

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

204654Orig1s000

PHARMACOLOGY REVIEW(S)

**Division of Reproductive and Urologic Products
Center for Drug Evaluation and Research**

Date: 5/16/2013

Reviewer: Alex Jordan, PhD

NDA #/SS#/date: 204654

Sponsor: Warner Chilcott

Drug Product: Norethindrone acetate/ethinyl estradiol/FE tablets

Indication: Contraception

Recommended Action: Approval

Background: I agree with the primary reviewer Dr. Raheja that NDA 204654 is approvable for contraception from a pharmacology standpoint.

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/s/

ALEXANDER W JORDAN
05/16/2013

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

PHARMACOLOGY/TOXICOLOGY NDA/BLA REVIEW AND EVALUATION

Application number: 204654
Supporting document/s: e-submission
Applicant's letter date: 9/27/2012
CDER stamp date: 9/28/2012
Product: Norethindrone acetate (NA) / Ethinyl estradiol
(EE)/FE tablets (b) (4)
Indication: Prevention of pregnancy
Applicant: Warner Chilcott
Review Division: RUDP
Reviewer: Krishan L. Raheja, D.V.M., Ph.D.
Supervisor/Team Leader: Alex Jordan, Ph.D.
Division Director: Hylton, Joffe, M.D. MMSc
Project Manager: Pamela K. Lucarelli

Review entered in DARRTS: 4/19/2013

Disclaimer

Except as specifically identified, all data and information discussed below and necessary for approval of NDA 204654 are owned by Warner Chilcott or are data for which Warner Chilcott has obtained a written right of reference. Any information or data necessary for approval of NDA 204654 that Warner Chilcott does not own or have a written right to reference constitutes one of the following: (1) published literature, or (2) a prior FDA finding of safety or effectiveness for a listed drug, as reflected in the drug's approved labeling. Any data or information described or referenced below from reviews or publicly available summaries of a previously approved application is for descriptive purposes only and is not relied upon for approval of NDA 204654.

1 Executive Summary

1.1 Introduction: This NDA provides for a new method of administration for a low dose oral contraceptive consisting of one chewable tablet containing 1 mg norethindrone acetate and 10 ug ethinyl estradiol ((b) (4) 1/10 chewable tablets) taken daily for 24 days followed by one tablet containing 10 ug ethinyl estradiol alone taken daily for 2 days, and one ferrous fumarate tablet taken daily for 2 days to facilitate 28-day regimen. (b) (4) 1/10 chewable tablets may be (b) (4) chewed before swallowing and followed with liquid; the 4 remaining tablets are swallowed. In lieu of nonclinical pharmacology and toxicology information, this application makes reference to sponsor's NDA 022501 approved on 10/20/2010 for Lo Loestrin Fe which consists of the same regimen and daily doses of active ingredients as in (b) (4) but in which all 28 tablets are swallowed.

1.2 Brief Discussion of Nonclinical Findings: All nonclinical pharmacology/toxicology information referred to sponsor's approved NDA 022501 for Lo Loestrin Fe.

1.3 Recommendations:

1.3.1 Approvability: Pharmacology/Toxicology recommends approval of (b) (4) under NDA 204654 for the indication of prevention of pregnancy

1.3.2 Additional Non Clinical Recommendations: None

1.3.3 Labeling: Sponsor has provided drug label in PLR format which is acceptable from the Pharmacology/Toxicology perspective.

2 Drug Information

2.1 Drug

CAS Registry Number (Optional)

For norethindrone acetate CAS number: 51-98-9

For ethinyl estradiol CAS number: 57-63-6

Generic Name: Norethindrone acetate, ethinyl estradiol, ferrous fumarate

Code Name: (b) (4)

Chemical Name:

For norethindrone acetate- 19-Norpregn-4-en-20-yn-3-one, 17-(acetyloxy- (17 α)
17-Hydroxy-19-nor-17 α -pregn-4-en-20-yn-3-one acetate

For ethinyl estradiol 19- Norpregna-1,3,5(10)-trien-20-yne-3,17-diol, (17 α)-
19-No-17 α -pregna-1,3,5(10)-trien-20-yne-3,17-diol

Molecular Formula/Molecular Weight

For norethindrone acetate- C₂₂ H₂₈ O₃ (340.46)

For ethinyl estradiol- C₂₀ H₂₄ O₂ (296.40)

Structure or Biochemical Description: Norethindrone acetate/ethinyl estradiol is an oral contraceptive.

Pharmacologic Class: Norethindrone acetate is a progestin and ethinyl estradiol is an estrogen

Relevant INDs, NDAs, BLAs and DMFs : NDA 022501 (Lo Loestrin, which has the same daily doses as (b) (4). DMF (b) (4) for norethindrone acetate USP); DMF (b) (4) for ethinyl estradiol; DMF (b) (4) (b) (4) for norethindrone acetate); DMF (b) (4) for ethinyl estradiol).

Warner Chilcott has also referred to their other approved NDAs using active ingredients as in (b) (4) tablets shown in table below:

Warner Chilcott NDAs Using Active Ingredients in (b) (4) Tablets

Inactive ingredients	Product	Regimen ^a NA(mg) / EE(mg)	Indication(s)
NDA 022501	Lo Loestrin Fe	1 / 0.10x 24 days 0 / 0.10 x 2 days	Prevention of pregnancy
NDA 21-871	Loestrin 24 Fe	1 / 0.020x 24 days	Prevention of pregnancy
NDA 17-876	Loestrin 21	1 / 0.020 x 21 days	Prevention of pregnancy
NDA 17-875	Loestrin 21 1.5/30	1.5 / 0.030 x 21 days	Prevention of pregnancy
NDA 17-354	Loestrin Fe	1 / 0.020 x 21 days	Prevention of pregnancy
NDA 17-355	Loestrin Fe 1.5/30	1.5 / 0.030 x 21 days	Prevention of pregnancy
NDA 20-130	Estrostep [®] Fe	1 / 0.020 x 5 days 1/ 0.030 x 7 days 1 / 0.035 x 9 days	Prevention of pregnancy
(b) (4)	Estrostep Fe	1 / 0.020 x 5 days 1/ 0.030 x 7 days 1/ 0.035 x 9 days	Prevention of pregnancy
NDA 21-065	Femhrt [®]	0.5 / 0.0025 x 28 days 1/ 0.005 x 28 days	Treatment of vasomotor symptoms Prevention of osteoporosis

2.3 Drug Formulation: Tablets

2.4 Comments on Novel Excipients: None

Inactive ingredients: All inactive ingredients in (b) (4) 1/10 chewable tablets, WC3016 EE10 tablets and ferrous fumarate tablets are described as either compendial or generally recognized as safe per 21 CFR regulations and are listed in the FDA Inactive Ingredients Database, which provides the maximum amount of inactive ingredient for each route/dosage form of FDA-approved drug products containing that ingredient. As shown in tables below, all inactive ingredients in (b) (4) 1/10 chewable tablets, WC3016 EE10 tablets and ferrous fumarate tablets have quantities equal to or below those listed in the database for a chewable oral tablet or an oral tablet.

Quantities of inactive ingredients in (b) (4) 1 /10 chewable tablets

Inactive ingredient	Quantity per (b) (4) 1/10 tablet (mg)	Maximum potency in FDA database (mg) ^a
Mannitol, USP (b) (4)	(b) (4)	(b) (4)
Mannitol, USP (b) (4)	(b) (4)	(b) (4)
Microcrystalline cellulose, NF (b) (4)	(b) (4)	(b) (4)
FD&C Blue No. 1 aluminum Lake		
Sodium starch glycolate, NF		
Magnesium stearate, NF		
Povidone, USP (b) (4)	(b) (4)	(b) (4)
Vitamin E, USP (b) (4)	(b) (4)	(b) (4)
Lactose monohydrate, NF, (b) (4)	(b) (4)	(b) (4)
Spearmint flavor		
Sucralose, NF		

a For an uncoated chewable tablet unless otherwise noted.

b maximum potency for an oral tablet (not available for an uncoated, chewable **tablet**)

Quantities of inactive ingredients in WC3016 EE10 tablets

Inactive ingredient	Quantity per WC3016 EE10 tablet (mg)	Maximum potency in FDA database ^a
Mannitol, USP (b) (4)	(b) (4)	(b) (4)
Mannitol, USP (b) (4)	(b) (4)	(b) (4)
Microcrystalline cellulose, NF (b) (4)	(b) (4)	(b) (4)
Sodium starch glycolate, NF		
Magnesium strearte, NF		
Povidone, USP (b) (4)	(b) (4)	(b) (4)
Vitamin E, USP (b) (4)	(b) (4)	(b) (4)
Lactose monohydrate, (b) (4)	(b) (4)	(b) (4)

^a for a tablet unless otherwise noted

Quantities of inactive ingredients in ferrous fumarate tablets

Inactive ingredient	Quantity per ferrous fumarate tablet (mg)	Maximum potency in FDA database (mg) ^a
Ferrous fumarate, USP	75.0	75
Mannitol, USP (b) (4)	(b) (4)	(b) (4)

Povidone, USP	(b) (4)	(b) (4)	(b) (4)
Microcrystalline cellulose, NF	(b) (4)	(b) (4)	(b) (4)
(b) (4)	(b) (4)	(b) (4)	(b) (4)
Sodium starch glycolate, NF	(b) (4)	(b) (4)	(b) (4)
Magnesium stearate, NF	(b) (4)	(b) (4)	(b) (4)
Sucralose, NF	(b) (4)	(b) (4)	(b) (4)
Spearmint flavor	(b) (4)	(b) (4)	(b) (4)

^a for an oral tablet unless otherwise specified

^b maximum potency for povidone (b) (4)

2.5 Comments on Impurities/Degradants of Concern: None

2.6 Proposed Clinical Population and Dosing Regimen: Clinical population will include women who want to use low dose COC. The dosing regimen consists of a chewable tablet containing 1 mg NA and 10 ug EE taken daily for 24 days followed by one tablet containing 10 ug EE alone taken daily for 2 days, and one ferrous fumarate tablet (placebo) taken daily for 2 days to complete 28-day regimen.

2.7 Regulatory Background: -

3 Studies Submitted: None. All referred to NDA 022501 for Lo Loestrin Fe.

12 Appendix/Attachments: None

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/s/

KRISHAN L RAHEJA
04/19/2013

ALEXANDER W JORDAN
04/19/2013

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

NDA Number: 204654

Date: 10-11-2012

Drug Name: Norethindrone acetate/EE/FE (b)(4)

Reviewer: Krishan L. Raheja

Sponsor: Warner Chilcott

Date CDER Received: 9-28-2012

Filing Date: 11-12-2012

User Fee Date: 7-28-2013

Expected Date of Draft Review: 3-15-2013

On initial overview of the Pharm/Tox portion of the NDA application

	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?		This NDA provides for a new method of administration for low dose OC consisting of one chewable tablet containing 1 mg NETA and 10 ug EE (b)(4) 1/10) taken daily for 24 days followed by one tablet containing 10 ug EE alone taken daily for 2 days, and one ferrous fumarate tablet taken daily for 2 days to facilitate 28-day regimen. (b)(4) 1/10 chewable tablets may be (b)(4) chewed before swallowing and followed with liquid; the 4 remaining tablets are swallowed. In leu of nonclinical pharmacology and toxicology information, this application makes reference to sponsor's NDA 022501 approved on 10/20/2010 for Lo Loestrin Fe which consists of the same regimen and daily doses of active ingredients as in (b)(4) but in which all 28 tablets are swallowed.
2)	Is the Pharm/Tox section of the NDA indexed and paginated in a manner to allow substantive review to begin?	NA	
3)	On its face, is the Pharm/Tox section of the NDA legible so that substantive review can being? Has the data been presented in an appropriate manner?	NA	
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?	NA	

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	
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?	NA	
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	
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	
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 ² or comparative serum/plasma AUC levels?	Yes Yes NA	
10)	From a Pharm/Tox perspective, is this NDA fileable? If not, please state in item #11 below why it is not.	YES	
11)	Reasons for refusal to file:		

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/s/

KRISHAN L RAHEJA
10/15/2012

ALEXANDER W JORDAN
10/15/2012