

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:
022573Orig1s000

PHARMACOLOGY REVIEW(S)



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

PHARMACOLOGY/TOXICOLOGY REVIEW AND EVALUATION

NDA NUMBER: 022573
SERIAL NUMBER: 000
DATE RECEIVED BY CENTER: 11/25/09
PRODUCT: (b) (4) (Norethindrone and ethinyl estradiol)
chewable and ferrous fumarate tablets
INTENDED CLINICAL POPULATION: Prevention of pregnancy
SPONSOR: Warner Chilcott Company, LLC
DOCUMENTS REVIEWED: Electronic submission
REVIEW DIVISION: Division of Reproductive and Urologic
Products (HFD-580)
PHARM/TOX REVIEWER: Krishan L. Raheja, D.V.M., Ph.D.
PHARM/TOX SUPERVISOR: Alex Jordan, Ph.D.
DIVISION DIRECTOR: Scott Monroe, M.D.
PROJECT MANAGER: Pamela K. Lucarelli

Date of review submission to Division File System (DFS): 1-21-2010

EXECUTIVE SUMMARY

I. Recommendations

- A. Recommendation on approvability: Pharmacology/toxicology recommends approval of NDA 022573 for contraception.
- B. Recommendation for nonclinical studies: The nonclinical pharmacology and toxicology of norethindrone and ethinyl estradiol are cross-referenced to Warner Chilcott's approved NDA 17-576 for Ovcon® 50 (norethindrone and ethinyl estradiol tablets, USP); the approved Ovcon 50 regimen includes the administration of 21 active tablets each containing the combination of 1 mg NE and 0.05 mg EE. The nonclinical pharmacology and toxicology of the inactive ingredients in (b) (4) are addressed by showing that the quantity of each inactive ingredients used in the manufacture of the tablets is below the maximum potency outlined in FDA's Inactive Ingredients Database or otherwise that the inactive ingredient is generally recognized as safe per 21 CFR regulations.
- C. Recommendations on labeling: Draft labeling is in accordance with PLR and provided in SPL format.

II. Summary of nonclinical findings

- A. Brief overview of nonclinical findings: In lieu of nonclinical pharmacology and toxicology information on the active ingredients in (b) (4), norethindrone and ethinyl estradiol, the sponsor has made reference to Warner Chilcott's NDA 17-576 for Ovcon (norethindrone 1 mg and ethinyl estradiol 50 ug tablets, USP) which received FDA approval on August 28, 1975. Sponsor has stated that NDA 17-576 is annually updated with relevant published abstracts obtained from the nonclinical and clinical literature.
- B. Pharmacologic activity: Norethindrone and ethinyl estradiol exhibit progestogenic and estrogenic activities, respectively.
- C. Nonclinical safety issues relevant to clinical use: None

2.6 PHARMACOLOGY/TOXICOLOGY REVIEW

2.6.1 INTRODUCTION AND DRUG HISTORY

NDA number: 02573

Review number: 1

Sequence number/date/type of submission: 000/11-25-09/ original submission

Information to sponsor: Yes () No ()

Sponsor and/or agent: Warner Chilcott Company, LLC

Manufacturer for drug substance: (b) (4)

for both ethinyl estradiol and norethindrone.

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

Division name: Reproductive and Urologic Products

HFD #: 580

Review completion date: 1-20-2010

Drug:

Trade name: (b) (4)

Generic name: Norethisterone and ethinyl estradiol

Code name: WC3026

Chemical name for norethisterone: 17-hydroxy-19-nor-17 α -pregn-4-en-20-yn-3-one

CAS registry number: 68-22-4

Molecular formula/molecular weight: C₂₀H₂₆O₂/298.41

Structure:

Chemical name for ethinyl estradiol: 19-norpregna-1,3,5(10)-trien-20-yne-3,17-diol, (17 α)- or
19-nor-17 α -pregna-1,3,5(10)-trien-20-yne-3,17-diol

CAS registry number: 57-63-6

Molecular formula/molecular weight: C₂₀H₂₄O₂/296.40

Structure:

Relevant INDs/NDAs/DMFs: IND 76,629; NDA17-576; DMFs (b) (4), respectively for ethinyl estradiol and norethindrone and DMF (b) (4), respectively for ethinyl estradiol and norethindrone.

Drug class: Norethindrone is a progestin and ethinyl estradiol is an estrogen

Intended clinical population: For prevention of pregnancy

Clinical formulation: Tablets.

Dosing regimen: WC3026 is a 28-tablet oral contraceptive regimen consisting of 24 tablets of WC3026-5C tablets (norethindrone, 0.8 mg and ethinyl estradiol, 25 ug/tablet) and 4 tablets of ferrous fumarate tablets (containing 75 mg of ferrous fumarate per tablet)

Quantitative composition of the WC3026-5C tablets is given in table below:

| Components | Function | mg/tablet | %w/w |
|--|----------------------------------|--------------|---------|
| EE (b) (4) | Active pharmaceutical ingredient | (b) (4) | (b) (4) |
| Norethindrone, USP | Active pharmaceutical ingredient | 0.80 | (b) (4) |
| Mannitol, USP (b) (4) | | | (b) (4) |
| Mannitol, USP (b) (4) | | | (b) (4) |
| Microcrystalline cellulose, NF (b) (4) | | | (b) (4) |
| FD&C Yellow # 6 Aluminum Lake | | | (b) (4) |
| FD7C Blue # 1 Aluminum Lake | | | (b) (4) |
| D&C Yellow # 10 (b) (4) | | | (b) (4) |
| Spearmint Flavor (b) (4) | | | (b) (4) |
| Sodium Starch Glycolate, NF | | | (b) (4) |
| Sucralose, NF | | | (b) (4) |
| Magnesium stearate, NF | | | (b) (4) |
| Total | | 70.00 | (b) (4) |

Composition of the ethinyl estradiol (b) (4) is given in table below:

| Component | Function | % w/w |
|-------------------------------------|----------------------------------|---------|
| Ethinyl estradiol, USP ¹ | Active pharmaceutical ingredient | (b) (4) |
| (b) (4) | | |

(b) (4)

Quantities of excipients in ferrous fumarate tablets in comparison to maximum potency in FDA database is given in table below:

| Excipient | Quantity per ferrous fumarate tablet (mg) | Maximum potency in FDA database (mg) |
|-------------------------------|---|--------------------------------------|
| Ferrous fumarate, USP | 75.0 | 75.0 |
| Mannitol, USP | (b) (4) | 600.0 |
| Povidone, USP (b) (4) | (b) (4) | 10.0 |
| Microcrystallin cellulose, NF | (b) (4) | 570.0 |
| Sodium starch glycolate, NF | (b) (4) | 50.0 |
| Mgnesium stearate, NF | (b) (4) | 50.0 |
| Sucralose, NF | (b) (4) | 1 88 |
| Spearmint flavor (b) (4) | (b) (4) | N/A for chewable tablets |

Impurities

The following related substances of ethinyl estradiol are monitored by (b) (4)

:
[Redacted]

[Redacted] (b) (4)

Route of administration: Oral

Disclaimer: Tabular and graphical information are constructed by the reviewer unless cited otherwise.

Data reliance : Except as specifically identified below, all data and information discussed below and necessary for approval of NDA 22-573 are owned by Warner-Chilcott Company or are data for which Warner Chilcott Company has obtained a written right of reference. Any information or data necessary for approval of NDA 22-573 that Warner Chilcott Company 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 described in the drug's approved labeling. Any data or information described or referenced below from a previously approved application that Warner Chilcott Company does not own (or from FDA reviews or summaries of a previously approved application) is for descriptive purposes only and is not relied upon for approval of NDA 22-573.

Studies reviewed within this submission: None. All nonclinical pharmacology and toxicology of ethinyl estradiol and norethindrone are well established in the literature and documented in Warner Chilcott's NDA 17-576 for Ovcon® 50 (norethindrone and ethinyl estradiol tablets, USP), 28-Day. Therefore, reference is made to NDA 17-576.

Studies not reviewed within this submission: -

OVERALL CONCLUSIONS AND RECOMMENDATIONS

Conclusions: Norethindrone (NE) and ethinyl estradiol (EE) are well known chemical entities used for decades in combination oral contraceptives and hormone therapy products. The nonclinical pharmacology and toxicology of NE and EE, the active ingredients in (b) (4) (WC2036-5C) tablets, are documented in Warner Chilcott's approved NDA 17-576 for Ovcon® 50 (norethindrone and ethinyl estradiol tablets, USP),

28 day. Ovcon 50 contains 1.0 mg NE and 0.05 mg EE administered over 21 days followed by 7 placebo tablets. The daily and per 28-day cycle doses of NE and EE found in Ovcon 50 are higher than those in (b)(4) and establishes the safety of WC3026-5C tablets. The safety of inactive ingredients is established by the fact that each of the inactive ingredients are found in similar or higher amounts in previously approved oral tablets or are otherwise generally recognized as safe in accordance with 21 CFR regulations.

Unresolved toxicology issues (if any): None

Recommendations: Pharmacology recommends approval of NDA 22-573 for the sponsor's proposed indication for prevention of pregnancy.

Suggested labeling: Suggested draft labeling is presented in accordance with PLR and provided in SPL format and is acceptable.

Application
Type/Number

Submission
Type/Number

Submitter Name

Product Name

NDA-22573

ORIG-1

WARNER
CHILCOTT INC

(b) (4) (norethindrone and ethinyl
estradiol tablets, chewable and
ferrous fumarate tablets)

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/s/

KRISHAN L RAHEJA
01/22/2010

ALEXANDER W JORDAN
01/22/2010