

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

21-871

CHEMISTRY REVIEW(S)

NDA 21-871

Loestrin 24 Fe
(norethindrone acetate/ethinyl estradiol tablets,
USP and ferrous fumarate tablets)
1 mg/20 mcg

Tablets

Warner Chilcott Company, Inc.

Rajiv Agarwal

DIVISION OF PRE-MARKETING DRUG QUALITY ASSESSMENT
(Branch III, Division II)

For

Division of Reproductive and Urologic Products

Chemistry Review Data Sheet

Chemistry Review Data Sheet

1. NDA 21-871
2. REVIEW # 1
3. REVIEW DATE: 16-Feb-2006
4. REVIEWER: Rajiv Agarwal
5. PREVIOUS DOCUMENTS: N/A
6. SUBMISSION(S) BEING REVIEWED:

<u>Submission(s) Reviewed</u>	<u>Document Date</u>
ORIGINAL	18-APR-2005
AMENDMENT	29-JUL-2005
AMENDMENT	13-OCT-2005
AMENDMENT	07-DEC-2005
AMENDMENT	13-DEC-2005
AMENDMENT	24-JAN-2006
AMENDMENT	02-FEB-2006
AMENDMENT	13-FEB-2006
AMENDMENT	15-FEB-2006
AMENDMENT	16-FEB-2006

7. NAME & ADDRESS OF APPLICANT:

Name: Warner Chilcott Company, Inc.

Address: Union Street

Representative: Mr. Alvin Howard

Telephone: 973-442-3233

8. DRUG PRODUCT NAME/CODE/TYPE:

- | | |
|---|---|
| a) Proprietary Name: | Loestrin 24 Fe |
| b) Non-Proprietary Name (USAN): | Norethindrone acetate and ethinyl estradiol tablets, USP and Ferrous Fumarate tablets |
| c) Code Name/# (ONDQA only): | None |
| d) Chem. Type/Submission Priority (ONDQA only): | |

- Chem. Type: 3
- Submission Priority: Standard

9. LEGAL BASIS FOR SUBMISSION: Not applicable

10. PHARMACOL. CATEGORY: Prevention of pregnancy in women who elect to use oral

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contraceptives as a method of contraception.

11. DOSAGE FORM: Immediate release tablets
12. STRENGTH/POTENCY: (1 mg) norethindrone acetate and (20 mcg) ethinyl estradiol
13. ROUTE OF ADMINISTRATION: Oral
14. Rx/OTC DISPENSED: Rx OTC
15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):

SPOTS product – Form Completed

Not a SPOTS product

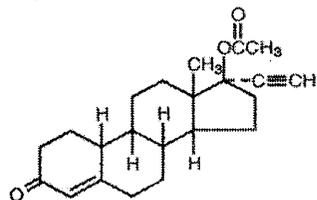
16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

I. Active Tablets:

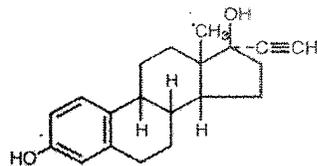
Chemical Name:

- *Norethindrone acetate:* 19-Norpregn-4-en-20-yn-3-one, 17-(acetyloxy)-, (17 α)
- *Ethinyl Estradiol:* 19-Norpregna-1, 3, 5 (10)-trien-20-yne-3, 17-diol, (17 α)-

Structural formula:



Norethindrone Acetate



Ethinyl Estradiol

Molecular Formula:

- Norethindrone acetate: $C_{22}H_{28}O_3$
- Ethinyl Estradiol: $C_{20}H_{24}O_2$

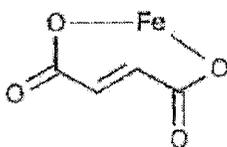
Molecular weight:

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- Norethindrone acetate: 340.46
- Ethinyl Estradiol: 296.40

II. Inert tablets:

Chemical name: 2-Butenedioic acid (E)-, iron (2+) salt
Established name: Ferrous Fumarate, USP
Molecular formula: C₄H₂FeO₄
Molecular weight: 169.90
Structural formula:



17. RELATED/SUPPORTING DOCUMENTS:

- EES inspection report: Acceptable 17-JUN-2005 (see the attached EER report; **Appendix -1**)
- Chemistry review of NDA 17-354.

Type/Number	Subject	Holder	Status	Review Date	Letter Date
DMF # _____	Norethindrone acetate	_____	Adequate, Reviewed by Dr. Jean Salemme for NDA _____ (no change since 2002)	16-SEP-2002	17-DEC-2004
DMF # _____	Ethinyl estradiol	_____	Adequate, Reviewed by this reviewer.	30-NOV-2005	17-DEC-2004
[]	Adequate, Reviewed by Dr. Donald Klein for NDA _____	03-NOV-2004	10-JAN-2005
[]	Adequate, Reviewed by Dr. Donal Klein for NDA _____	29-SEP-2005	15-DEC-2004
[]	Adequate, Reviewed by Dr. Arthur Shaw for NDA _____	04-NOV-2005	15-DEC-2004
[]	Adequate, Reviewed by this reviewer.	06-DEC-2005	28-MAR-2005

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DMF # [Adequate, Reviewed by this reviewer	06-DEC-2005	18-OCT-2004
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18. STATUS:

ONDQA:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
EES	Acceptable	17-JUN-2005	Ms. J D Ambrogio
DMETS	Acceptable*	10-FEB-2006	Ms. Alina Mahmud

* The trade name "Loestrin 24 Fe" is acceptable to DMETS and Clinical Division (see attchement).

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The Chemistry Review for NDA 21-871

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability:

This NDA may be **approved** from the CMC point of view.

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

None

II. Summary of Chemistry Assessments

A. Description of the Drug Product(s) and Drug Substance(s)

Drug Product:

Loestrin 24 Fe is a new dosing regimen containing the same active and inactive tablets present in the currently approved Loestrin Fe 1/20 tablets (NDA 17-354 approved on 30-APR-1973). The approved Loestrin Fe 1/20 regimen consists of twenty one (21) Loestrin 1/20 tablets and seven (7) 75-mg Ferrous Fumerate tablets as inactive tablets. The current dosing regimen is now twenty four (24) active (i.e. Loestrin 1/20) tablets and four (4) ferrous fumarate tablets.

The active ingredients in the **active tablets** are norethindrone acetate (1 mg) and ethinyl estradiol (20 mcg) and inactive excipients are acacia _____, lactose _____, magnesium stearate, _____ starch, confectioner's sugar, and talc.

The ingredients in the **inactive tablets (75 mg)** are ferrous fumarate, compressible sugar, povidone, microcrystalline cellulose, sodium starch glycolate, and magnesium stearate.

The drug product is manufactured at Warner Chilcott Company, Inc. Fajardo, Puerto Rico and the facility is in compliance with cGMP. The **EER** was forwarded to the Office of Compliance on 10-JUN-2005 for NDA 21-871 and an **acceptable** recommendation was issued on 17-JUN-2005 (see **Appendix 1**).

The drug product and placebo tablets are packaged into a blister card. The Loestrin 24 Fe container closure system consists of a blister card (_____) placed in a foil pouch with a _____ desiccant pack. The primary packaging for the current product is identical to that for approved product with additional protection provided by enclosing the blister card in a foil pouch with a _____ desiccant pack.

The approved shelf life for Loestrin Fe 1/20 is 24 months (NDA 17-354). A six month stability data under all three ICH storage conditions for the three batches of current dosing regimen, in a more protective secondary container including _____ desiccant pack, is provided. The historical stability data on already approved product (same product) and the six month stability data (using a secondary packaging and a desiccant) under all three ICH storage conditions support the requested **24 months expiry date**.

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The trade name Loestrin 24 Fe is acceptable to DMETS.

Drug Substance:

Drug substances (norethindrone acetate and ethinyl estradiol) are manufactured by _____ . All facilities are in compliance with cGMP

B. Description of How the Drug Product is Intended to be Used

Loestrin 24 Fe provides a continuous dosage regimen consisting of 24 oral contraceptive (active) tablets and 4 ferrous fumarate (placebo) tablets. Each active tablet contains 1 mg norethindrone acetate and 20 mcg ethinyl estradiol. The ferrous fumarate tablets, which are present to facilitate ease of drug administration via a 28-day regimen, are non-hormonal, and do not serve any therapeutic purpose. Earlier, the drug product was packaged in a blister card, later it was deemed that the primary packaging should be enclosed in a more protective _____ foil pouch along with a desiccant to avoid degradation of ethinyl estradiol. The secondary packaging does provide additional protection as evident by the stability studies. The drug product is deemed to be stable for 24 months when stored at USP recommended storage conditions [25°C (77°F); excursions permitted to 15 – 30°C (59-86°F)].

C. Basis for Approvability or Not-Approval Recommendation:

- Except for a dosing regimen, the composition, manufacturing process and specification are the same as the originally approved product.
- It has been demonstrated via stability studies that a new secondary packaging, which also contains a desiccant, provides better protection than the original primary container closure system alone.
- The final recommendation from the Office of Compliance for all the manufacturing and testing sites is ACCEPTABLE.

III. Administrative**A. Reviewer's Signature Electronically captured in DFS****B. Endorsement Block**

Rajiv Agarwal/Moo-Jhong Rhee/Kar/Nenita Crisostomo:
Date 16-FEB-2006

C. CC Block

HFD-580/Division File/NDA 21-871

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/s/

Rajiv Agarwal
2/16/2006 12:11:28 PM
CHEMIST

Moo-Jhong Rhee
2/16/2006 01:28:54 PM
CHEMIST
Chief, Branch III

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