

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**203667Orig1s000**

**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: NDA 203667 Original submission  
Supporting document/s: e-submission  
Applicant's letter date: 7/9/2012  
CDER stamp date: 7/9/2012  
Product: Norethindrone acetate/ethinyl estradiol  
Indication: Prevention of pregnancy  
Applicant: Warner Chilcott, Rockaway, NJ  
Review Division: RUDP  
Reviewer: Krishan L. Raheja, D.V.M., Ph.D.  
Supervisor/Team Leader: Alex Jordan, Ph.D.  
Division Director: Hylton,Jeffe, M.D. MMS  
Project Manager: Maria Wasilik,

*Entered in DARRTS: 3/1/2013*

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Except as specifically identified, all data and information discussed below and necessary for approval of NDA 203667 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 203667 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 203667

# 1 Executive Summary

## 1.1 Introduction

This NDA is for a new method of administration for oral contraception consisting of one chewable tablet containing 1 mg norethindrone acetate and 0.020 mg ethinyl estradiol (formulation WC3040-1F) taken daily for 24 days followed by one ferrous fumarate (placebo) tablet taken daily for 4 days. Tablets may be chewed (followed with liquid) or swallowed.

Norethindrone acetate and ethinyl estradiol are synthetic hormones used widely as components of combination oral contraceptives and hormone therapy products. Doses of these ingredients are similar to those for currently approved oral contraceptives.

## 1.2 Brief Discussion of Nonclinical Findings

In lieu of nonclinical pharmacology and toxicology information, the sponsor has made reference to their NDA 21-871 for Loestrin® 24 Fe (norethindrone acetate and ethinyl estradiol tablets, USP and ferrous fumarate tablets), and has addressed the safety of the inactive ingredients by showing that the quantity of inactive ingredients used in the manufacture of tablets is below the maximum concentration outlined in FDA's Inactive Ingredients Database or otherwise that inactive ingredients are generally recognized as safe per 21 CFR regulations.

## 1.3 Recommendations

**1.3.1 Approvability:** From the Pharmacology/Toxicology viewpoint, NDA 203667 is recommended for approval.

**1.3.2 Additional Non Clinical Recommendations:** None. The pharmacology and toxicology of the active ingredients in WC3040 tablets are well documented in the NDAs for the Warner Chilcott products listed in table below:

Table-1

Warner Chilcott NDA	Product	Regimen <sup>a</sup> NA (mg)/EE (mg)	Indication(s)
NDA 21-871	Loestrin 24 Fe	1/0.020 x 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
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

<sup>a</sup> Per 28-day cycle; in some products placebo reminder pills complete the 28-day cycle.

**1.3.3 Labeling:** Labeling for Carcinogenesis, Mutagenesis, Impairment of Fertility; Pregnancy and Nursing Mothers will be identical to the label for Loestrin<sup>®24</sup> Fe. Label has not been reviewed yet.

## 2 Drug Information

### 2.1 Drug

CAS Registry Number (Optional)

Generic Name: Norethindrone acetate and ethinyl estradiol

Code Name: WC3040-1F

Chemical Name for norethindrone acetate is as given below:

[19-Norpregn-4-en-20yn-3-one, 17-(acetyloxy)- (17 $\alpha$ )-]

Molecular formula is: C<sub>22</sub>H<sub>28</sub>O<sub>3</sub>

Molecular weight is: 340.47

Chemical name for ethinyl estradiol is as given below:

19 Nor-1,3,5 (10), 17 $\alpha$ -pregnatriene-20-yne-3, 17-diol

Molecular formula is: C<sub>20</sub>H<sub>24</sub>)<sub>2</sub>

Molecular weight is: 296.40

Structure or Biochemical Description: Norethindrone acetate and ethinyl estradiol are synthetic hormones which act as contraceptives by suppressing gonadotropins secretion. The primary effect of this action is inhibition of ovulation primarily mediated by

the progestin component of the combination. Other mechanisms involve thickening of cervical mucus, which hinders sperm's penetration and thinning of the endometrium which hinders implantation. The concomitant administration of estrogen allows regular withdrawal bleeding and less breakthrough bleeding.

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

**2.2 Relevant INDs, NDAs, BLAs and DMFs:** The referred NDA 21-871 and other NDAs described in table 1.

### 2.3 Drug Formulation: Tablet

Composition of WC3040-1F chewable tablets is given in table 2 below:

Table-2

Component	Quality standard	Function	Quantity (mg/tablet)
Norethindrone acetate	USP	Active pharmaceutical ingredient	1.00
Ethinyl estradiol	USP	Active pharmaceutical ingredient	0.02
Acacia (b) (4)	NF	(b) (4)	(b) (4)
Lactose monohydrate	NF		
Magnesium stearate	NF		
Starch	NF		
Confectioner's sugar	NF		
Talc (b) (4)	USP		

Composition of the ferrous fumarate tablets is given in table 3 below:

Table-3

Component	Quality standard	Function	Quantity (mg/ tablet)
Ferrous fumarate	USP	Primary component	75.0
Mannitol (b) (4)	USP	(b) (4)	(b) (4)
Povidone (b) (4)	USP		
Microcrystalline cellulose (b) (4)	NF		
Sodium starch	NF		

glycolate		(b) (4)
Magnesium stearate	NF	
Sucralose	NF	
Spearmint flavor	In-house	
(b) (4)		

Quantities of inactive ingredients and corresponding FDA maximum concentration are given in table 4 below:

Table-4

Inactive ingredient	Quantity per WC3040-1F active tablet (mg)	Maximum concentration in FDA database (mg) <sup>a</sup>
Acacia (b) (4), NF	(b) (4)	(b) (4)
(b) (4) monohydrate, NF		
Magnesium stearate, NF		
Starch, NF		
Confectioner's sugar, NF		
Talc (b) (4) USP		

<sup>a</sup> For an uncoated, oral chewable tablet.

**2.4 Comments on Novel Excipients:** There are no novel excipients

**2.5 Comments on Impurities/Degradants of Concern:** None described

## 2.6 Proposed Clinical Population and Dosing Regimen

One chewable tablet containing 1 mg norethindrone acetate and 0.020 mg ethinyl estradiol (formulation WC3040-1F) taken daily for 24 days followed by one ferrous fumarate (placebo) tablet taken daily for 4 days. Tablets may be chewed (followed with liquid) or swallowed.

**2.7 Regulatory Background:** -

**3 Studies Submitted:** None

**12 Appendix/Attachments:** None

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/s/  
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KRISHAN L RAHEJA  
03/01/2013

ALEXANDER W JORDAN  
03/01/2013

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

**NDA Number: 203667**

**Date: 7-12-2012**

**Drug Name: Norethindrone acetate (NA)/EE/Fe**

**Reviewer: Krishan L. Raheja**

**Sponsor: Warner Chilcott**

**Date CDER Received: 7-9-2012**

**Filing Date: 8-28-2012**

**User Fee Date:**

**Expected Date of Draft Review: 1-15-2013**

**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?	NA  This NDA seeks approval of a new method of administration for oral contraception consisting of one chewable tablet containing 1 mg NA and 0.020 mg EE taken daily for 24 days followed by one ferrous fumarate tablet taken daily for 4 days by which WC3040 active tablets may be chewed (followed with liquid or swallowed.  In lieu of nonclinical pharmacology and toxicology information, sponsor has made reference to Warner Chilcott approved NDA 21871 for Loestrin 24 FE (NA and EE tablets & ferrous fumarate tablets), which has the same amount of active ingredients and dosing regimen as for the proposed NDA formulation. Moreover, the nonclinical pharmacology and toxicology of NA and EE is well established in the literature.
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 begin? 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?		The formulation to be marketed under the proposed NDA is similar to that of sponsor's approved NDA 21871 except for the new method of administration.
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 <sup>2</sup> 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/  
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07/25/2012

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07/25/2012