CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

022501Orig1s000

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

Department of Health and Human Services
Food and Drug Administration

PATENT INFORMATION SUBMITTED WITH THE FILING OF AN NDA, AMENDMENT, OR SUPPLEMENT

For Each Patent That Claims a Drug Substance (Active Ingredient), Drug Product (Formulation and Composition) and/or Method of Use

Form Approved: OMB No. 0910-0513
Expiration Date: 04/30/10
See OMB Statement on Page 3.

NDA NUMBER
22-501

NAME OF APPLICANT / NDA HOLDER
Warner Chilcott Company, Inc.

The following is provided in accordance with Section 505(b) and (c) of the Federal Food, Drug, and Cosmetic Act.

TRADE NAME (OR PROPOSED TRADE NAME)
(b) (4)

ACTIVE INGREDIENT(S)	STRENGTH(S)
Norethindrone acetate / ethinyl estradiol	1 mg / 10mcg

DOSAGE FORM
Oral Tablet

This patent declaration form is required to be submitted to the Food and Drug Administration (FDA) with an NDA application, amendment, or supplement as required by 21 CFR 314.53 at the address provided in 21 CFR 314.53(d)(4).
Within thirty (30) days after approval of an NDA or supplement, or within thirty (30) days of issuance of a new patent, a new patent declaration must be submitted pursuant to 21 CFR 314.53(c)(2)(ii) with all of the required information based on the approved NDA or supplement. The information submitted in the declaration form submitted upon or after approval will be the only information relied upon by FDA for listing a patent in the Orange Book.

For hand-written or typewriter versions (only) of this report: If additional space is required for any narrative answer (i.e., one that does not require a "Yes" or "No" response), please attach an additional page referencing the question number.

FDA will not list patent information if you file an incomplete patent declaration or the patent declaration indicates the patent is not eligible for listing.

For each patent submitted for the pending NDA, amendment, or supplement referenced above, you must submit all the information described below. If you are not submitting any patents for this pending NDA, amendment, or supplement, complete above section and sections 5 and 6.

1. GENERAL

a. United States Patent Number	b. Issue Date of Patent	c. Expiration Date of Patent
5,552,394	9/3/1996	7/22/2014

d. Name of Patent Owner	Address *(of Patent Owner)*	
Warner Chilcott Company, Inc.	Union Street, Road 195, km 1.1	
	City/State: Fajardo, Puerto Rico	
	ZIP Code: 00738	FAX Number *(if available)*: (787) 863-5355
	Telephone Number: (787) 863-1850	E-Mail Address *(if available)*

e. Name of agent or representative who resides or maintains a place of business within the United States authorized to receive notice of patent certification under section 505(b)(3) and (j)(2)(B) of the Federal Food, Drug, and Cosmetic Act and 21 CFR 314.52 and 314.95 (if patent owner or NDA applicant/holder does not reside or have a place of business within the United States)	Address *(of agent or representative named in 1.e.)*	
☞ Warner Chilcott (US), LLC	100 Enterprise Drive	
	City/State: Rockaway, New Jersey	
	ZIP Code: 07866	FAX Number *(if available)*: (973) 442.3280
	Telephone Number: (973) 442.3200	E-Mail Address *(if available)*: ahoward@wcrx.com

f. Is the patent referenced above a patent that has been submitted previously for the approved NDA or supplement referenced above? ☐ Yes ☒ No

g. If the patent referenced above has been submitted previously for listing, is the expiration date a new expiration date? ☐ Yes ☒ No

PSC Graphics: (301) 443-1090 EF

For the patent referenced above, provide the following information on the drug substance, drug product and/or method of use that is the subject of the pending NDA, amendment, or supplement.

2. Drug Substance (Active Ingredient)

2.1	Does the patent claim the drug substance that is the active ingredient in the drug product described in the pending NDA, amendment, or supplement?	☐ Yes	☒ No
2.2	Does the patent claim a drug substance that is a different polymorph of the active ingredient described in the pending NDA, amendment, or supplement?	☐ Yes	☒ No
2.3	If the answer to question **2.2** is "Yes," do you certify that, as of the date of this declaration, you have test data demonstrating that a drug product containing the polymorph will perform the same as the drug product described in the NDA? The type of test data required is described at 21 CFR 314.53(b).	☐ Yes	☐ No
2.4	Specify the polymorphic form(s) claimed by the patent for which you have the test results described in **2.3**.		
2.5	Does the patent claim only a metabolite of the active ingredient pending in the NDA or supplement? (Complete the information in section 4 below if the patent claims a pending method of using the pending drug product to administer the metabolite.)	☐ Yes	☒ No
2.6	Does the patent claim only an intermediate?	☐ Yes	☒ No
2.7	If the patent referenced in **2.1** is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.)	☐ Yes	☐ No

3. Drug Product (Composition/Formulation)

3.1	Does the patent claim the drug product, as defined in 21 CFR 314.3, in the pending NDA, amendment, or supplement?	☐ Yes	☒ No
3.2	Does the patent claim only an intermediate?	☐ Yes	☒ No
3.3	If the patent referenced in **3.1** is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.)	☐ Yes	☐ No

4. Method of Use

Sponsors must submit the information in section 4 for each method of using the pending drug product for which approval is being sought that is claimed by the patent. For each pending method of use claimed by the patent, provide the following information:

4.1	Does the patent claim one or more methods of use for which approval is being sought in the pending NDA, amendment, or supplement?	☒ Yes	☐ No

4.2	Patent Claim Number(s) *(as listed in the patent)* Claims 1, 7 to 12 (the following information applies to each claim)	Does (Do) the patent claim(s) referenced in **4.2** claim a pending method of use for which approval is being sought in the pending NDA, amendment, or supplement?	☒ Yes ☐ No
4.2a	If the answer to **4.2** is "Yes," identify with specificity the use with reference to the proposed labeling for the drug product.	Use: *(Submit indication or method of use information as identified specifically in the approved labeling.)* (b) (4) is indicated for the prevention of pregnancy in women (b) (4) (b) (4)	

5. No Relevant Patents

	For this pending NDA, amendment, or supplement, there are no relevant patents that claim the drug substance (active ingredient), drug product (formulation or composition) or method(s) of use, for which the applicant is seeking approval and with respect to which a claim of patent infringement could reasonably be asserted if a person not licensed by the owner of the patent engaged in the manufacture, use, or sale of the drug product.	☐ Yes

6. Declaration Certification

6.1 ***The undersigned declares that this is an accurate and complete submission of patent information for the NDA, amendment, or supplement pending under section 505 of the Federal Food, Drug, and Cosmetic Act. This time-sensitive patent information is submitted pursuant to 21 CFR 314.53. I attest that I am familiar with 21 CFR 314.53 and this submission complies with the requirements of the regulation. I verify under penalty of perjury that the foregoing is true and correct.***

Warning: A willfully and knowingly false statement is a criminal offense under 18 U.S.C. 1001.

6.2 Authorized Signature of NDA Applicant/Holder or Patent Owner *(Attorney, Agent, Representative or other Authorized Official) (Provide Information below)*	Date Signed
	3/23/09

NOTE: Only an NDA applicant/holder may submit this declaration directly to the FDA. A patent owner who is not the NDA applicant/holder is authorized to sign the declaration but may not submit it directly to FDA. 21 CFR 314.53(c)(4) and (d)(4).

Check applicable box and provide information below.

☐ NDA Applicant/Holder	☒ NDA Applicant's/Holder's Attorney, Agent (Representative) or other Authorized Official
☐ Patent Owner	☐ Patent Owner's Attorney, Agent (Representative) or Other Authorized Official

Name Alvin Howard, Senior Vice President, Regulatory Affairs, Warner Chilcott (US), LLC	
Address 100 Enterprise Drive	City/State Rockaway, New Jersey
ZIP Code 07866	Telephone Number (973) 442-3233
FAX Number *(if available)* (973) 442-3280	E-Mail Address *(if available)* ahoward@wcrx.com

The public reporting burden for this collection of information has been estimated to average 20 hours per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:

Food and Drug Administration
CDER (HFD-007)
5600 Fishers Lane
Rockville, MD 20857

An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number.

EXCLUSIVITY SUMMARY

NDA # 022501 SUPPL # 000 HFD # 580

Trade Name: Lo Loestrin Fe

Generic Name: norethindrone acetate and ethinyl estradiol tablets, ethinyl estradiol tablets, and ferrous fumarate tablets

Applicant Name : Warner Chilcott Company, Inc

Approval Date, If Known: October 21, 2010

PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, and all efficacy supplements. Complete PARTS II and III of this Exclusivity Summary only if you answer "yes" to one or more of the following questions about the submission.

a) Is it a 505(b)(1), 505(b)(2) or efficacy supplement?

YES ☒ NO ☐

If yes, what type? Specify 505(b)(1), 505(b)(2), SE1, SE2, SE3,SE4, SE5, SE6, SE7, SE8

505(b)(1)

c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "no.")

YES ☒ NO ☐

If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

d) Did the applicant request exclusivity?

YES ☒ NO ☐

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

3

e) Has pediatric exclusivity been granted for this Active Moiety?

YES ☐ NO ☒

If the answer to the above question in YES, is this approval a result of the studies submitted in response to the Pediatric Written Request?

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS AT THE END OF THIS DOCUMENT.

2. Is this drug product or indication a DESI upgrade?

YES ☐ NO ☒

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (even if a study was required for the upgrade).

PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES
(Answer either #1 or #2 as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES ☐ NO ☐

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

2. Combination product.

If the product contains more than one active moiety(as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES ☒ NO ☐

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

See attached list

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8. (Caution: The questions in part II of the summary should only be answered "NO" for original approvals of new molecular entities.)
IF "YES," GO TO PART III.

PART III THREE-YEAR EXCLUSIVITY FOR NDAs AND SUPPLEMENTS

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2 was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

YES ☒ NO ☐

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials,

such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

(a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES ☒ NO ☐

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval AND GO DIRECTLY TO SIGNATURE BLOCK ON PAGE 8:

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES ☐ NO ☒

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES ☐ NO ☒

If yes, explain:

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES ☐ NO ☒

If yes, explain:

(c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

Protocol PR-05806

Studies comparing two products with the same ingredient(s) are considered to be bioavailability studies for the purpose of this section.

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

YES ☐ NO ☒

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

b) For each investigation identified as "essential to the approval", does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

YES ☐ NO ☒

If you have answered "yes" for one or more investigation, identify the NDA in which a similar investigation was relied on:

c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

Protocol PR-05806

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean

providing 50 percent or more of the cost of the study.

a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

IND # 073510	YES ☒	NO ☐ Explain:

(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

Investigation #1	
YES ☐	NO ☐
Explain:	Explain:
Investigation #2	
YES ☐	NO ☐
Explain:	Explain:

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES ☐ NO ☒

If yes, explain:

==========

Name of person completing form: Karl Stiller, R.Ph.
Title: Regulatory Health Project Manager
Date: October 15, 2010

Name of Office/Division Director signing form: Scott Monroe, M.D.
Title: Director, Division of Reproductive and Urologic Products

Form OGD-011347; Revised 05/10/2004; formatted 2/15/05

List of approved drug product(s) containing the active moiety from Section II, question 2.

N016659	NORINYL 1+50 28-DAY
N016954	MICRONOR
N017060	NOR-QD
N017354	LOESTRIN FE 1/20
N017355	LOESTRIN FE 1.5/30
N017565	NORINYL 1+35 21-DAY
N017565	NORINYL 1+35 28-DAY
N017576	OVCON-50
N017716	OVCON-35
N017735	MODICON 28
N017743	BREVICON 28-DAY
N017875	LOESTRIN 21 1.5/30
N017876	LOESTRIN 21 1/20
N017919	ORTHO-NOVUM 1/35-28
N018405	AYGESTIN
N018977	TRI-NORINYL 28-DAY
N018985	ORTHO-NOVUM 7/7/7-28
N020130	ESTROSTEP FE
N020870	COMBIPATCH
N020870	COMBIPATCH
N020907	ACTIVELLA
N020907	ACTIVELLA
N021065	FEMHRT
N021065	FEMHRT
N021490	FEMCON FE
N021871	LOESTRIN 24 FE
N020071	DESOGEN
N021090	CYCLESSA
N020301	ORTHO-CEPT
N020713	MIRCETTE
N021676	YAZ
N021098	YASMIN
N022532	BEYAZ
N021187	NUVARING
N022262	LOSEASONIQUE
N021840	SEASONIQUE
N021544	SEASONALE
N021864	LYBREL
N018782	NORDETTE-28
N021180	ORTHO EVRA
N021490	FEMCON FE
N017565	NORINYL 1+35 21-DAY

N018985	ORTHO-NOVUM 7/7/7-28
N017735	MODICON 28
N017919	ORTHO-NOVUM 1/35-28
N017716	OVCON-35
N017576	OVCON-50
N018977	TRI-NORINYL 28-DAY
N017743	BREVICON 28-DAY
N017565	NORINYL 1+35 28-DAY
N021065	FEMHRT
N021065	FEMHRT
N021871	LOESTRIN 24 FE
N017876	LOESTRIN 21 1/20
N017875	LOESTRIN 21 1.5/30
N020130	ESTROSTEP FE
N017354	LOESTRIN FE 1/20
N017355	LOESTRIN FE 1.5/30
N021241	ORTHO TRI-CYCLEN LO
N019697	ORTHO TRI-CYCLEN
N019653	ORTHO CYCLEN-28
N017802	LO/OVRAL-28

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

/s/

KARL J STILLER
10/21/2010

SCOTT E MONROE
10/21/2010

Stiller, Karl

From: Greeley, George
Sent: Tuesday, January 19, 2010 10:00 AM
To: Stiller, Karl
Cc: Stowe, Ginneh D.
Subject: NDA 22-501 (b) (4)

Importance: High

Follow Up Flag: Follow up
Flag Status: Yellow

Hi Karl,

The (b) (4) (norethrine acetate and ethinyl estradiol) partial waiver and extrapolation was reviewed by the PeRC PREA Subcommittee on November 04, 2009. The Division recommended a partial waiver because studies would be impossible or highly impracticable because the disease/condition does not exist in children.

The PeRC agreed with the Division to grant a partial waiver for this product and that the extrapolation of efficacy will occur for pediatric patients 12 years of age and older.

Thank you.

George Greeley
Regulatory Health Project Manager
Pediatric and Maternal Health Staff
Office of New Drugs
FDA/CDER
10903 New Hampshire Ave.
Bldg #22, Room 6467
Silver Spring, MD 20993-0002
301.796.4025

Please consider the environment before printing this e-mail.

3. DEBARMENT CERTIFICATION

I hereby certify that Warner Chilcott Company, Inc. did not and will not use in any capacity the services of any person debarred under section 306(a) and (b) of the Federal Food, Drug and Cosmetic Act in connection with this New Drug Application.

3/23/09

Alvin Howard
Senior Vice President, Regulatory Affairs
Warner Chilcott (US), LLC on behalf of
Warner Chilcott Company, Inc.

Date

ACTION PACKAGE CHECKLIST

APPLICATION INFORMATION[1]		
NDA # 22501 BLA #	NDA Supplement # BLA STN #	If NDA, Efficacy Supplement Type: Orig
Proprietary Name: Lo Loestrin Fe Established/Proper Name: norethindrone acetate (NA) and ethinyl estradiol (EE) 1 mg NA/10 mcg EE, 10 mcg EE Dosage Form: tablet		Applicant: Warner Chilcott Company, Inc. Agent for Applicant (if applicable):
RPM: Karl Stiller		Division: DRUP

NDAs:
NDA Application Type: ☒ 505(b)(1) ☐ 505(b)(2)
Efficacy Supplement: ☐ 505(b)(1) ☐ 505(b)(2)

(A 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). Consult page 1 of the 505(b)(2) Assessment or the Appendix to this Action Package Checklist.)

505(b)(2) Original NDAs and 505(b)(2) NDA supplements:
Listed drug(s) relied upon for approval (include NDA #(s) and drug name(s)):

Provide a brief explanation of how this product is different from the listed drug.

If no listed drug, explain.
- ☐ This application relies on literature.
- ☐ This application relies on a final OTC monograph.
- ☐ Other (explain)

Two months prior to each action, review the information in the 505(b)(2) Assessment and submit the draft to CDER OND IO for clearance. Finalize the 505(b)(2) Assessment at the time of the approval action.

On the day of approval, check the Orange Book again for any new patents or pediatric exclusivity.

☐ No changes ☐ Updated Date of check:

If pediatric exclusivity has been granted or the pediatric information in the labeling of the listed drug changed, determine whether pediatric information needs to be added to or deleted from the labeling of this drug.

❖ Actions	
• Proposed action • User Fee Goal Date is October 21, 2010	☒ AP ☐ TA ☐ CR
• Previous actions *(specify type and date for each action taken)*	☐ None CR - January 26, 2010

[1] The **Application Information** section is (only) a checklist. The **Contents of Action Package** section (beginning on page 5) lists the documents to be included in the Action Package.

❖ If accelerated approval or approval based on efficacy studies in animals, were promotional materials received? Note: Promotional materials to be used within 120 days after approval must have been submitted (for exceptions, see http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm069965.pdf). If not submitted, explain _____	☐ Received
❖ Application Characteristics [2]	

Review priority: ☒ Standard ☐ Priority
Chemical classification (new NDAs only):

☐ Fast Track
☐ Rolling Review
☐ Orphan drug designation
☐ Rx-to-OTC full switch
☐ Rx-to-OTC partial switch
☐ Direct-to-OTC

NDAs: Subpart H
☐ Accelerated approval (21 CFR 314.510)
☐ Restricted distribution (21 CFR 314.520)
Subpart I
☐ Approval based on animal studies

BLAs: Subpart E
☐ Accelerated approval (21 CFR 601.41)
☐ Restricted distribution (21 CFR 601.42)
Subpart H
☐ Approval based on animal studies

☐ Submitted in response to a PMR
☐ Submitted in response to a PMC
☐ Submitted in response to a Pediatric Written Request

REMS: ☐ MedGuide
☐ Communication Plan
☐ ETASU
☐ REMS not required

Comments: On January 26, 2010, this application received a CR letter due to deficiencies at a drug substance manufacturing facility and a control testing laboratory which resulted in an overall "withold" recommendation from the Office of Compliance. The previously idendified deficiencies were corrected and on April 21, 201, the Applicant submitted a Class 2 Resubmission.

❖ BLAs only: Ensure *RMS-BLA Product Information Sheet for TBP* and *RMS-BLA Facility Information Sheet for TBP* have been completed and forwarded to OPI/OBI/DRM (Vicky Carter)	☐ Yes, dates
❖ BLAs only: Is the product subject to official FDA lot release per 21 CFR 610.2 *(approvals only)*	☐ Yes ☐ No
❖ Public communications *(approvals only)*	
• Office of Executive Programs (OEP) liaison has been notified of action	☐ Yes ☐ No
• Press Office notified of action (by OEP)	☐ Yes ☐ No
• Indicate what types (if any) of information dissemination are anticipated	☐ None ☐ HHS Press Release ☐ FDA Talk Paper ☐ CDER Q&As ☐ Other

[2] Answer all questions in all sections in relation to the pending application, i.e., if the pending application is an NDA or BLA supplement, then the questions should be answered in relation to that supplement, not in relation to the original NDA or BLA. For example, if the application is a pending BLA supplement, then a new *RMS-BLA Product Information Sheet for TBP* must be completed.

❖ Exclusivity	
• Is approval of this application blocked by any type of exclusivity?	☒ No ☐ Yes
• NDAs and BLAs: Is there existing orphan drug exclusivity for the "same" drug or biologic for the proposed indication(s)? *Refer to 21 CFR 316.3(b)(13) for the definition of "same drug" for an orphan drug (i.e., active moiety). This definition is NOT the same as that used for NDA chemical classification.*	☒ No ☐ Yes If, yes, NDA/BLA # and date exclusivity expires:
• (b)(2) NDAs only: Is there remaining 5-year exclusivity that would bar effective approval of a 505(b)(2) application)? *(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)*	☐ No ☐ Yes If yes, NDA # and date exclusivity expires:
• (b)(2) NDAs only: Is there remaining 3-year exclusivity that would bar effective approval of a 505(b)(2) application? *(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)*	☐ No ☐ Yes If yes, NDA # and date exclusivity expires:
• (b)(2) NDAs only: Is there remaining 6-month pediatric exclusivity that would bar effective approval of a 505(b)(2) application? *(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)*	☐ No ☐ Yes If yes, NDA # and date exclusivity expires:
• NDAs only: Is this a single enantiomer that falls under the 10-year approval limitation of 505(u)? *(Note that, even if the 10-year approval limitation period has not expired, the application may be tentatively approved if it is otherwise ready for approval.)*	☒ No ☐ Yes If yes, NDA # and date 10-year limitation expires:
❖ Patent Information (NDAs only)	
• Patent Information: Verify that form FDA-3542a was submitted for patents that claim the drug for which approval is sought. If the drug is an old antibiotic, skip the Patent Certification questions.	☒ Verified ☐ Not applicable because drug is an old antibiotic.
• Patent Certification [505(b)(2) applications]: Verify that a certification was submitted for each patent for the listed drug(s) in the Orange Book and identify the type of certification submitted for each patent.	21 CFR 314.50(i)(1)(*i*)(A) ☐ Verified 21 CFR 314.50(i)(1) ☐ (ii) ☐ (iii)
• [505(b)(2) applications] If the application includes a **paragraph III** certification, it cannot be approved until the date that the patent to which the certification pertains expires (but may be tentatively approved if it is otherwise ready for approval).	☐ No paragraph III certification Date patent will expire
• [505(b)(2) applications] For **each paragraph IV** certification, verify that the applicant notified the NDA holder and patent owner(s) of its certification that the patent(s) is invalid, unenforceable, or will not be infringed (review documentation of notification by applicant and documentation of receipt of notice by patent owner and NDA holder). *(If the application does not include any paragraph IV certifications, mark "N/A" and skip to the next section below (*Summary Reviews*)).*	☐ N/A (no paragraph IV certification) ☐ Verified

- [505(b)(2) applications] For **each paragraph IV** certification, based on the questions below, determine whether a 30-month stay of approval is in effect due to patent infringement litigation.

  Answer the following questions for **each** paragraph IV certification:

  (1) Have 45 days passed since the patent owner's receipt of the applicant's notice of certification? ☐ Yes ☐ No

  (Note: The date that the patent owner received the applicant's notice of certification can be determined by checking the application. The applicant is required to amend its 505(b)(2) application to include documentation of this date (e.g., copy of return receipt or letter from recipient acknowledging its receipt of the notice) (see 21 CFR 314.52(e))).

  *If "**Yes**," skip to question (4) below. If "**No**," continue with question (2).*

  (2) Has the patent owner (or NDA holder, if it is an exclusive patent licensee) submitted a written waiver of its right to file a legal action for patent infringement after receiving the applicant's notice of certification, as provided for by 21 CFR 314.107(f)(3)? ☐ Yes ☐ No

  *If "**Yes**," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip the rest of the patent questions.*

  *If "**No**," continue with question (3).*

  (3) Has the patent owner, its representative, or the exclusive patent licensee filed a lawsuit for patent infringement against the applicant? ☐ Yes ☐ No

  (Note: This can be determined by confirming whether the Division has received a written notice from the (b)(2) applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2))).

  *If "**No**," the patent owner (or NDA holder, if it is an exclusive patent licensee) has until the expiration of the 45-day period described in question (1) to waive its right to bring a patent infringement action or to bring such an action. After the 45-day period expires, continue with question (4) below.*

  (4) Did the patent owner (or NDA holder, if it is an exclusive patent licensee) submit a written waiver of its right to file a legal action for patent infringement within the 45-day period described in question (1), as provided for by 21 CFR 314.107(f)(3)? ☐ Yes ☐ No

  *If "**Yes**," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next section below (*Summary Reviews*).*

  *If "**No**," continue with question (5).*

(5) Did the patent owner, its representative, or the exclusive patent licensee bring suit against the (b)(2) applicant for patent infringement within 45 days of the patent owner's receipt of the applicant's notice of certification? (Note: This can be determined by confirming whether the Division has received a written notice from the (b)(2) applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2)). If no written notice appears in the NDA file, confirm with the applicant whether a lawsuit was commenced within the 45-day period). *If "**No**," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next section below (*Summary Reviews*).* *If "**Yes**," a stay of approval may be in effect. To determine if a 30-month stay is in effect, consult with the OND ADRA and attach a summary of the response.*	☐ Yes ☐ No
CONTENTS OF ACTION PACKAGE	
❖ Copy of this Action Package Checklist[3]	Yes
Officer/Employee List	
❖ List of officers/employees who participated in the decision to approve this application and consented to be identified on this list *(approvals only)*	☒ Included
Documentation of consent/non-consent by officers/employees	☒ Included
Action Letters	
❖ Copies of all action letters *(including approval letter with final labeling)*	Action(s) and date(s) AP - October 21, 2010 CR - January 26, 2010
Labeling	
❖ Package Insert *(write submission/communication date at upper right of first page of PI)*	
• Most recent draft labeling. If it is division-proposed labeling, it should be in track-changes format.	October 19, 2010
• Original applicant-proposed labeling	March 26, 2009
• Example of class labeling, if applicable	Beyaz - September 24, 2010 Natazia - May 6, 2010

[3] Fill in blanks with dates of reviews, letters, etc.

Medication Guide/Patient Package Insert/Instructions for Use/Device Labeling *(write submission/communication date at upper right of first page of each piece)*	☐ Medication Guide ☒ Patient Package Insert ☐ Instructions for Use ☐ Device Labeling ☐ None
• Most-recent draft labeling. If it is division-proposed labeling, it should be in track-changes format.	October 19, 2010
• Original applicant-proposed labeling	March 26, 2009
• Example of class labeling, if applicable	See Package Insert
❖ Labels (**full color** carton and immediate-container labels) *(write submission/communication date on upper right of first page of each submission)*	
• Most-recent draft labeling	October 19, 2010
❖ Proprietary Name • Acceptability/non-acceptability letter(s) *(indicate date(s))* • Review(s) *(indicate date(s))*	Approval - October 8, 2010 Approval - January 21, 2010 Review - January 19, 2010 Denial - July 8, 2009 Review - July 8, 2009
❖ Labeling reviews *(indicate dates of reviews and meetings)*	☐ RPM ☒ DMEPA January 14, 2010 ☒ DRISK January 19, 2010 ☒ DDMAC December 10, 2009 October 4, 2010 ☐ CSS ☒ Other reviews Clincal - October 21, 2010 SEALD October 19, 2010 (2) CMC - September 16, 2010 (see Product Quality Discipline tab) ClinPharm - November 27, 2009 and October 12, 2010 (see Clinical Pharmacology Reviews tab) Clinical - January 9, 2010 and October 12, 2010 (see Clinical Reviews tab) Clinical - October 21, 2010

Administrative / Regulatory Documents	
❖ Administrative Reviews *(e.g., RPM Filing Review[4]/Memo of Filing Meeting) (indicate date of each review)* ❖ All NDA (b)(2) Actions: Date each action cleared by (b)(2) Clearance Cmte ❖ NDA (b)(2) Approvals Only: 505(b)(2) Assessment *(indicate date)*	PharmTox Filing Review - April 30, 2009 PharmTox Filing Memo - April 30, 2009 Stats Filing Review - May 5, 2009 Clinical Filing Review - May 5, 2009 CMC Filing Review - May 7, 2009 ClinPharm Filing Review - May 11, 2009 RPM Filing Review - January 20, 2010 ☐ Not a (b)(2) ☐ Not a (b)(2)
❖ NDAs only: Exclusivity Summary *(signed by Division Director)*	☒ Included
❖ Application Integrity Policy (AIP) Status and Related Documents http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm	
• Applicant is on the AIP	☐ Yes ☒ No
• This application is on the AIP o If yes, Center Director's Exception for Review memo *(indicate date)* o If yes, OC clearance for approval *(indicate date of clearance communication)*	☐ Yes ☒ No ☐ Not an AP action
❖ Pediatrics *(approvals only)* • Date reviewed by PeRC November 4, 2009 If PeRC review not necessary, explain: _____ • Pediatric Page/Record *(approvals only, must be reviewed by PERC before finalized)*	☒ Included
❖ Debarment certification (original applications only): verified that qualifying language was not used in certification and that certifications from foreign applicants are cosigned by U.S. agent *(include certification)*	☒ Verified, statement is acceptable
❖ Outgoing communications *(letters (except action letters), emails, faxes, telecons)*	October 19, 2010 - Labeling Negotiation October 15, 2010 - Labeling Negotiation May 3, 2010 - Resubmission Acknowledgement letter January 21, 2010 - Proprietary Name Granted letter January 15, 2010 - Labeling Communication January 7, 2010 - Advice email December 14, 2009 - CMC Teleconference and emails November 30, 2009 - Advice/Information Request letter September 3, 2009 -

[4] Filing reviews for scientific disciplines should be filed behind the respective discipline tab.

	Advice/Information Request letter June 8, 2009 - Filing letter April 3, 2009 - Acknowledgement letter
❖ Internal memoranda, telecons, etc.	
❖ Minutes of Meetings	
• Regulatory Briefing *(indicate date of mtg)*	☒ No mtg
• If not the first review cycle, any end-of-review meeting *(indicate date of mtg)*	☒ N/A or no mtg
• Pre-NDA/BLA meeting *(indicate date of mtg)*	☒ No mtg
• EOP2 meeting *(indicate date of mtg)*	☒ No mtg
• Other milestone meetings (e.g., EOP2a, CMC pilots) *(indicate dates of mtgs)*	Responses to Pre-IND questions - September 1, 2006
❖ Advisory Committee Meeting(s)	☒ No AC meeting
• Date(s) of Meeting(s)	
• 48-hour alert or minutes, if available *(do not include transcript)*	
Decisional and Summary Memos	
❖ Office Director Decisional Memo *(indicate date for each review)*	☒ None
Division Director Summary Review *(indicate date for each review)*	☐ None October 21, 2010 January 26, 2010
Cross-Discipline Team Leader Review *(indicate date for each review)*	☐ None October 20, 2010 January 26, 2010
PMR/PMC Development Templates *(indicate total number)*	☒ None
Clinical Information[5]	
❖ Clinical Reviews	
• Clinical Team Leader Review(s) *(indicate date for each review)*	See CDTL Review under Decisional and Summary Memos tab
• Clinical review(s) *(indicate date for each review)*	October 12, 2010 January 9, 2010 May 5, 2009
• Social scientist review(s) (if OTC drug) *(indicate date for each review)*	☒ None
❖ Financial Disclosure reviews(s) or location/date if addressed in another review OR If no financial disclosure information was required, check here ☐ and include a review/memo explaining why not *(indicate date of review/memo)*	p. 12 of January 9, 2010 review
❖ Clinical reviews from immunology and other clinical areas/divisions/Centers *(indicate date of each review)*	☒ None
❖ Controlled Substance Staff review(s) and Scheduling Recommendation *(indicate date of each review)*	☒ Not applicable

[5] Filing reviews should be filed with the discipline reviews.

❖ Risk Management • REMS Documents and Supporting Statement *(indicate date(s) of submission(s))* • REMS Memo(s) and letter(s) *(indicate date(s))* • Risk management review(s) and recommendations (including those by OSE and CSS) *(indicate date of each review and indicate location/date if incorporated into another review)*	☒ None
❖ DSI Clinical Inspection Review Summary(ies) *(include copies of DSI letters to investigators)*	☒ None requested
Clinical Microbiology ☒ None	
❖ Clinical Microbiology Team Leader Review(s) *(indicate date for each review)*	☐ None
Clinical Microbiology Review(s) *(indicate date for each review)*	☐ None
Biostatistics ☐ None	
❖ Statistical Division Director Review(s) *(indicate date for each review)*	☒ None
Statistical Team Leader Review(s) *(indicate date for each review)*	☒ None
Statistical Review(s) *(indicate date for each review)*	☐ None October 18, 2010 December 28, 2009 May 5, 2009
Clinical Pharmacology ☐ None	
❖ Clinical Pharmacology Division Director Review(s) *(indicate date for each review)*	☒ None
Clinical Pharmacology Team Leader Review(s) *(indicate date for each review)*	☒ None
Clinical Pharmacology review(s) *(indicate date for each review)*	☐ None October 12, 2010 November 27, 2009 May 11, 2009
❖ DSI Clinical Pharmacology Inspection Review Summary *(include copies of DSI letters)*	☒ None
Nonclinical ☐ None	
❖ Pharmacology/Toxicology Discipline Reviews	
• ADP/T Review(s) *(indicate date for each review)*	☐ None
• Supervisory Review(s) *(indicate date for each review)*	☐ None
• Pharm/tox review(s), including referenced IND reviews *(indicate date for each review)*	☐ None September 20, 2010 June 22, 2009 April 30, 2009(2)
❖ Review(s) by other disciplines/divisions/Centers requested by P/T reviewer *(indicate date for each review)*	☒ None
❖ Statistical review(s) of carcinogenicity studies *(indicate date for each review)*	☒ No carc
❖ ECAC/CAC report/memo of meeting	☒ None Included in P/T review, page
❖ DSI Nonclinical Inspection Review Summary *(include copies of DSI letters)*	☒ None requested

Product Quality ☐ None	
❖ Product Quality Discipline Reviews	
• ONDQA/OBP Division Director Review(s) *(indicate date for each review)*	☒ None
• Branch Chief/Team Leader Review(s) *(indicate date for each review)*	☐ None May 7, 2009
• Product quality review(s) including ONDQA biopharmaceutics reviews *(indicate date for each review)*	☐ None September 16, 2010 January 25, 2010 January 8, 2010 May 7, 2009
❖ Microbiology Reviews ☐ NDAs: Microbiology reviews (sterility & pyrogenicity) (OPS/NDMS) *(indicate date of each review)* ☐ BLAs: Sterility assurance, microbiology, facilities reviews (DMPQ/MAPCB/BMT) *(indicate date of each review)*	☐ Not needed November 25, 2009
❖ Reviews by other disciplines/divisions/Centers requested by CMC/quality reviewer *(indicate date of each review)*	☒ None
❖ Environmental Assessment (check one) (original and supplemental applications)	
☐ Categorical Exclusion *(indicate review date)(all original applications and all efficacy supplements that could increase the patient population)*	January 8, 2010
☐ Review & FONSI *(indicate date of review)*	
☐ Review & Environmental Impact Statement *(indicate date of each review)*	
❖ Facilities Review/Inspection	
☒ NDAs: Facilities inspections (include EER printout) *(date completed must be within **2 years** of action date) (only original NDAs and supplements that include a new facility or a change that affects the manufacturing sites[6])*	Date completed: May 26, 2010 ☒ Acceptable ☐ Withhold recommendation ☐ Not applicable
☐ BLAs: TB-EER *(date of most recent TB-EER must be within **30 days** of action date) (original and supplemental BLAs)*	Date completed: ☐ Acceptable ☐ Withhold recommendation
❖ NDAs: Methods Validation *(check box only, do not include documents)*	☐ Completed ☐ Requested ☒ Not yet requested ☐ Not needed (per review)

[6] I.e., a new facility or a change in the facility, or a change in the manufacturing process in a way that impacts the Quality Management Systems of the facility.

Appendix to Action Package Checklist

An NDA or NDA supplemental 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) **Or** 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.
(3) **Or** 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) **And** 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.
(3) **And** 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) **Or** 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.
(3) **Or** 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 ODE's ADRA.

MEMORANDUM

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

DATE: October 19, 2010

TO: Warner Chilcott Company, LLC

THROUGH : Ileana Brown, Director, Regulatory Affairs

FROM: DRUP

SUBJECT: Package Insert/Patient Package Insert and Carton and Container negotiation

APPLICATION/DRUG: NDA 022501 Lo Loestrin Fe

The Applicant submitted draft Package Insert/Patient Package Insert and Carton and Container labeling as part of their Class 2 resubmission on April 20, 2010 (received April 21, 2010).

Proposed changes to the Carton and Container labeling were sent to the Applicant on October 14, 2010, and fully incorporated and returned to the Division on October 19, 2010 (attached).

Proposed changes to the Package Insert/Patient Package Insert were sent to the Applicant, fully incorporated into the labeling by the Applicant, and returned to the Division on October 19, 2010 (attached).

Proposed changes to the Carton and Container labeling from the Division

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From: Stiller, Karl
Sent: Thursday, October 14, 2010 4:30 PM
To: 'Ileana Brown'
Subject: NDA 022501 Carton and Container Labeling comments

Refer to your April 21, 2010, Class 2 Resubmission. We have the following comments and request that you resubmit labeling after making these changes.

Container Labels: Blister Card: Trade and Sample (28 tablets)

1. Remove the (b) (4) separating the proprietary name from the established name as this line is considered intervening matter and violates 21 CFR 201.10(a).
2. Increase the prominence of the proprietary name. As currently presented, it has less prominence than the manufacturer's logo.
3. Present the product strength on the blister card. As currently presented, the strength is missing.

Carton Labeling: Trade (5 blister cards per carton); Sample (1 blister card per carton; 6 cartons per tray)

1. Remove the (b) (4) separating the proprietary name from the established name as this line is considered intervening matter and violates 21 CFR 201.10(a).
2. On the trade carton, relocate the statement "Ferrous fumarate tablets are not USP for dissolution and assay" (located in the upper left-hand corner of the principal display panel) to the back panel. As currently presented, this information is extraneous.
3. Present the product strength immediately after the established name on the principal display panel. As currently presented, the strength is only located on a side panel.

LCDR Karl Stiller, R.Ph.
Regulatory Health Project Manager
Division of Reproductive and Urologic Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research
301-796-1993

Proposed changes to the Carton and Container labeling Accepted by the Applicant

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From: Ileana Brown [mailto:IBrown@wcrx.com]
Sent: Tuesday, October 19, 2010 12:23 PM
To: Stiller, Karl
Subject: NDA 022501 Lo Loestrin Fe - Complete Set of Carton/Container Labels

Karl,

Attached is the complete set of draft carton/container labels for Lo Loestrin Fe. For completion I am also providing the day label as provided in the NDA; the Division did not request any changes to this label.

The clean draft labeling text will be sent to you shortly in a separate e-mail

Ileana

********** WC Confidentiality Note: **********

This email transmission and any documents accompanying this email transmission contain information from Warner Chilcott, PLC, which is confidential. The information is intended only for the use of the intended recipient. If you are not the intended recipient, you are hereby notified that any disclosure, copying, distribution or the taking of any action in reliance on the contents of this email information is strictly prohibited, and that the documents should be returned to Warner Chilcott immediately. If you have received this email in error please notify us immediately by replying to the email address set forth above.

********** Thank you **********


Lo Loestrin Fe 0420G031 Day Label.


Lo Loestrin Fe Sample Tray 0420C03


Lo Loestrin Fe Sample Carton 0420C


Lo Loestrin Fe Sample Credit Card 0


Lo Loestrin Fe Trade Carton 0420C018 rev


Lo Loestrin Fe Trade Credit Card 0420G05

<ATTACHMENTS FROM OCTOBER 19, 2010, EMAIL FROM APPLICANT>

APPEARS THIS WAY ON ORIGINAL

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

Proposed changes to the Package Insert/Patient Package Insert from the Division

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From: Stiller, Karl
Sent: Tuesday, October 19, 2010 12:56 PM
To: 'Ileana Brown'
Subject: FW: Proposed Lo Loestrin Fe labeling

Ms. Brown:

There is one additional change that the review team requests that you make before returning the PI/PPI. Please ensure that the Full Prescribing Information title begins on a new page and is separated from the TOC with a horizontal line. See 21 CFR 201.57(d)(2).

Karl

From: Stiller, Karl
Sent: Tuesday, October 19, 2010 11:30 AM
To: 'Ileana Brown'
Subject: Proposed Lo Loestrin Fe labeling

Ms. Brown:

Please review the attached PI/PPI with tracked changes. If you agree with our proposed edits, accept tracked changes, remove comments, and return to me by COB today. Please note that when viewed as "final showing mark-up," the Highlights section does not display properly. However, when viewed as "final" it appears correctly.

LCDR Karl Stiller, R.Ph.
Regulatory Health Project Manager
Division of Reproductive and Urologic Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research
301-796-1993

NDA 22501 Draft Labeling from ...

<ATTACHMENT FROM OCTOBER 19, 2010, EMAIL FROM DIVISION>

APPEARS THIS WAY ON ORIGINAL

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

Proposed changes to the Package Insert/Patient Package Insert labeling Accepted by the Applicant

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From: Ileana Brown [mailto:IBrown@wcrx.com]
Sent: Tuesday, October 19, 2010 1:16 PM
To: Stiller, Karl
Subject: Re: Proposed Lo Loestrin Fe labeling

Karl,

The changes received today have been accepted and there are no additional changes from the company; therefore, the attached draft labeling text in MS WORD is a clean copy.
Thank you.

Ileana

NDA 22501 Draft Labeling WC Oct 19 2

<ATTACHMENT FROM OCTOBER 19, 2010, EMAIL FROM APPLICANT>

APPEARS THIS WAY ON ORIGINAL

27 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/ TS) immediately 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.

/s/

KARL J STILLER
10/19/2010

MEMORANDUM

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

DATE: October 15, 2010

TO: Warner Chilcott Company, LLC

THROUGH : Ileana Brown, Director, Regulatory Affairs

FROM: DRUP

SUBJECT: Carton and container negotiation

APPLICATION/DRUG: NDA 022501 Lo Loestrin Fe

Included in the October 8, 2010, review from DMEPA reviewer Tara Turner were comments for the Applicant pertaining to carton and container labeling changes. These comments were sent to the Applicant on October 14, 2010.

On October 15, 2010, the Applicant requested that the Division (b) (4)

From: Stiller, Karl
Sent: Friday, October 15, 2010 2:35 PM
To: 'Ileana Brown'
Subject: RE: NDA 022501 Carton and Container Labeling comments REVISED REQUEST

Ms. Brown:

(b) (4)
(b) (4)

LCDR Karl Stiller, R.Ph.
Regulatory Health Project Manager
Division of Reproductive and Urologic Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research
301-796-1993

From: Toyer, Denise P
Sent: Friday, October 15, 2010 2:25 PM
To: Turner, Tara; Kober, Margaret; Stiller, Karl
Cc: Tang, Yubing; Christner, Donna; Soule, Lisa; Oleszczuk, Zachary; Holquist, Carol A
Subject: RE: NDA 022501 Carton and Container Labeling comments REVISED REQUEST

Karl,

To clarify, we recommend the changes be made (b) (4). Such changes (e.g., lack of strength on blister and location of strength on carton) are safety related and will ensure that the proprietary name, established name and strength are the most prominent information presented. At least one of the recommendations is required by the regulations.

Denise

From: Soule, Lisa
Sent: Friday, October 15, 2010 2:20 PM
To: Stiller, Karl
Subject: FW: NDA 022501 Carton and Container Labeling comments REVISED REQUEST

Even if we have not heard from CMC, with both Margie and DMEPA unwilling to accept the sponsor's proposal, I think we should go ahead and deny it.

Thanks,
Lisa

From: Turner, Tara
Sent: Friday, October 15, 2010 2:17 PM
To: Kober, Margaret; Stiller, Karl
Cc: Tang, Yubing; Christner, Donna; Soule, Lisa; Oleszczuk, Zachary; Toyer, Denise P; Holquist, Carol A
Subject: RE: NDA 022501 Carton and Container Labeling comments REVISED REQUEST

Hi Karl,

I spoke with Carol and Denise. We suggest that the Applicant make the recommended labeling changes (b) (4).

Thanks,
Tara

From: Kober, Margaret
Sent: Friday, October 15, 2010 12:58 PM
To: Stiller, Karl; Turner, Tara
Cc: Tang, Yubing; Christner, Donna; Soule, Lisa
Subject: RE: NDA 022501 Carton and Container Labeling comments REVISED REQUEST

Given the nature of the deficiencies in the propsed labeling, (b) (4) (b) (4).

From: Stiller, Karl
Sent: Friday, October 15, 2010 12:47 PM
To: Turner, Tara
Cc: Kober, Margaret; Tang, Yubing; Christner, Donna; Soule, Lisa
Subject: FW: NDA 022501 Carton and Container Labeling comments REVISED REQUEST

~~Roche~~ Warner Chilcott has revised their request.

Let me know what you would like to tell the Applicant.

Karl

From: Ileana Brown [mailto:IBrown@wcrx.com]
Sent: Friday, October 15, 2010 12:33 PM
To: Stiller, Karl
Subject: NDA 022501 Carton and Container Labeling comments REVISED REQUEST

Hi Karl,

(b) (4)

Thanks in advance Karl.

Regards,

Ileana

----- Forwarded by Ileana Brown/RK/NA/WCRX on 10/15/2010 11:11 AM -----

From: Ileana Brown/RK/NA/WCRX
To: "Stiller, Karl" <Karl Stiller@fda hhs gov>
Date: 10/14/2010 06:31 PM
Subject: Re: NDA 022501 Carton and Container Labeling comments

---

Hi Karl,

We received the Division's request this afternoon to make the container label changes indicated in the e-mail below. We plan to make the changes requested (b) (4)

Karl, would it be possible to find out tomorrow (Friday) whether or not this is acceptable to the Division? (b) (4)

Thanks very much.

Ileana

From: "Stiller, Karl" <Karl Stiller@fda hhs gov>
To: "'Ileana Brown'" <IBrown@wcrx com>
Date: 10/14/2010 04:34 PM
Subject: NDA 022501 Carton and Container Labeling comments

Refer to your April 21, 2010, Class 2 Resubmission. We have the following comments and request that you resubmit labeling after making these changes.

Container Labels: Blister Card: Trade and Sample (28 tablets)

1. Remove the (b) (4) separating the proprietary name from the established name as this line is considered intervening matter and violates 21 CFR 201.10(a).
2. Increase the prominence of the proprietary name. As currently presented, it has less prominence than the manufacturer's logo.
3. Present the product strength on the blister card. As currently presented, the strength is missing.

Carton Labeling: Trade (5 blister cards per carton); Sample (1 blister card per carton; 6 cartons per tray)

1. Remove the (b) (4) separating the proprietary name from the established name as this line is considered intervening matter and violates 21 CFR 201.10(a).
2. On the trade carton, relocate the statement "Ferrous fumarate tablets are not USP for dissolution and assay" (located in the upper left-hand corner of the principal display panel) to the back panel. As currently presented, this information is extraneous.
3. Present the product strength immediately after the established name on the principal display panel. As currently presented, the strength is only located on a side panel.

LCDR Karl Stiller, R.Ph.
Regulatory Health Project Manager
Division of Reproductive and Urologic Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research
301-796-1993

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/s/

KARL J STILLER
10/15/2010

Memo to the file

Date: 9-20-2010

NDA #: 22-501 Draft Labeling Text Resubmission

Date of submission: 04/20/2010

Sponsor: Warner Chilcott Company, LLC

Drug Product: Lo Loestrin Fe (norethindrone acetate and ethinyl estradiol

Code name: WC3016

Strength: 1mg NA/10 ug EE, 10 ug EE

Dosage form: Tablet

Route of administration: Oral

Indication: Prevention of pregnancy

Subject: Draft Labeling Text Resubmission

Background: Draft labeling submitted with the original NDA application dated 3/26/09 (b) (4) sponsor was requested to include this information in the labeling resubmission. (b) (4) in the Drat labeling Test Resubmission and refers to Warning and Precautions (5.2, 5.3).

Regulatory action: The new resubmitted label for Lo Loestrin Fe is acceptable from the P/T perspective .

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/s/

KRISHAN L RAHEJA
09/20/2010

ALEXANDER W JORDAN
09/20/2010

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 022501

ACKNOWLEDGE CLASS 2 RESPONSE

Warner Chilcott Company, LLC
Attention: Alvin Howard
Senior Vice President, Regulatory Affairs
100 Enterprise Drive
Rockaway, NJ 07866

Dear Mr. Howard:

We acknowledge receipt on April 21, 2010, of your April 20, 2010, resubmission to your new drug application for Lo Loestrin Fe (norethindrone acetate and ethinyl estradiol tablets/ethinyl estradiol tablets/ferrous fumarate) tablets.

We consider this a complete, class 2 response to our January 26, 2010, action letter. Therefore, the user fee goal date is October 21, 2010.

If you have any questions, call Karl Stiller, Regulatory Project Manager, at (301) 796-1993.

Sincerely,

{See appended electronic signature page}

Margaret Kober, R.Ph., M.P.A.
Chief, Project Management Staff
Division of Reproduction and Urologic Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

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

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/s/

MARGARET M KOBER
05/03/2010
Chief, Project Management Staff

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Silver Spring, MD 20993

NDA 022501

PROPRIETARY NAME REQUEST
CONDITIONALLY ACCEPTABLE

Warner Chilcott Company, LLC
100 Enterprise Drive
Rockaway, New Jersey 07866

ATTENTION: Ileana Brown
Director, Regulatory Affairs

Dear Ms. Brown:

Please refer to your New Drug Application (NDA) dated March 26, 2009, received March 26, 2009, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Norethindrone Acetate and Ethinyl Estradiol Tablets 1 mg/10 mcg, Ethinyl Estradiol Tablets 10 mcg and Ferrous Fumarate Tablets 75 mg.

We also refer to your November 30, 2009, correspondence, received December 2, 2009, requesting review of your proposed proprietary name, Lo Loestrin Fe. We have completed our review of the proposed proprietary name, Lo Loestrin Fe and have concluded that it is acceptable.

If **any** of the proposed product characteristics as stated in your November 30, 2009 submission are altered prior to approval of the marketing application, the proprietary name should be resubmitted for review.

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, contact Maria Wasilik, Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (301) 796-0567. For any other information regarding this application contact the Office of New Drugs (OND) Regulatory Project Manager, Karl Stiller at (301) 796-1993.

Sincerely,

{See appended electronic signature page}

Carol Holquist, RPh
Director
Division of Medication Error Prevention and Analysis
Office of Surveillance and Epidemiology
Center for Drug Evaluation and Research

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

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/s/

CAROL A HOLQUIST
01/21/2010

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation ODEIII

FACSIMILE TRANSMITTAL SHEET

DATE: January 15, 2010

To: Ileana Brown, Director, Regulatory Affairs	**From:** Nenita Crisostomo, R.N. Regulatory Health Project Manager
Company: Warner Chilcott Company, LLC	Division of Reproductive and Urologic Products
Fax number: 973-442-3280	**Fax number:** 301-796-9897
Phone number: 973-442-3200	**Phone number:** 301-796-0875

Subject: NDA 22501 norethindrone acetate/ethinyl estradiol: DMEPA's Recommendations to Revise Container and Carton Labeling

Total no. of pages including cover: 2

Dear Ileana,

Attached below are recommendations to revise the container and carton labeling following the review of the Division of Medication Error Prevention and Analysis for this pending NDA. Please submit your response, including the mock labels, on or before the close of business on January 19, 2010. If you have any questions regarding this communication, please do not hesitate to contact me. Otherwise, please contact Karl Stiller, Regulatory Health Project Manager, at 301-796-1993.

Best Regards,
Nita

Document to be mailed: ❑ **YES** ☑ **NO**

THIS DOCUMENT IS INTENDED ONLY FOR THE USE OF THE PARTY TO WHOM IT IS ADDRESSED AND MAY CONTAIN INFORMATION THAT IS PRIVILEGED, CONFIDENTIAL, AND PROTECTED FROM DISCLOSURE UNDER APPLICABLE LAW.

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RECOMMENDATIONS TO REVISE

CONTAINER AND CARTON LABELING

January 15, 2010

NDA 022501 norethindrone acetate/ethinyl estradiol

A. Container Labels: Blister Card: Trade and Sample (28 tablets)

1. Increase the prominence of the established name by increasing the font size and weight, to comply with 21 CFR 201.10(g)(2).
2. Delete the [redacted] (b) (4) presentation of strength. Alternatively, present the strength as follows:

   Norethindrone acetate and Ethinyl estradiol tablets 1 mg/10 mcg

   Ethinyl estradiol tablets 10 mcg

   Ferrous fumarate tablets 75 mg

   To improve contrast and readability, for information that appears in the color-shaded portion of the label, change the font from white to black. Also, ensure that the strength does not intersect the purple and green areas. As currently presented, the change in colors is distracting and distorts the appearance of the letters and numbers.
3. To accommodate the revised statement of strength and decrease crowding, delete the statement "Lo Loestrin Fe provides 26 days of active therapy."
4. Ensure that calendar strips are provided with each container, as described in the insert labeling, for ease of administration on alternate start days. These were not provided in the current submission.

B. Carton Labeling: Trade (5 blister cards per carton); Sample (1 blister card per carton; 6 cartons per tray)

1. Increase the prominence of the established name by increasing the font size and weight, to comply with 21 CFR 201.10(g)(2).
2. Delete the superimposed presentation of the product strength [redacted] (b) (4) Present the product strength immediately after the established name as follows:

   Each blue tablet contains Norethindrone acetate and Ethinyl estradiol 1 mg/10 mcg

   Each white tablet contains Ethinyl estradiol 10 mcg

   Each brown tablet contains Ferrous fumarate 75 mg
3. On the trade carton, delete the numbers [redacted] (b) (4) located in the upper left-hand corner of the principal display panel. The numbers are ambiguous and provide no useful information to healthcare practitioners or patients.

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

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/s/

NENITA I CRISOSTOMO
01/15/2010

MEMORANDUM

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

DATE: January 7, 2010

TO: Warner Chilcott Company, Inc.
100 Enterprise Drive
Rockaway, NJ 07866

THROUGH : Ileana Brown, Director, Regulatory Affairs

FROM: The Division of Reproductive and Urologic Products

SUBJECT: December 23, 2009, Labeling Proposal

APPLICATION/DRUG: NDA 022501/norethindrone acetate and ethinyl estradiol tablets, ethinyl estradiol tablets, and ferrous fumarate tablets

On January 6, 2010, the information contained in the second email was requested to be sent to the Applicant for NDA 022501.

From: Soule, Lisa
Sent: Wednesday, January 06, 2010 5:32 PM
To: Apparaju, Sandhya; Stiller, Karl
Cc: Kim, Myong-Jin
Subject: RE: Loestrin Label

Karl - let's send these to the Sponsor by email as Sandhya recommends. We can also include them in the label revision, which I will now plan to send back to the Sponsor on Tuesday if DRISK indeed gets us their comments by Mon.

Lisa M. Soule, M.D.
Clinical Team Leader
Division of Reproductive & Urologic Products

NEW EMAIL ADDRESS: lisa.soule@fda.hhs.gov

From: Apparaju, Sandhya
Sent: Wednesday, January 06, 2010 2:58 PM
To: Soule, Lisa; Stiller, Karl
Cc: Kim, Myong-Jin
Subject: RE: Loestrin Label

Hi Lisa and Karl,

MJ and I just discussed the sponsor's response to our recommended labeling edits and we have the following comments to be communicated (preferably as soon as possible via e-mail to expedite the process in case further action is needed):

Comments for the sponsor:

Comment # 1: Regarding the reporting of T1/2 values in the labeling, we request that you report arithmetic mean T1/2 values for norethindrone and ethinyl estradiol (b) (4) (b) (4) *. Please modify the label with this information.*

Comment # 2: With regard to literature references that were submitted in support of the labeling statement shown below, we have the following comments and proposal for revision:

Based on the references provided, it appears that the extent of metabolic conversion of norethindrone to ethinyl estradiol as reported is variable. We recommend that you refrain from including (b) (4) *in the labeling and revise the statement in section 12.0 as shown:*

A small amount of norethindrone acetate is metabolically converted to ethinyl estradiol~~,~~ (b) (4)

Comment # 3: Modify the figure legends as shown below:

Figure 1. Mean **(± SD)** plasma ethinyl estradiol concentration versus time profiles following single- and multiple-dose oral administration ~~of~~ (**of** norethindrone acetate and ethinyl estradiol tablets, ethinyl estradiol tablets and ferrous fumarate tablets) to healthy female volunteers (n = 15)

Figure 2. Mean **(± SD)** plasma norethindrone concentration versus time profiles following single- and multiple-dose oral administration ~~of~~ (**of** norethindrone acetate and ethinyl estradiol tablets, ethinyl estradiol tablets and ferrous fumarate tablets) to healthy female volunteers (n = 15)

Thanks,
Sandhya

From: Soule, Lisa
Sent: Tuesday, January 05, 2010 6:19 PM
To: Apparaju, Sandhya
Cc: Kim, Myong-Jin
Subject: Loestrin Label

Sandhya - this label came back from the Sponsor just before the holidays. They accepted virtually everything we revised, but did ask for justification of one of the PK parameters you had revised. Ron and I are done w/the clinical review of it...when do you think you'll be able to look at it? I think the next

time we send it to them, it will likely be finalized, and then everyone can put an update memo in DARRTS indicating that labeling is acceptable.

Thanks,
Lisa

On January 7, 2010, an email was sent to Ileana Brown, Director, Regulatory Affairs for Warner Chilcott Company, Inc.

From: Stiller, Karl
Sent: Thursday, January 07, 2010 12:49 PM
To: 'Ileana Brown'
Cc: Stiller, Karl
Subject: NDA 022501 Labeling Proposal

Dear Ms. Brown:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for your product containing norethindrone acetate and ethinyl estradiol tablets, ethinyl estradiol tablets, and ferrous fumarate tablets.

We also refer to your December 23, 2009, submission, containing your response to labeling changes proposed by the Division.

We have reviewed the referenced material and have the following comments and recommendations. Additions to current labeling are shown by underlined text and deletions are shown by ~~strike-through~~ text.

1. Regarding the reporting of T1/2 values in the labeling, we request that you report arithmetic mean T1/2 values for norethindrone and ethinyl estradiol (EE) (b) (4) (b) (4) Modify the labeling with this information.
2. With regard to literature references submitted in support of your labeling statement, it appears that the extent of metabolic conversion of norethindrone to ethinyl estradiol as reported is variable. We recommend that you refrain from including (b) (4) (b) (4) in the labeling and revise the statement in **Section 12.2 Pharmacokinetics**, *Metabolism* as shown:

   Norethindrone undergoes extensive biotransformation, primarily via reduction, followed by sulfate and glucuronide conjugation. The majority of metabolites in the circulation are sulfates, with glucuronides accounting for most of the urinary metabolites. A small amount of norethindrone acetate is metabolically converted to ethinyl estradiol~~,~~ (b) (4)

3. Modify the figure legends as shown below:

   Figure 1. - Mean (± SD) plasma ethinyl estradiol concentration versus time profiles following single- and multiple-dose oral administration ~~of~~ (of norethindrone acetate and ethinyl estradiol tablets, ethinyl estradiol tablets and ferrous fumarate tablets) to healthy female volunteers (n = 15)

   Figure 2. - Mean (± SD) plasma norethindrone concentration versus time profiles following single- and multiple-dose oral administration ~~of~~ (of norethindrone acetate and ethinyl estradiol tablets, ethinyl estradiol tablets and ferrous fumarate tablets) to healthy female volunteers (n = 15)

If you have any questions, call me, at (301) 796-1993.

LCDR Karl Stiller, R.Ph.
Regulatory Health Project Manager
Division of Reproductive and Urologic Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research
301-796-1993

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

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/s/

KARL J STILLER
01/07/2010

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 022501

PROPRIETARY NAME REQUEST
WITHDRAWN

Warner Chilcott Company, LLC
100 Enterprise Drive
Rockaway, New Jersey 07866

ATTENTION: Ms. Ileana Brown,
Director, Regulatory Affairs

Dear Ms. Brown:

Please refer to your New Drug Application (NDA) dated March 26, 2009, received March 26, 2009, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Norethindrone Acetate and Ethinyl Estradiol Tablets 1 mg/10 mcg, Ethinyl Estradiol Tablets 10 mcg and Ferrous Fumarate Tablets 75 mg.

We acknowledge receipt of your November 20, 2009 correspondence, on November 23, 2009, notifying us that you are withdrawing your November 11, 2009 request for a review of the proposed proprietary name (b) (4). This proposed proprietary name request is considered withdrawn as of November 23, 2009.

We also acknowledge that you have proposed an alternate proprietary name, Lo Loestrin FE, in your submission dated December 2, 2009.

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, call Maria Wasilik, Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (301) 796-0567. For any other information regarding this application, contact the Office of New Drugs (OND) Regulatory Project Manager, Karl Stiller at (301) 796-1993.

Sincerely,

{See appended electronic signature page}

Carol Holquist, RPh
Director
Division of Medication Error Prevention and Analysis
Office of Surveillance and Epidemiology
Center for Drug Evaluation and Research

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

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/s/

DENISE P TOYER on behalf of CAROL A HOLQUIST
12/29/2009

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 022501

PROPRIETARY NAME REQUEST
WITHDRAWN

Warner Chilcott Company, LLC
100 Enterprise Drive
Rockaway, New Jersey 07866

ATTENTION: Ms. Ileana Brown
Director, Regulatory Affairs

Dear Ms. Brown:

Please refer to your New Drug Application (NDA) dated March 26, 2009, received March 26, 2009, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Norethindrone Acetate and Ethinyl Estradiol 1 mg/10 mcg Tablets, Ethinyl Estradiol 10 mcg Tablets and Ferrous Fumarate 75 mg Tablets.

We acknowledge receipt of your November 10, 2009, correspondence, on November 12, 2009, notifying us that you are withdrawing your September 21, 2009 request for a review of the proposed proprietary name (b) (4) This proposed proprietary name request is considered withdrawn as of November 12, 2009.

We also acknowledge that you have proposed an alternate proprietary name, Lo Loestrin FE, in your submission dated December 2, 2009.

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, call Maria Wasilik, Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (301) 796-0567. For any other information regarding this application, contact the Office of New Drugs (OND) Regulatory Project Manager, Karl Stiller at (301) 796-1993.

Sincerely,
{See appended electronic signature page}

Carol Holquist, RPh
Director
Division of Medication Error Prevention and Analysis
Office of Surveillance and Epidemiology
Center for Drug Evaluation and Research

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

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/s/

CAROL A HOLQUIST
12/23/2009

MEMORANDUM OF TELECON

DATE: December 14, 2009

APPLICATION NUMBER: NDA 22-501 (b) (4)
(norethindrone acetate/ethinyl estradiol) Tablets

BETWEEN:

Name: Geoff Millington, M.S., Director , Regulatory Affairs
Olu Aloba, Ph.D., Director, Pharmaceutical Development
Robert Kessler, Ph.D., Sr Manager, Pharmaceutical Development

Phone: 973-442-3256, office (Geoff Millington)

Representing: Warner Chilcott

AND

Name: ***Office of New Drug Quality Assessment***
Yubing Tang, Ph.D., Review Chemist
Donna Christner, Ph.D., Pharmaceutical Assessment Lead
Jeannie David, M.S., Regulatory Health Project Manager

Office of Pharmaceutical Sciences, New Drug Microbiology Staff
Vinayak Pawar, Ph.D., Product Microbiology Reviewer

SUBJECT:

Background:
Warner Chilcott submitted an original NDA on March 26, 2009. Upon completion of review of the Drug Microbiology sections of the NDA, the following point was provided to Warner Chilcott from Jeannie David, Project Manager in FDA/ONDQA, to Ileana Brown and Geoff Millington, Warner Chilcott, by email on December 9, 2009, in preparation for the December 14, 2009, teleconference:

The product specification should state that the product meets the requirements of USP <61>, <62>, and <1111> if tested. The batch release criteria should identify the specific manufacturing process tests and criteria used to assess the finished product as microbiologically suitable for release. These tests and criteria should include, for example:

- *Microbial limits data for critical raw materials,*
- *Microbiological environmental monitoring data for critical processing steps, and*
- *In-process control parameters (e.g., heat, drying, washing) that may affect product quality microbiology.*

Discussion:
The Agency stated that non-performance of the Microbial Limits test was a concern because high amounts of compendial (b) (4) excipients in the capsule and an

increase in moisture content over time could be conducive to the proliferation of microbial contaminants. The Agency is not concerned about the frequency of testing but that the drug product specification should state that it meets the Microbial Limits requirements of USP <61>, <62> and <1111> if tested.

Warner Chilcott attempted to justify non-performance of the Microbial Limits test based on: (b) (4) .

Warner Chilcott in conclusion agreed to include the Microbial Limits test statement in the product release specification and agreed to notify the Agency of their decision to monitor microbial limits at product release and at expiry.

The call ended.

Jeannie David
Regulatory Project Manager
Office of New Drug Assessment
Center for Drug Evaluation and Research

Edits and Concurrence:
V. Pawar 12/17/09
Y. Tang 12/17/09

Follow-up emails with Warner Chilcott, attached:

David, Jeannie C

From: Geoffrey Millington [GMillington@wcrx.com]
Sent: Thursday, December 17, 2009 9:34 AM
To: David, Jeannie C
Subject: RE: NDA 22-501

Dear Jeannie,

The Warner Chilcott participants at the December 14th teleconference were:

Robert Kessler, Ph.D - Senior Manager, Pharmaceutical Development
Olu Aloba, Ph. D - Director, Pharmaceutical Development
Geoffrey Millington, M.S. - Director, Regulatory Affairs

As agreed, we are revising our finished product specifications for the drug product to include Microbial Limits. In order to provide this information to you rapidly, as you requested, we will submit the revised specifications with a cover letter and form to you today (I will forward a pdf file of the submission to your email today).

If you have any questions you can reach me at 973-442-3256.

Thanks.

Geoff Millington
Warner Chilcott

"David, Jeannie C" ---12/16/2009 05:35:14 PM---Dear Geoff:

From: "David, Jeannie C" <Jeannie.David@fda hhs.gov>
To: "Geoffrey Millington" <GMillington@wcrx.com>
Cc: "Ileana Brown" <IBrown@wcrx.com>, "Stiller, Karl" <Karl.Stiller@fda hhs.gov>
Date: 12/16/2009 05:35 PM
Subject: RE: NDA 22-501

Dear Geoff:

Reference is made to the teleconference held between representatives of FDA and Warner Chilcott on December 14, 2009, wherein Warner Chilcott agreed to the Agency's request to revise the drug product specification. When you revise the specification for your drug product, please update the acceptance criteria for the related substances that you had agreed upon in your amendment dated October 16, 2009.

The following is a list of FDA participants for the December 14, 2009 teleconference. We would appreciate a list of participants from Warner Chilcott.

Yubing Tang, Ph.D. Review Chemist
Donna Christner, Ph.D. Pharmaceutical Assessment Lead
Vinayak Pawar, Ph.D. Product Microbiology Reviewer
Jeannie David, M.S. Regulatory Project Manager

In order to facilitate our review in light of upcoming leave schedules, we would like to request that your amendment (or at least an electronic courtesy copy of the intended amendment) be provided by this Friday, December 18, 2009. Please let me know if you have any further questions.

Thank you,

Jeannie

Jeannie David, M.S.
Regulatory Project Manager
Food and Drug Administration
Center for Drug Evaluation and Research
Office of New Drug Quality Assessment
10903 New Hampshire Avenue
Building 22, Mail Room 1491
Silver Spring, MD 20993
Phone: (301) 796-4247
Fax: (301) 796-9877

jeannie.david@fda.hhs.gov

From: Geoffrey Millington [mailto:GMillington@wcrx.com]
Sent: Wednesday, December 09, 2009 4:52 PM
To: David, Jeannie C
Subject: RE: NDA 22-501

Jeannie,

I have been able to arrange with the appropriate colleagues to have the teleconference with you on **Monday, Dec. 14, from 12-12:30.**

The number to call is my office at **973-442-3256.**

Please let me know if anything changes.

Thanks.

Geoff Millington
Director, Regulatory Affairs
Warner Chilcott
973-442-3256

"David, Jeannie C" ---12/09/2009 01:49:29 PM---Dear Ms. Brown,

From:	"David, Jeannie C" <Jeannie.David@fda.hhs.gov>
To:	"Ileana Brown" <IBrown@wcrx.com>
Cc:	"Stiller, Karl" <Karl.Stiller@fda.hhs.gov>, "Geoffrey Millington" <GMillington@wcrx.com>
Date:	12/09/2009 01:49 PM
Subject:	RE: NDA 22-501

Dear Ms. Brown,

Please refer to Warner Chilcott's New Drug Application (NDA) 22-501 submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for [redacted] (b) (4) (norethindrone acetate/ethinyl estradiol) Tablets. As discussed, we are reviewing the Chemistry, Manufacturing and Controls sections of Warner Chilcott's submission and request a teleconference to discuss a deficiency related to the Drug Product Microbiological Attributes. For your convenience, the topic for discussion is provided below:

The product specification should state that the product meets the requirements of USP <61>, <62>, and

<1111> if tested. The batch release criteria should identify the specific manufacturing process tests and criteria used to assess the finished product as microbiologically suitable for release. These tests and criteria should include, for example:

- *Microbial limits data for critical raw materials,*
- *Microbiological environmental monitoring data for critical processing steps, and*
- *In-process control parameters (e.g., heat, drying, washing) that may affect product quality microbiology.*

We request a half-hour (1/2 hr) teleconference within the following timeframes. We would appreciate if you can provide a call in number for the teleconference.

- Monday, December 14, 10:00 - 10:30 AM EST
- Monday, December 14, 12:00 - 12:30 PM EST

As discussed, after review of the questions we would appreciate if you can reply to this email to inform us if Warner Chilcott would like to proceed with the proposed teleconference, or if instead Warner Chilcott would intend to submit an amendment to address the issues.

Thank you for your assistance.

Regards,

Jeannie

Jeannie David, M.S.
Regulatory Project Manager
Food and Drug Administration
Center for Drug Evaluation and Research
Office of New Drug Quality Assessment
10903 New Hampshire Avenue
Building 22, Mail Room 1491
Silver Spring, MD 20993
Phone: (301) 796-4247
Fax: (301) 796-9877

jeannie.david@fda.hhs.gov

From: Ileana Brown [mailto:IBrown@wcrx.com]
Sent: Tuesday, December 08, 2009 1:26 PM
To: David, Jeannie C
Cc: Stiller, Karl; Geoffrey Millington
Subject: NDA 22-501

Hi Jeannie,

As discussed, please forward the microbiology comments on the drug product for this NDA. Please include Geoff in your reply e-mail since he will follow-up with you next week; I will be out of the office next week.

Regards,

Ileana

********** WC Confidentiality Note: **********
This email transmission and any documents accompanying this email transmission contain information from Warner Chilcott, PLC, which is confidential. The information is intended only for the use of the intended recipient. If you are not the intended recipient, you are hereby notified that any disclosure, copying, distribution or the taking of any action in reliance on the contents of this email information is strictly prohibited, and that the documents should be returned to Warner Chilcott immediately. If you have received this email in error please notify us immediately by replying to the email address set forth above.

********** Thank you **********

********** WC Confidentiality Note: **********
This email transmission and any documents accompanying this email transmission contain information from Warner Chilcott, PLC, which is confidential. The information is intended only for the use of the intended recipient. If you are not the intended recipient, you are hereby notified that any disclosure, copying, distribution or the taking of any action in reliance on the contents of this email information is strictly prohibited, and that the documents should be returned to Warner Chilcott immediately. If you have received this email in error please notify us immediately by replying to the email address set forth above.
********** Thank you **********

********** WC Confidentiality Note: **********
This email transmission and any documents accompanying this email transmission contain information from Warner Chilcott, PLC, which is confidential. The information is intended only for the use of the intended recipient. If you are not the intended recipient, you are hereby notified that any disclosure, copying, distribution or the taking of any action in reliance on the contents of this email information is strictly prohibited, and that the documents should be returned to Warner Chilcott immediately. If you have received this email in error please notify us immediately by replying to the email address set forth above.
********** Thank you **********

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

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

/s/

JEANNIE C DAVID
12/17/2009

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 022501

INFORMATION REQUEST

Warner Chilcott Company, Inc.
Attention: Ileana Brown
Director, Regulatory Affairs
100 Enterprise Drive
Rockaway, NJ 07866

Dear Ms. Brown:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for your product containing norethindrone acetate and ethinyl estradiol tablets, ethinyl estradiol tablets, and ferrous fumarate tablets.

We are reviewing the Clinical section of your submission and have the following information requests. We request a prompt written response in order to continue our evaluation of your NDA. In reference to your Phase 3 Study PR-05806:

1. Provide data regarding how many of the 28 pregnancies occurred despite "perfect use" of the product.
2. Provide data identifying how many pills were missed and on which days of the cycle the pills were missed during the cycle that conception occurred for each of these 28 subjects.

If you have any questions, call Karl Stiller, Regulatory Project Manager, at (301) 796-1993.

Sincerely,

{See appended electronic signature page}

Jennifer Mercier
Chief, Project Management Staff
Division of Reproduction and Urologic Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

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

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/s/

JENNIFER L MERCIER
11/30/2009

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

REQUEST FOR CONSULTATION

TO *(Office/Division)*: David Hussong/Jim McVey/Sylvia Gantt
NEW DRUG MICROBIOLOGY STAFF
OC/OO/CDER/OPS/NDMS - HFD-805

FROM (*Name, Office/Division, and Phone Number of Requestor)*: Jeannie David, Office of New Drug Quality Assessment, 301-796-4247

DATE	IND NO.	NDA NO.	TYPE OF DOCUMENT	DATE OF DOCUMENT
September 16, 2009		22-501	Pending NDA	March 26, 2009

NAME OF DRUG	PRIORITY CONSIDERATION	CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE
Norethindrone acetate and ethinyl estradiol tablets, ethinyl estradiol tablets, and ferrous fumarate tablets	HIGH		Wednesday, September 30, 2009

NAME OF FIRM: Warner Chilcott Company, Inc.

REASON FOR REQUEST

I. GENERAL

- ☐ NEW PROTOCOL
- ☐ PROGRESS REPORT
- ☐ NEW CORRESPONDENCE
- ☐ DRUG ADVERTISING
- ☐ ADVERSE REACTION REPORT
- ☐ MANUFACTURING CHANGE / ADDITION
- ☐ MEETING PLANNED BY
- ☐ PRE-NDA MEETING
- ☐ END-OF-PHASE 2a MEETING
- ☐ END-OF-PHASE 2 MEETING
- ☐ RESUBMISSION
- ☐ SAFETY / EFFICACY
- ☒ PAPER NDA
- ☐ CONTROL SUPPLEMENT
- ☐ RESPONSE TO DEFICIENCY LETTER
- ☐ FINAL PRINTED LABELING
- ☐ LABELING REVISION
- ☐ ORIGINAL NEW CORRESPONDENCE
- ☐ FORMULATIVE REVIEW
- ☐ OTHER *(SPECIFY BELOW)*:

II. BIOMETRICS

- ☐ PRIORITY P NDA REVIEW
- ☐ END-OF-PHASE 2 MEETING
- ☐ CONTROLLED STUDIES
- ☐ PROTOCOL REVIEW
- ☐ OTHER (SPECIFY BELOW):
- ☐ CHEMISTRY REVIEW
- ☐ PHARMACOLOGY
- ☐ BIOPHARMACEUTICS
- ☐ OTHER (SPECIFY BELOW):

III. BIOPHARMACEUTICS

- ☐ DISSOLUTION
- ☐ BIOAVAILABILTY STUDIES
- ☐ PHASE 4 STUDIES
- ☐ DEFICIENCY LETTER RESPONSE
- ☐ PROTOCOL - BIOPHARMACEUTICS
- ☐ IN-VIVO WAIVER REQUEST

IV. DRUG SAFETY

- ☐ PHASE 4 SURVEILLANCE/EPIDEMIOLOGY PROTOCOL
- ☐ DRUG USE, e.g., POPULATION EXPOSURE, ASSOCIATED DIAGNOSES
- ☐ CASE REPORTS OF SPECIFIC REACTIONS (List below)
- ☐ COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP
- ☐ REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY
- ☐ SUMMARY OF ADVERSE EXPERIENCE
- ☐ POISON RISK ANALYSIS

V. SCIENTIFIC INVESTIGATIONS

- ☐ CLINICAL
- ☐ NONCLINICAL

COMMENTS / SPECIAL INSTRUCTIONS: We request Product Quality Micro review of the acceptability of the applicant's proposal for no microbial testing in their pending NDA. Background and relevant information are attached to this consult request.

SIGNATURE OF REQUESTOR
{see electronic signature}

METHOD OF DELIVERY (Check one)
☐ DFS ☒ EMAIL ☐ MAIL ☐ HAND

PRINTED NAME AND SIGNATURE OF RECEIVER

PRINTED NAME AND SIGNATURE OF DELIVERER

To our microbiological consultant:

We have recently received NDA 22-501 for drug product, (b) (4) (norethindrone acetate and ethinyl estradiol tablets, ethinyl estradiol tablets and ferrous fumarate tablets) submitted by *Warner Chilcott* for women to prevent pregnancy.

The applicant proposes (b) (4)

However, after reviewing the application, I have following concerns.

- Not all ingredients, including drug substances and other excipients in the (b) (4) step of the manufacturing (see below for (b) (4)), are tested for microbes.
- The stability test results for ferrous fumarate tablets showed a stead increase in moisture level (e.g. in one case, increased from 1.7% to 3.3% and in the other case from 2.6% to 3.4%, for three months for both cases). It is indicative to me that the tablets pick up moisture during the storage. Although there is no moisture data for other two tablets, it is reasonable to argue that similar trend exists. If this trend is true, will the moisture facilitate microbial growth?

I have provided relevant information below. We would like to know, from your perspective, whether applicant's proposal, no microbial test, is acceptable. We'd very appreciate your help.

Also, this is a paper NDA, if you need any additional information, please let me know so I will scan whatever section you need and e-mail to you.

Thanks,

Yubing Tang, Ph. D.
CMC Reviewer
OPS/ONDQA/DPMAII

RELEVANT INFORMATION

NDA: 22-501
OND Division: Division of Reproductive and Urologic Products
Applicant: Warner Chilcott
Trademark: (b) (4)
Established Name: norethindrone acetate, ethinyl estradiol
Dosage Form: Tablets
Route of Administration: Oral
Indication: Pregnancy Prevention

The proposed drug product, (b) (4) (norethindrone acetate (NA) and ethinyl estradiol (EE) tables, ethinyl estradiol tablets and ferrous fumarate tables), is a low dose oral contraceptive.

The following compendial excipients are contained in Loestrin® 1/10 Fe: mannitol, USP, microcrystalline cellulose, NF, FD&C Blue No. 1 Aluminum Lake (FD&C certified), sodium starch glycolate, NF, magnesium stearate, NF, povidone, USP, vitamin E, USP, lactose monohydrate, NF and sucralose, NF. The spearmint flavor in ferrous fumarate tablets is a non-compendial excipient.

Loestrin® 1/10 Fe active tablets are (b) (4)

Container closure system for (b) (4) tablet regimen is a unit-dose blister consisting of a (b) (4) blister lidding and aluminum foil/ (b) (4) (b) (4) backing.

Batch Formula for NA Tablets

(b) (4)

(b) (4)

Table 2: Batch Formula for WC3016 Ethinyl Estradiol (b) (4) 0.2% w/w Formulation Number WC3016 (b) (4)

Component	Quality Standard	Amount per batch (kg)
Ethinyl estradiol[a]	USP	(b) (4)
Povidone (b) (4)	USP	
Vitamin E	USP	
Lactose monohydrate (b) (4)	NF	
(b) (4)	N/A	
(b) (4)	USP	
Total	N/A	

(b) (4)

Table 3: Batch Formula for WC3016 1/10 Tablet Blend

Component	Quality Standard	Amount per batch (kg)
Ethinyl estradiol (b) (4) 0.2% w/w Formulation number WC3016 (b) (4)	N/A	(b) (4)
Norethindrone acetate	USP	
Mannitol (b) (4)	USP	
Mannitol (b) (4)	USP	
Microcrystalline cellulose, (b) (4) (b) (4)	NF	
FD&C blue No. 1 aluminum lake	FD&C certified	
Sodium starch glycolate	NF	
Magnesium stearate	NF	
Total	N/A	

Batch Formula for EE Tablets ([redacted]

Table 2: Batch Formula for WC3016 Ethinyl Estradiol [redacted] 0.2% w/w Formulation Number WC3016-[redacted]

Component	Quality Standard	Amount per batch (kg)
Ethinyl estradiol[a]	USP	[redacted]
Povidone [redacted]	USP	
Vitamin E	USP	
Lactose monohydrate [redacted]	NF	
[redacted]	N/A	
	USP	
Total	N/A	

[redacted]

Table 3: Batch Formula for WC3016 EE10 Tablet Blend

Component	Quality Standard	Amount per batch (kg)
Ethinyl estradiol [redacted] 0.2% w/w Formulation number WC3016-[redacted]	N/A	[redacted]
Mannitol [redacted]	USP	
Mannitol [redacted]	USP	
Microcrystalline cellulose, [redacted]	NF	
Sodium starch glycolate	NF	
Magnesium stearate	NF	
Total	N/A	

2 Page(s) have been Withheld in Full as b4 (CCI/TS) immediately following this page

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

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/s/

JEANNIE C DAVID
09/16/2009

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 22-501

ADVICE/INFORMATION REQUEST

Warner Chilcott Company, Inc.
Attention: Ileana Brown
Director, Regulatory Affairs
100 Enterprise Drive
Rockaway, New Jersey 07866

Dear Ms. Brown:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for your product containing norethindrone acetate and ethinyl estradiol tablets, ethinyl estradiol tablets, and ferrous fumarate tablets.

We also refer to your July 22, 2009, submission, containing responses to our June 8, 2009, Filing Communication.

We are reviewing your submissions and have the following comments and information requests regarding the Clinical, and Chemistry, Manufacturing, and Controls (CMC) sections. We request a prompt written response in order to continue our evaluation of your NDA.

CLINICAL

1. The Pearl Index point estimate and confidence interval (based on the 28 pregnancies determined at this point in the review to have occurred "on-drug") is a significant concern.
2. According to the Case Report Form (CRF) for Subject 025-017, this subject took her last dose of study drug on 12/22/07. There is a note written by the Principal Investigator in the "Suspected Pregnancy" section of the CRF that states that the subject had a positive pregnancy test on 12/28/07, which would have been 6 days after her last dose.. Therefore, we have determined that this subject had an "on-drug" pregnancy and will be included in the Pearl Index calculation. The total number of "on-drug" pregnancies on which the Pearl Index is calculated is now 28.
3. Provide the CRF for Subject 011-010. This subject was included in Data Listing 16.2.14 on page 7352 of 22444 under Suspected Pregnancies, All Enrolled Subjects.
4. Provide, at a minimum, the mean, median, and range for the number of observed days of 1) intracyclic bleeding only, 2) intracyclic spotting only and 3) intracyclic bleeding/spotting combined, within each cycle. Provide the same data for withdrawal

bleeding/spotting. Provide figures displaying the number of subjects on the y-axis and the number of days of (1) intracyclic bleeding only, (2) intracyclic spotting only, and (3) intracyclic bleeding/spotting combined on the x-axes for each cycle. (Refer to Mishell et al., Contraception 75: 11-15, 2007 for examples.)

5. Provide the following information about hematologic indices:
    a. Provide shift tables of hemoglobin and hematocrit laboratory values, classifying subjects as low, normal, or high at baseline and end of study.
    b. Provide data on hematologic indices at baseline and end of study for subjects who withdrew due to bleeding-related adverse reactions.
6. Subject 043-004 is listed in Table 24 on page 88 of 22444 as having a transverse sinus thrombosis, yet her CRF data indicates that her final diagnosis was transverse sigmoid sinus stenosis. Clarification is requested.
7. Clarify what instructions were given to subjects regarding condom use during the phase 3 clinical trial and verify that subjects who used condoms during this trial were not included in the MITT population.

CMC

1. There is inconsistency in your description of the ferrous fumarate tablets. The specification describes the tablets as "… brown tablets debossed with (b) (4) on one side and '624' on the other side." In the **Prescribing Information** section under Item 3. DOSAGE FORM AND STRENGTH, the tablets are described as "…brown tablet is imprinted with WC on one side and 624 on the other." Clarify whether (b) (4) or "WC" is correct.
2. The impurity specifications for your drug product are not justified by the release data and stability results. Revise the acceptance criteria for the impurities as recommended below.

(b) (4)

3. Labeling
   - The lot number and expiration date are missing on the blister packs (both for trade and sample). Revise the blister packs to include this information.
   - The statement "Rx only" cannot be found in the submitted carton label. Revise the carton label to include this statement.

If you have any questions, call Karl Stiller, Regulatory Project Manager, at (301) 796-1993.

Sincerely,

{See appended electronic signature page}

Margaret Kober, R.Ph., M.P.A.
Chief, Project Management Staff
Division of Reproduction and Urologic Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

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

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/s/

MARGARET M KOBER
09/03/2009
Chief, Project Management Staff

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADM NISTRATION

REQUEST FOR DDMAC LABELING REVIEW CONSULTATION

Please send immediately following the Filing/Planning meeting

TO:

CDER-DDMAC-RPM

FROM: (Name/Title, Office/Division/Phone number of requestor) Karl Stiller/RPM, ODEIII/DRUP 301-796-1993

REQUEST DATE	IND NO.	NDA/BLA NO.	TYPE OF DOCUMENTS (PLEASE CHECK OFF BELOW)
8-6-2010		022501	

NAME OF DRUG	PRIORITY CONSIDERATION	CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE (Generally 1 week before the wrap-up meeting)
Lo Loestrin Fe	Standard		9-30-2010

NAME OF FIRM:

PDUFA Date: 10-21-2010

TYPE OF LABEL TO REVIEW

TYPE OF LABELING:
(Check all that apply)
X PACKAGE INSERT (PI)
X PATIENT PACKAGE INSERT (PPI)
X CARTON/CONTAINER LABELING
☐ MEDICATION GUIDE
☐ INSTRUCTIONS FOR USE(IFU)

TYPE OF APPLICATION/SUBMISSION
X ORIGINAL NDA/BLA
☐ IND
☐ EFFICACY SUPPLEMENT
☐ SAFETY SUPPLEMENT
☐ LABELING SUPPLEMENT
☐ PLR CONVERSION

REASON FOR LABELING CONSULT
☐ INITIAL PROPOSED LABELING
X LABELING REVISION

EDR link to submission:
\\fdswa150\nonectd\N22501\N_000\2010-04-20
Substantially complete labeling will be provided around the time of the labeling meeting(s).

Please Note: There is no need to send labeling at this time. DDMAC reviews substantially complete labeling, which has already been marked up by the CDER Review Team. The DDMAC reviewer will contact you at a later date to obtain the substantially complete labeling for review.

COMMENTS/SPECIAL INSTRUCTIONS:

Mid-Cycle Meeting: None scheduled

Labeling Meetings: September 20 and 28, 2010

Wrap-Up Meeting: None scheduled

SIGNATURE OF REQUESTER Karl Stiller

SIGNATURE OF RECEIVER

METHOD OF DELIVERY (Check one)
X eMAIL ☐ HAND

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

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/s/

KARL J STILLER
08/06/2010

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 22-501

PROPRIETARY NAME REQUEST
UNACCEPTABLE

Warner Chilcott Company, Inc.
100 Enterprise Drive
Rockaway, New Jersey 07866

Attention: Ileana Brown
Director, Regulatory Affairs

Dear Ms. Brown:

Please refer to your New Drug Application (NDA) dated March 26, 2009, received March 26, 2009, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for norethindrone acetate and ethinyl estradiol tablets, ethinyl estradiol tablets and ferrous fumarate tablets.

We also refer to your April 9, 2009, correspondence, received April 10, 2009, requesting review of your proposed proprietary name, (b) (4). We have completed our review of the proposed proprietary name, (b) (4), and have concluded that this name is unacceptable because it does not provide adequate distinction from other combination products in the Loestrin product line.

(b) (4) This is misleading and may cause confusion with the other Loestrin products.

In the absence of data to support that the (b) (4) would not inadvertently introduce a source of error, we do not recommend the proposed proprietary name, (b) (4).

You have not proposed an alternate proprietary name for review. If you intend to have a proprietary name for this product, we recommend that you submit a new request for a proposed proprietary name review. (See the draft Guidance for Industry, *Complete Submission for the Evaluation of Proprietary Names*, HTTP://www.fda.gov/cder/guidance/7935dft.pdf and "PDUFA Reauthorization Performance Goals and Procedures Fiscal Years 2008 through 2012".)

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, call Maria Wasilik, Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (301) 796-0757. For any other information regarding this application, contact Karl Stiller, Regulatory Project Manager in the Office of New Drugs (OND) at (301) 796-1993.

Sincerely,

{See appended electronic signature page}

Carol Holquist, RPh.
Director
Division of Medication Error Prevention and Analysis
Office of Surveillance and Epidemiology
Center for Drug Evaluation and Research

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/s/

Carol Holquist

7/8/2009 06:20:26 PM

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

REQUEST FOR CONSULTATION

TO *(Office/Division)*: CDER OSE CONSULTS

FROM (*Name, Office/Division, and Phone Number of Requestor)*: Karl Stiller, Project Manager, Division of Reproductive and Urologic Products, HFD-580
301-796-1993

DATE	IND NO.	NDA NO.	TYPE OF DOCUMENT	DATE OF DOCUMENT
29-Jun-09		22-501	NDA	25-May-09

NAME OF DRUG	PRIORITY CONSIDERATION	CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE
(b) (4) (norethindrone acetate/ethinyl estradiol)	S		30-Oct-09

NAME OF FIRM: Warner Chilcott

REASON FOR REQUEST

I. GENERAL

- ☐ NEW PROTOCOL
- ☐ PROGRESS REPORT
- ☐ NEW CORRESPONDENCE
- ☐ DRUG ADVERTISING
- ☐ ADVERSE REACTION REPORT
- ☐ MANUFACTURING CHANGE / ADDITION
- ☐ MEETING PLANNED BY
- ☐ PRE-NDA MEETING
- ☐ END-OF-PHASE 2a MEETING
- ☐ END-OF-PHASE 2 MEETING
- ☐ RESUBMISSION
- ☐ SAFETY / EFFICACY
- ☐ PAPER NDA
- ☐ CONTROL SUPPLEMENT
- ☐ RESPONSE TO DEFICIENCY LETTER
- ☐ FINAL PRINTED LABELING
- ☐ LABELING REVISION
- ☐ ORIGINAL NEW CORRESPONDENCE
- ☐ FORMULATIVE REVIEW
- ☒ OTHER *(SPECIFY BELOW)*:

II. BIOMETRICS

- ☐ PRIORITY P NDA REVIEW
- ☐ END-OF-PHASE 2 MEETING
- ☐ CONTROLLED STUDIES
- ☐ PROTOCOL REVIEW
- ☐ OTHER (SPECIFY BELOW):
- ☐ CHEMISTRY REVIEW
- ☐ PHARMACOLOGY
- ☐ BIOPHARMACEUTICS
- ☐ OTHER (SPECIFY BELOW):

III. BIOPHARMACEUTICS

- ☐ DISSOLUTION
- ☐ BIOAVAILABILTY STUDIES
- ☐ PHASE 4 STUDIES
- ☐ DEFICIENCY LETTER RESPONSE
- ☐ PROTOCOL - BIOPHARMACEUTICS
- ☐ IN-VIVO WAIVER REQUEST

IV. DRUG SAFETY

- ☐ PHASE 4 SURVEILLANCE/EPIDEMIOLOGY PROTOCOL
- ☐ DRUG USE, e.g., POPULATION EXPOSURE, ASSOCIATED DIAGNOSES
- ☐ CASE REPORTS OF SPECIFIC REACTIONS (List below)
- ☐ COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP
- ☐ REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY
- ☐ SUMMARY OF ADVERSE EXPERIENCE
- ☐ POISON RISK ANALYSIS

V. SCIENTIFIC INVESTIGATIONS

- ☐ CLINICAL
- ☐ NONCLINICAL

COMMENTS / SPECIAL INSTRUCTIONS: This is an electronic submission. All labeling can be found in Module 1.14.1 at \\FDSWA150\NONECTD\N2250N_000\2009-03-26 .

SIGNATURE OF REQUESTOR
Karl Stiller

METHOD OF DELIVERY (Check one)
☒ DFS ☐ EMAIL ☐ MAIL ☐ HAND

PRINTED NAME AND SIGNATURE OF RECEIVER

PRINTED NAME AND SIGNATURE OF DELIVERER

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

/s/

Karl Stiller

6/29/2009 03:00:53 PM

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

REQUEST FOR CONSULTATION

TO *(Office/Division)*: Division of Drug Marketing, Advertising and Communications (DDMAC) HFD-42, BLD WO 51 Room 3251
Attn: Janice Maniwang

FROM (*Name, Office/Division, and Phone Number of Requestor)*: Karl Stiller, Project Manager, Division of Reproductive and Urologic Products, HFD-580
301-796-1993

DATE	IND NO.	NDA NO.	TYPE OF DOCUMENT	DATE OF DOCUMENT
29-Jun-09		22-501	NDA	25-May-09

NAME OF DRUG	PRIORITY CONSIDERATION	CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE
(b) (4) (norethindrone acetate/ethinyl estradiol)	S		30-Oct-09

NAME OF FIRM: Warner Chilcott

REASON FOR REQUEST

I. GENERAL

- ☐ NEW PROTOCOL
- ☐ PROGRESS REPORT
- ☐ NEW CORRESPONDENCE
- ☐ DRUG ADVERTISING
- ☐ ADVERSE REACTION REPORT
- ☐ MANUFACTURING CHANGE / ADDITION
- ☐ MEETING PLANNED BY
- ☐ PRE-NDA MEETING
- ☐ END-OF-PHASE 2a MEETING
- ☐ END-OF-PHASE 2 MEETING
- ☐ RESUBMISSION
- ☐ SAFETY / EFFICACY
- ☐ PAPER NDA
- ☐ CONTROL SUPPLEMENT
- ☐ RESPONSE TO DEFICIENCY LETTER
- ☐ FINAL PRINTED LABELING
- ☐ LABELING REVISION
- ☐ ORIGINAL NEW CORRESPONDENCE
- ☐ FORMULATIVE REVIEW
- ☒ OTHER *(SPECIFY BELOW)*:

II. BIOMETRICS

- ☐ PRIORITY P NDA REVIEW
- ☐ END-OF-PHASE 2 MEETING
- ☐ CONTROLLED STUDIES
- ☐ PROTOCOL REVIEW
- ☐ OTHER (SPECIFY BELOW):
- ☐ CHEMISTRY REVIEW
- ☐ PHARMACOLOGY
- ☐ BIOPHARMACEUTICS
- ☐ OTHER (SPECIFY BELOW):

III. BIOPHARMACEUTICS

- ☐ DISSOLUTION
- ☐ BIOAVAILABILTY STUDIES
- ☐ PHASE 4 STUDIES
- ☐ DEFICIENCY LETTER RESPONSE
- ☐ PROTOCOL - BIOPHARMACEUTICS
- ☐ IN-VIVO WAIVER REQUEST

IV. DRUG SAFETY

- ☐ PHASE 4 SURVEILLANCE/EPIDEMIOLOGY PROTOCOL
- ☐ DRUG USE, e.g., POPULATION EXPOSURE, ASSOCIATED DIAGNOSES
- ☐ CASE REPORTS OF SPECIFIC REACTIONS (List below)
- ☐ COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP
- ☐ REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY
- ☐ SUMMARY OF ADVERSE EXPERIENCE
- ☐ POISON RISK ANALYSIS

V. SCIENTIFIC INVESTIGATIONS

- ☐ CLINICAL
- ☐ NONCLINICAL

COMMENTS / SPECIAL INSTRUCTIONS: This is an electronic submission. The the PI can be found at \\FDSWA150\NONECTD\N22501\N_000\2009-03-26 .

Each dosing regimen is comprised of 24 tablets containing 1 mg norethindrone acetate and 10 mcg ethinyl estradiol, 2 tablets containing 10 mcg ethinyl estradiol, and 2 ferrous fumarate tablets.

SIGNATURE OF REQUESTOR	METHOD OF DELIVERY (Check one)
Karl Stiller	☒ DFS ☐ EMAIL ☐ MAIL ☐ HAND
PRINTED NAME AND SIGNATURE OF RECEIVER	PRINTED NAME AND SIGNATURE OF DELIVERER

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/s/

Karl Stiller

6/29/2009 03:05:23 PM

DEPARTMENT OF HEALTH & HUMAN SERVICES
Public Health Service
Food and Drug Administration
Rockville, MD 20857

FILING COMMUNICATION

NDA 22-501

Warner Chilcott Company, Inc. c/o Warner Chilcott (US), LLC
Attention: Alvin Howard
Senior Vice President Regulatory Affairs
100 Enterprise Drive
Rockaway, NJ 07866

Dear Mr. Howard:

Please refer to your new drug application (NDA) dated and received March 26, 2009, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act, for (b) (4) (norethindrone acetate [NA] and ethinyl estradiol [EE] 1 mg NA/10 mcg EE, 10 mcg EE), tablets.

We have completed our filing review and have determined that your application is sufficiently complete to permit a substantive review. Therefore, in accordance with 21 CFR 314.101(a), this application is considered filed 60 days after the date we received your application. The review classification for this application is **Standard**. Therefore, the user fee goal date is January 26, 2010.

We are reviewing your application according to the processes described in the Guidance for Review Staff and Industry: Good Review Management Principles and Practices for PDUFA Products. Therefore, we have established internal review timelines as described in the guidance, which includes the timeframes for FDA internal milestone meetings (e.g., filing, planning, midcycle, team, and wrap-up meetings). Please be aware that the timelines described in the guidance are flexible and subject to change based on workload and other potential review issues (e.g., submission of amendments). We will inform you of any necessary information requests or status updates following the milestone meetings or at other times, as needed, during the process. If major deficiencies are not identified during the review, we plan to communicate proposed labeling and, if necessary, any postmarketing commitment requests by December 15, 2009.

During our filing review of your application, we identified the following potential review issues:

1. We do not agree with your definitions of the pregnancy intent-to-treat cohort (PITT) population and "on-drug pregnancies."

   We define the PITT as including women aged 18 to less than 36 years at the time of enrollment in the clinical trial. The PITT cohort is the principal analysis cohort for pregnancy evaluation. Subjects in this group should not be censored on their 36th birthday in the pregnancy assessment. Therefore, the pregnancies occurring in Subject 001-104 and Subject 017-022 should be included in the pregnancy assessment.

We define "on-drug pregnancies" as all conceptions that occur from Day 1 (the initiation of taking study drug) to seven days after the final tablet (i.e., the second Fe tablet) in the pill pack is taken. If the pills are stopped prior to completing a 28-day pack, we define "on-drug pregnancies" as all conceptions from Day 1 to seven days after the final tablet is taken. Thus, Subject 028-055 should be included in the pregnancy assessment.

Based on the above definitions of the PITT population and "on-drug pregnancies," you are requested to submit a recalculation of the Pearl Index and life table pregnancy rates.

2. Section 13: Nonclinical Toxicology and Section 13.1 Carcinogenesis, Mutagenesis and Impairment of Fertility (b) (4) (b) (4) If there is no information regarding potential drug-related effects on carcinogenicity, mutagenicity, and fertility, then the label must clearly indicate the lack of data.

We are providing the above comments to give you preliminary notice of potential review issues. Our filing review is only a preliminary evaluation of the application and is not indicative of deficiencies that may be identified during our review. Issues may be added, deleted, expanded upon, or modified as we review the application.

We have the following additional comments and information requests:

1. Provide a stratification of all the pregnancies included in the Pearl Index calculations by weight and BMI deciles.

2. The text of the Clinical Study Report (e.g., Table 6) refers to a Pearl Index calculation in the subgroup of women aged 18 to 35 years in the MITT population as being 2.554. However, various tables in the submission (e.g., Table 14.2.1.1) list the Pearl Index in this subgroup to be 2.544. Please clarify this discrepancy.

3. Provide the Case Report Form (CRF) for Subject 025-017, who was lost to follow-up but was described as a "possible pregnancy."

4. Your pregnancy narratives typically refer to "last active pill." Clarify whether this refers to the last combination pill or the last EE-alone pill.

If you have not already done so, you must submit the content of labeling [21 CFR 314.50(l)(1)(i)] in structured product labeling (SPL) format as described at http://www.fda.gov/oc/datacouncil/spl.html. The content of labeling must be in the Prescribing Information (physician labeling rule) format.

Please respond only to the above requests for additional information. While we anticipate that any response submitted in a timely manner will be reviewed during this review cycle, such review decisions will be made on a case-by-case basis at the time of receipt of the submission.

REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication in pediatric patients unless this requirement is waived, deferred, or inapplicable.

We acknowledge receipt of your request for a full waiver of pediatric studies for this application. Once we have reviewed your request, we will notify you if the full waiver request is denied and a pediatric drug development plan is required.

If you have any questions, call Karl Stiller, Regulatory Project Manager, at (301) 796-1993.

Sincerely,

{See appended electronic signature page}

Scott Monroe, M.D.
Director
Division of Reproductive and Urologic Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

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/s/

Scott Monroe
6/8/2009 12:12:55 PM

Memo to the file

Date: 4-13-09

NDA #: 22-501

Date of submission: 3-25-09

Sponsor: Warner Chilcott Company, Inc.

Drug Product: Loestrin tablet (1 mg NA10 ug EE, 10 ug EE**)**

Indication: Contraception

Subject: NDA filling meeting

Reviewer: Krishan L. Raheja, D.V.M., Ph.D.

Through P/T Supervisor: Lynnda Reid, Ph.D.

Regulatory action: NDA 22-501 is filable from the P/T perspective.

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/s/

Krishan L. Raheja
4/30/2009 11:53:14 AM
PHARMACOLOGIST

Lynnda Reid
4/30/2009 12:20:09 PM
PHARMACOLOGIST

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 22-501

NDA ACKNOWLEDGMENT

Warner Chilcott Company, Inc. c/o Warner Chilcott (US), LLC
Attention: Alvin Howard
Senior Vice President Regulatory Affairs
100 Enterprise Drive
Rockaway, NJ 07866

Dear Mr. Howard:

We have received your new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for the following:

Name of Drug Product:	[redacted] (b) (4) (norethindrone acetate (NA) and ethinyl estradiol (EE) 1 mg NA/10 mcg EE, 10 mcg EE), tablets
Date of Application:	March 26, 2009
Date of Receipt:	March 26, 2009
Our Reference Number:	NDA 22-501

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, we will file the application on May 25, 2009 in accordance with 21 CFR 314.101(a).

If you have not already done so, promptly submit the content of labeling [21 CFR 314.50(l)(1)(i)] in structured product labeling (SPL) format as described at http://www.fda.gov/oc/datacouncil/spl.html. Failure to submit the content of labeling in SPL format may result in a refusal-to-file action under 21 CFR 314.101(d)(3). The content of labeling must conform to the content and format requirements of revised 21 CFR 201.56-57.

The NDA number provided above should be cited at the top of the first page of all submissions to this application. Send all submissions, electronic or paper, including those sent by overnight mail or courier, to the following address:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Reproductive and Urologic Products
5901-B Ammendale Road
Beltsville, MD 20705-1266

All regulatory documents submitted in paper should be three-hole punched on the left side of the page and bound. The left margin should be at least three-fourths of an inch to assure text is not obscured in the fastened area. Standard paper size (8-1/2 by 11 inches) should be used; however, it may occasionally be necessary to use individual pages larger than standard paper size. Non-standard, large pages should be folded and mounted to allow the page to be opened for review without disassembling the jacket and refolded without damage when the volume is shelved. Shipping unbound documents may result in the loss of portions of the submission or an unnecessary delay in processing which could have an adverse impact on the review of the submission. For additional information, please see http:www.fda.gov/cder/ddms/binders.htm.

If you have any questions, call Karl Stiller, Regulatory Project Manager, at (301) 796-1993.

Sincerely,

{See appended electronic signature page}

Jennifer Mercier
Chief, Project Management Staff
Division of Reproduction and Urologic Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

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/s/

Jennifer L. Mercier
4/3/2009 11:25:53 AM