

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

203667Orig1s000

STATISTICAL REVIEW(S)

Memorandum of Statistical Review

NDA Number: 203667 / Supporting Document # 000

Drug Name: Norethindrone acetate (NA) 1 mg and ethinyl estradiol (EE) 0.02 mg chewable tablets and ferrous fumarate (FE) 75 mg tablets

Indication(s): Prevention of pregnancy

Applicant: Warner Chilcott Co., LLC

Date(s): Letter Date: July 9, 2012 PDUFA Date: May 9, 2013

Review Priority: 1 Standard

Biometrics Division: Division of Biometrics 3

Biometrics Reviewer: Sonia Castillo, Ph.D.

Biometrics Team Leader: Mahboob Sobhan, Ph.D.

Medical Division: Division of Reproductive and Urologic Drug Products

Clinical Team: Gerald Willett, M.D., Medical Reviewer
Lisa Soule, M.D., Team Leader

Project Manager: Jennifer Mercier

Key Words: NDA review

This submission is for a new method of administration by which norethindrone acetate (NA) and ethinyl estradiol (EE) and ferrous fumarate (FE) tablets may be swallowed or chewed. The approved regimen for Warner Chilcott's Loestrin® 24 Fe (NE and EE tablets, USP and ferrous fumarate tablets) is for swallowed pills. This submission is based on studies to show bioequivalence of the chewed regimen to the currently approved swallowed regimen. These bioequivalence studies are reviewed by the Clinical Pharmacology team. There are no new efficacy issues to address in this application, so no statistical review of efficacy is necessary.

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/s/

SONIA CASTILLO
12/13/2012

STATISTICS FILING CHECKLIST FOR A NEW NDA

NDA Number: 203667 / Supporting Doc. 000

Applicant: Warner Chilcott Co., LLC

Drug Name: Norethindrone acetate (NA) 1 mg and ethinyl estradiol (EE) 0.02 mg chewable tablets and ferrous fumarate (FE) 75 mg tablets

Indication: Prevention of pregnancy

NDA Type: Standard

Stamp Date: 7-9-2012

According to the Applicant's cover letter:

The Application provides for a new method of administration for oral contraception by which norethindrone acetate (NA)/ethinyl estradiol (EE) tablets may be swallowed or chewed followed with liquid. The regimen consists of one active tablet containing 1 mg NA and 0.020 mg EE taken daily for 24 days followed by one ferrous fumarate tablet (placebo) taken daily for 4 days to facilitate a 28-day regimen. The proposed regimen, and consequently the exposure to norethindrone and EE, is the same as the approved regimen for Warner Chilcott's Loestrin® 24 Fe (norethindrone acetate and ethinyl estradiol tablets, USP and ferrous fumarate tablets) which received approval as an oral contraceptive on February 17, 2006 under NDA 21-871; the active tablets in Loestrin 24 Fe are referred to in this Application as WC2061 tablets. The Application contains results of Study PR-08507 (Report RR-00508) which show that WC2061 tablets swallowed (the currently approved method of administration for Loestrin 24 Fe) are bioequivalent to WC2061 tablets chewed ...

The safety and efficacy of NA and EE in the prevention of pregnancy is documented in NDA 21-871 for Loestrin 24 Fe. Reference is made therefore to NDA 21-871 in Section 1.4.4 Cross Reference to Other Applications. To support the oral safety of chewing active tablets containing 1 mg NA, this Application contains the results of Study PR-10007 / Report RR-01708, an oral irritation study conducted with WC2061 tablets chewed daily for 24 days ... Results of a comparative bioavailability study (Study PR-07411 / Report RR-00112) conducted with an alternate formulation are submitted for completeness of safety information; however, approval of this other formulation is not sought in this Application.

Based on the information cited above and after discussion with the clinical reviewer, there are no new efficacy issues to address in this application. Therefore, no statistical review of efficacy is necessary and there are no statistical requests to the Applicant for the 74-day letter.

On **initial** overview of the NDA application for RTF:

	Content Parameter for RTF	Yes	No	NA
1A	Paper Submission			X
1B	Electronic Submission: Indexing and reference links within electronic submission are sufficient to permit navigation through the submission, including access to reports, tables, data, etc.	X		
2	ISS, ISE, and complete study reports are available (original protocols, amendments, etc.)	X		
3	Safety and efficacy were investigated for gender, racial, and geriatric subgroups.			X
4	Data sets in EDR are accessible and conform to applicable guidances.	X		

THE STATISTICAL SECTION OF THE APPLICATION IS FILEABLE Yes

Because there are no efficacy issues to review in this submission, all items in the following table are not applicable.

Content Parameter (possible review concerns for 74-day letter)
Designs utilized are appropriate for the indications requested.
Endpoints and methods of analysis are specified in the protocols/statistical analysis plans.
Interim analyses are pre-specified and appropriate adjustments in significance level made. DSMB meeting minutes and data are available.
Appropriate references for novel statistical methodology are included.
Safety data organized to permit analyses across clinical trials in the NDA.
Applicant's investigation of effect of dropouts on statistical analyses appears adequate.

Sonia Castillo, Ph.D. Reviewing Statistician

Mahboob Sobhan, Ph.D. Team Leader

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/s/

SONIA CASTILLO
08/30/2012

MAHBOOB SOBHAN
08/30/2012