			
Other attendees	Audrey Gassman		

**FILING MEETING DISCUSSION:**

<p><b>GENERAL</b></p> <ul style="list-style-type: none"> <li>• 505(b)(2) filing issues?</li> </ul> <p><b>If yes, list issues:</b></p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> <li>• Per reviewers, are all parts in English or English translation?</li> </ul> <p><b>If no, explain:</b></p>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> <li>• Electronic Submission comments</li> </ul> <p><b>List comments:</b></p>	<input type="checkbox"/> Not Applicable
<p><b>CLINICAL</b></p> <p><b>Comments:</b></p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<ul style="list-style-type: none"> <li>• Clinical study site(s) inspections(s) needed?</li> </ul> <p><b>If no, explain:</b> BE studies conducted</p>	<input type="checkbox"/> YES <input checked="" type="checkbox"/> NO
<ul style="list-style-type: none"> <li>• Advisory Committee Meeting needed?</li> </ul> <p><b>Comments:</b></p> <p><i>If no, for an NME NDA or original BLA, include the reason. For example:</i></p> <ul style="list-style-type: none"> <li>○ <i>this drug/biologic is not the first in its class</i></li> <li>○ <i>the clinical study design was acceptable</i></li> </ul>	<input type="checkbox"/> YES Date if known: <input checked="" type="checkbox"/> NO <input type="checkbox"/> To be determined Reason: Not an NME

<ul style="list-style-type: none"> <li>○ <i>the application did not raise significant safety or efficacy issues</i></li> <li>○ <i>the application did not raise significant public health questions on the role of the drug/biologic in the diagnosis, cure, mitigation, treatment or prevention of a disease</i></li> </ul>	
<ul style="list-style-type: none"> <li>• Abuse Liability/Potential</li> </ul> <p><b>Comments:</b></p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE  <input type="checkbox"/> Review issues for 74-day letter
<ul style="list-style-type: none"> <li>• If the application is affected by the AIP, has the division made a recommendation regarding whether or not an exception to the AIP should be granted to permit review based on medical necessity or public health significance?</li> </ul> <p><b>Comments:</b></p>	<input type="checkbox"/> Not Applicable <input type="checkbox"/> YES <input type="checkbox"/> NO
<p><b>CLINICAL MICROBIOLOGY</b></p> <p><b>Comments:</b></p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE  <input type="checkbox"/> Review issues for 74-day letter
<p><b>CLINICAL PHARMACOLOGY</b></p> <p><b>Comments:</b></p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE  <input type="checkbox"/> Review issues for 74-day letter
<ul style="list-style-type: none"> <li>• Clinical pharmacology study site(s) inspections(s) needed?</li> </ul>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<p><b>BIOSTATISTICS</b></p> <p><b>Comments:</b></p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE  <input type="checkbox"/> Review issues for 74-day letter
<p><b>NONCLINICAL (PHARMACOLOGY/TOXICOLOGY)</b></p> <p><b>Comments:</b></p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE  <input type="checkbox"/> Review issues for 74-day letter

<p><b>IMMUNOGENICITY (BLAs/BLA efficacy supplements only)</b></p> <p>Comments:</p>	<p>X Not Applicable  <input type="checkbox"/> FILE  <input type="checkbox"/> REFUSE TO FILE  <input type="checkbox"/> Review issues for 74-day letter</p>
<p><b>PRODUCT QUALITY (CMC)</b></p> <p>Comments:</p>	<p><input type="checkbox"/> Not Applicable  X FILE  <input type="checkbox"/> REFUSE TO FILE  <input type="checkbox"/> Review issues for 74-day letter</p>
<p><b><u>Environmental Assessment</u></b></p> <ul style="list-style-type: none"> <li>• Categorical exclusion for environmental assessment (EA) requested?   <b>If no</b>, was a complete EA submitted?   <b>If EA submitted</b>, consulted to EA officer (OPS)?</li> </ul> <p>Comments:</p>	<p><input type="checkbox"/> Not Applicable   <input type="checkbox"/> YES  <input type="checkbox"/> NO   <input type="checkbox"/> YES  <input type="checkbox"/> NO   <input type="checkbox"/> YES  <input type="checkbox"/> NO</p>
<p><b><u>Quality Microbiology (for sterile products)</u></b></p> <ul style="list-style-type: none"> <li>• Was the Microbiology Team consulted for validation of sterilization? (NDAs/NDA supplements only)</li> </ul> <p>Comments:</p>	<p>X Not Applicable   <input type="checkbox"/> YES  <input type="checkbox"/> NO</p>
<p><b><u>Facility Inspection</u></b></p> <ul style="list-style-type: none"> <li>• Establishment(s) ready for inspection?</li> <li>▪ Establishment Evaluation Request (EER/TBP-EER) submitted to OMPQ?</li> </ul> <p>Comments:</p>	<p><input type="checkbox"/> Not Applicable   X YES  <input type="checkbox"/> NO   X YES  <input type="checkbox"/> NO</p>
<p><b><u>Facility/Microbiology Review (BLAs only)</u></b></p> <p>Comments:</p>	<p>X Not Applicable  <input type="checkbox"/> FILE  <input type="checkbox"/> REFUSE TO FILE  <input type="checkbox"/> Review issues for 74-day letter</p>

<b><u>CMC Labeling Review</u></b>	
<b>Comments:</b>	<input type="checkbox"/> Review issues for 74-day letter
<b>REGULATORY PROJECT MANAGEMENT</b>	
<b>Signatory Authority:</b> Hylton Joffe	
<b>Date of Mid-Cycle Meeting</b> (for NME NDAs/BLAs in “the Program” PDUFA V): February 25, 2013	
<b>21<sup>st</sup> Century Review Milestones (see attached)</b> (listing review milestones in this document is optional):	
<b>Comments:</b>	
<b>REGULATORY CONCLUSIONS/DEFICIENCIES</b>	
X	The application is unsuitable for filing. Explain why:
X	The application, on its face, appears to be suitable for filing.  <u>Review Issues:</u>  X No review issues have been identified for the 74-day letter.  <input type="checkbox"/> Review issues have been identified for the 74-day letter. List (optional):  <u>Review Classification:</u>  X Standard Review  <input type="checkbox"/> Priority Review
<b>ACTIONS ITEMS</b>	
<input type="checkbox"/>	Ensure that any updates to the review priority (S or P) and classifications/properties are entered into tracking system (e.g., chemical classification, combination product classification, 505(b)(2), orphan drug).
<input type="checkbox"/>	If RTF, notify everybody who already received a consult request, OSE PM, and Product Quality PM (to cancel EER/TBP-EER).
<input type="checkbox"/>	If filed, and the application is under AIP, prepare a letter either granting (for signature by Center Director) or denying (for signature by ODE Director) an exception for review.
<input type="checkbox"/>	BLA/BLA supplements: If filed, send 60-day filing letter
<input type="checkbox"/>	If priority review:

	<ul style="list-style-type: none"> <li>• notify sponsor in writing by day 60 (For BLAs/BLA supplements: include in 60-day filing letter; For NDAs/NDA supplements: see CST for choices)</li> <li>• notify OMPQ (so facility inspections can be scheduled earlier)</li> </ul>
X	Send review issues/no review issues by day 74
X	Conduct a PLR format labeling review and include labeling issues in the 74-day letter
<input type="checkbox"/>	Update the PDUFA V DARRTS page (for NME NDAs in “the Program”)
<input type="checkbox"/>	BLA/BLA supplements: Send the Product Information Sheet to the product reviewer and the Facility Information Sheet to the facility reviewer for completion. Ensure that the completed forms are forwarded to the CDER RMS-BLA Superuser for data entry into RMS-BLA one month prior to taking an action [These sheets may be found in the CST eRoom at: <a href="http://eroom.fda.gov/eRoom/CDER2/CDERStandardLettersCommittee/0_1685f">http://eroom.fda.gov/eRoom/CDER2/CDERStandardLettersCommittee/0_1685f</a> ]
<input type="checkbox"/>	Other

## Appendix A (NDA and NDA Supplements only)

NOTE: The term "original application" or "original NDA" as used in this appendix denotes the NDA submitted. It does not refer to the reference drug product or "reference listed drug."

An original application is likely to be a 505(b)(2) application if:

- (1) it relies on published literature to meet any of the approval requirements, and the applicant does not have a written right of reference to the underlying data. If published literature is cited in the NDA but is not necessary for approval, the inclusion of such literature will not, in itself, make the application a 505(b)(2) application,
- (2) it relies for approval on the Agency's previous findings of safety and efficacy for a listed drug product and the applicant does not own or have right to reference the data supporting that approval, or
- (3) it relies on what is "generally known" or "scientifically accepted" about a class of products to support the safety or effectiveness of the particular drug for which the applicant is seeking approval. (Note, however, that this does not mean *any* reference to general information or knowledge (e.g., about disease etiology, support for particular endpoints, methods of analysis) causes the application to be a 505(b)(2) application.)

Types of products for which 505(b)(2) applications are likely to be submitted include: fixed-dose combination drug products (e.g., heart drug and diuretic (hydrochlorothiazide) combinations); OTC monograph deviations (see 21 CFR 330.11); new dosage forms; new indications; and, new salts.

An efficacy supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2).

An efficacy supplement is a 505(b)(1) supplement if the supplement contains all of the information needed to support the approval of the change proposed in the supplement. For example, if the supplemental application is for a new indication, the supplement is a 505(b)(1) if:

- (1) The applicant has conducted its own studies to support the new indication (or otherwise owns or has right of reference to the data/studies),
- (2) No additional information beyond what is included in the supplement or was embodied in the finding of safety and effectiveness for the original application or previously approved supplements is needed to support the change. For example, this would likely be the case with respect to safety considerations if the dose(s) was/were the same as (or lower than) the original application, and.
- (3) All other "criteria" are met (e.g., the applicant owns or has right of reference to the data relied upon for approval of the supplement, the application does not rely

for approval on published literature based on data to which the applicant does not have a right of reference).

An efficacy supplement is a 505(b)(2) supplement if:

- (1) Approval of the change proposed in the supplemental application would require data beyond that needed to support our previous finding of safety and efficacy in the approval of the original application (or earlier supplement), and the applicant has not conducted all of its own studies for approval of the change, or obtained a right to reference studies it does not own. For example, if the change were for a new indication AND a higher dose, we would likely require clinical efficacy data and preclinical safety data to approve the higher dose. If the applicant provided the effectiveness data, but had to rely on a different listed drug, or a new aspect of a previously cited listed drug, to support the safety of the new dose, the supplement would be a 505(b)(2),
- (2) The applicant relies for approval of the supplement on published literature that is based on data that the applicant does not own or have a right to reference. If published literature is cited in the supplement but is not necessary for approval, the inclusion of such literature will not, in itself, make the supplement a 505(b)(2) supplement, or
- (3) The applicant is relying upon any data they do not own or to which they do not have right of reference.

If you have questions about whether an application is a 505(b)(1) or 505(b)(2) application, consult with your OND ADRA or OND IO.

-----  
**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/  
-----

JENNIFER L MERCIER  
11/14/2012

**Department of Health and Human Services  
Public Health Service  
Food and Drug Administration  
Center for Drug Evaluation and Research  
Office of Surveillance and Epidemiology  
Office of Medication Error Prevention and Risk Management**

**Label, Labeling and Packaging Review**

Date: May 21, 2013

Reviewers: Alison Park, Pharm.D.  
Manizheh Siahpoushan, Pharm.D.  
Division of Medication Error Prevention and Analysis

Acting Team Leader: James Schlick, RPh., MBA  
Division of Medication Error Prevention and Analysis

Division Director: Carol Holquist, RPh  
Division of Medication Error Prevention and Analysis

Drug Names and Strengths: Norethindrone Acetate and Ethinyl Estradiol  
Chewable Tablets, Ethinyl Estradiol Tablets, and  
Ferrous Fumarate Tablets  
1 mg/10 mcg and 10 mcg and 75 mg

Application Type/Number: NDA 204654

Applicant: Warner Chilcott Company, LLC

OSE RCM #: 2013-1

\*\*\* This document contains proprietary and confidential information that should not be released to the public.\*\*\*

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## 1 INTRODUCTION

This review evaluates the proposed container labels, carton, and insert labeling for Norethindrone Acetate and Ethinyl Estradiol Chewable Tablets, Ethinyl Estradiol Tablets, and Ferrous Fumarate Tablets, NDA 204654, for areas of vulnerability that could lead to medication errors.

### 1.1 REGULATORY HISTORY

New Drug Application (NDA) 204654 was submitted by the Applicant, Warner Chilcott LLC, under Section 505(b)(1) for Norethindrone Acetate and Ethinyl Estradiol Chewable Tablets, Ethinyl Estradiol Tablets, and Ferrous Fumarate Tablets on September 28, 2012. This NDA provides for a new method of administration for low dose oral contraception consisting of mint-flavored, chewable tablets containing 1 mg norethindrone acetate and 10 mcg ethinyl estradiol taken daily for 24 days followed by tablets containing 10 mcg ethinyl estradiol alone taken daily for 2 days and 75 mg ferrous fumarate taken daily for 2 days. The proposed regimen (i.e., 24 active tablets containing 1 mg of norethindrone acetate and 10 mcg ethinyl estradiol, 2 active tablets containing 10 mcg ethinyl estradiol, and 2 tablets containing 75 mg ferrous fumarate) is the same as the approved regimen for Lo Loestrin Fe (NDA 022501, approved October 21, 2010) by Applicant holder, Warner Chilcott LLC. The main difference with NDA 204654 is that the first 24 active tablets may be chewed before swallowing and followed with liquid or may be swallowed whole.

On April 4, 2013, the Applicant submitted a request for proprietary name review for (b) (4) for NDA 204654 which is being reviewed under a separate cover by DMEPA.

### 1.2 PRODUCT INFORMATION

The following product information is provided in the September 28, 2012 submission.

- Active Ingredient: Norethindrone Acetate/Ethinyl Estradiol (NA/EE), Ethinyl Estradiol (EE), and Ferrous Fumarate
- Indication of Use: Prevention of Pregnancy
- Route of Administration: Oral
- Dosage Form: Chewable Tablets (Norethindrone Acetate and Ethinyl Estradiol) Tablets (Ethinyl Estradiol), and Tablets (Ferrous Fumarate)
- Strength: 1 mg/10 mcg, 10 mcg, and 75 mg
- Dose and Frequency: Take one tablet by mouth at the same time every day. The blue tablet may be swallowed whole or chewed and swallowed. If the blue tablet is chewed, the patient should drink a full glass (8 ounces) of liquid immediately after swallowing. The white tablet and the brown tablet are swallowed whole.
- How Supplied: Carton of 5 blister cards; each blister card contains 24 blue, round (active) chewable tablets containing 1 mg norethindrone and 10 mcg ethinyl estradiol, 2 white hexagonal (active) tablets containing 10 mcg ethinyl estradiol, and 2 brown, round (non-hormonal placebo) tablets containing 75 mg ferrous fumarate.

- Storage: Store at 25°C (77°F); excursions permitted to 15 to 30°C (59 to 86°F)
- Container and Closure System: Primary packaging consists of unit-dose blisters consisting of (b) (4) blister film and an aluminum (b) (4) lidding. Secondary packaging consists of a rigid (b) (4) card bonded to the unit-dose blister, prescriber and patient package inserts, and (b) (4) cartons.

## 2 METHODS AND MATERIALS REVIEWED

DMEPA searched the FDA Adverse Event Reporting System (FAERS) database for Lo Loestrin Fe medication error reports. We also reviewed the Norethindrone Acetate and Ethinyl Estradiol Chewable Tablets, Ethinyl Estradiol Tablets, and Ferrous Fumarate Tablets labels and package insert labeling submitted by the Applicant.

### 2.1 SELECTION OF MEDICATION ERROR CASES

We searched the FAERS database using the strategy listed in Table 1.

<b>Table 1: FAERS Search Strategy</b>	
Date of Search	February 25, 2013
Drug Names	Trade name: LO LOESTRIN FE Verbatim: LO LOESTRIN%
MedDRA Search Strategy	Medication Errors (HLGT) Product Packaging Issues HLT Product Label Issues HLT Product Quality Issues (NEC) HLT

The FAERS database search identified five cases. Each case was reviewed for relevancy and duplication. After individual review, two cases were not included in the final analysis for the following reasons:

- Product Quality issue (i.e., possibility of “bad batch” due to an adverse event of heavy bleeding)
- Adverse Event and not a medication error (i.e., patient experienced blood clot in leg)

### 2.2 MATERIALS REVIEWED

Using the principals of human factors and Failure Mode and Effects Analysis,<sup>1</sup> along with post marketing medication error data, the Division of Medication Error Prevention and Analysis (DMEPA) evaluated the following:

- Trade and professional sample blister card labels submitted April 4, 2013 (Appendix B)
- Trade and professional sample carton labeling submitted April 4, 2013 (Appendix C)

<sup>1</sup> Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

- Professional sample tray labeling submitted April 4, 2013 (Appendix D)
- Insert Labeling submitted April 4, 2013

### **3 MEDICATION ERROR RISK ASSESSMENT**

The following sections describe the results of our FAERS search and the risk assessment of the Norethindrone Acetate and Ethinyl Estradiol Chewable Tablets, Ethinyl Estradiol Tablets, and Ferrous Fumarate Tablets product design as well as the associated labels and labeling.

#### **3.1 MEDICATION ERROR CASES**

Following exclusions as described in section 2.1, three Lo Loestrin Fe medication error cases remained for our detailed analysis. Two cases described dispensing errors. The first case (Case #8668651v.1) described an error in which Lo Loestrin Fe was dispensed instead of Loestrin 24 Fe. The patient detected the error at home and returned the wrong drug before any were taken. The second case (Case # 8362429v.1) described an error in which Loestrin 24 Fe was dispensed instead of Lo Loestrin Fe. Similar product name is identified as a contributing factor in the narrative which states that “a different name would have not led to this error.”

The third case (Case #8382122v.1) described a potential for medication error due to drug name confusion between Loestrin 24 Fe and Lo Loestrin Fe. The reporter states “the manufacturer should have named the second drug something different to avoid confusion.”

#### **3.2 INTEGRATED SUMMARY OF MEDICATION ERROR RISK ASSESSMENT**

The Applicant is proposing a chewable form of their currently approved Lo Loestrin Fe product. The Applicant does not indicate in the September 28, 2012 submission if it intends to discontinue marketing of Lo Loestrin Fe upon approval of the proposed product or if this NDA represents an extension to the Loestrin product line. Two cases of dispensing errors and one case of complaint concerning the similarity of the names have been identified between Loestrin 24 Fe and Lo Loestrin Fe. Our assessment of the labels and labeling found that the two products are adequately differentiated by the use of different colors (Appendix E and F). However, similar product name is identified as a root cause of the medication error in two of the three cases. The Applicant submitted the proposed proprietary name, (b) (4) for this product. This should minimize the risk of confusion; however, the Applicant is proposing a similar trade dress for the proposed product as the Lo Loestrin Fe (Appendix E). This is concerning because similar trade dress may create continued errors within this company line. Therefore, it is important that we ensure adequate differentiation of this product from others within the Loestrin product line.

Reference is made to the Applicant’s currently marketed NDA 022501 for Lo Loestrin Fe tablets which are swallowed whole. In this proposed Application for a new method of administration, it is noted that only the combination of 1 mg norethindrone acetate and 10 mcg ethinyl estradiol are supposed to be chewed. However, the remaining tablets (containing 10 mcg ethinyl estradiol and the 75 mg ferrous fumarate tablets) are intended to be swallowed whole as per the currently approved method of administration for Lo Loestrin Fe. Although the Applicant has reflected this in the proposed container labels

(i.e., boxed in statement “**DO NOT CHEW**”) and insert labeling (i.e., **Section 2.1** under **Dosage and Administration** states “The blue tablet [REDACTED] (b) (4) chewed and swallowed” and “The white tablet and the brown tablet are swallowed”), the possibility exists for incorrect route of administration errors in which the 10 mcg ethinyl estradiol and 75 mg ferrous fumarate tablets may be inadvertently chewed. Also, dose omission errors may occur in which the patient may skip the last four tablets mistaking all of them for inactive pills instead of just the last two non-hormonal placebo ferrous fumarate tablets.

The medical officer stated, via email, the two 10 mcg ethinyl estradiol tablets are intended to improve efficacy and breakthrough bleeding/spotting but there is little evidence for such an effect. Therefore, there would be no issues in safety and efficacy if the 10 mcg ethinyl estradiol tablets are not taken or are chewed and swallowed. Additionally, the CMC reviewer and medical officer noted that the non-hormonal placebo ferrous fumarate tablets are flavored and sweetened so they could be chewed or not taken without affecting safety or efficacy. Although there does not appear to be any serious effects from incorrect route of administration or dose omission errors with the proposed product, the blister card label can be improved to minimize these types of errors.

The Applicant is proposing [REDACTED] (b) (4)

[REDACTED] This is concerning because similar trade dress among products within a company line are vulnerable to selection errors. Moreover, previous reviews noted a report of confusion with the Loestrin product line. Although we could not definitively link the confusion to the similar trade dress, we could not rule it out as a contributing factor to the error. Therefore, it is important that we ensure adequate differentiation of this product from others within the Loestrin product line.

Additionally, deficiencies are noted in the container labels (blister cards), carton, and insert labeling. We provide recommendations in Section 5 to help minimize the risk of medication errors.

#### **4 CONCLUSIONS**

DMEPA concludes that the proposed labels and labeling can be improved to increase the readability and prominence of important information on the label to promote the safe use of the product, to mitigate confusion, and to clarify information.

#### **5 RECOMMENDATIONS**

Based on this review, DMEPA recommends the following be implemented prior to approval of this NDA:

##### **A. All Labels and Labeling**

1. Remove the proprietary name, [REDACTED] (b) (4) from all labels and labeling because this name was found unacceptable by DMEPA.
2. Revise the trade dress of your proposed product to appear different than your currently marketed product, Lo Loestrin Fe. Both the proposed product and Lo loestrin Fe use the same colors [REDACTED] (b) (4) and are difficult to differentiate. This can lead to selection errors when dispensing these products. Thus, we recommend as part of your future product development, you consider using color prudently to bring attention to the

product name, strength, and important warnings across your entire product line or within a line of related products.

3. Revise all instances of the usual dosage statement “Usual Dosage- One tablet daily for 28 days as directed by physician. See Package Insert for Full Prescribing Information.” to read “Usual Dosage: See package insert for full prescribing information.” As it is currently presented, the usual dosage statement is not complete and does not capture the full instructions patients are supposed to follow (i.e., One blue tablet daily chewed or swallowed taken at the same time every day for 24 days. If chewed follow with 8 ounces of liquid. One white tablet daily swallowed taken at the same time every day for 2 days. One brown tablet daily swallowed taken at the same time every day for 2 days.”

**B. Blister Card Labels (trade and professional sample blister cards)**

Revise the boxed-in statement (b) (4) to use positive language. Negative statements may have the opposite of the intended meaning because the word “not” can be overlooked. The revised statement reads “Swallow tablets whole. Do not chew.” Additionally, we recommend highlighting this section to emphasize the importance of the warning statement ‘Swallow tablets whole. Do not chew.’”

If you have further questions or need clarifications, please contact Marcus Cato, project manager, at 301-796-3903.

## 6 REFERENCES

Siahpoushan, M., OSE Review #2012-1506 and 2012-2290 Label, Labeling and Packaging Review for Minastrin 24 Fe (Norethindrone Acetate and Ethinyl Estradiol Soft Gelatin Capsules, and Ferrous Fumarate Soft Gelatin Capsules), November 5, 2012.

## APPENDICES

### APPENDIX A. DATABASE DESCRIPTIONS

#### **FDA Adverse Event Reporting System (FAERS)**

The FDA Adverse Event Reporting System (FAERS) is a database that contains information on adverse event and medication error reports submitted to FDA. The database is designed to support the FDA's post-marketing safety surveillance program for drug and therapeutic biologic products. The informatic structure of the database adheres to the international safety reporting guidance issued by the International Conference on Harmonisation. Adverse events and medication errors are coded to terms in the Medical Dictionary for Regulatory Activities (MedDRA) terminology. The suspect products are coded to valid tradenames or active ingredients in the FAERS Product Dictionary (FPD).

FDA implemented FAERS on September 10, 2012, and migrated all the data from the previous reporting system (AERS) to FAERS. Differences may exist when comparing case counts in AERS and FAERS. FDA validated and recoded product information as the AERS reports were migrated to FAERS. In addition, FDA implemented new search functionality based on the date FDA initially received the case to more accurately portray the follow up cases that have multiple receive dates.

FAERS data have limitations. First, there is no certainty that the reported event was actually due to the product. FDA does not require that a causal relationship between a product and event be proven, and reports do not always contain enough detail to properly evaluate an event. Further, FDA does not receive reports for every adverse event or medication error that occurs with a product. Many factors can influence whether or not an event will be reported, such as the time a product has been marketed and publicity about an event. Therefore, FAERS data cannot be used to calculate the incidence of an adverse event or medication error in the U.S. population.

13 Pages of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

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/s/  
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MANIZHEH SIAHPOUSHAN  
05/21/2013

JAMES H SCHLICK  
05/21/2013

CAROL A HOLQUIST  
05/21/2013

# REGULATORY PROJECT MANAGER PHYSICIAN'S LABELING RULE (PLR) FORMAT REVIEW OF THE PRESCRIBING INFORMATION

**Application: 204654**

**Application Type: New NDA**

**Name of Drug: norethindrone acetate/ethinyl estradiol chewable tablets/ethinyl estradiol tablets and FE tablets**

**Applicant: Warner Chilcott, LLC**

**Submission Date: September 27, 2012**

**Receipt Date: September 28, 2012**

## **Review of the Prescribing Information (PI)**

This review is based on the applicant's submitted Microsoft Word format of the PI. The applicant's proposed PI was reviewed in accordance with the labeling format requirements listed in the "Selected Requirements for Prescribing Information (SRPI)" checklist (see the Appendix).

## **Conclusions/Recommendations**

SRPI format deficiencies were identified in the review of this PI. For a list of these deficiencies see the Appendix.

All SRPI format deficiencies of the PI and other labeling issues identified above will be conveyed to the applicant in the 74-day letter/an advice letter. The applicant will be asked to correct these deficiencies and resubmit the PI in Word format by January 4, 2012. The resubmitted PI will be used for further labeling review.

## **Appendix**

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### **Selected Requirements of Prescribing Information (SRPI)**

The Selected Requirement of Prescribing Information (SRPI) version 2 is a 48-item, drop-down checklist of critical format elements of the prescribing information (PI) based on labeling regulations (21 CFR 201.56 and 201.57) and labeling guidances.

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## **Highlights (HL)**

### **GENERAL FORMAT**

- YES** 1. Highlights (HL) must be in two-column format, with ½ inch margins on all sides and in a minimum of 8-point font.

## Selected Requirements of Prescribing Information (SRPI)

- NO** 2. The length of HL must be less than or equal to one-half page (the HL Boxed Warning does not count against the one-half page requirement) unless a waiver has been granted in a previous submission (i.e., the application being reviewed is an efficacy supplement).

Instructions to complete this item: If the length of the HL is less than or equal to one-half page then select “YES” in the drop-down menu because this item meets the requirement. However, if HL is longer than one-half page:

➤ **For the Filing Period (for RPMs)**

- *For efficacy supplements:* If a waiver was previously granted, select “YES” in the drop-down menu because this item meets the requirement.
- *For NDAs/BLAs and PLR conversions:* Select “NO” in the drop-down menu because this item does not meet the requirement (deficiency). The RPM notifies the Cross-Discipline Team Leader (CDTL) of the excessive HL length and the CDTL determines if this deficiency is included in the 74-day or advice letter to the applicant.

➤ **For the End-of Cycle Period (for SEALD reviewers)**

- The SEALD reviewer documents (based on information received from the RPM) that a waiver has been previously granted or will be granted by the review division in the approval letter.

- YES** 3. All headings in HL must be presented in the center of a horizontal line, in UPPER-CASE letters and **bolded**.

- YES** 4. White space must be present before each major heading in HL.

- YES** 5. Each summarized statement in HL must reference the section(s) or subsection(s) of the Full Prescribing Information (FPI) that contains more detailed information. The preferred format is the numerical identifier in parenthesis [e.g., (1.1)] at the end of each information summary (e.g. end of each bullet).

- YES** 6. Section headings are presented in the following order in HL:

Section	Required/Optional
• <b>Highlights Heading</b>	Required
• <b>Highlights Limitation Statement</b>	Required
• <b>Product Title</b>	Required
• <b>Initial U.S. Approval</b>	Required
• <b>Boxed Warning</b>	Required if a Boxed Warning is in the FPI
• <b>Recent Major Changes</b>	Required for only certain changes to PI*
• <b>Indications and Usage</b>	Required
• <b>Dosage and Administration</b>	Required
• <b>Dosage Forms and Strengths</b>	Required
• <b>Contraindications</b>	Required (if no contraindications must state “None.”)
• <b>Warnings and Precautions</b>	Not required by regulation, but should be present
• <b>Adverse Reactions</b>	Required
• <b>Drug Interactions</b>	Optional

## Selected Requirements of Prescribing Information (SRPI)

• Use in Specific Populations	Optional
• Patient Counseling Information Statement	Required
• Revision Date	Required

\* RMC only applies to the Boxed Warning, Indications and Usage, Dosage and Administration, Contraindications, and Warnings and Precautions sections.

- YES** 7. A horizontal line must separate HL and Table of Contents (TOC).

### HIGHLIGHTS DETAILS

#### Highlights Heading

- YES** 8. At the beginning of HL, the following heading must be **bolded** and appear in all UPPER CASE letters: “**HIGHLIGHTS OF PRESCRIBING INFORMATION**”.

#### Highlights Limitation Statement

- NO** 9. The **bolded** HL Limitation Statement must be on the line immediately beneath the HL heading and must state: “**These highlights do not include all the information needed to use (insert name of drug product in UPPER CASE) safely and effectively. See full prescribing information for (insert name of drug product in UPPER CASE).**”

#### Product Title

- NO** 10. Product title in HL must be **bolded**.

#### Initial U.S. Approval

- YES** 11. Initial U.S. Approval in HL must be placed immediately beneath the product title, **bolded**, and include the verbatim statement “**Initial U.S. Approval:**” followed by the **4-digit year**.

#### Boxed Warning

- YES** 12. All text must be **bolded**.

- YES** 13. Must have a centered heading in UPPER-CASE, containing the word “**WARNING**” (even if more than one Warning, the term, “**WARNING**” and not “**WARNINGS**” should be used) and other words to identify the subject of the Warning (e.g., “**WARNING: SERIOUS INFECTIONS**”).

- YES** 14. Must always have the verbatim statement “*See full prescribing information for complete boxed warning.*” centered immediately beneath the heading.

- YES** 15. Must be limited in length to 20 lines (this does not include the heading and statement “*See full prescribing information for complete boxed warning.*”)

## Selected Requirements of Prescribing Information (SRPI)

- YES** 16. Use sentence case for summary (combination of uppercase and lowercase letters typical of that used in a sentence).

### Recent Major Changes (RMC)

- YES** 17. Pertains to only the following five sections of the FPI: Boxed Warning, Indications and Usage, Dosage and Administration, Contraindications, and Warnings and Precautions.

- YES** 18. Must be listed in the same order in HL as they appear in FPI.

- YES** 19. Includes heading(s) and, if appropriate, subheading(s) of labeling section(s) affected by the recent major change, together with each section's identifying number and date (month/year format) on which the change was incorporated in the PI (supplement approval date). For example, "Dosage and Administration, Coronary Stenting (2.2) --- 3/2012".

- YES** 20. Must list changes for at least one year after the supplement is approved and must be removed at the first printing subsequent to one year (e.g., no listing should be one year older than revision date).

### Indications and Usage

- YES** 21. If a product belongs to an established pharmacologic class, the following statement is required in the Indications and Usage section of HL: [(Product) is a (name of class) indicated for (indication)]."

### Dosage Forms and Strengths

- YES** 22. For a product that has several dosage forms, bulleted subheadings (e.g., capsules, tablets, injection, suspension) or tabular presentations of information is used.

### Contraindications

- YES** 23. All contraindications listed in the FPI must also be listed in HL or must include the statement "None" if no contraindications are known.

- YES** 24. Each contraindication is bulleted when there is more than one contraindication.

### Adverse Reactions

- YES** 25. For drug products other than vaccines, the verbatim **bolded** statement must be present: "**To report SUSPECTED ADVERSE REACTIONS, contact (insert name of manufacturer) at**

## Selected Requirements of Prescribing Information (SRPI)

(insert manufacturer’s U.S. phone number) or FDA at 1-800-FDA-1088 or [www.fda.gov/medwatch](http://www.fda.gov/medwatch)”.

### Patient Counseling Information Statement

**YES** 26. Must include one of the following three **bolded** verbatim statements (without quotation marks):

If a product **does not** have FDA-approved patient labeling:

- “**See 17 for PATIENT COUNSELING INFORMATION**”

If a product **has** FDA-approved patient labeling:

- “**See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.**”
- “**See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.**”

### Revision Date

**YES** 27. **Bolded** revision date (i.e., “**Revised: MM/YYYY or Month Year**”) must be at the end of HL.

---

## Contents: Table of Contents (TOC)

### GENERAL FORMAT

**YES** 28. A horizontal line must separate TOC from the FPI.

**YES** 29. The following **bolded** heading in all UPPER CASE letters must appear at the beginning of TOC: “**FULL PRESCRIBING INFORMATION: CONTENTS**”.

**YES** 30. The section headings and subheadings (including title of the Boxed Warning) in the TOC must match the headings and subheadings in the FPI.

**YES** 31. The same title for the Boxed Warning that appears in the HL and FPI must also appear at the beginning of the TOC in UPPER-CASE letters and **bolded**.

**YES** 32. All section headings must be **bolded** and in UPPER CASE.

**YES** 33. All subsection headings must be indented, not bolded, and in title case.

**YES** 34. When a section or subsection is omitted, the numbering does not change.

**YES** 35. If a section or subsection from 201.56(d)(1) is omitted from the FPI and TOC, the heading “**FULL PRESCRIBING INFORMATION: CONTENTS**” must be followed by an asterisk

## Selected Requirements of Prescribing Information (SRPI)

and the following statement must appear at the end of TOC: “\*Sections or subsections omitted from the Full Prescribing Information are not listed.”

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### Full Prescribing Information (FPI)

#### GENERAL FORMAT

- YES** 36. The following heading must appear at the beginning of the FPI in UPPER CASE and **bolded**: “**FULL PRESCRIBING INFORMATION**”.
- YES** 37. All section and subsection headings and numbers must be **bolded**.
- YES** 38. The **bolded** section and subsection headings must be named and numbered in accordance with 21 CFR 201.56(d)(1) as noted below. If a section/subsection is omitted, the numbering does not change.

<b>Boxed Warning</b>
<b>1 INDICATIONS AND USAGE</b>
<b>2 DOSAGE AND ADMINISTRATION</b>
<b>3 DOSAGE FORMS AND STRENGTHS</b>
<b>4 CONTRAINDICATIONS</b>
<b>5 WARNINGS AND PRECAUTIONS</b>
<b>6 ADVERSE REACTIONS</b>
<b>7 DRUG INTERACTIONS</b>
<b>8 USE IN SPECIFIC POPULATIONS</b>
<b>8.1 Pregnancy</b>
<b>8.2 Labor and Delivery</b>
<b>8.3 Nursing Mothers</b>
<b>8.4 Pediatric Use</b>
<b>8.5 Geriatric Use</b>
<b>9 DRUG ABUSE AND DEPENDENCE</b>
<b>9.1 Controlled Substance</b>
<b>9.2 Abuse</b>
<b>9.3 Dependence</b>
<b>10 OVERDOSAGE</b>
<b>11 DESCRIPTION</b>
<b>12 CLINICAL PHARMACOLOGY</b>
<b>12.1 Mechanism of Action</b>
<b>12.2 Pharmacodynamics</b>
<b>12.3 Pharmacokinetics</b>
<b>12.4 Microbiology (by guidance)</b>
<b>12.5 Pharmacogenomics (by guidance)</b>
<b>13 NONCLINICAL TOXICOLOGY</b>
<b>13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility</b>
<b>13.2 Animal Toxicology and/or Pharmacology</b>
<b>14 CLINICAL STUDIES</b>
<b>15 REFERENCES</b>
<b>16 HOW SUPPLIED/STORAGE AND HANDLING</b>
<b>17 PATIENT COUNSELING INFORMATION</b>

## Selected Requirements of Prescribing Information (SRPI)

- YES** 39. FDA-approved patient labeling (e.g., Medication Guide, Patient Information, or Instructions for Use) must not be included as a subsection under Section 17 (Patient Counseling Information). All patient labeling must appear at the end of the PI upon approval.
- YES** 40. The preferred presentation for cross-references in the FPI is the section heading (not subsection heading) followed by the numerical identifier in italics. For example, [*see Warnings and Precautions (5.2)*].
- N/A** 41. If RMCs are listed in HL, the corresponding new or modified text in the FPI sections or subsections must be marked with a vertical line on the left edge.

### FULL PRESCRIBING INFORMATION DETAILS

#### Boxed Warning

- YES** 42. All text is **bolded**.
- YES** 43. Must have a heading in UPPER-CASE, containing the word “**WARNING**” (even if more than one Warning, the term, “**WARNING**” and not “**WARNINGS**” should be used) and other words to identify the subject of the Warning (e.g., “**WARNING: SERIOUS INFECTIONS**”).
- YES** 44. Use sentence case (combination of uppercase and lowercase letters typical of that used in a sentence) for the information in the Boxed Warning.

#### Contraindications

- N/A** 45. If no Contraindications are known, this section must state “None”.

#### Adverse Reactions

- YES** 46. When clinical trials adverse reactions data is included (typically in the “Clinical Trials Experience” subsection of Adverse Reactions), the following verbatim statement or appropriate modification should precede the presentation of adverse reactions:

*“Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice.”*

- YES** 47. When postmarketing adverse reaction data is included (typically in the “Postmarketing Experience” subsection of Adverse Reactions), the following verbatim statement or appropriate modification should precede the presentation of adverse reactions:

*“The following adverse reactions have been identified during post-approval use of (insert drug name). Because these reactions are reported voluntarily from a population of uncertain size, it*

## Selected Requirements of Prescribing Information (SRPI)

*is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.”*

### Patient Counseling Information

- NO** 48. Must reference any FDA-approved patient labeling, include the type of patient labeling, and use one of the following statements at the beginning of Section 17:
- “See FDA-approved patient labeling (Medication Guide)”
  - “See FDA-approved patient labeling (Medication Guide and Instructions for Use)”
  - “See FDA-approved patient labeling (Patient Information)”
  - “See FDA-approved patient labeling (Instructions for Use)”
  - “See FDA-approved patient labeling (Patient Information and Instructions for Use)”
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JENNIFER L MERCIER  
10/31/2012

**REQUEST FOR OPDP (previously DDMAC) LABELING REVIEW  
CONSULTATION**

DEPARTMENT OF HEALTH AND HUMAN SERVICES  
PUBLIC HEALTH SERVICE  
FOOD AND DRUG ADMINISTRATION

**\*\*Please send immediately following the Filing/Planning meeting\*\***

TO: Olga Salis

**CDER-DDMAC-RPM**

FROM: (Name/Title, Office/Division/Phone number of requestor)

Jennifer Mercier  
Division of Reproductive and Urologic Products

REQUEST DATE  
October 9, 2012

IND NO.

NDA/BLA NO.  
204654

TYPE OF DOCUMENTS  
(PLEASE CHECK OFF BELOW)

NAME OF DRUG  
Norethindrone acetate and ethinyl estradiol  
chewable tablets/ethinyl estradiol/FE tablets

PRIORITY CONSIDERATION

CLASSIFICATION OF DRUG

DESIRED COMPLETION DATE  
(Generally 1 week before the wrap-up meeting)

NAME OF FIRM:  
Warner Chilcott

PDUFA Date: July 28, 2013

**TYPE OF LABEL TO REVIEW**

**TYPE OF LABELING:**

(Check all that apply)

- PACKAGE INSERT (PI)
- PATIENT PACKAGE INSERT (PPI)
- CARTON/CONTAINER LABELING
- MEDICATION GUIDE
- INSTRUCTIONS FOR USE (IFU)

**TYPE OF APPLICATION/SUBMISSION**

- ORIGINAL NDA/BLA
- IND
- EFFICACY SUPPLEMENT
- SAFETY SUPPLEMENT
- LABELING SUPPLEMENT
- PLR CONVERSION

**REASON FOR LABELING CONSULT**

- INITIAL PROPOSED LABELING
- LABELING REVISION

**EDR link to submission:**

EDR Location: <\\CDSESUB1\EVSPROD\NDA204654\0000>

**Please Note:** There is no need to send labeling at this time. OPDP reviews substantially complete labeling, which has already been marked up by the CDER Review Team. After the disciplines have completed their sections of the labeling, a full review team labeling meeting can be held to go over all of the revisions. Within a week after this meeting, "substantially complete" labeling should be sent to OPDP. Once the substantially complete labeling is received, OPDP will complete its review within 14 calendar days.

**COMMENTS/SPECIAL INSTRUCTIONS:**

Mid-Cycle Meeting: February 25, 2013  
Labeling Meetings: March 7, 2013 (Labeling Planning) May 27, 2013 (Wrap up with Labeling) June 11, 2013 (Labeling)  
Wrap-Up Meeting: May 27, 2013

SIGNATURE OF REQUESTER

SIGNATURE OF RECEIVER

METHOD OF DELIVERY (Check one)

- eMAIL
- HAND

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/s/  
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JENNIFER L MERCIER  
10/09/2012