

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:
022573Orig1s000

OTHER REVIEW(S)

SEALD LABELING: PI SIGN-OFF REVIEW

APPLICATION NUMBER	NDA 022573
APPLICANT	Warner Chilcott, Inc
DRUG NAME	Norethindrone and ethinyl estradiol chewable tablets and ferrous fumarate chewable tablets
SUBMISSION DATE	November 26, 2009
PDUFA DATE	December 23, 2010
SEALD SIGN-OFF DATE	December 20, 2010
OND ASSOCIATE DIRECTOR FOR LABELING	Ann Marie Trentacosti for Laurie Burke

This memo confirms that all critical prescribing information (PI) deficiencies found in the SEALD Labeling Review filed December 20, 2010, for this application have been addressed. SEALD agrees that the PI is ready for approval at this time.

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/s/

ANN M TRENTACOSTI
12/20/2010

SEALD LABELING REVIEW

This SEALD Labeling Review identifies major aspects of the draft labeling that do not meet the requirements of 21 CFR 201.56 and 201.57 and related CDER labeling policies.

APPLICATION NUMBER	NDA 022573
APPLICANT	Warner Chilcott, Inc.
PRODUCT NAME	Norethindrone and ethinyl estradiol chewable tablets and ferrous fumarate chewable tablets
SUBMISSION DATE	11/26/2009
PDUFA DATE	12/23/2010
SEALD REVIEW DATE	12/20/2010
SEALD LABELING REVIEWER	Jun Yan, Pharm.D.

The following checked Selected Requirements for Prescribing Information items are outstanding labeling issues that must be corrected before the final draft labeling is approved.

Selected Requirements for Prescribing Information

For other regulatory requirements, see 21 CFR 201.56 and 201.57.

Highlights (HL)

- **General comments**

- Highlights is in 8-point font, two-column format, with ½ inch margins.
- Highlights is limited in length to one-half page. If greater than one-half page, a waiver has been granted previously or has been requested by the applicant in this submission.
- There is no redundancy of information.
- If a Boxed Warning is present, it must be limited to 20 lines. (Boxed Warning lines do not count against the one-half page requirement.)
- A horizontal line must separate the HL and TOC
- All headings must be presented in the center of a horizontal line in upper-case letters and **bold** type.
- Each summarized statement must reference the section(s) or subsection(s) of the Full Prescribing Information (FPI) that contains more detailed information.
- Includes the following headings in the following order:

• Highlights Limitation Statement (required statement)
• Drug names, dosage form, route of administration, and controlled substance symbol, if applicable (required information)
• Initial U.S. Approval (required information)
• Boxed Warning (if applicable)
• Recent Major Changes (for a supplement)
• Indications and Usage (required information)
• Dosage and Administration (required information)
• Dosage Forms and Strengths (required information)
• Contraindications (required heading – if no contraindications are known, it must state “None”)
• Warnings and Precautions
• Adverse Reactions (required AR contact reporting statement)
• Drug Interactions (optional heading)
• Use in Specific Populations (optional heading)
• Patient Counseling Information Statement (required statement)
• Revision Date (required information)

- **Highlights Limitation Statement**
 - Must be **bolded** and placed at the beginning of Highlights and read as follows: “**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].**” **Please use UPPER CASE for the established name in the statement.**
- **Product Title**
 - Must be **bolded** and include the proprietary and nonproprietary drug names, followed by the drug’s dosage form, route of administration (ROA), and, if applicable, controlled substance symbol.
- **Initial U.S. Approval**
 - Must include the 4-digit year of the initial U.S. approval of the new molecular entity (NME), new biological product, or new combination of active ingredients. If this is an NME, the year corresponds to the current approval action.
- **Boxed Warning**
 - All text in the boxed warning is **bolded**.
 - Summary must not exceed a length of 20 lines.
 - Requires a heading in upper-case bolded letters, containing the word “WARNING” and other words to identify the subject of the warning (e.g., “**WARNING: LIFE-THREATENING ADVERSE REACTIONS**”).
 - Must have the verbatim statement “*See full prescribing information for complete boxed warning.*” If Highlights boxed warning is identical to FPI boxed warning, this statement is not necessary.
- **Recent Major Changes (RMC)**
 - Applies only to supplements and is limited to five sections: Boxed Warning, Indications and Usage, Dosage and Administration, Contraindications, Warnings and Precautions.
 - The heading and, if appropriate, subheading of each labeling section affected by the change must be listed with the date (MM/YYYY format) of supplement approval. For example, “Dosage and Administration, Coronary Stenting (2.2) --- 2/2010.”
 - For each RMC listed, the corresponding new or modified text in the FPI must be marked with a vertical line (“margin mark”) on the left edge.
 - A changed section must be listed in HL for at least one year after the supplement is approved and must be removed at the first printing subsequent to one year.
 - Removal of a section or subsection should be noted. For example, “Dosage and Administration, Coronary Stenting (2.2) --- removal 2/2010.”

Contents: Table of Contents (TOC)

- The heading – **FULL PRESCRIBING INFORMATION: CONTENTS** – must appear at the beginning of the TOC in UPPER CASE and **bold** type.
- The headings and subheadings (including the title of boxed warning) in the TOC must match the headings and subheadings in the FPI.
- All section headings must be in **bold** type, and subsection headings must be indented and not bolded.
- When a section or subsection is omitted, the numbering does not change. For example, under Use in Specific Populations, if the subsection 8.2 (Labor and Delivery) is omitted, it must read:
 - 8.1 Pregnancy
 - 8.3 Nursing Mothers (not 8.2)
 - 8.4 Pediatric Use (not 8.3)
 - 8.5 Geriatric Use (not 8.4)
- When a section or subsection 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 the Contents: “*Sections or subsections omitted from the Full Prescribing Information are not listed.”

Full Prescribing Information (FPI)

• General Format

- A horizontal line must separate the TOC and FPI
- The heading – **FULL PRESCRIBING INFORMATION** – must appear at the beginning in UPPER CASE and **bold** type.
- The section and subsection headings must be named and numbered in accordance with 21 CFR 201.56(d)(1).

• Boxed Warning

- Must have a heading, in UPPER CASE **bold** type, containing the word “**WARNING**” and other words to identify the subject of the warning. Use **bold** type and lower-case letters for the summary.
- Must include a brief, concise summary of critical information and cross-reference to more detailed discussion in other sections (e.g., Contraindications, Warnings and Precautions).

• Contraindications

- For Pregnancy Category X drugs, list pregnancy as a contraindication.

• Warnings and Precautions

- For Pregnancy Category D drugs, list pregnancy as a Warning and Precaution.

- **Adverse Reactions**

- Only “adverse reactions” as defined in 21 CFR 201.57(c)(7) should be included in labeling. Other terms, such as “adverse events” or “treatment-emergent adverse events,” cannot be used.

- For the “Clinical Trials Experience” subsection, the following verbatim statement 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.” Please change the word (b) (4) to “rates” and add “clinical.”

- For the “Postmarketing Experience” subsection, the listing must be separate from the listing of adverse reactions identified in clinical trials and include the following verbatim statement:

- “The following adverse reactions have been identified during post approval use of drug X. 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.”

- **Use in Specific Populations**

- Subsections 8.4 Pediatric Use and 8.5 Geriatric Use are required.

- **Patient Counseling Information**

- This section is required and cannot be omitted.

- Must reference any FDA-approved patient labeling, including the type of patient labeling. The statement “See FDA-approved patient labeling (insert type of patient labeling).” should appear at the beginning of Section 17 for prominence. For example:

- “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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/s/

JUN YAN
12/20/2010

ANN M TRENTACOSTI
12/20/2010



**Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology**

Date: December 17, 2010

Application Type/Number: NDA# 022573

To: Scott Monroe, MD, Division Director
Division of Reproductive and Urology Products (DRUP)

Through: Todd Bridges, RPh, Team Leader
Denise Toyer, Pharm.D., Deputy Director
Division of Medication Error Prevention and Analysis (DMEPA)

From: Denise V. Baugh, PharmD, BCPS, Safety Evaluator
Division of Medication Error Prevention and Analysis (DMEPA)

Subject: Label and Labeling Review

Drug Name(s): Norethindrone and Ethinyl Estradiol Chewable Tablets and
Ferrous Fumarate Chewable Tablets
0.8 mg/25 mcg

Applicant: Warner Chilcott Company, LLC

OSE RCM #: 2010-2169

1 INTRODUCTION

This review responds to a request from the Division of Reproductive and Urology Products (DRUP) for a review of the revised label and labeling for Norethindrone and Ethinyl Estradiol Chewable Tablets and Ferrous Fumarate Chewable Tablets submitted on December 10, 2010, in response to the Division of Medication Error Prevention and Analysis' previous comments to the Applicant.

No proprietary name has been found acceptable for this product at this time. Thus, the revised label and labeling do not contain a proprietary name.

2 MATERIAL REVIEWED

The Applicant provided revised label and labeling on December 10, 2010. We also reviewed the recommendations in OSE Review # 2010-78 dated August 26, 2010.

3 DISCUSSION

Review of the revised documents show that the Applicant implemented DMEPA's recommendations in OSE Review # 2010-78. The Applicant's revisions did not introduce any additional areas of vulnerability that could lead to medication errors.

4 CONCLUSIONS AND RECOMMENDATIONS

The revised label and labeling submitted by the Applicant adequately addresses our concerns from a medication error perspective. We do not have any additional comments at this time.

If you have further questions or need clarifications, please contact Maria Wasilik, OSE Project Manager, at 301-796-0567.

5 REFERENCES

OSE Review # 2010-78, Label and Labeling Review for ^{(b) (4)} (Norethindrone and Ethinyl Estradiol Chewable Tablets and Ferrous Fumarate Chewable Tablets) 0.8 mg/25 mcg, Baugh, D; August 26, 2010.

6 APPENDICES

Appendix A:

Overwrap



5 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

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/s/

TODD D BRIDGES on behalf of DENISE V BAUGH
12/17/2010

TODD D BRIDGES
12/17/2010

DENISE P TOYER
12/17/2010

SEALD LABELING REVIEW

This review identifies aspects of the draft labeling that do not meet the requirements of 21 CFR 201.56 and 201.57 and related CDER labeling policies.

APPLICATION NUMBER	NDA 022573
APPLICANT	Warner Chilcott, Inc.
DRUG NAME	(b) (4) (norethindrone and ethinyl estradiol chewable tablets and ferrous fumarate chewable tablets)
SUBMISSION DATE	November 26, 2009
PDUFA DATE	September 26, 2010
SEALD REVIEW DATE	September 21, 2010
SEALD LABELING REVIEWER	Jun Yan, Pharm.D.

Outlined below are the following outstanding labeling issues that must be corrected before the final draft labeling is approved. Issues are listed in the order mandated by the regulations or guidance.

If there are no issues for a particular heading in highlights (HL) or for sections in the full prescribing information (FPI), “none” is stated. If clearly inapplicable sections are omitted from the FPI, “not applicable” is stated. In addition, “not applicable” is stated if optional headings (i.e., Drug Interactions or Use in Specific Populations) are omitted from HL.

Highlights (HL):

- **Highlights Limitation Statement:** None.
- **Product Title Line:** None.
- **Initial U.S. Approval:** None.
- **Boxed Warning:** None.
- **Recent Major Changes:** N/A.
- **Indications and Usage:** None.
- **Dosage and Administration:** None.
- **Dosage Forms and Strengths:** None.
- **Contraindications:** None.
- **Warnings and Precautions:** None.

SEALD LABELING REVIEW

- **Adverse Reactions:** None.
- **Drug Interactions:** None.
- **Use in Specific Populations:** None.
- **Patient Counseling Information Statement:** None.
- **Revision Date:** None.

Table of Contents (TOC):

Should be presented in double columns.

Full Prescribing Information:

Boxed Warning: N/A.

1 Indications and Usage: None.

2 Dosage and Administration: None.

3 Dosage Forms and Strengths: None.

4 Contraindications: None.

5 Warnings and Precautions: None.

6 Adverse Reactions: None.

7 Drug Interactions: None.

8 Use in Specific Populations: None.

9 Drug Abuse and Dependence: N/A.

10 Overdosage: None.

11 Description: None.

12 Clinical Pharmacology: Section 12.2: Ensure “Tradename” is changed to the approved proprietary name at the time of approval.

SEALD LABELING REVIEW

13 Nonclinical Toxicology: None.

14 Clinical Studies: None.

15 References: N/A.

16 How Supplied/Storage and Handling: None.

17 Patient Counseling Information: None.

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/s/

JUN YAN
09/21/2010

LAURIE B BURKE
09/22/2010

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Food and Drug Administration
Center for Drug Evaluation and Research
Division of Drug Marketing, Advertising, and Communications

*****PRE-DECISIONAL AGENCY MEMO*****

Date: September 13, 2010

To: Pam Lucarelli, Regulatory Project Manager
Division of Reproductive and Urologic Products (DRUP)

From: Janice Maniwang, Pharm.D., M.B.A., Regulatory Review Officer
Carrie Newcomer, Pharm.D., Regulatory Review Officer
Division of Drug Marketing, Advertising, and Communications (DDMAC)

Re: **NDA 022573**
DDMAC labeling comments for Tradename (norethindrone and ethinyl estradiol chewable tablets and ferrous fumarate chewable tablets)

Background

This consult is in response to DRUP's August 12, 2010 request for DDMAC's review on labeling materials for Tradename (norethindrone and ethinyl estradiol chewable tablets and ferrous fumarate chewable tablets) (norethindrone/ethinyl estradiol/ferrous fumarate). DDMAC has reviewed the following labeling materials for norethindrone/ethinyl estradiol/ferrous fumarate:

Healthcare Provider Directed:

- Prescribing Information (PI)

Consumer Directed:

- Patient Product Information (PPI)

Please note that our comments are based on the substantially complete version of the draft label sent to DDMAC on September 9, 2010. In addition, we have considered the Loestrin 24 Fe PI (approved February 2006) in our review of the draft norethindrone acetate/ethinyl estradiol labeling.

We offer the following comments:

PI & PPI

Please see our attached comments.

DDMAC appreciates the opportunity to provide comments on these materials. If you have any questions, please contact:

- Janice Maniwang (Professional directed materials)
(301) 796-3821, or janice.maniwang@fda.hhs.gov
- Carrie Newcomer (Consumer directed materials)
(301) 796-1233, or carrie.newcomer@fda.hhs.gov

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(CCI/TS) immediately following this page

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22573	ORIG-1	WARNER CHILCOTT INC	(b) (4) (norethindrone and ethinyl estradiol tablets, chewable and ferrous fumarate tablets)

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/s/

JANICE L MANIWANG
09/14/2010

CARRIE A NEWCOMER
09/14/2010

MEMORANDUM

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

CLINICAL INSPECTION SUMMARY

DATE: July 23, 2010

TO: Pam Lucarelli, Regulatory Project Manager
Gerald Willett, M.D., Medical Officer
Division of Reproductive and Urologic Products

FROM: Roy Blay, Ph.D.
Good Clinical Practice Branch II
Division of Scientific Investigations

THROUGH: Tejashri Purohit-Sheth, M.D.
Branch Chief
Good Clinical Practice Branch II
Division of Scientific Investigations

SUBJECT: Evaluation of Clinical Inspections.

NDA: 22-573

APPLICANT: Warner Chilcott
100 Enterprise Drive
Rockaway, NJ 07866
Attn: Ileana Brown
Director, Regulatory Affairs
973-442-3229

DRUG: (b) (4)

NME: No

THERAPEUTIC
CLASSIFICATION: Standard Review

INDICATION: Contraception

CONSULTATION
REQUEST DATE: March 15, 2010

DIVISION ACTION
GOAL DATE: September 24, 2010

PDUFA DATE: September 26, 2010

I. BACKGROUND:

The conduct of Protocol #PR-00207, entitled “An Open Label Study of the Contraceptive Efficacy of an Extended Regimen of Norethindrone and Ethinyl Estradiol” was inspected. The primary objective of this study was to assess the efficacy of (b)(4) in the prevention of pregnancy.

The primary measure of efficacy was the pregnancy rate, expressed using the Pearl Index, defined as the number of pregnancies per 100 women-years of treatment, and by life table methods.

These clinical sites were selected for inspection because of their high enrollments and neither having a history of previous inspections.

II. RESULTS (by Site):

Name of CI, Location	Protocol #/ # of Subjects/	Inspection Dates	Final Classification
Site # 205 Dr. Joe Blumenau Research Across America RHD Professional Plaza 4 9 Medical Parkway, Suite 202 Dallas, TX 75234 972-241-1222	PR-00207/ 46 (enrolled)/	26 Apr - 3 May 2010	NAI
Site # 246 Dr. Robert Lamar Parker 2927 Lyndhurst Avenue Winston Salem, NC 27103 336-765-9350	PR-00207/ 51 (enrolled)/	22-25 Jun 2010	NAI

Key to Classifications

NAI = No deviation from regulations.

VAI = Deviation(s) from regulations.

OAI = Significant deviations from regulations. Data unreliable.

Pending = Preliminary classification based on information in 483 or preliminary communication with the field;
 EIR has not been received from the field and complete review of EIR is pending.

1. Site # 205

Dr. Joe Blumenau
 Research Across America
 RHD Professional Plaza 4
 9 Medical Parkway, Suite 202
 Dallas, TX 75234

- a. **What was inspected:** At this site, 60 subjects were screened, 46 were enrolled and 24 completed the study. The records of 23 subjects were audited, including, but not limited to, consent forms, subject binders, Case Report Forms, monitor, sponsor, and IRB correspondence, test article accountability, adverse events, and financial disclosure.

- b. General observations/commentary:** A Form FDA 483 was not issued at the conclusion of the inspection. Review of the records noted above revealed no significant discrepancies or regulatory violations.
- c. Assessment of data integrity:** The data appear acceptable in support of the respective application.

2. Site # 246

Dr. Robert Lamar Parker
2927 Lyndhurst Avenue
Winston Salem, NC 27103

- a. What was inspected:** At this site, 51 subjects were enrolled with 30 completing the study. Consent forms were present and signed for all enrolled subjects. The Case Report Forms of 17 subjects were audited and compared with the corresponding source documents. CRFs were verified for protocol adherence, deviations, concomitant medications adverse events, and laboratory findings.
- b. General observations/commentary:** A Form FDA 483 was not issued at the conclusion of the inspection. Review of the records noted above revealed no significant discrepancies or regulatory violations.
- c. Assessment of data integrity:** The data appear acceptable in support of the respective application.

III. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

The clinical investigator sites of Drs. Blumenau and Parker were inspected in support of this NDA. The study appears to have been conducted adequately, and the data generated by these clinical sites appear acceptable in support of the respective indication.

{See appended electronic signature page}

Roy Blay, Ph.D.
Good Clinical Practice Branch II
Division of Scientific Investigations

CONCURRENCE:

{See appended electronic signature page}

Tejashri Purohit-Sheth, M.D.
Branch Chief
Good Clinical Practice Branch II
Division of Scientific Investigations

Application
Type/Number

Submission
Type/Number

Submitter Name

Product Name

NDA-22573

ORIG-1

WARNER
CHILCOTT INC

(b) (4) (norethindrone and ethinyl
estradiol tablets, chewable and
ferrous fumarate tablets)

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/s/

ROY A BLAY
07/27/2010

TEJASHRI S PUROHIT-SHETH
07/27/2010