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RESEARCH**

APPLICATION NUMBER:

204426Orig1s000

PHARMACOLOGY REVIEW(S)

**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: 204426
Supporting document/s: e-submission
Applicant's letter date: 6-21-2012
CDER stamp date: 6-21-2012
Product: Norethindrone acetate/ethinyl estradio/Fe
Indication: Prevention of Pregnancy
Applicant: Warner Chilcott
Review Division: Reproductive and Urologic Products
Reviewer: Krishan L. Raheja, D.V.M. Ph.D.
Supervisor/Team Leader: Alex Jordan, Ph.D.
Division Director: Hylton, Joffe, M.D., M.M.Sc.
Project Manager: Pamela K. Lucarelli

Review entered in DARRTS: 11/23/2012

Disclaimer

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1 Executive Summary

1.1 Introduction: This NDA application for norethindrone acetate (NA) and ethinyl estradiol (EE) soft gelatin capsules, and ferrous fumarate soft gelatin capsules provides for a new dosage form for oral contraception consisting of one soft gelatin capsule of 1 mg NA and 0.020 mg EE taken daily for 24 days followed by one ferrous fumarate (placebo) soft gelatin capsule taken daily for 4 days to facilitate a 28-day regimen. The proposed dosing regimen under this NDA and consequently the exposure to NA and EE, is the same as the approved regimen for Warner Chilcott's Loestrin[®] 24 Fe, approved on 2/17/2006 under NDA 21-871, which had the same amount of active ingredients, NA and EE and of placebo ferrous fumarate as tablets. For nonclinical pharmacology and toxicology sponsor has cross referenced NDA 21-871 to support approval of present NDA 204426.

To further support the safety of active ingredients used under present NDA 204426, sponsor has provided reference to various sponsor's approved NDAs as shown in table below:

Warner Chilcott NDA	Product	Regimen ^a NA (mg)/EE (mg)	Indication(s)
NDA 21-871	Loestrin 24 Fe	1/0.020 x 24 days	Prevention of pregnancy
NDA 17-876		1/0.020 x 21	Prevention of pregnancy
NDA 17-875	Loestrin 21 1.5/0.030	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
NDA 21-276	Estrostep Fe	1/ 0.020 x 5 days 1 / 0.030 x 7 days 1 / 0.035 x 9 days	Treatment of acne
NDA 21-065	femhrt [®]	0.5 / 0.0025 x 28 days 1 / 0.005 x 28 days	Treatment of vasomotor symptoms Prevention of osteoporosis

^a Per 28-cycle; in some products placebo reminder pills complete the 28-day regimen

1.2 Brief Discussion of Nonclinical Findings: No new nonclinical data is submitted and pharmacology and toxicology is referenced to sponsor's approved NDA 21-871. Moreover, it is stated that both NA and EE are synthetic hormones which are widely used as components of both combined oral contraceptives (COCs) and hormone replacement therapy. Also daily doses of NA and EE proposed under present application are found in currently approved COCs. The inactive ingredients used in active capsules and in the ferrous fumarate capsules are compendial and are listed in the FDA's Inactive Ingredients Database.

1.3 Recommendations:

1.3.1 Approvability: Pharmacology/Toxicology recommends approval of NDA 204426 as a COC for prevention of pregnancy.

1.3.2 Additional Non Clinical Recommendations: None

1.3.3 Labeling: Sponsor has submitted Draft Labeling

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 and ethinyl estradiol capsules and ferrous fumarate capsules

Indication: Prevention of pregnancy

Dosage form: Capsule, soft gelatin

Route of administration: Oral

Code Name: WC3042

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

Chemical name: For ethinyl estradiol

19-Norpregna-1,3,5(10)-trien-20-yne-3,17-diol, (17 α)-
19-Nor-17 α -pregna-1,3,5(10)-trien-20-yne-3,17-diol.

Molecular Formula/Molecular Weight

Norethindrone acetate- C₂₂H₂₈O₃ (340.46)

Ethinyl estradiol- C₂₀H₂₄O₂ (296.40)

Structure or Biochemical Description: Norethindrone acetate is a nor-testosterone derivative and ethinyl estradiol is a synthetic estrogen.

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

2.2 Relevant INDs, NDAs, BLAs and DMFs: NDA 21-871 for Loestrin 24 Fe, (b) (4) DMF (b) (4) for norethindrone acetate, (b) (4) DMF (b) (4) for ethinyl estradiol

2.3 Drug Formulation and dosing regimen: This application provides for a new dosage form for oral contraception consisting of one soft gelatin capsule containing 1 mg NA and 0.020 mg EE taken daily for 24 days followed by one ferrous fumarate soft gelatin capsule taken daily for 4 days for a 28-day regimen. The proposed formulation is the same as the approved regimen for sponsor's Loestrin 24 Fe tablet formulation approved as an oral contraceptive on 2/17/2006 under NDA 21-871.

2.4 Comments on Novel Excipients: There are no novel excipients in the proposed formulation.

2.5 Comments on Impurities/Degradants of Concern: None described. The quantity (mg/capsule) of the inactive ingredients (b) (4) in the oral soft gelatin NA and EE capsules, which include sesame oil, NF; linoleoyl (b) (4) glycerides, NF; (b) (4) and dehydrated alcohol, USP are below the maximum potency found in previously in soft gelatin capsules and that given in the FDA Inactive Ingredient Database for soft gelatin capsule.

Similarly the quantity (mg/capsule) of the inactive ingredients (b) (4) in ferrous fumarate soft gelatin capsule which include ferrous fumarate, USP; soybean oil, NF; lecithin, NF and yellow wax, NF are below the maximum potency in FDA Inactive Ingredients Database for oral soft gelatin capsule.

2.6 Proposed Clinical Population and Dosing Regimen: Proposed clinical population includes women who prefer to use the proposed NA/EE formulation for contraception. The dosing regimen consists of taking one soft gelatin capsule containing 1 mg norethindrone acetate (NA) and 0.020 mg ethinyl estradiol (EE) (WC3042-05 active capsules) taken daily for 24 days followed by one ferrous fumarate capsule (WC4032-08P0 (placebo) taken daily for 4 days.

2.7 **Regulatory Background:** Warner-Chilcott has number of approved and under review submissions which have the same active and inactive ingredients as in the present NDA 204426. As such sponsor has stated that in lieu of nonclinical pharmacology and toxicology information, this application makes reference to Warner-Chilcott's NDA 21-871 for Loestrin[®] 24 Fe (norethindrone acetate and ethinyl estradiol tablets, USP and ferrous fumarate tablets) and addresses the safety of the inactive ingredients by showing that the quantity of inactive ingredients is below the maximum potency outlined in FDA's Inactive Ingredients Database.

3 Studies Submitted: None

12 Appendix/Attachments: None

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/s/

KRISHAN L RAHEJA
11/23/2012

ALEXANDER W JORDAN
11/23/2012

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

NDA Number: 204426

Date: 7/9/2012

Drug Name: Norethindrone acetate/ethinyl estradiol

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

Soft gelatin capsules & ferrous fumarate soft gelatin capsules (WC3042)

Sponsor: Warner Chilcott (US), LLC, Rockaway, NJ

Date CDER Received: 6/21/2012

Filing Date: 8/5/2012

User Fee Date:

Expected Date of Draft Review: 11/1/2012

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

ITEM	YES / NO	COMMENTS
1)		This submission is for a new dosage form for oral contraception consisting of one soft gelatin capsule containing 1 mg NA and 0.020 mg EE, taken daily for 24 days followed by one ferrous fumarate soft gelatin capsule taken daily for 4 days to complete 28-day regimen. The proposed regimen, and the exposure to NA and EE is the same as approved regimen for Warner Chilcott's Loestrin 24Fe which has the same dosage for NA, EE and ferrous fumarate in tablet formulation, approved under NDA 21-871. No nonclinical Pharm//Tox studies have been conducted under present NDA and are instead referred to their approved NDA 21871.
2)	NA	
3)	NA	
4)	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?		No preclinical toxicology studies using proposed capsule formulation have been conducted. Sponsor however, has conducted bioequivalence studies, which show that NA/EE in capsules are bioequivalent to Loestrin 24 Fe tablets.
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
07/09/2012

ALEXANDER W JORDAN
07/09/2012