

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**21-871**

**ADMINISTRATIVE and CORRESPONDENCE  
DOCUMENTS**

**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**

NDA NUMBER

21-871

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)

Loestrin 24

ACTIVE INGREDIENT(S)

Norethindrone Acetate/Ethinyl Estradiol

STRENGTH(S)

1mg/20mcg

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

5,552,394

b. Issue Date of Patent

9/3/1996

c. Expiration Date of Patent

7/22/2014

d. Name of Patent Owner

Warner Chilcott Company, Inc.

Address (of Patent Owner)

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)

☐ Warner Chilcott (US), Inc.

Address (of agent or representative named in 1.e.)

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

**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 separately for each patent claim claiming a method of using the pending drug product for which approval is being sought. For each method of use claim referenced, 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 (as listed in the patent) Claims 1-12 (The following information applies to each claim)	Does the patent claim referenced in 4.2 claim a pending method of use for which approval is being sought in the pending NDA, amendment, or supplement? <input checked="" type="checkbox"/> Yes <input type="checkbox"/> 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.) Loestrin 24 is indicated for use by women to lower the risk of becoming pregnant.
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**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



4/15/05

**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, Vice President, Regulatory Affairs, Warner Chilcott (US), Inc.

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 9 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.*

**WARNER  
CHILCOTT**

NDA 21-871  
Loestrin 24 (norethindrone acetate 1 mg/ethinyl estradiol 20  
mcg tablets, USP and ferrous fumarate tablets)

Item 14  
Patent Certification

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#### **14. PATENT CERTIFICATION**

Not applicable for a 505(b)(1) application in accordance with 21 CFR 314.50(i).

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On Original**

## EXCLUSIVITY SUMMARY

NDA # 21-871

SUPPL #

HFD # 580

Trade Name Loestrin® 24 Fe

Generic Name norethindrone acetate/ethinyl estradiol and ferrous fumarate tablets.

Applicant Name Warner Chilcott Company, Inc.

Approval Date, If Known February 17, 2006

### **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?

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).

NDA#

NDA#

NDA#

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).

NDA# 17-354	Loestrin® Fe 1/20 (norethindrone acetate ethinyl estradiol /tablets, USP and ferrous fumarate) tablets
NDA# 21-065	fmhrt® (ethinyl estradiol and norethindrone acetate) tablets
NDA# 17-355	NDA 17-355/S-46 Loestrin_ Fe 1.5/30 (norethindrone and ethinyl estradiol) tablets, USP and ferrous fumarate tablets

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:

Study RR-10104.0

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.")

Investigation #1 YES  NO

Investigation #2 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?

Investigation #1 YES  NO

Investigation #2 YES  NO

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

NDA 17-354 Loestrin® Fe 1/20 (norethindrone acetate ethinyl estradiol /tablets, USP and ferrous fumarate) tablets

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"):

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?

Investigation #1  
IND # 64817      YES       ! NO   
! Explain:

Investigation #2  
IND #      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: Nenita Crisostomo, R.N.  
Title: Regulatory Health Project Manager  
Date: February 17, 2006

Name of Office/Division Director signing form: Daniel Shames, M.D.  
Title: Director

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

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this page is the manifestation of the electronic signature.**  
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/s/

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Daniel A. Shames  
2/17/2006 04:33:11 PM

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## PEDIATRIC PAGE

(Complete for all filed original applications and efficacy supplements)

DA #: 21-871 Supplement Type (e.g. SE5): \_\_\_\_\_ Supplement Number: \_\_\_\_\_

Stamp Date: April 18, 2005 Action Date: February 17, 2006

HFD 580 Trade and generic names/dosage form: Loestrin® 24 Fe (norethindrone acetate/ethinyl estradiol) tablets

Applicant: Warner Chilcott Company, Inc., Therapeutic Class: 3S

Indication(s) previously approved:

**Each approved indication must have pediatric studies: Completed, Deferred, and/or Waived.**

Number of indications for this application(s): 1

Indication #1: Prevention of pregnancy in women who elect to use oral contraceptives as a method of contraception.

Is there a full waiver for this indication (check one)?

- Yes: Please proceed to Section A.
- No: Please check all that apply: \_\_\_ Partial Waiver \_\_\_ Deferred \_\_\_ Completed  
NOTE: More than one may apply  
Please proceed to Section B, Section C, and/or Section D and complete as necessary.

### Section A: Fully Waived Studies

Reason(s) for full waiver:

- Products in this class for this indication have been studied/labeled for pediatric population
- Disease/condition does not exist in children
- Too few children with disease to study
- There are safety concerns
- Other: Safety and efficacy of Loestrin 24 Fe tablets have been established in women of reproductive age. Safety and efficacy are expected to be the same for postpubertal adolescents under the age of 16 and for users 16 years and older. Use of this product before menarche is not indicated.

*If studies are fully waived, then pediatric information is complete for this indication. If there is another indication, please see Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.*

### Section B: Partially Waived Studies

Age/weight range being partially waived:

Min \_\_\_\_\_ kg \_\_\_\_\_ mo. \_\_\_\_\_ yr. \_\_\_\_\_ Tanner Stage \_\_\_\_\_  
Max \_\_\_\_\_ kg \_\_\_\_\_ mo. \_\_\_\_\_ yr. \_\_\_\_\_ Tanner Stage \_\_\_\_\_

Reason(s) for partial waiver:

- Products in this class for this indication have been studied/labeled for pediatric population
- Disease/condition does not exist in children
- Too few children with disease to study
- There are safety concerns
- Adult studies ready for approval
- Formulation needed

Other: \_\_\_\_\_

*If studies are deferred, proceed to Section C. If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.*

**Section C: Deferred Studies**

Age/weight range being deferred:

Min \_\_\_\_\_ kg \_\_\_\_\_ mo. \_\_\_\_\_ yr. \_\_\_\_\_ Tanner Stage \_\_\_\_\_  
Max \_\_\_\_\_ kg \_\_\_\_\_ mo. \_\_\_\_\_ yr. \_\_\_\_\_ Tanner Stage \_\_\_\_\_

Reason(s) for deferral:

- Products in this class for this indication have been studied/labeled for pediatric population
- Disease/condition does not exist in children
- Too few children with disease to study
- There are safety concerns
- Adult studies ready for approval
- Formulation needed

Other: \_\_\_\_\_

Date studies are due (mm/dd/yy): \_\_\_\_\_

*If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.*

**Section D: Completed Studies**

Age/weight range of completed studies:

Min \_\_\_\_\_ kg \_\_\_\_\_ mo. \_\_\_\_\_ yr. \_\_\_\_\_ Tanner Stage \_\_\_\_\_  
Max \_\_\_\_\_ kg \_\_\_\_\_ mo. \_\_\_\_\_ yr. \_\_\_\_\_ Tanner Stage \_\_\_\_\_

Comments:

*If there are additional indications, please proceed to Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.*

This page was completed by:

*{See appended electronic signature page}*

Nenita Crisostomo, R.N.  
Regulatory Project Manager

cc: NDA 21-871  
HFD-960/ Grace Carmouze

**FOR QUESTIONS ON COMPLETING THIS FORM CONTACT THE DIVISION OF PEDIATRIC DRUG DEVELOPMENT, HFD-960, 301-594-7337.**

(revised 12-22-03)

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

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Nenita Crisostomo  
2/17/2006 11:51:48 AM

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**ITEM 20. REQUEST FOR FULL WAIVER OF PEDIATRIC STUDIES**

Application: NDA 21-871

Drug: Loestrin 24 Tablets (norethindrone acetate/ethinyl estradiol tablets and ferrous fumarate tablets)

Sponsor: Warner Chilcott Company, Inc.

Indication: For use by women to lower the risk of becoming pregnant.

In accordance with 21CFR 314.55(c)(2), Warner Chilcott Company, Inc. hereby requests a full waiver of the requirement for pediatric studies associated with the submission of this NDA.

Loestrin 24 Tablets are not indicated before menarche regardless of the age of the adolescent. It is Warner Chilcott's belief that the onset of menarche in an adolescent and not her actual age is the factor that defines the characteristics of this population. It is therefore expected that the efficacy and safety of Loestrin 24 tablets in postpubertal females under the age of 18 would be the same as that established in women aged 18 to 35.

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**ITEM 16. CERTIFICATION ABOUT THE USE OF A DEBARRED PERSON**

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 for Loestrin<sup>®</sup> 24 (norethindrone acetate 1mg/ ethinyl estradiol 20 mcg tablets and ferrous fumarate tablets).



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

4/15/05

Date

Appears This Way  
On Original

## NDA/EFFICACY SUPPLEMENT ACTION PACKAGE CHECKLIST

Applicable Information		
NDA 21-871	Efficacy Supplement Type SE-	Supplement Number
Drug: Loestrin® 24 Fe (norethindrone acetate/ethinyl estradiol) tablets		Applicant: Warner Chilcott Company, Inc.
RPM: Karen Kirchberg, R.N. Nenita Crisostomo, R.N.		HFD-580      Phone # : 301-796-0933 301-796-0875
<p>Application Type: <input checked="" type="checkbox"/> 505(b)(1)   <input type="checkbox"/> 505(b)(2)                      (This can be determined by consulting page 1 of the NDA Regulatory Filing Review for this application or Appendix A to this Action Package Checklist.)</p> <p><b>If this is a 505(b)(2) application, please review and confirm the information previously provided in Appendix B to the NDA Regulatory Filing Review. Please update any information (including patent certification information) that is no longer correct.</b></p> <p><input checked="" type="checkbox"/> Confirmed and/or corrected</p>		Listed drug(s) referred to in 505(b)(2) application (NDA #(s), Drug name(s)):
<b>❖ Application Classifications:</b>		
• Review priority		<input checked="" type="checkbox"/> Standard <input type="checkbox"/> Priority
• Chem class (NDAs only)		3S
• Other (e.g., orphan, OTC)		N/A
User Fee Goal Dates		February 17, 2006
<b>❖ Special programs (indicate all that apply)</b>		
		<input checked="" type="checkbox"/> None <input type="checkbox"/> Subpart H <input type="checkbox"/> 21 CFR 314.510 (accelerated approval) <input type="checkbox"/> 21 CFR 314.520 (restricted distribution) <input type="checkbox"/> Fast Track <input type="checkbox"/> Rolling Review <input type="checkbox"/> CMA Pilot 1 <input type="checkbox"/> CMA Pilot 2
<b>❖ User Fee Information</b>		
• User Fee		<input checked="" type="checkbox"/> Paid   UF ID number PD3006055
• User Fee waiver		<input type="checkbox"/> Small business <input type="checkbox"/> Public health <input type="checkbox"/> Barrier-to-Innovation <input type="checkbox"/> Other (specify)
• User Fee exception		<input type="checkbox"/> Orphan designation <input type="checkbox"/> No-fee 505(b)(2) (see NDA Regulatory Filing Review for instructions) <input type="checkbox"/> Other (specify)
<b>❖ Application Integrity Policy (AIP)</b>		
• Applicant is on the AIP		<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No
• This application is on the AIP		<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No



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 box below (Exclusivity).

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

- (5) Did the patent owner, its representative, or the exclusive patent licensee bring suit against the applicant for patent infringement within 45 days of the patent owner's receipt of the applicant's notice of certification?

Yes  No

(Note: This can be determined by confirming whether the Division has received a written notice from the 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 box below (Exclusivity).

If "Yes," a stay of approval may be in effect. To determine if a 30-month stay is in effect, consult with the Director, Division of Regulatory Policy II, Office of Regulatory Policy (HFD-007) and attach a summary of the response.

❖ Exclusivity (approvals only)			
<ul style="list-style-type: none"> <li>Exclusivity summary</li> <li>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.)</li> </ul>		2/17/06	
<ul style="list-style-type: none"> <li>Is there existing orphan drug exclusivity protection for the "same drug" 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.</li> </ul>		<input type="checkbox"/> Yes, Application # <input checked="" type="checkbox"/> No	
❖ Administrative Reviews (Project Manager, ADRA) (indicate date of each review)			7/1/05

<b>❖ Actions</b>	
• Proposed action	<input checked="" type="checkbox"/> AP <input type="checkbox"/> TA <input type="checkbox"/> AE <input type="checkbox"/>
• Previous actions (specify type and date for each action taken)	N/A
• Status of advertising (approvals only)	<input checked="" type="checkbox"/> Materials requested in AP letter <input type="checkbox"/> Reviewed for Subpart H
<b>❖ Public communications</b>	
• Press Office notified of action (approval only)	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> Not applicable
• Indicate what types (if any) of information dissemination are anticipated	<input checked="" type="checkbox"/> None <input type="checkbox"/> Press Release <input type="checkbox"/> Talk Paper <input type="checkbox"/> Dear Health Care Professional Letter
<b>❖ Labeling (package insert, patient package insert (if applicable), MedGuide (if applicable))</b>	
• Division's proposed labeling (only if generated after latest applicant submission of labeling)	
• Most recent applicant-proposed labeling	2/17/06
• Original applicant-proposed labeling	4/15/05
• Labeling reviews (including DDMAC, DMETS, DSRCS) and minutes of labeling meetings ( <i>indicate dates of reviews and meetings</i> )	
• DDMAC	9/8/05
• DMETS	Reviews: 8/19/05, 12/22/05 Mtg Minutes: 2/10/06
• DSRCS	7/11/05
• Other relevant labeling (e.g., most recent 3 in class, class labeling)	
<b>❖ Labels (immediate container &amp; carton labels)</b>	
• Division proposed (only if generated after latest applicant submission)	
• Most recent applicant-proposed	2/17/06
• Applicant proposed	4/15/06
• Reviews	DMETS review—12/22/06 CMC review—2/16/06 Clinical Review—2/17/06
<b>❖ Post-marketing commitments</b>	
• Agency request for post-marketing commitments	N/A
• Documentation of discussions and/or agreements relating to post-marketing commitments	N/A
• Outgoing correspondence (i.e., letters, E-mails, faxes)	4/26/05, 6/13/05, 10/3/05, 10/4/05, 11/21/05, 2/3/06, 2/7/06
<b>❖ Memoranda and Telecons</b>	
<b>❖ Minutes of Meetings</b>	
• Pre-IND	9/17/03
• EOP2 meeting (indicate date)	
• Pre-NDA meeting (indicate date)	3/17/04 (CMC), 11/15/04
• Pre-Approval Safety Conference (indicate date; approvals only)	

• Other: Filing Meeting	6/17/05
• Other: Trade Name Meeting	2/10/06
❖ Advisory Committee Meeting	
• Date of Meeting	N/A
• 48-hour alert	N/A
❖ Federal Register Notices, DESI documents, NAS/NRC reports (if applicable)	N/A
<b>Summary Applications Review</b>	
❖ Summary Reviews (e.g., Office Director, Division Director, Medical Team Leader) ( <i>indicate date for each review</i> )	Clinical Team Leader 2/17/06
<b>Clinical Information</b>	
❖ Clinical review(s) ( <i>indicate date for each review</i> )	2/17/06
❖ Microbiology (efficacy) review(s) ( <i>indicate date for each review</i> )	N/A
❖ Safety Update review(s) ( <i>indicate date or location if incorporated in another review</i> )	SEE CLINICAL REVIEW
❖ Risk Management Plan review(s) ( <i>indicate date/location if incorporated in another rev</i> )	N/A
❖ Pediatric Page(separate page for each indication addressing status of all age groups)	2/17/06
❖ Demographic Worksheet ( <i>NME approvals only</i> )	N/A
❖ Statistical review(s) ( <i>indicate date for each review</i> )	2/15/06
❖ Biopharmaceutical review(s) ( <i>indicate date for each review</i> )	2/17/06
❖ Controlled Substance Staff review(s) and recommendation for scheduling ( <i>indicate date for each review</i> )	N/A
Clinical Inspection Review Summary (DSI)	
• Clinical studies	see Clinical Memo 10/25/05
• Bioequivalence studies	N/A
<b>CMC Information</b>	
❖ CMC review(s) ( <i>indicate date for each review</i> )	2/16/06
❖ Environmental Assessment	
• Categorical Exclusion ( <i>indicate review date</i> )	Filing review, 9/19/06
• Review & FONSI ( <i>indicate date of review</i> )	Filing review, 9/19/06
• Review & Environmental Impact Statement ( <i>indicate date of each review</i> )	CMC review 2/16/06, pg. 15
❖ Microbiology (validation of sterilization & product sterility) review(s) ( <i>indicate date for each review</i> )	N/A
❖ Facilities inspection (provide EER report): CMC review, pages 18-20	Date completed: 6/17/05 (✓) Acceptable ( ) Withhold recommendation
❖ Methods validation	( ) Completed ( ) Requested (✓) Not yet requested
<b>Nonclinical Pharm/Tox Information</b>	
❖ Pharm/tox review(s), including referenced IND reviews ( <i>indicate date for each review</i> )	1/12/96
❖ Nonclinical inspection review summary	N/A
❖ Statistical review(s) of carcinogenicity studies ( <i>indicate date for each review</i> )	N/A
CAC/ECAC report	N/A

**Appendix A to NDA/Efficacy Supplement Action Package Checklist**

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

- (1) it relies on literature to meet any of the approval requirements (unless the applicant has a written right of reference to the underlying data)
- (2) it relies on the Agency's previous approval of another sponsor's drug product (which may be evidenced by reference to publicly available FDA reviews, or labeling of another drug sponsor's drug product) to meet any of the approval requirements (unless the application includes a written right of reference to data in the other sponsor's NDA)
- (3) it relies on what is "generally known" or "scientifically accepted" about a class of products to support the safety or effectiveness of the particular drug for which the applicant is seeking approval. (Note, however, that this does not mean *any* reference to general information or knowledge (e.g., about disease etiology, support for particular endpoints, methods of analysis) causes the application to be a 505(b)(2) application.)
- (4) it seeks approval for a change from a product described in an OTC monograph and relies on the monograph to establish the safety or effectiveness of one or more aspects of the drug product for which approval is sought (see 21 CFR 330.11).

Products that may be likely to be described in a 505(b)(2) application include combination drug products (e.g., heart drug and diuretic (hydrochlorothiazide) combinations), OTC monograph deviations, new dosage forms, new indications, and new salts.

If you have questions about whether an application is a 505(b)(1) or 505(b)(2) application, please consult with the Director, Division of Regulatory Policy II, Office of Regulatory Policy (HFD-007).

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Center for Drug Evaluation and Research  
Office of Drug Evaluation ODEIII

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**FACSIMILE TRANSMITTAL SHEET**

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**DATE: February 17, 2006**

<b>To:</b> Alvin Howard Vice President, Regulatory Affairs	<b>From:</b> Nenita Crisostomo, R.N. Regulatory Health Project Manager
<b>Company:</b> Warner Chilcott, Inc.	Division of Reproductive and Urologic Products
<b>Fax number:</b> 973-442-3280	<b>Fax number:</b> 301-796-0875
<b>Phone number:</b> 973-442-3233	<b>Phone number:</b> 301-796-0875

**Subject:** NDA 21-871: Approval Letter dated 2/17/06

**Total no. of pages including cover:** 44

**Comments:**

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**Document to be mailed:**       YES       NO

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DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration  
Rockville, MD 20857

NDA 21-871

Warner Chilcott  
Attention: Alvin D. Howard  
Vice President, Regulatory Affairs  
100 Enterprise Drive  
Rockaway, NJ 07866

Dear Mr. Howard:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Loestrin 24 Fe (norethindrone acetate/ethinyl estradiol) Tablets.

We also refer to the meeting between representatives of your firm and the FDA on February 10, 2006. The purpose of the meeting was to discuss the proposed tradename submitted with your NDA.

The official minutes of that meeting are enclosed. You are responsible for notifying us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call Nenita Crisostomo, Regulatory Project Manager, at (301) 796-0875.

Sincerely,

*{See appended electronic signature page}*

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

Enclosure

## Teleconference Meeting Minutes

**Date:** February 10, 2006      **Time:** 2:00 – 2:45 PM      **Location:** White Oak; C/R 5201

**NDA 21-871**                      **Drug Name:** Loestrin 24 Fe (norethindrone/ethinyl estradiol)  
Tablets

**Sponsor:** Warner Chilcott

**Indication:** Prevention of pregnancy

**Type of Meeting:** C (Label and Tradename Guidance)

**FDA Lead:** Scott Monroe, M.D. – Deputy Director, Division of Reproductive and Urologic Products (DRUP)

**Minutes Recorder:** Jennifer Mercier

### **FDA Attendees:**

Scott Monroe, M.D. – Deputy Director, DRUP

Daniel Davis, M.D. - Medical Officer, DRUP

Carol Holquist – Director, Division of Medication Errors and Technical Support (DMETS)  
Office of Drug Safety (ODS)

Denise Toyer - Deputy Director, DMETS, ODS

Alina Mahmud - Team Leader, DMETS, ODS

Diane C. Smith - Project Manager, DMETS, ODS

Jennifer Mercier – Chief, Project Management Staff, DRUP

### **External Attendees:**

Fang Li, Ph.D. - Manager, Regulatory Affairs

Alvin Howard - Senior Vice President, Regulatory Affairs

### **Discussion/Decisions Reached:**

- DRUP and DMETS informed the Applicant that the Agency still had concerns with the proposed tradename of Loestrin Fe 24. The basis for this concern was based largely on the identifier “24” being placed at the end of the name, thereby making it more likely to be omitted from a prescription. To address this concern, the Agency suggested that the proposed name be modified to Loestrin 24 Fe since the identifier “Fe” was of lesser importance and not unique to the new drug product. The Applicant agreed to the suggestion and will submit new mock-ups of the proposed container labeling and revised product labeling by the close of business on Tuesday, February 14, 2006.
- DMETS discussed with the Applicant the need for an educational program at the time of product launch to educate pharmacists and physicians on this new product that contains 24-days of active dosing. The sponsor concurred with the recommendation and is revising their program to educate healthcare providers about the product, especially in regard to the meaning of the number “24” in the tradename.

### **Action Item:**

Send meeting minutes to sponsor within 30 days.

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Office of Drug Evaluation ODEIII

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**FACSIMILE TRANSMITTAL SHEET**

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**DATE: February 7, 2006**

<b>To:</b> Fang Li Manager, Regulatory Affairs	<b>From:</b> Nenita Crisostomo, R.N. Regulatory Health Project Manager
<b>Company:</b> Warner Chilcott Company, Inc.	Division of Reproductive and Urologic Products
<b>Fax number:</b> 973-442-3280	<b>Fax number:</b> 301-796-0875
<b>Phone number:</b> 973-442-3237	<b>Phone number:</b> 301-796-0875
<b>Subject:</b> NDA 21-871 Loestrin Fe 24: Clinical Information Request--Cumulative Pregnancy Rate	

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**Total no. of pages including cover: 1**

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**Comments:**

Dear Ms. Li,

Please provide the cumulative pregnancy rate using the Life Table method for all women using Loestrin 24 [including the one unconfirmed pregnancy in subject 022/011] and in the subset of women age 18-35 using Loestrin 24. This should be calculated with and without the undocumented pregnancy that occurred in subject 022/011 — The sponsor should assume that this subject became pregnant in Cycle 6.

If this has been done and is in the NDA submission, the sponsor may direct me to the information.

Thank you,  
Nenita Crisostomo

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 Office of Drug Evaluation ODEIII

## FACSIMILE TRANSMITTAL SHEET

**DATE: February 3, 2006**

<b>To:</b> Fang Li, Ph.D., R.A.C.	<b>From:</b> Nenita Crisostomo, R.N. Regulatory Health Project Manager
<b>Company:</b> Warner Chilcott Company, Inc.	Division of Reproductive and Urologic Products
<b>Fax number:</b> 973-442-3280	<b>Fax number:</b> 301-796-9897
<b>Phone number:</b> 973-442-3237	<b>Phone number:</b> 301-796-0875
<b>Subject:</b> NDA 21-871: Information Request--Clinical	

**Total no. of pages including cover: 2**

**Comments:**

Dear Dr. Li,

As we discussed via teleconference today, here are the list of information requests made by the Clinical Team. Please provide your responses by close of business on February 6, 2006. If you have any questions, please do not hesitate to call me.

Thank you very much,

Nenita Crisostomo, RN

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A. Was there any follow-up done (lab testing or otherwise) for the following 3 subjects with markedly abnormal triglyceride values at the end of study:

1. Site 1, subject #20- triglyceride 707 on Day 194
2. Site 3, subject #4- triglyceride 511 on Day 201
3. Site 23, subject #5- triglyceride 291 on Day 181

Were their other chemistry lab values normal?

If no follow-up was obtained, why was it not obtained?

B. What Volume(s) of the paper submission contain Report RR 10104.0, Section 14 with all the Tables with a 14.x.y.z denotation?

C. Provide a table for the Loestrin 1/20 MITT population similar to Table 5 (on page 28 of 46 in the ISE) for the Loestrin 24 MITT population.

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# Memo

**To:** Daniel Shames, MD  
Director, Division of Reproductive and Urologic Products, HFD-520

**From:** Kimberly Pedersen, RPh, Safety Evaluator  
Alina Mahmud, RPh, MS, Team Leader  
Denise Toyer, PharmD, Deputy Director  
Carol Holquist, RPh, Director  
Division of Medication Errors and Technical Support, Office of Drug Safety, HFD-420

**Date:** December 22, 2005

**Re:** ODS Consult 05-0303 and 05-0304; Loestrin FE 24 (Norethindrone Acetate/Ethinyl Estradiol and Ferrous Fumarate Tablets 1mg/20 mcg/75 mg); NDA 21-871

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This memorandum is in response to the sponsor's December 7, 2005 submission in which they responded to a six questions outlined in an Agency information request letter dated 21 November 2005. These questions were formulated following an internal meeting between DMETS and DRUP. This memorandum will respond to each of the six sponsor responses.

1. DMETS acknowledges the sponsor added "FE" to the name to comply with regulations. However, the sponsor's graphic presentation (Attachment A) shows "FE" in a smaller font size than the "Loestrin" and "24". Please increase the font to be consistent with both "Loestrin" and "24." Revising in this manner will make the name appear as one. This will minimize the potential omission of the iron component in prescribing.
2. DMETS was concerned that patients and practitioners would not understand the meaning of "24", as this is a novel number of "active" tablets for oral contraceptives. The Drug Safety Institute analysis merely analyzed the proposed names, not the meaning of "24" or even the various ways it may be confused. Thus, DMETS does not believe the sponsor addressed the agency's question. The sponsor should conduct a survey that addresses if the new proprietary name conveys the meaning of 24 active tablets.
3. DMETS has no comment.
4. DMETS concurs with the proposed methods to educate prescribers and pharmacists. We appreciated the note that the Pharmacy Information Sheet will highlight "the 24 days of active therapy and 4 days of ferrous fumarate." DMETS would like to review a copy of this proposed Pharmacy Information Sheet. In addition, DMETS assumes major pharmacy and obstetrics/gynecological journals will be the "relevant journals" where the advertising campaign will be launched. Additionally, following the survey supplementary educational components may become apparent.
5. Although the sponsor noted there were no intentions of developing other 24-day regimens "at this time", this phrasing denotes an issue may remain for potential future confusion (i.e., what would you name a Loestrin 1.5/30 24 day product?). DMETS would like to acknowledge that any future development could result in difficulty preventing inter-brand confusion due to this chosen naming convention.

6. DMETS has no comment.

If you have any questions or need clarification, please contact the medication errors Project Manager, Diane Smith at 301-796-0538.

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DRUG SAFETY OFFICE REVIEWER

Carol Holquist  
12/23/2005 01:37:01 PM  
DRUG SAFETY OFFICE REVIEWER

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NDA 21-871

**INFORMATION REQUEST LETTER**

Warner Chilcott U.S., Inc.  
Attention: Alvin D. Howard  
Vice President, Regulatory Affairs  
100 Enterprise Drive  
Rockaway, NJ 07866

Dear Mr. Howard:

Please refer to your new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Loestrin<sup>®</sup> 24 (norethindrone/ethinyl estradiol and ferrous fumarate) Tablets.

We also refer to your correspondence dated October 12, 2005. You propose two alternative trade names: Loestrin<sup>®</sup> 24 day active therapy and Loestrin<sup>®</sup> 1/20 24 day active therapy.

The Division of Reproductive and Urologic Products (DRUP) and the Division of Medical Errors and Technical Support (DMETS) have the following comments and questions:

1. If this product is to contain iron in the placebo pills, this must be displayed in the proprietary name; otherwise it is misleading [see 21 CFR 201.10 (c)(2)].
2. We recommend that you conduct a survey of your proposed trade name(s), modified to include reference to "ferrous fumarate" (i.e. FE), with a sufficient number of prescribers and pharmacists to determine how the new product and new proprietary name will be prescribed, scripted, and interpreted. It is important to obtain feedback to determine if the proposed name conveys the intended meaning of 24 active tablets. It is also necessary to determine if this name is the best representation to assure distinctiveness to minimize prescribing, selection, and dispensing errors. In addition, these data could aid in the development of an effective educational campaign to alleviate confusion and error, especially in the first year of marketing. We request that you submit to the NDA the results of your survey. The findings from your survey will be considered by DRUP and DMETS in our determination of the acceptability of the trade name(s) that you propose for the product.

3. DRUP and DMETS agree that the new carton label color and design are distinctive and acceptable. For our assurance, please provide a visual layout of all your marketed containers for Loestrin and state that you have no plans to revise other Loestrin products to incorporate a similar appearance.
4. How do you plan to educate prescribers and pharmacists about your new product to minimize prescribing, selection, and dispensing errors?
5. Please clarify if you intend to develop a dosing regimen of 24 active tablets for any of the other Loestrin products?
6. Do you plan to discontinue marketing of Loestrin 1/20 (with or without iron) if the proposed new product is approved for marketing?

If you have any questions, call Karen Kirchberg, NP, Project Manager, at (301) 796-0933.

Sincerely,

*{see appended electronic signature page}*

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

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Office of Drug Evaluation ODE III

**FACSIMILE TRANSMITTAL SHEET**

**DATE:** October 4, 2005

<b>To:</b> Fang Li	<b>From:</b> Karen Kirchberg, NP
Warner Chilcott Regulatory Affairs	Division of Reproductive and Urologic Drug Products
<b>Fax number:</b> (973) 442-3280	<b>Fax number:</b> (301) 796-9897
<b>Phone number:</b> (973) 442-3237	<b>Phone number:</b> (301) 796-0933
<b>Subject:</b> NDA 21-871 Information Request	

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NDA 21-871 for Loestrin (norethindrone acetate/ethinyl estradiol) Tablets

Please submit to the NDA a table (or list) of the clinical sites detailing the number of subjects enrolled and the number of subjects who completed the study at each site. We are aware that site #4 and #8 did not enroll any subjects.

Please send and fax the response in to the NDA. Our fax number is (301) 796-9897.

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NDA 21-871

**INFORMATION REQUEST LETTER**

Warner Chilcott U.S., Inc.  
Attention: Alvin D. Howard  
Vice President, Regulatory Affairs  
100 Enterprise Drive  
Rockaway, NJ 07866

Dear Mr. Howard:

Please refer to your new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Loestrin<sup>®</sup> 24 (norethindrone/ethinyl estradiol and ferrous fumarate) Tablets.

Your trade name request, Loestrin<sup>®</sup> 24, was reviewed by the Division of Medical Errors and Technical Support (DMETS). DMETS did not find the trade name acceptable and the Division of Reproductive and Urologic Products concurs with that decision. DMETS had the following comments:

Loestrin 24 represents an extension of the Loestrin FE 1/20 (NDA 17-876) product line. The concerns are as follows:

- referencing the number "24" in the trade name (the number does not reflect the dose but only the number of active tablets)
- the potential confusion with the use of "24" with 21/28 (total number of tablets in the pack) or 24-hour duration drug products
- no representation of the iron ingredient in the trade name

We request that you submit an alternative trade name or names for reconsideration.

If you have any questions, call Karen Kirchberg, NP, Project Manager, at (301) 796-0933.

Sincerely,

*{see appended electronic signature page}*

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

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Jennifer L. Mercier  
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5	Is a statement provided that all facilities are ready for GMP inspection?	x		
6	Has an environmental assessment report or categorical exclusion been provided?	x		
7	Does the section contain controls for the drug substance?	x		DMF (ethinyl estradiol) and (Norethindrone) contains all the relevant information on drug substances. LOAs are provided.
8	Does the section contain controls for the drug product?	x		
9	Has stability data and analysis been provided to support the requested expiration date?	x		
10	Has all information requested during the IND phase, and at the pre-NDA meetings been included?	x		
11	Have draft container labels been provided?	x		
12	Has the draft package insert been provided?	x		
13	Has an investigational formulations section been provided?	x		Loestrin 1/20 tablets batches are used in Phase I and II clinical studies.
14	Is there a Methods Validation package?	x		
15	Is a separate microbiological section included?		x	Not applicable

This application **meets the filing requirement** from the CMC point of view. This application is adequate to review from the CMC standpoint.

**Review Chemist:** Rajiv Agarwal, Ph.D date: 19-SEP-2005

**Team Leader:** Moo-Jhong Rhee, Ph.D date: 19-SEP-2005

Original NDA 21-871  
HFD-580/ NDA 21-871/Division File  
HFD-580/Chem/RAgarwal/MRhee  
HFD-580/PM/Kkirchberg

**Have all DMF References been Identified? YES**

DMF Number	Holder	Description	LOA	Status
		Ethinyl Estradiol	17-DEC-2004	Active

Norethindrone acetate	17-DEC-2004	Active
	28-MAR-2005	Active
	10-JAN-2005	Active
	15-DEC-2004	Active
	18-OCT-2004	Active

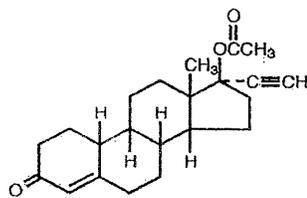
### SUMMARY

**Background:** Loestrin 1/20, approved under NDA 17-876, differs from Loestrin-24 in that administration, also consisting of a 28-day regimen, is comprised of 21 oral contraceptive tablets and 7 placebo (inactive) tablets. Loestrin-24, however, consists of 24 oral contraceptive tablets and 4 placebo tablets. Placebo tablets in both the cases are ferrous fumarate tablets.

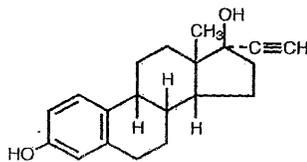
### DRUG SUBSTANCE (Norethindrone Acetate and ethinyl Estradiol):

The active ingredients in the "Loestrin 24", are **Norethindrone Acetate** and **Ethinyl Estradiol**. \_\_\_\_\_ manufactures the drug substances. Detailed information regarding the synthesis and characterization of Norethindrone Acetate and Ethinyl Estradiol is provided in their representative Drug Master Files. Letters authorizing Warner Chilcott to cross-reference the DMFs are provided in the submission. The following information on the drug substance is also provided in the NDA submission.

### Structural formulas (for Active):

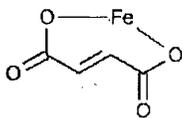


Norethindrone Acetate



Ethinyl Estradiol

**Structural formula of Ferrous Fumarate (placebo):**



**DRUG PRODUCT:**

**Active tablets:** Loestrin 24 tablets are white, oval, beveled-edge, debossed with the PD logo on one side and 145 on the other side.

**Placebo tablets:** Ferrous Fumarate Tablets, 75 mg, are brown, round, flat faced tablets with “PD-622” debossed on one side.

**Dosage form:** Tablet  
**Strength:** 1.0 mg Norethindrone/20 µg ethinyl estradiol  
**Route of Administration:** Oral

**Components and composition of unit dose (Active):**

**Table 5. Unit dose Composition of Loestrin 1/20 Tablets**

Component	Grade	Function	Theoretical Amount per Tablet (mg)
Norethindrone Acetate	USP	Drug Substance	1.00
Ethinyl Estradiol	USP	Drug Substance	0.02
Acacia	NF		
Lactose	NF		
Magnesium Stearate	NF		
Starch	NF		
Confectioner's Sugar	NF		
Talc	USP		
Total Tablet Weight:			73.00

**Components and composition of unit dose (Placebo):**

Component	Function	Batch Qty (kg)	Per Tablet (mg)
Ferrous Fumarate, USP	--	┌	└
Compressible Sugar, NF	—		
Povidone, USP	—		
Microcrystalline Cellulose, NF	—		
Sodium Starch Glycolate, NF	—		
Magnesium Stearate, NF	—		
Total			

<sup>1</sup> Contains approximately 1.35% excess

**Manufacturers:**

**Drug Substances (Norethindrone Acetate and ethinyl Estradiol):**

\_\_\_\_\_  
\_\_\_\_\_  
\_\_\_\_\_

**Drug Product:**

*Manufactured, in-process testing, packaged, and released at:*

Warner Chilcott Company, Inc.  
Union Station  
Road 195 Km. 1.1  
Fajardo, Puerto Rico 00738

*Stability testing and release testing is performed at:*

Warner Chilcott UK  
Old Belfast Road  
Millbrook, Larne, County Antrim  
Northern Ireland, BT 40 2SH

**Specifications for Loestrin 1/20 tablets:**

Test	Specification	Method
Description		
Identification		
Uniformity of Dosage Units		
Assay		
Degradation Products/ Impurities  Norethindrone Acetate		
Degradation Products/ Impurities  Ethinyl Estradiol		
Dissolution		

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Specifications for Ferrous Fumarate tablets (placebo):

TABLE 201 - REVISION SPECIFICATIONS FOR FERROUS FUMARATE TABLETS, 75 MG

Test	Specification	Method Number
Description	┌	
Identification		
Uniformity of Dosage Units		
Weight Variation		
Dissolution		
Assay		

Stability:

24 months of **expiration date** is requested for the drug product and placebo packaged in blister (24 active tablets and 4 placebo tablet /card in foil with desiccant). The primary stability data on active and placebo is provided in the submission:

- **Active tablets (three commercial scale batches):**
  - **Long term and intermediate:** 0, 3 and 6 months
  - **Accelerated:** 0, 1, 2, 3, and 6 months
  
- **Placebo tablets (two commercial scale batches of Ferrous fumarate tablets):**
  - **Long term and intermediate:** 0 and 3 months
  - **Accelerated:** 0, 1, 2, and 3 months

**Comment:**

The stability data on 3 commercial scale batches (80114F1, 80114F2, and 80114F3) of the active and two commercial scale batches of placebo (80174F1 and 80174F3) manufactured to date and packaged in a blister card ( ) and blister card is placed in a foil pouch with a desiccant pack is provided.

The container closure system is identical to that of Loestrin 1/20 tablets (approved

NDA 17-354). However, the applicant has made some improvement on how the current product is packaged. For the current NDA an additional protection (secondary packaging) is provided by enclosing the blister card in a foil pouch with a ~~desiccant~~ desiccant pack.

Earlier, the **approved shelf life of Loestrin 1/20 was 24 months**. Based on the historical stability data on the approved product and current stability data on the same product packaged in a more protective packaging, **it may be possible** to grant a 24 months of expiration dating.

**Overall comment:**

This NDA is being filed in support the use of an already approved product under NDA **17-876**. Loestrin 1/20, approved under NDA 17-876, differs from Loestrin-24 in that administration, also consisting of a 28-day regimen, is comprised of 21 oral contraceptive tablets and 7 placebo (inactive) tablets. Loestrin-24, however, consists of 24 oral contraceptive tablets and 4 placebo tablets. Placebo tablets in both the cases are ferrous fumarate tablets.

The following information is included in the NDA and will be reviewed or consulted.

- All the excipients used in the manufacture of this product (Loestrin-24) are used in other pharmaceutical applications and are also used in the approved product (Loestrin 1/20).
- Drug substance and drug product manufacturing sites are identical to the approved application.
- There is no change in the manufacturing process of the drug product.
- Container closure system is identical to Loestrin 1/20.
- Manufacturing sites are entered in the EES.
- Trade name consult and container closure labels will be sent to DMETS, once the NDA is filed.

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/s/

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Rajiv Agarwal  
9/19/2005 01:21:55 PM  
CHEMIST

Moo-Jhong Rhee  
9/19/2005 01:25:03 PM  
CHEMIST  
I concur

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**Division of Medication Errors and Technical Support (DMETS)  
Office of Drug Safety  
HFD-420; PKLN Rm. 6-34  
Center for Drug Evaluation and Research**

**PROPRIETARY NAME REVIEW**

**DATE OF REVIEW:** July 22, 2005

**NDA #:** 21-871

**NAME OF DRUG:** **Loestrin® 24** (Norethindrone Acetate and Ethinyl Estradiol Tablets and Ferrous Fumarate Tablets) 1 mg/20 mcg/75 mg

**NDA HOLDER:** Warner Chilcott, Inc.

**I. INTRODUCTION:**

This consult was written in response to a request from the Division of Reproductive and Urologic Drug Products, for a review of the proprietary name "Loestrin 24" with regard to potential name confusion with other proprietary or established drug names. The proposed container labels, carton and insert labeling were submitted for review and comment.

**PRODUCT INFORMATION**

Loestrin 24 represents an extension of the Loestrin FE 1/20 (NDA 17-876, approved 1976) product line. Loestrin 24 contains norethindrone and ethinyl estradiol in twenty-four tablets with ferrous fumarate in the remaining four tablets. Loestrin 24 is indicated for women to lower the risk of becoming pregnant. Patients are recommended to take one tablet daily, at the same time each day. Single missed tablets should be taken as soon as possible. Menstruation usually begins two to three days after starting the ferrous fumarate tablets; however, this could occur as late as the fourth or fifth day. Regardless, the next course of tablets should be started without interruption. After several months of treatment, bleeding may be reduced to a point of virtual absence.

**II. RISK ASSESSMENT:**

The medication error staff of DMETS conducted a search of several standard published drug product reference texts<sup>1,2</sup> as well as several FDA databases<sup>3</sup> for existing drug names which sound-alike or look-alike to Loestrin 24 to a degree where potential confusion between drug names could occur under the usual clinical practice settings. A search of the electronic online version of the U.S. Patent and Trademark Office's Text and Image Database was also conducted<sup>4</sup>. The Saegis Pharma-In-Use database<sup>5</sup> was searched for drug names with potential for confusion. An expert panel discussion was conducted to review all findings from the searches.

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<sup>1</sup> MICROMEDEX Integrated Index, 2005, MICROMEDEX, Inc., 6200 South Syracuse Way, Suite 300, Englewood, Colorado 80111-4740, which includes all products/databases within ChemKnowledge, DrugKnowledge, and RegsKnowledge Systems.

<sup>2</sup> Facts and Comparisons, online version, Facts and Comparisons, St. Louis, MO.

<sup>3</sup> AMF Decision Support System [DSS], the Division of Medication Errors and Technical Support [DMETS] database of Proprietary name consultation requests, New Drug Approvals 98-05, and the electronic online version of the FDA Orange Book.

<sup>4</sup> WWW location <http://tess2.uspto.gov/bin/gate.exe?f=searchstr&state=m2pu5u.1.1>

<sup>5</sup> Data provided by Thomson & Thomson's SAEGIS™ Online Service, available at [www.thomson-thomson.com](http://www.thomson-thomson.com)

**A. EXPERT PANEL DISCUSSION**

An Expert Panel discussion was held by DMETS to gather professional opinions on the safety of the proprietary name Loestrin 24. Potential concerns regarding drug marketing and promotion related to the proposed names were also discussed. This group is composed of DMETS Medication Errors Prevention Staff and representation from the Division of Drug Marketing, Advertising, and Communications (DDMAC). The group relies on their clinical and other professional experiences and a number of standard references when making a decision on the acceptability of a proprietary name.

1. The Expert Panel identified two names that were thought to have the potential for confusion with the name Loestrin 24. These products are listed along with the dosage forms available and usual FDA-approved dosage in Table 1 (see below). In addition, the panel had concerns regarding the new formulation, drug presentation, and nomenclature. There were concerns referencing the use of a number in the tradename, the lack of representation of iron in the tradename, and the potential confusion with the use of "24" (with 21/28 day or 24-hour duration drug products).
2. DDMAC did not have concerns with Loestrin 24 in regard to promotional claims.

Table 1: Potential Sound-Alike/Look-Alike Names Identified by DMETS Expert Panel

Product Name	Established name, Dosage Form(s), Strength(s)	Usual adult dose*	Other**
Loestrin® 24	Norethindrone Acetate/Ethinyl Estradiol and Ferrous Fumarate Tablets, 1 mg/20 mcg/75 mg	One tablet daily	
Loestrin® 1.5/30	Norethindrone Acetate/Ethinyl Estradiol 1.5 mg/30 mcg	One tablet daily.	LA/SA
Loestrin® FE 1.5/30	Above with 75 mg Ferrous Fumarate Tablets		
Loestrin® 1/20	Norethindrone Acetate/Ethinyl Estradiol 1 mg/20 mcg		
Loestrin® FE 1/20	Above with 75 mg Ferrous Fumarate Tablets		
Livostin®	Levocabastine Hydrochloride 0.05%, 5 mL and 10 mL	One drop into affected eyes four times per day	LA

\*Frequently used, not all-inclusive.  
 \*\*L/A (look-alike), S/A (sound-alike)

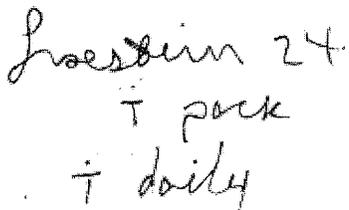
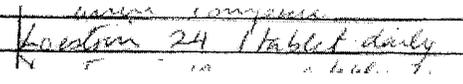
**B. PHONETIC ORTHOGRAPHIC COMPUTER ANALYSIS (POCA)**

As part of the name similarity assessment, proposed names are evaluated via a phonetic/orthographic algorithm. The proposed proprietary name is converted into its phonemic representation before it runs through the phonetic algorithm. Likewise, an orthographic algorithm exists which operates in a similar fashion. No additional names of concern were identified in POCA that were not discussed in EPD.

C. PRESCRIPTION ANALYSIS STUDIES

Methodology:

Three separate studies were conducted within the Centers of the FDA for the proposed proprietary name to determine the degree of confusion of Loestrin 24 with marketed U.S. drug names (proprietary and established) due to similarity in visual appearance with handwritten prescriptions or verbal pronunciation of the drug name. These studies employed a total of 121 health care professionals (pharmacists, physicians, and nurses) for each. This exercise was conducted in an attempt to simulate the prescription ordering process. An inpatient order and outpatient prescription was written, each consisting of a combination of marketed and unapproved drug products and a prescription for Loestrin 24 (see below). The prescriptions were optically scanned and one was delivered to a random sample of the participating health professionals via e-mail. In addition, the outpatient order was recorded on voice mail, which was sent to a random sample of the participating health professionals for their review and interpretation. After receiving either the written or verbal prescription order, the participants sent their interpretations of the orders via e-mail to the medication error staff.

HANDWRITTEN PRESCRIPTION	VERBAL PRESCRIPTION
<p>Outpatient RX:</p> 	<p>Loestrin 24 1 pack One daily</p>
<p>Inpatient RX:</p> 	

Results:

Three participants in the Rx study (five voice and one inpatient) identified the name as Loestrin, a currently marketed product. The participants did not indicate the modifier. See appendix A for the complete listing of interpretations from the verbal and written studies.

C. SAFETY EVALUATOR RISK ASSESSMENT

In reviewing the proprietary name Loestrin 24, the primary concerns related to look-alike and sound-alike confusion with the currently marketed Loestrin product line and Livostin. In addition to look-alike and sound-alike concerns, DMETS does not believe the proposed name adequately reflects the iron component of this product. We also have concerns with potential misinterpretation of the "24" modifier.

Loestrin 1.5/30 (NDA 17-355) was approved in 1973 and Loestrin 1/20 was approved in 1976. As there are other Loestrin products currently approved and marketed, a search of the FDA Adverse Event Reporting System (AERS) database and the DQRS (Drug Quality Reporting System) for any post-marketing safety reports was prudent. The search criteria consisted of the tradename and

verbatim term of “Loes%<sup>6</sup>” and the reactions included under the system organ class of “Injury, Poisoning and Procedural Complications.” The search revealed eighteen cases, ten of which involved adverse events such as stroke, thrombus and fetal demise. An additional case remarked on the possible interaction of Loestrin and infliximab. These cases will not be discussed further. The remaining eight cases described confusion in the product line between the two strengths (1/20 and 1.5/30) and subsequent dispensing of the incorrect Loestrin drug product. These cases will be discussed in further detail below. In addition, DMETS searched the Drug Quality Reporting System (DQRS) for reports involving Loestrin. Thirty-one cases were found, of which three were considered relevant to the labeling of this proposed drug product. The remaining cases were duplicates of the AERS reports or related to the stability or content uniformity of the tablets.

## 1. Look-Alike and Sound-Alike Concerns

- a. Loestrin 24 is the latest addition to the Loestrin product line. The proposed and currently marketed products share the proprietary name of Loestrin with different modifying numbers (24, 1.5/30 and 1/20). For the marketed products, these numbers represent the presentation of strength; thus, the practitioner would need to indicate this on the prescription for proper order completion. Although there are differences in strength, a post-marketing search found eight (n=8) errors involving confusion with the currently marketed Loestrin 1.5/30 and Loestrin 1/20 (dates ranging from 1995 to 2002). The majority of the errors did not indicate the etiology of the error or what type of prescription (new or refill), but most were noted to be in the retail/community pharmacy level (n=5). Causality was provided for a few cases, which are as follows: understaffed pharmacy, similar names, too many people involved in process, and did not check the prescription properly. Of the known outcomes, most patients noticed the error prior to ingestion (n=5) with only two patients taking the incorrect medication. One of these patients received the incorrect medication on initial fill of the prescription, thus having no reference for how the medication should appear. Of note from the data available, the confusion was comparable for the 1.5/30 and the 1/20 strengths; since four prescriptions were filled for 1.5/30 when 1/20 was intended and three were filled vice-versa. Due to this data, DMETS expects that similar confusion may occur with the introduction of this new formulation (Loestrin 24) to the product line.

The currently marketed and proposed Loestrin product line share the overlapping characteristics of active ingredients, route of administration (oral), indication for use (prevention of pregnancy), dosage form (tablet), dosing regimen (one daily) and strength (1/20). To add further confusion, Loestrin FE 1/20 and Leostrin 24 differ only in the number of ferrous fumarate tablets contained in each cycle. The overlap in strength and shared root name may be a problem in selection errors and computer selection errors, especially if a physician were to write “Loestrin 24 1/20.” DMETS believes there is the potential for confusion. Upon prescription filling, patients may not realize the incorrect formulation was dispensed and may believe that the label and labeling differences are due to updates or revisions. Thus, the patient may not question the difference. If a patient was expecting tablets that would gradually eliminate menstruation, but instead received the seven iron tablets; the patient would menstruate, but the chance of pregnancy does not change. Thus, the likelihood for patient harm is minimal. DMETS recommends that the sponsor provide educational material about the availability of the new formulation upon product launch. Additionally, DMETS refers the sponsor to labeling recommendations in Section III of this review. DMETS believes the possibility for confusion and harm to be minimal if adequate product packaging differentiation and proper provider and patient education is provided.

- b. Livostin may look similar to Loestrin when scripted. Livostin contains levacavastin hydrochloride as a 0.5% ophthalmic suspension for the temporary relief of the signs and

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<sup>6</sup>- Wildcard code for searching of the Adverse Event Reporting System (AERS) database that helps to capture variations in spellings and blatant misspellings.

symptoms of seasonal allergic conjunctivitis. Recommended dosing is one drop into affected eye four times per day. The orthographic similarities stem from the shared leading "L", central "st" and concluding "in." This may be compounded by the possibility for an open "o" of Loestrin to resemble the "v" of Livostin.

*Loestrin*  
*Livostin*

The products also differ in route of administration (ocular compared to oral) and directions for use (one drop to affected eye four times daily compared to one tablet daily). Although both drug products may be written as "UD" or use as directed with a quantity of #1, Livostin is available in two size bottles that may be indicated on the prescription. However, it is not uncommon to see this omission on prescriptions and often, pharmacists will pick what size bottle that is in stock. Since Livostin was approved in 1993 and Loestrin has been in the marketplace since 1973, a review of the AERS and DQRS databases would be a good gauge to the possibility for confusion. A review of these databases did not find any reports of confusion between these two currently marketed proprietary names, Loestrin and Livostin. Furthermore, the multiple strengths and packaging configurations of Loestrin require that some additional identification be represented for accurate order completion. Due to the differing strengths of Loestrin and lack of any current reports of confusion between Livostin and Loestrin, DMETS believes the possibility for confusion to be minimal.

## 2. Representation of Ferrous Fumarate in Proprietary Name

The proprietary name Loestrin 24, as currently proposed, does not adequately reflect the active ingredient of ferrous fumarate. Per 21 CFR 201.10c (2), all ingredients must be represented. Oral contraceptives containing iron traditionally use the modifier "FE" in the proprietary name to represent the iron portion (e.g. Loestrin FE 1.5/30, Estrostep Fe). The proposed name is also misleading as the existing 21 and 28 day Loestrin drug products contains reference to the ferrous fumarate in the name, Loestrin FE. Therefore, not including FE in the proposed name would lead one to believe the product does not contain the active ingredient ferrous fumarate.

## 3. Safety concerns with the modifier "24"

Loestrin 24 is the newest proposed extension to the Loestrin product line that contains twenty-four tablets of norethindrone acetate/estradiol and 4 tablets of ferrous fumarate for a total of twenty-eight tablets. DMETS has concerns that the modifier "24" does not follow the standard naming practice of oral contraceptives and as a result, may be misinterpreted.

Traditionally, when numerical modifiers are used in conjunction with the proprietary name, it is used to either indicate the strength of the active ingredients (e.g. Ortho-Novum 1/35, Norinyl 1/50), number of tablets of each active ingredient (e.g. in biphasic products Necon 10/11 and Ortho-Novum 10/11 and tri-phasics, Ortho-Novum 777 and Necon 777) or the total number of tablets contained in the cycle (Loestrin 21 1/20). Loestrin 24 does not follow this naming convention as there are 28 tablets total in the packaging. DMETS has concerns that the modifier "24" may be misinterpreted as the total number of tablets in the package (in lieu of 28) or as a presentation of strength for an ingredient (e.g. 24 mcg). In addition, there are currently marketed drug products that utilize "24" in their proprietary names. The modifier of "24" was found in the proprietary name of five drug products listed in the electronic Orange Book, which were as follows: Clarinex D 24 hour (Rx), Theo-24 (Rx), Claritin-D 24 hour (OTC), Efidac 24 Pseudoephedrine HCl/Brompheniramine Maleate (OTC) and Efidac 24 Pseudoephedrine HCl (OTC). In all these examples, the numerical modifier "24" indicates a 24 hour dosing schedule may ultimately cause confusion among practitioners. DMETS is also concerned that

the modifier does not follow the accepted naming convention of the currently marketed Loestrin products and that the modifier "24" does not accurately convey its meaning, which may ultimately cause confusion among practitioners and patients.

We recognize that the sponsor will need to distinguish the differences between Loestrin FE 1/20 and the proposed product. However, what has been proposed may not convey these differences and contribute to error. Thus, if the sponsor is allowed to use the name Loestrin 24, health care practitioners and patients should be surveyed to determine if the modifier conveys what they are intending (i.e. 24 active tablets), that the "24" is not misinterpreted for the total days of therapy or some other misinterpretation, and if Loestrin 24 conveys the presence of ferrous fumarate. The sponsor should also ask health care providers how best to differentiate this product from the existing Loestrin FE 1/20 and Loestrin 1/20 drug products.

### **III. LABELING, PACKAGING, AND SAFETY RELATED ISSUES:**

In the review of the container labels, carton and insert labeling of Loestrin 24, DMETS has attempted to focus on safety issues relating to possible medication errors. As there has been confusion with the currently marketed Loestrin drug products, DMETS has identified several areas of possible improvement that might minimize potential user error.

#### **A. CONTAINER LABEL**

1. Please assure that the established name is at least  $\frac{1}{2}$  the size of the proprietary name per 21 CFR 201.10(g)(2).
2. The DQRS search found three reports from 1990, 1995 and 1998 that complain of issues with the expiration on blister cards and the containers. Two noted difficulty reading the data and one reported conflicting dates on the carton and container; although the dates were Jan and Jun96, which may be extrapolated to difficulty in reading the dates on the carton and container due to the likeness of Jan and Jun. Assure that the expiration and lot number are readable on the blister cards and the containers.
3. Remove the graphic art (green circle) around the proprietary name as this is distracting.
4. The dual color scheme for the proprietary name of Loestrin is distracting. Revise using one color for all the letters.
5. Please assure that the "new" statement is only present for the first six months of marketing

#### **B. CARTON LABELING**

1. See comments A 1-4.
2. Add the "Rx only" statement per Section 503(b)(4) of the Federal Food, Drug, and Cosmetic Act. DMETS prefers the addition to the principal display panel.
3. On the physician's sample carton, please add the strength to the proprietary and established name to the side panels to help aid in proper identification.
4. On physician's sample tray, please decrease the prominence of the "6" of six pouches to decrease the possible confusion with strength or number of tablets.

### C. INSERT LABELING

#### Dosage and Administration Section

Consider rearranging the content of this section, since this is a unique approach for oral contraceptives. Move from the eighth paragraph "Loestrin 24 provides a continuous administration regimen consisting of 24 ....." to appear as the first paragraph. In addition, the one paragraph under "Special Notes on Administration" should also be moved to just after the aforementioned paragraph. The last paragraph in the section "After several months on treatment, bleeding may....." should be moved as the third paragraph. Thus, the resulting leader in this section would include the drug content first to be followed by initial results second and expect final result. Due to the unique nature of this drug product, increased number of active tablets, DMETS believes this more pertinent information should be placed earlier in this section, as this is pertinent information to the nature of the drug product.

### D. PATIENT PACKAGE INSERT

Consider the addition of a simplified version of the proposed introductory paragraph in the Dosage and Administration section of the package insert, which contains drug content, initial expected results and final expected result. This information would be of importance to patients as this is a unique days supply of active tablets; thus changing the expected outcomes and/or side effects.

### E. PATIENT AND PROVIDER EDUCATION

DMETS requests that the sponsor provide an educational program for providers and patients. This education program will help to educate pharmacists to the existence of and mechanism of this drug product and it should also describe how the product differs from the currently marketed Loestrin FE. Patient education should provide a picture of the actual packaging of Loestrin 24 to help prevent error and confusion.

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**III. RECOMMENDATIONS:**

1. DMETS does not recommend the use of the proprietary name Loestrin 24.
2. DMETS recommends implementation of the label and labeling revisions outlined in section III of this review to minimize potential errors with the use of this product.
2. DDMAC finds the proprietary name, Loestrin 24, acceptable from a promotional perspective.

DMETS would appreciate feedback of the final outcome of this consult. We would be willing to meet with the Division for further discussion, if needed. If you have further questions or need clarifications, please contact Diane Smith, project manager, at 301-827-1998.

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Kimberly Culley, RPh  
Safety Evaluator  
Division of Medication Errors and Technical Support  
Office of Drug Safety

Concur:

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Alina Mahmud, R.Ph., MS  
Team Leader  
Division of Medication Errors and Technical Support  
Office of Drug Safety

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Appendix A: DMETS Prescription Study Results

<b>INPATIENT</b>	<b>OUTPATIENT</b>	<b>VOICE</b>
Loestrin 2.4	Loestrin 24	Lorestrin
Loestrin 24	Loestrin 24	Loestrin
Loestrin 24	Loestrin 24	Lorestrin
Loestrin	Loestrin 24	Loestrin 24
Loestrin 24	Loestrin 24	Lorestrin
Loestrin 24	Loestrin 24	Loestrin
Loestrin 24	Loestrin 24	Lorestrin 24
Loestrin 24	Loestrin 24	Zolestrin 24
Loestrin 24	Loestrin 24	Lo-Estrin 24
Loestrin 24	Loestrin 24	Loestrin 24
Loestrin 24	Loestrin 24	Loestrin 24
Loestrin 24	Loestrin 24	Loestrin 24
Loestrin 24	Loestrin 24	Loestrin-24
Loestrin 24	Loestrin 24	Loestrin 24
Loestrin 24	Lisestrin 24	Loestrin 24
Loestrin 24	Loestrin 24	
Loestrin 24	Lorestrin 24	
Loestrin 24	Loestrin 24	
Loestrin 24		

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/s/

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Kimberly Culley  
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DRUG SAFETY OFFICE REVIEWER

Alina Mahmud  
8/19/2005 11:40:43 AM  
DRUG SAFETY OFFICE REVIEWER

Carol Holquist  
8/19/2005 01:42:38 PM  
DRUG SAFETY OFFICE REVIEWER

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**MEMORANDUM**

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

**DATE:** July 11, 2005

**TO:** Daniel Shames, M.D., Director  
Division of Reproductive and Urologic Drug Products  
HFD-580

**VIA:** Karen Kirchberg, N.P., Regulatory Project Manager  
Division of Reproductive and Urologic Drug Products  
HFD-580

**FROM:** Jeanine Best, M.S.N., R.N., P.N.P.  
Patient Product Information Specialist  
Division of Surveillance, Research, and Communication Support  
HFD-410

**THROUGH:** Gerald Dal Pan, M.D., M.H.S., Director  
Division of Surveillance, Research, and Communication Support  
HFD-410

**SUBJECT:** DSRCs Review of Patient Labeling for Loestrin 24 (norethindrone acetate/ethinyl estradiol and ferrous fumarate) Tablets, NDA 21-871

**Background and Summary:**

The sponsor submitted NDA 21-871 on April 15, 2005, Loestrin 24 (norethindrone acetate/ethinyl estradiol and ferrous fumarate) Tablets. Loestrin 24 is a combination oral contraceptive product has a requirement under §310.501 for a patient package insert (PPI). The sponsor submitted a PPI following the March 2004, Draft Guidance; *Guidance for Industry: Labeling for Combined Oral Contraceptives*.

**Comments and recommendations:**

1. The format and content of the proposed PPI are acceptable from a patient comprehension perspective. The Flesch-Kincaid reading level is 7.6 and the Flesch reading ease is 67%.
2. Avoid the use of all UPPER CASE letters to emphasize statements or important information. Upper case lettering is difficult to read. Use upper and lower case letters and, bold or increase the font size for word or statement emphasis. The tradename and headings are the exception to this recommendation and may be in all upper case letters.

Please call us if you have any questions.

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/s/

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Jeanine Best  
7/11/05 03:03:35 PM  
DRUG SAFETY OFFICE REVIEWER

Toni Piazza Hepp  
7/11/05 04:52:14 PM  
DRUG SAFETY OFFICE REVIEWER  
for Gerald Dal Pan

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       Trade Secret / Confidential

✓ Draft Labeling

       Deliberative Process

**NDA REGULATORY FILING REVIEW**  
**(Including Memo of Filing Meeting)**

NDA # 21-871

Supplement # 000

Efficacy Supplement Type SE-

Trade Name: Loestrin®

Established Name: (norethindrone acetate/ethinyl estradiol and ferrous fumarate) Tablets

Strengths: 1mg/20mcg/75 mg

Applicant: Warner Chilcott Company, Inc.

Agent for Applicant: Warner Chilcott (US), Inc.

Date of Application: April 15, 2005

Date of Receipt: April 17, 2005

Date clock started after UN:

Date of Filing Meeting: June 1, 2005

Filing Date: June 17, 2005

Action Goal Date (optional): February 17, 2005

User Fee Goal Date: February 17, 2005

Indication(s) requested: Oral Contraception

Type of Original NDA: (b)(1)  (b)(2)

OR

Type of Supplement: (b)(1)  (b)(2)

**NOTE:**

(1) If you have questions about whether the application is a 505(b)(1) or 505(b)(2) application, see Appendix A. 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). If the application is a (b)(2), complete Appendix B.

(2) If the application is a supplement to an NDA, please indicate whether the NDA is a (b)(1) or a (b)(2) application:

NDA is a (b)(1) application OR  NDA is a (b)(2) application

Therapeutic Classification: S

P

Resubmission after withdrawal?

Resubmission after refuse to file?

Chemical Classification: (1,2,3 etc.) 3

Other (orphan, OTC, etc.)

Form 3397 (User Fee Cover Sheet) submitted: YES  NO

User Fee Status: Paid  Exempt (orphan, government)   
Waived (e.g., small business, public health)

**NOTE:** If the NDA is a 505(b)(2) application, and the applicant did not pay a fee in reliance on the 505(b)(2) exemption (see box 7 on the User Fee Cover Sheet), confirm that a user fee is not required. The applicant is required to pay a user fee if: (1) the product described in the 505(b)(2) application is a new molecular entity or (2) the applicant claims a new indication for a use that has not been approved under section 505(b). Examples of a new indication for a use include a new indication, a new dosing regime, a new patient population, and an Rx-to-OTC switch. The best way to determine if the applicant is claiming a new indication for a use is to compare the applicant's proposed labeling to labeling that has already been approved for the product described in the application. Highlight the differences between the proposed and approved labeling.

Version: 12/15/2004

This is a locked document. If you need to add a comment where there is no field to do so, unlock the document using the following procedure. Click the 'View' tab; drag the cursor down to 'Toolbars'; click on 'Forms.' On the forms toolbar, click the lock/unlock icon (looks like a padlock). This will allow you to insert text outside the provided fields. The form must then be relocked to permit tabbing through the fields.

If you need assistance in determining if the applicant is claiming a new indication for a use, please contact the user fee staff.

- Is there any 5-year or 3-year exclusivity on this active moiety in an approved (b)(1) or (b)(2) application? YES  NO   
If yes, explain:
- Does another drug have orphan drug exclusivity for the same indication? YES  NO
- If yes, is the drug considered to be the same drug according to the orphan drug definition of sameness [21 CFR 316.3(b)(13)]? YES  NO

If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy (HFD-007).

- Is the application affected by the Application Integrity Policy (AIP)? YES  NO   
If yes, explain:
- If yes, has OC/DMPQ been notified of the submission? YES  NO
- Does the submission contain an accurate comprehensive index? YES  NO
- Was form 356h included with an authorized signature? YES  NO   
**If foreign applicant, both the applicant and the U.S. agent must sign.**
- Submission complete as required under 21 CFR 314.50? YES  NO   
If no, explain:
- If an electronic NDA, does it follow the Guidance? N/A  YES  NO   
**If an electronic NDA, all forms and certifications must be in paper and require a signature.**  
Which parts of the application were submitted in electronic format? labeling

Additional comments:

- If an electronic NDA in Common Technical Document format, does it follow the CTD guidance? N/A  YES  NO
- Is it an electronic CTD (eCTD)? N/A  YES  NO   
**If an electronic CTD, all forms and certifications must either be in paper and signed or be electronically signed.**

Additional comments:

- Patent information submitted on form FDA 3542a? YES  NO
- Exclusivity requested? YES, \_\_\_\_\_ Years NO   
*NOTE: An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.*
- Correctly worded Debarment Certification included with authorized signature? YES  NO   
**If foreign applicant, both the applicant and the U.S. Agent must sign the certification.**

**NOTE:** Debarment Certification should use wording in FD&C Act section 306(k)(1) i.e.,  
 “[Name of applicant] hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application.” Applicant may not use wording such as “To the best of my knowledge . . . .”

- Financial Disclosure forms included with authorized signature? YES  NO   
 (Forms 3454 and 3455 must be included and must be signed by the APPLICANT, not an agent.)  
**NOTE:** Financial disclosure is required for bioequivalence studies that are the basis for approval.
- Field Copy Certification (that it is a true copy of the CMC technical section)? Y  NO
- PDUFA and Action Goal dates correct in COMIS? YES  NO   
 If not, have the document room staff correct them immediately. These are the dates EES uses for calculating inspection dates.
- Drug name and applicant name correct in COMIS? If not, have the Document Room make the corrections. Ask the Doc Rm to add the established name to COMIS for the supporting IND if it is not already entered.
- List referenced IND numbers: 64,817
- End-of-Phase 2 Meeting(s)? Date(s) \_\_\_\_\_ NO   
 If yes, distribute minutes before filing meeting.
- Pre-NDA Meeting(s)? Date(s) \_\_\_\_\_ NO   
 If yes, distribute minutes before filing meeting.

**Project Management**

- Was electronic “Content of Labeling” submitted? YES  NO   
 If no, request in 74-day letter.
- All labeling (PI, PPI, MedGuide, carton and immediate container labels) consulted to DDMAC? YES  NO
- Risk Management Plan consulted to ODS/IO? N/A  YES  NO
- Trade name (plus PI and all labels and labeling) consulted to ODS/DMETS? Y  NO
- MedGuide and/or PPI (plus PI) consulted to ODS/DSRCS? N/A  YES  NO
- If a drug with abuse potential, was an Abuse Liability Assessment, including a proposal for scheduling, submitted? N/A  YES  NO

**If Rx-to-OTC Switch application:**

- OTC label comprehension studies, all OTC labeling, and current approved PI consulted to ODS/DSRCS? N/A  YES  NO
- Has DOTCDP been notified of the OTC switch application? YES  NO

**Clinical**

- If a controlled substance, has a consult been sent to the Controlled Substance Staff? YES  NO

**Chemistry**

- Did applicant request categorical exclusion for environmental assessment? YES  NO   
If no, did applicant submit a complete environmental assessment? YES  NO   
If EA submitted, consulted to Florian Zielinski (HFD-357)? YES  NO
- Establishment Evaluation Request (EER) submitted to DMPQ? YES  NO
- If a parenteral product, consulted to Microbiology Team (HFD-805)? YES  NO

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ATTACHMENT

MEMO OF FILING MEETING

DATE: 6.17.05

BACKGROUND: Loestrin 1/20 is an already approved product. Watner Chilcott purchased the NDA from Pfizer. This NDA submission provides for a new dosing regimen.

(Provide a brief background of the drug, e.g., it is already approved and this NDA is for an extended-release formulation; whether another Division is involved; foreign marketing history; etc.)

ATTENDEES: Jennifer Mercier-CPMS, Scott Monroe, M.D.-Team leader, Dan Davis, M.D.-Medical Reviewer

ASSIGNED REVIEWERS (including those not present at filing meeting) :

<u>Discipline</u>	<u>Reviewer</u>
Medical:	Scott Monroe, MD - Medical Team Leader
Secondary Medical:	Daniel Davis, MD - Medical Officer
Statistical:	Shahla Farr, Ph.D. - Statistical Reviewer
Pharmacology:	Lynnda Reid, Ph.D. - Pharmacology Spervisor
Statistical Pharmacology:	
Chemistry:	Raj Agarwal, Ph.D. - Chemistry Reviewer
Environmental Assessment (if needed):	
Biopharmaceutical:	Myong-Jin Kim - Pharmacokinetics Reviewer
Microbiology, sterility:	
Microbiology, clinical (for antimicrobial products only):	
DSI:	
Regulatory Project Management:	Karen Kirchberg, NP
Other Consults:	

Per reviewers, are all parts in English or English translation? YES  NO

If no, explain:

CLINICAL FILE  REFUSE TO FILE

• Clinical site inspection needed? YES  NO

• Advisory Committee Meeting needed? YES, date if known \_\_\_\_\_ NO

• If the application is affected by the AIP, has the division made a recommendation regarding whether or not an exception to the AIP should be granted to permit review based on medical necessity or public health significance? N/A  YES  NO

CLINICAL MICROBIOLOGY N/A  FILE  REFUSE TO FILE

STATISTICS N/A  FILE  REFUSE TO FILE

BIOPHARMACEUTICS FILE  REFUSE TO FILE

- Biopharm. inspection needed? YES  NO

PHARMACOLOGY N/A  FILE  REFUSE TO FILE

- GLP inspection needed? YES  NO

CHEMISTRY FILE  REFUSE TO FILE

- Establishment(s) ready for inspection? YES  NO
- Microbiology YES  NO

**ELECTRONIC SUBMISSION:**

Any comments:

**REGULATORY CONCLUSIONS/DEFICIENCIES:**  
(Refer to 21 CFR 314.101(d) for filing requirements.)

- The application is unsuitable for filing. Explain why:
- The application, on its face, appears to be well-organized and indexed. The application appears to be suitable for filing.
  - No filing issues have been identified.
  - Filing issues to be communicated by Day 74. List (optional):

**ACTION ITEMS:**

1.  If RTF, notify everybody who already received a consult request of RTF action. Cancel the EER.
2.  If filed and the application is under the AIP, prepare a letter either granting (for signature by Center Director) or denying (for signature by ODE Director) an exception for review.
3.  Convey document filing issues/no filing issues to applicant by Day 74.

Karen Kirchberg  
Regulatory Project Manager, HFD-580

## Appendix A to NDA Regulatory Filing Review

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

- (1) it relies on literature to meet any of the approval requirements (unless the applicant has a written right of reference to the underlying data)
- (2) it relies on the Agency's previous approval of another sponsor's drug product (which may be evidenced by reference to publicly available FDA reviews, or labeling of another drug sponsor's drug product) to meet any of the approval requirements (unless the application includes a written right of reference to data in the other sponsor's NDA)
- (3) it relies on what is "generally known" or "scientifically accepted" about a class of products to support the safety or effectiveness of the particular drug for which the applicant is seeking approval. (Note, however, that this does not mean *any* reference to general information or knowledge (e.g., about disease etiology, support for particular endpoints, methods of analysis) causes the application to be a 505(b)(2) application.)
- (4) it seeks approval for a change from a product described in an OTC monograph and relies on the monograph to establish the safety or effectiveness of one or more aspects of the drug product for which approval is sought (see 21 CFR 330.11).

Products that may be likely to be described in a 505(b)(2) application include combination drug products (e.g., heart drug and diuretic (hydrochlorothiazide) combinations), OTC monograph deviations, new dosage forms, new indications, and new salts.

If you have questions about whether an application is a 505(b)(1) or 505(b)(2) application, please consult with the Director, Division of Regulatory Policy II, Office of Regulatory Policy (HFD-007).

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**Appendix B to NDA Regulatory Filing Review  
Questions for 505(b)(2) Applications**

1. Does the application reference a listed drug (approved drug)? YES  NO

*If "No," skip to question 3.*

2. Name of listed drug(s) referenced by the applicant (if any) and NDA/ANDA #(s):
3. The purpose of this and the questions below (questions 3 to 5) is to determine if there is an approved drug product that is equivalent or very similar to the product proposed for approval and that should be referenced as a listed drug in the pending application.

- (a) Is there a pharmaceutical equivalent(s) to the product proposed in the 505(b)(2) application that is already approved?

YES  NO

*(Pharmaceutical equivalents are drug products in identical dosage forms that: (1) contain identical amounts of the identical active drug ingredient, i.e., the same salt or ester of the same therapeutic moiety, or, in the case of modified release dosage forms that require a reservoir or overage or such forms as prefilled syringes where residual volume may vary, that deliver identical amounts of the active drug ingredient over the identical dosing period; (2) do not necessarily contain the same inactive ingredients; and (3) meet the identical compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times, and/or dissolution rates. (21 CFR 320.1(c))*

*If "No," skip to question 4. Otherwise, answer part (b).*

- (b) Is the approved pharmaceutical equivalent(s) cited as the listed drug(s)? YES  NO   
(The approved pharmaceutical equivalent(s) should be cited as the listed drug(s).)

*If "Yes," skip to question 6. Otherwise, answer part (c).*

- (c) Have you conferred with the Director, Division of Regulatory Policy II, Office of Regulatory Policy (ORP) (HFD-007)? YES  NO

*If "No," please contact the Director, Division of Regulatory Policy II, ORP. Proceed to question 6.*

4. (a) Is there a pharmaceutical alternative(s) already approved? YES  NO

*(Pharmaceutical alternatives are drug products that contain the identical therapeutic moiety, or its precursor, but not necessarily in the same amount or dosage form or as the same salt or ester. Each such drug product individually meets either the identical or its own respective compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times and/or dissolution rates. (21 CFR 320.1(d)) Different dosage forms and strengths within a product line by a single manufacturer are thus pharmaceutical alternatives, as are extended-release products when compared with immediate- or standard-release formulations of the same active ingredient.)*

*If "No," skip to question 5. Otherwise, answer part (b).*

- (b) Is the approved pharmaceutical alternative(s) cited as the listed drug(s)? YES  NO   
(The approved pharmaceutical alternative(s) should be cited as the listed drug(s).)

**NOTE:** *If there is more than one pharmaceutical alternative approved, consult the Director, Division of*

*Regulatory Policy II, Office of Regulatory Policy (ORP) (HFD-007) to determine if the appropriate pharmaceutical alternatives are referenced.*

*If "Yes," skip to question 6. Otherwise, answer part (c).*

- (c) Have you conferred with the Director, Division of Regulatory Policy II, ORP? YES  NO

*If "No," please contact the Director, Division of Regulatory Policy II, ORP. Proceed to question 6.*

5. (a) Is there an approved drug product that does not meet the definition of "pharmaceutical equivalent" or "pharmaceutical alternative," as provided in questions 3(a) and 4(a), above, but that is otherwise very similar to the proposed product? YES  NO

*If "No," skip to question 6.*

*If "Yes," please describe how the approved drug product is similar to the proposed one and answer part (b) of this question. Please also contact the Director, Division of Regulatory Policy II, Office of Regulatory Policy (HFD-007), to further discuss.*

- (b) Is the approved drug product cited as the listed drug? YES  NO
6. Describe the change from the listed drug(s) provided for in this (b)(2) application (for example, "This application provides for a new indication, otitis media" or "This application provides for a change in dosage form, from capsules to solution").
7. Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA? (Normally, FDA will refuse-to-file such NDAs (see 21 CFR 314.101(d)(9)).) YES  NO
8. Is the extent to which the active ingredient(s) is absorbed or otherwise made available to the site of action less than that of the reference listed drug (RLD)? (See 314.54(b)(1)). If yes, the application should be refused for filing under 21 CFR 314.101(d)(9). YES  NO
9. Is the rate at which the product's active ingredient(s) is absorbed or otherwise made available to the site of action unintentionally less than that of the RLD (see 21 CFR 314.54(b)(2))? If yes, the application should be refused for filing under 21 CFR 314.101(d)(9). YES  NO
10. Are there certifications for each of the patents listed for the listed drug(s)? YES  NO
11. Which of the following patent certifications does the application contain? (Check all that apply and identify the patents to which each type of certification was made, as appropriate.)
- 21 CFR 314.50(i)(1)(i)(A)(1): The patent information has not been submitted to FDA. (Paragraph I certification)  
Patent number(s):
- 21 CFR 314.50(i)(1)(i)(A)(2): The patent has expired. (Paragraph II certification)  
Patent number(s):

- 21 CFR 314.50(i)(1)(i)(A)(3): The date on which the patent will expire. (Paragraph III certification)  
Patent number(s):
- 21 CFR 314.50(i)(1)(i)(A)(4): The patent is invalid, unenforceable, or will not be infringed by the manufacture, use, or sale of the drug product for which the application is submitted. (Paragraph IV certification)  
Patent number(s):

**NOTE:** *IF FILED, and if the applicant made a "Paragraph IV" certification [21 CFR 314.50(i)(1)(i)(A)(4)], the applicant must **subsequently** submit a signed certification stating that the NDA holder and patent owner(s) were notified the NDA was filed [21 CFR 314.52(b)]. The applicant must also submit documentation showing that the NDA holder and patent owner(s) received the notification [21 CFR 314.52(e)].*

- 21 CFR 314.50(i)(1)(ii): No relevant patents.
- 21 CFR 314.50(i)(1)(iii): The patent on the listed drug is a method of use patent and the labeling for the drug product for which the applicant is seeking approval does not include any indications that are covered by the use patent as described in the corresponding use code in the Orange Book. Applicant must provide a statement that the method of use patent does not claim any of the proposed indications. (Section viii statement)  
Patent number(s):
- 21 CFR 314.50(i)(3): Statement that applicant has a licensing agreement with the patent owner (must also submit certification under 21 CFR 314.50(i)(1)(i)(A)(4) above).  
Patent number(s):
- Written statement from patent owner that it consents to an immediate effective date upon approval of the application.  
Patent number(s):

12. Did the applicant:

- Identify which parts of the application rely on information (e.g. literature, prior approval of another sponsor's application) that the applicant does not own or to which the applicant does not have a right of reference?  
YES  NO
- Submit a statement as to whether the listed drug(s) identified has received a period of marketing exclusivity?  
YES  NO
- Submit a bioavailability/bioequivalence (BA/BE) study comparing the proposed product to the listed drug?  
N/A  YES  NO
- Certify that it is seeking approval only for a new indication and not for the indications approved for the listed drug if the listed drug has patent protection for the approved indications and the applicant is requesting only the new indication (21 CFR 314.54(a)(1)(iv).)?  
N/A  YES  NO

13. If the (b)(2) applicant is requesting 3-year exclusivity, did the applicant submit the following information required by 21 CFR 314.50(j)(4):

- Certification that at least one of the investigations included meets the definition of "new clinical investigation" as set forth at 314.108(a). YES  NO

- A list of all published studies or publicly available reports that are relevant to the conditions for which the applicant is seeking approval. YES  NO

- EITHER

The number of the applicant's IND under which the studies essential to approval were conducted.

IND# \_\_\_\_\_ NO

OR

A certification that the NDA sponsor provided substantial support for the clinical investigation(s) essential to approval if it was not the sponsor of the IND under which those clinical studies were conducted?

YES  NO

14. Has the Associate Director for Regulatory Affairs, OND, been notified of the existence of the (b)(2) application?

YES  NO

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CSO

Karen Kirchberg  
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CSO

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DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration  
Rockville, MD 20857

**FILING COMMUNICATION**

NDA 21-871

Warner Chilcott, Inc.  
Attention: Alvin D. Howard  
Vice President, Regulatory Affairs  
100 Enterprise Way  
Rockaway, New Jersey 07866

Dear Mr. Howard

Please refer to your April 15, 2005 new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Loestrin® 24 (norethindrone acetate/ethinyl estradiol and ferrous fumarate) Tablets.

We have completed our filing review and have determined that your application is sufficiently complete to permit a substantive review. Therefore, this application will be filed under section 505(b) of the Act on June 17, 2005 in accordance with 21 CFR 314.101(a).

At this time, we have not identified any potential filing 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.

If you have any questions, call Karen Kirchberg, N.P., Regulatory Health Project Manager, at (301) 827-4254.

Sincerely,

*{See appended electronic signature page}*

Donna Griebel, M.D.  
Deputy Director  
Division of Reproductive and Urologic Drug  
Products  
Office of Drug Evaluation III  
Center for Drug Evaluation and Research

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**45 Day NDA Meeting Checklist  
Pharmacology/Toxicology**

**NDA Number:** 21-871

**Drug Name:** Loestrin® 24 (norethindrone acetate/ethinyl estradiol)

**Sponsor:** Warner Chilcott

**Date:** June 1, 2005

**Reviewer:** Lynnda Reid

**Date CDER Received:** April 18, 2005

**Filing Date:** June 17, 2005

**User Fee Date:** February 18, 2006

**Expected Date of Draft Review:** August 1, 2005

**On initial overview of the Pharm/Tox portion of the NDA application, PT finds the NDA fileable.**

ITEM	YES/NO	COMMENTS	
1)	On its face, is the Pharm/Tox section of the NDA organized in a manner to allow substantive review to begin?	YES	PT data was waived based on the extensive nonclinical and clinical data for norethindrone acetate and ethinyl estradiol.
2)	Is the Pharm/Tox section of the NDA indexed and paginated in a manner to allow substantive review to begin?	NA	Appears This Way On Original
3)	On its face, is the Pharm/Tox section of the NDA legible so that substantive review can begin? Has the data been presented in an appropriate manner?	YES	Appears This Way On Original
4)	Are all necessary and appropriate studies for this agent, including special studies/data requested by the Division during pre-submission communications/discussions, completed and submitted in this NDA?	YES	Appears This Way On Original
5)	If the formulation to be marketed is not identical to the formulation used in the toxicology studies (including the impurity profiles), has the Sponsor clearly defined the differences and submitted reviewable supportive data?	NA	Appears This Way On Original
6)	Does the route of administration used in animal studies appear to be the same as the intended human exposure? If not, has the sponsor submitted supportive data and/or an adequate scientific rationale to justify the alternative route?	YES	Appears This Way On Original

7)	Has the sponsor submitted a statement(s) that all the pivotal Pharm/Tox studies have been performed in accordance with the GLP regulations (21 CFR 58) or an explanation for any significant deviations?	NA	Appears This Way On Original
8)	Has the sponsor submitted a statement(s) that the Pharm/Tox studies have been performed using acceptable, state-of-the-art protocols which also reflect agency animal welfare concerns?	NA	Appears This Way On Original
9)	Has the proposed draft labeling been submitted?  Are the appropriate sections for the product included and generally in accordance with 21 CFR 201.57?  Is information available to express human dose multiples in either mg/m <sup>2</sup> or comparative serum/plasma AUC levels?	YES  YES  YES	Similar to labeling for other OC containing norethindrone acetate and ethinyl estradiol.  Appears This Way On Original
10)	From a Pharm/Tox perspective, is this NDA fileable? If not, please state in item #11 below why it is not.	YES	Appears This Way On Original
11)	Reasons for refusal to file:	Appears This Way On Original	

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PHARMACOLOGIST

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DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration  
Rockville, MD 20857

NDA 21-871

Warner Chilcott, Inc.  
Attention: Alvin D. Howard  
Vice President, Regulatory Affairs  
100 Enterprise Way  
Rockaway, New Jersey 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 for the following:

Name of Drug Product:	Loestrin <sup>®</sup> 24 (norethindrone acetate/ethinyl estradiol and ferrous fumarate) Tablets
Review Priority Classification:	Standard (S)
Date of Application:	April 15, 2005
Date of Receipt:	April 18, 2005
Our Reference Number:	NDA 21-871

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 June 17, 2005 in accordance with 21 CFR 314.101(a). If the application is filed, the user fee goal date will be February 17, 2006.

All applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred. We note that you have not fulfilled the requirement. We are waiving the requirement for pediatric studies for this application.

Please cite the NDA number listed above at the top of the first page of any communications concerning this application. Send all electronic or mixed electronic and paper submissions to the Central Document Room at the following address:

Food and Drug Administration  
Center for Drug Evaluation and Research  
Central Document Room (CDR)  
5901-B Ammendale Road  
Beltsville, MD 20705-1266

If your submission only contains paper, send it to the following address:

U.S. Postal Service or Courier/Overnight Mail:

Food and Drug Administration  
Center for Drug Evaluation and Research  
Division of Reproductive and Urologic Drug Products  
Attention: Division Document Room, 8B45  
5600 Fishers Lane  
Rockville, Maryland 20857

If you have any questions, call Karen Kirchberg, N.P., Regulatory Project Manager, at (301) 827-4254.

Sincerely,

*{See appended electronic signature page}*

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

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/s/

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Jennifer L. Mercier  
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**ORIGINAL**

Form Approved: OMB No. 0910 - 0297 Expiration Date: December 31, 2006 See instructions for OMB Statement.

DEPARTMENT OF HEALTH AND HUMAN SERVICES FOOD AND DRUG ADMINISTRATION	<b>PRESCRIPTION DRUG USER FEE COVERSHEET</b>
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A completed form must be signed and accompany each new drug or biologic product application and each new supplement. See exceptions on the reverse side. If payment is sent by U.S. mail or courier, please include a copy of this completed form with payment. Payment instructions and fee rates can be found on CDER's website: <http://www.fda.gov/cder/pdufa/default.htm>

1. APPLICANT'S NAME AND ADDRESS  WARNER CHILCOTT INC Alvin Howard 100 ENTERPRISE DR SUITE 280 ROCKAWAY NJ 07866 US	4. BLA SUBMISSION TRACKING NUMBER (STN) / NDA NUMBER  21-871
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2. TELEPHONE NUMBER 973-442-3233	5. DOES THIS APPLICATION REQUIRE CLINICAL DATA FOR APPROVAL? <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO  IF YOUR RESPONSE IS "NO" AND THIS IS FOR A SUPPLEMENT, STOP HERE AND SIGN THIS FORM IF RESPONSE IS "YES", CHECK THE APPROPRIATE RESPONSE BELOW:  <input checked="" type="checkbox"/> THE REQUIRED CLINICAL DATA ARE CONTAINED IN THE APPLICATION  <input type="checkbox"/> THE REQUIRED CLINICAL DATA ARE SUBMITTED BY REFERENCE TO:
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3. PRODUCT NAME Loestrin 24 ( norethindrone acetate 1mg/ethinyl estradiol 20 mcg tablets, USP and ferrous fumarate tablets )	6. USER FEE I.D. NUMBER PD3006055
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7. IS THIS APPLICATION COVERED BY ANY OF THE FOLLOWING USER FEE EXCLUSIONS? IF SO, CHECK THE APPLICABLE EXCLUSION.

<input type="checkbox"/> A LARGE VOLUME PARENTERAL DRUG PRODUCT APPROVED UNDER SECTION 505 OF THE FEDERAL FOOD, DRUG, AND COSMETIC ACT BEFORE 9/1/92 (Self Explanatory)	<input type="checkbox"/> A 505(b)(2) APPLICATION THAT DOES NOT REQUIRE A FEE
<input type="checkbox"/> THE APPLICATION QUALIFIES FOR THE ORPHAN EXCEPTION UNDER SECTION 736(a)(1)(E) of the Federal Food, Drug, and Cosmetic Act	<input type="checkbox"/> THE APPLICATION IS SUBMITTED BY A STATE OR FEDERAL GOVERNMENT ENTITY FOR A DRUG THAT IS NOT DISTRIBUTED COMMERCIALY

8. HAS A WAIVER OF AN APPLICATION FEE BEEN GRANTED FOR THIS APPLICATION?  YES  NO

**Public reporting burden for this collection of information** is estimated to average 30 minutes 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:

Department of Health and Human Services Food and Drug Administration CBER, HFM-99 1401 Rockville Pike Rockville, MD 20852-1448	Food and Drug Administration CDER, HFD-94 12420 Parklawn Drive, Room 3046 Rockville, MD 20852	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.
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SIGNATURE OF AUTHORIZED COMPANY REPRESENTATIVE 	TITLE SUP	DATE 4/14/05
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9. USER FEE PAYMENT AMOUNT FOR THIS APPLICATION  
\$672,000.00

Form FDA 3397 (12/03)

(Close) (Print Cover sheet)

*Change to LCC 1  
616-40001*



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration  
Rockville, MD 20857

IND 64,817

Warner Chilcott Company, Inc.  
Attention: Fang Li, Ph.D.  
Manager, Regulatory Affairs  
Rockaway 80 Corporate Center  
100 Enterprise Drive, Suite 280  
Rockaway, NJ 07866

Dear Dr. Li:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for Loestrin® 24 (norethindrone/ethinyl estradiol) Tablets.

We also refer to the meeting request dated September 1, 2004 and the Pre-NDA meeting that was scheduled for November 3, 2004. The preliminary responses to your meeting questions were faxed to you on November 1, 2004. Since you agreed to accept the Division's responses, the meeting was canceled. Enclosed are the finalized responses. They will serve as the official minutes of that meeting.

If you have any questions, call Karen Kirchberg, Regulatory Project Manager, at (301) 827-4254.

Sincerely,

*{See appended electronic signature page}*

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

Enclosure

## MEMORANDUM OF MEETING MINUTES

The Pre-NDA meeting scheduled for November 3, 2004 was cancelled. The following are the official responses to the questions in the meeting package provided by the Division of Reproductive and Urologic Drug Products (DRUDP).

**SPONSOR:** Warner Chilcott  
**APPLICATION:** IND 64,817  
**DRUG NAME:** Loestrin<sup>®</sup> 24

### BACKGROUND

The Sponsor is planning to submit the Loestrin<sup>®</sup> 24 Tablet NDA application in the first half of 2005. The new dosing regimen consist of 24 days of active tablets (norethindrone acetate 1 mg and ethinyl estradiol 20mcg) followed by 4 days of placebo tablets with ferrous fumarate.

### MEETING OBJECTIVES

The purpose of the meeting is to seek concurrence from the Division that the information to be included in the NDA submission is adequate to evaluate the safety and efficacy of the product.

### DISCUSSION:

Questions:

CMC

1. *Does the agency concur with the content and outline proposed for CMC (item 4)?*

DRUDP Answer: Yes.

Pharmacology and Toxicology

2. *Does the Agency concur that both norethindrone acetate and ethinyl estradiol are well known chemical entities and no new pharmacology and toxicology information need be provided?*

DRUDP Answer: Yes.

3. *Does the Agency concur that the inactive ingredients in both the Loestrin 24 and Ferrous Fumarate tables are considered safe for use in an oral tablet dosage form, therefore, no pharmacology and toxicology information need be provided for these components?*

DRUDP Answer: Yes.

Human Pharmacokinetics and Bioavailability

4. *Does the Agency concur with the content and outline proposed for human pharmacokinetics and bioavailability (Item 6)?*

DRUDP Answer: Yes.

Clinical

5. *Does the Agency concur that the content and outline proposed for clinical (item 8) support the evaluation of the efficacy and safety for the proposed indication?*

DRUDP Answer: In general, yes. If the product is marketed elsewhere, your NDA should include a summary of postmarketing safety reports. There should also be a statement for each clinical study that was conducted in compliance with institutional review board regulation and

informed consent regulations. If you audited subject records, please provide a list identifying each study so audited.

We also request that you calculate and report

- The Pearl Index for the comparator product.
- Provide Pearl Indices for the subgroup of women between 18 and 35 years old at baseline using only those cycles in which no backup contraceptive method was used.
- Provide 2-sided 95% confidence intervals for all Pearl Indices.

6. *Does the Agency concur that the planned analysis for Study PR-03903 is appropriate to support a claim of reduced incidence of intracyclic bleeding compared to Loestrin 1/20?*

DRUDP Answer: This will be a review issue.

Statistical

7. *Does the Agency concur with the content and outline proposed for Statistics (item 10)?*

DRUDP Answer: Yes.

Case Report Tabulations

8. *Does the Agency concur with the proposal to provide individual patient data by parameter as part of the final study reports in the clinical section (item 8) in lieu of case report tabulations by patient in the case report tabulations (item 11)?*

DRUDP Answer: This should be acceptable since you are providing datasets electronically. Please follow the available guidance for electronic datasets. (See Guidance for Industry: Providing Regulatory Submission in Electronic Format – NDAs.) Each dataset should be a single file and each case report form domain should be provided as a single dataset. For example, demographic information, pregnancy test results, vital signs, adverse events, etc. should each be provided as individual datasets.

Case Report Forms

9. *Does the Agency concur with the proposal to provide required case report forms as part of the final study reports in the case report tabulations (item 8) and not in the case report forms (item 12)?*

DRUDP Answer: Yes. Please also provide CRFs for all women who became pregnant, in addition to all deaths and discontinuations due to adverse events.

10. *Does the Agency concur that only the following two types of components need to be submitted in the NDA in electronic format?*

- *Individual patient data in SAS transport file format for the pivotal clinical study (protocol PR03903)*
- *Draft labeling in MS WORD and PDF files*

DRUDP Answer: We prefer a fully electronic submission. However, we will accept a less-than-fully electronic submission. Also provide individual patient data for the two Phase 1 studies in SAS transport file format, with corresponding data definition files. (See Guidance for Industry: Providing Regulatory Submission in Electronic Format – NDAs).

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/s/

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NDA 21-871 [Lo-Estrin® 24 (norethindrone acetate and ethinyl estradiol tablets, USP and ferrous fumarate tablets)]

**Memo: site inspections**

**Date: October 25, 2005**

**I do not feel that any DSI inspections are warranted.**

**This is a very low-dose estrogen contraceptive product that has been around for many years and has a good safety profile. The new regimen proposed in the NDA represents a minor change [24 active pills instead of 21] from the currently approved regimen.**

**I reviewed the number of sites and their enrollment. Overall, there were 32 sites that screened 1,160 women, enrolled 939 (81% of those screened), and had 725 complete the study (77% of those enrolled). The mean enrollment was 29 women per site, and the 5 sites with the highest # had 63, 60, 60, 57, and 48 enrollees.**

**The principal investigator (PI) at a site stated on the financial disclosure that the PI owned 5,000 shares of Galen stock @ \$50 per share; the site screened women, enrolled , and completed. This enrollment represented , of the total number of women who completed the study, so any results from this one center should not significantly change the analysis or conclusions that the Division's reviewers will make.**

**Daniel Davis, MD  
Clinical reviewer**

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Daniel Davis  
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MEDICAL OFFICER

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## Teleconference Meeting Minutes

**Date:** September 17, 2003    **Time:** 9:00 – 10:00 AM    **Place:** PKLN Conf. Rm. 17B43

**IND:** 64,817

**Drug Name:** Loestrin® 24 (norethindrone acetate  
1 mg/ethinyl estradiol 20 mcg)

**Type of Meeting:** Pre-IND

**Indication:** Loestrin 24 is indicated for the prevention of pregnancy in women who elect to use oral contraceptives as a method of contraception.

**Sponsor:** Galen Holdings PLC

**FDA Lead:** Barbara Wesley, M.D.

**Meeting Recorder:** Charlene Williamson

### FDA Participants:

Daniel Shames, M.D., Director, Division of Reproductive and Urologic Drug Products  
(DRUDP)-HFD-580

Donna Griebel, M.D., Deputy Director, DRUDP– HFD-580

Scott Monroe, M.D., Medical Team Leader, DRUDP, HFD-580

Barbara Wesley, M.D., Medical Officer, DRUDP, HFD-580

Moo-Jhong Rhee, Ph.D., Chemistry Team Leader, Division of New Drug Chemistry II  
(DNDC II) @DRUDP (HFD-580)

Suzanne Thornton, Ph.D., Pharmacology Acting Supervisor, DRUDP – HFD-580

Kate Meaker, M.S. - Statistician, Division of Biometrics II (DBII) @  
DRUDP (HFD-580)

Karen Anderson, N.P., Regulatory Project Manager, DRUDP, HFD-580

Charlene Williamson, Regulatory Project Manager, DRUDP, HFD-580

### External Participants:

Tina deVries, Ph.D., Vice President, Pharmaceuticals

Herman Ellman, M.D., Senior Vice President, Clinical Development

---

Alvin D. Howard, Vice President, Regulatory Affairs

### Meeting Objectives:

To discuss the requirements for a combination oral contraceptive (COC) containing 1-mg norethindrone acetate (NETA) and 20-mcg ethinyl estradiol (EE) given for 24 days followed by 4 days of placebo.

- We expect that at least 600 subjects (resulting in 3600 cycles) who receive the study drug will complete this 6 month trial: 600 subjects is approximately 85% of your proposed enrollment of 700 subjects. If you anticipate a higher percentage of premature terminations, you will need to enroll more patients.

**Action Items:**

Meeting minutes to the sponsor within 30 days.

*(See appended electronic signature page)*

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Scott Monroe, M.D.  
Meeting Chair

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Cc:

Original IND 64,817

HFD-580/Wesley/Williamson/Monroe/Meaker

Drafted: CW/8.1.03

Revised/Initialed: Wesley, 10.6.03/Monroe, 10.7.03

Finalized: Williamson, 10.8.03

Filename: c:\documentsandsettings\williamsonc\mydocuments\nda\64817

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**MEMORANDUM OF TELECON      DRAFT**

**MEETING DATE:**                      March 17, 2004

**TIME:**                                      2:00 PM

**LOCATION:**                                Parklawn Building Rm. 18B-43

**APPLICATION NUMBER:**            IND 64,817 Loestrin 24 Tablets

**SPONSOR:**                                Galen Holding, PLC

**TYPE OF MEETING:**                Teleconference

**MEETING RECORDER:**              Charlene Williamson, Project Manager

**FDA ATTENDEES**

Jean Salemme, Ph.D., Chemistry Reviewer, Office of New Drug Chemistry (ONDC) @  
Division of Reproductive and Urologic Drug Products, (DRUDP); HFD – 580  
Charlene Williamson, Regulatory Project Manager, DRUDP; HFD-580

**EXTERNAL ATTENDEES**

Dr. Tina deVries, Vice President, Pharmaceuticals  
Alvin Howard, Vice President, Regulatory Affairs  
Fang Li, Manager, Regulatory Affairs  
Dr. Robert Kessler, Manager, Pharmaceuticals

**BACKGROUND:**

Loestrin 24 will be indicated for the prevention of pregnancy in women who elect to use oral contraceptives as a method of contraception. The medication regimen is for one active tablet to be taken for 24 days and then followed by a placebo for 4 days. The active tablet is the same formulation as the approved Loestrin 1/20.

**MEETING OBJECTIVES:**

Galen requested FDA's comments on stability data in anticipation of an NDA filing. Galen proposed to provide 3 months accelerated data on ~~one~~ batches of the drug product in new secondary packaging (pouch).

**DISCUSSION:**

- The secondary pouch as proposed is acceptable.
- The Division will accept 3 months of accelerated stability data at the time of submission, and an additional 3 months of accelerated stability data during the NDA review cycle, for a total of 6 months accelerated and 25° stability data.
- Loestrin was approved in 1970s; the specifications for impurities and dissolution should be revisited based on the batch analysis data. Especially, the acceptance

criterion for the dissolution test should be re-established based on dissolution profile of current production batches.

**ACTION ITEM:**

Official Minutes will be conveyed to the Sponsor

Minutes Preparer:

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Charlene Williamson  
Regulatory Project Manager

Chair Concurrence:

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Jean Salemme, Ph.D.  
Chemist

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cc: Original  
HFD-580/Div. Files  
HFD-580/Meeting Minutes files  
HFD-580/RPM

Concurrence: JSalemme/3.25.04/MRhee/3.25.04

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Z. Charlene Williamson  
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CSO

Jean Salemmé  
4/2/04 12:37:38 PM  
CHEMIST

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