CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

022501Orig1s000

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:	22-501
SERIAL NUMBER:	000
DATE RECEIVED BY CENTER:	3/26/09
PRODUCT:	(b) (4)
INTENDED CLINICAL POPULATION:	Prevention of pregnancy
SPONSOR:	Warner Chilcott Company Inc. Fajardo, PR
DOCUMENTS REVIEWED:	Vol. 1.1 – 1.3
REVIEW DIVISION:	Division of Reproductive and Urologic products (HFD- 580)
PHARM/TOX REVIEWER:	Krishan L. Raheja, D.V.M., Ph.D.
PHARM/TOX SUPERVISOR:	Lynnda Reid, Ph.D.
DIVISION DIRECTOR:	Scott Monroe, M.D.
PROJECT MANAGER:	Karl Stiller

Date of review submission to Division File System (DFS): 6-15-09

EXECUTIVE SUMMARY

I. Recommendations

A. Recommendation on approvability: Pharmacology/toxicology data support approval of NDA 22-501 for [redacted] (b) (4) for contraception.

B. Recommendation for nonclinical studies: All pharmacology/toxicology data were reviewed under the sponsor's approved NDA 21-871 for Loestrin® 24 Fe (norethindrone acetate and ethinyl estradiol tablets, USP and ferrous fumarate tablets) for the contraception indication.

C. Recommendations on labeling: As required the Labeling is in accordance with PLR and provided in SPL format.

II. Summary of nonclinical findings:

A. Brief overview of nonclinical findings: There are no new nonclinical findings. The safety of norethindrone acetate and ethinyl estradiol at concentrations of 1.0 mg and 0.010 mg, respectively, have been established in previously conducted nonclinical and clinical studies.

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

C. Nonclinical safety issues relevant to clinical use: None

2.6 PHARMACOLOGY/TOXICOLOGY REVIEW

2.6.1 INTRODUCTION AND DRUG HISTORY

NDA number: 22-501
Review number: 1
Sequence number/date/type of submission: 000/3-25-09/original submission
Information to sponsor: Yes ( ) No (*)
Sponsor and/or agent: Warner Chilcott Company Inc. Fajardo, Pueto Rico/
Warner Chilcott (US), LLC Rockaway, New Jersey

Manufacturer for drug substance: Norethindrone acetate and Ethinyl estradiol by (b) (4) (b) (4).

Reviewer name: Krishan L. Raheja, D.V.M., Ph.D.
Division name: Reproductive and Urologic Products
HFD #: 580
Review completion date: 5-5-09

Drug:

Trade name: (b) (4)
Generic name: Norethindrone acetate (NA) and ethinyl estradiol (EE)
(1 mg NA/10 ug EE, 10 ug EE) tablets
Code name: -
Chemical name, CAS registry number and molecular formula/molecular weight are provided in the following table:

Drug	Chemical name	CAS Registry No.	Emperical formula	Molecular weight
Norethindrone acetate	19-Norpregn-4-en-20-yn-3-one, 17-(acetyloxy)-, (17α)	51-98-9	$C_{22}H_{28}O_3$	340.46
Ethinyl estradiol	19-Norpregna-1,3,5(10)-trien-20-yne—3,17-diol, (17α)-	57-63-6	$C_{20}H_{24}O_2$	296.40

Relevant INDs/NDAs/DMFs: IND 73,510; NDA 21-871

Drug class: Norethindrone acetate, a progestin and Ethinyl estradiol, an estrogen

Intended clinical population: Prevention of pregnancy

Clinical formulation: Tablets

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 22-501 are owned by Warner Chilcott Company Inc. or are data for which Warner Chilcott Company Inc. has obtained a written right of reference. Any information or data necessary for approval of NDA 22-501 that Warner Chilcott, Inc. 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, Inc. 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 22-501.

Studies reviewed within this submission: None. All pharmacology/toxicology studies were referenced to the sponsor's approved NDA 21-871 for Loestrin ® 24 (norethindrone acetate/ethinyl estradiol) tablets for contraception.

Studies not reviewed within this submission: none

OVERALL CONCLUSIONS AND RECOMMENDATIONS

Conclusions: There are no safety concerns as the sponsor's product Loestrin® 24 has been previously approved for contraception under NDA 21-871. Both products have the same active ingredients. The amount of norethindrone acetate is 1 mg/tablet for both Loestrin® 24 and (b) (4) However, while the amount of ethinyl estradiol is 20 ug/tablet in the approved Loestrin® 24, it is reduced to 10 ug under NDA 22-501. The dosing regimen for both formulations consists of continuous dosing for 24 consecutive days followed by 4 days on placebo tablets containing 75 mg ferrous fumarate. The safety of inactive ingredients in (b) (4) is established by showing that the quantity of inactive ingredients used in the manufacture of tablets is below the maximum potency outlined in FDA's Inactive Ingredients Database or otherwise that the inactive ingredients are generally recognized as safe per 21 CFR regulations.

Unresolved toxicology issues (if any): None

Recommendations: Pharmacology /toxicology data support approval of NDA 22-501.

Suggested labeling: Suggested Labeling is in accord with PLR and provided in SPL format. Section No. 13 Nonclinical toxicology and 13.1 Carcinogenesis, Mutagenesis and Impairment of Fertility were not included in the draft labeling, which is mandatory and needs to be included. Sponsor will need to provide recommended labeling consistent with other combined oral contraceptives.

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