CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

022573Orig1s000

CHEMISTRY REVIEW(S)

MEMORANDUM

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

DATE: December 20, 2010

TO: Review #1 of NDA 22-573

FROM: Jane Chang, Ph.D.
Review Chemist, ONDQA

SUBJECT: Labeling Review
NDA 22-573
norethindrone and ethinyl estradiol chewable tablets and ferrous fumarate chewable tablets

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SUMMARY

After completion of CMC Review #1, revised labeling information was provided in the amendments dated 27-Sep-2010 and 16-Dec-2010. The information in the 16-Dec-2010 amendment confirms the previously agreed upon changes for Section 3 of Full Prescribing Information and Drug Listing Data Elements (see CMC Review #1, pages 116 and 121-122).

RECOMMENDATION

The labeling changes do no affect the conclusion and recommendation of Review #1. From a chemistry, manufacturing, and controls review perspective, this NDA may be approved.

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/s/

JANE L CHANG
12/20/2010

MARIE KOWBLANSKY on behalf of MOO JHONG RHEE
12/20/2010

NDA 22-573

(b) (4)

(norethindrone and ethinyl estradiol chewable tablets and ferrous fumarate chewable tablets)

Warner Chilcott Company, Inc.

Jane L. Chang, Ph.D.

Review Chemist

Office of New Drug Quality Assessment
Division of New Drug Quality Assessment II
Branch IV

For Division of Division of Reproductive and Urologic Drug Product
HFD-580

Table of Contents

Chemistry Review Data Sheet

1. NDA 22-573

2. REVIEW #: 1

3. REVIEW DATE: 09-Sep-2010

4. REVIEWER: Jane L. Chang, Ph.D.

5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date
None	N/A

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Original Submission	26-Nov-2009
Amendment (PS)	28-Apr-2010
Amendment	20-May-2010
Amendment (LC)	05-Jun-2010
Amendment	29-Jun-2010
Amendment	11-Aug-2010
Amendment (PS)	18-Aug-2010
Amendment	24-Aug-2010
Amendment (LC)	31-Aug-2010

7. NAME & ADDRESS OF APPLICANT:

Name:	Warner Chilcott Company, Inc.
Address:	Union Street, Road 195 Km 1.1 Fajardo, PR 00738-1005
Representative:	Alvin Howard, Senior Vice President Regulatory Affairs Warner Chilcott (US), LLC 100 Enterprise Drive Rockaway, NJ 07866
Telephone:	973-442-3200
Fax:	973-442-3280

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: (b) (4)
b) Non-Proprietary Name: norethindrone and ethinyl estradiol chewable tablets and ferrous fumarate chewable tablets
c) Code Name/# (ONDQA only): N/A
d) Chem. Type/Submission Priority (ONDQA only):

- Chem. Type: 5, New Formulation
- Submission Priority: S

**Review of the proposed proprietary name by DMEPA is still pending as of the date of this review.*

9. LEGAL BASIS FOR SUBMISSION: 505(b)(1)

10. PHARMACOL. CATEGORY: norethindrone and ethinyl estradiol, a synthetic progestin and estrogen, respectively.

11. DOSAGE FORM: chewable tablets

12. STRENGTH/POTENCY: 0.8 mg of norethindrone and 0.025 mg of ethinyl estradiol

13. ROUTE OF ADMINISTRATION: oral

14. Rx/OTC DISPENSED: __X__Rx ___OTC

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):

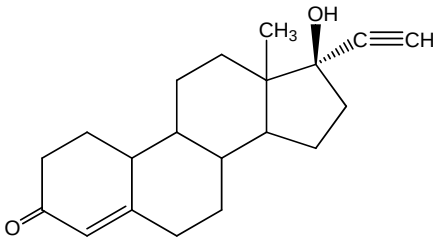
_____SPOTS product – Form Completed

__X___Not a SPOTS product

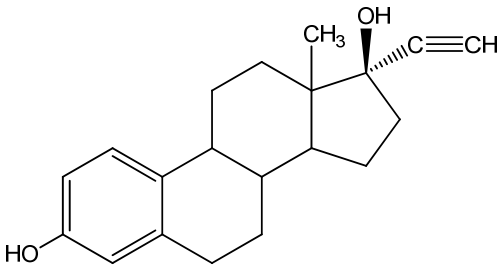
Chemistry Review Data Sheet

1. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

Active Tablets:

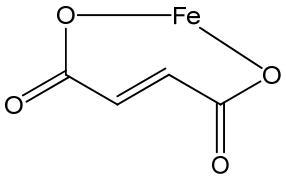


Norethindrone
$C_{20}H_{26}O_2$
MW 298.42



Ethinyl Estradiol
$C_{20}H_{24}O_2$
MW 296.40

Inert Tablets:



Ferrous Fumarate
$C_4H_2FeO_4$
MW 169.90

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
(b) (4)	II		(b) (4)	3	Adequate	11/04/2009	By V. S. Prabhu
	II			3	Adequate	6/30/2010	By P. Jin
	II			1	Adequate	3/12/2010	By J. Chang
	II			3	Adequate	7/7/2010	By P. Jin
	III			3	Adequate	3/19/2009	By B. Kurtyka
	III			1	Adequate	3/12/2010	By J. Chang
	IV			1	Adequate	6/11/2010	By J. Chang

[1] Action codes for DMF Table:
1 – DMF Reviewed.
Other codes indicate why the DMF was not reviewed, as follows:
2 –Type 1 DMF
3 – Reviewed previously and no revision since last review
4 – Sufficient information in application
5 – Authority to reference not granted
6 – DMF not available
7 – Other (explain under "Comments")

[2] Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
IND	76-629	norethindrone (NE) 0.8 mg and ethinyl estradiol (EE) 25 mcg
NDA	17-576	Ovcon® 50

18. STATUS:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	N/A		
EES	Acceptable	4/16/2010	A. Inyard
Pharm/Tox	N/A		
Biopharm	The dissolution method for NE/EE tablets is acceptable as interim, but the sponsor should develop a more discriminating dissolution method and to submit the results within a year of expedition of the request. The dissolution acceptance criteria for NE/EE tablets and ferrous fumarate tablets in the original submission are unacceptable.	7/29/2010	S. Suarez
	The dissolution method for NE/EE tablets is acceptable as interim. The sponsor agreed upon developing a more discriminating dissolution method and to submit the results within a year of expedition of the request. The dissolution acceptance criteria for NE/EE tablets and ferrous fumarate tablets revised in the 8/24/2010 amendment are acceptable.	8/31/2010	S. Suarez
Methods Validation	N/A (according to the current ONDQA policy)		
Office of Drug Safety	The 1st proposed proprietary name "(b) (4)" was denied due to vulnerability to name confusion.	4/5/2010	D. V. Baugh
	The 2nd proposed proprietary name "(b) (4)" was denied due to vulnerability to name confusion.	7/27/2010	D. V. Baugh
	"(b) (4)" was proposed as the proprietary name.	Pending*	
EA	Categorical exclusion (see review)	5/3/2010	J. Chang
Microbiology	N/A		

*"(b) (4)" was proposed as the proprietary name in the 8/18/2010 amendment. As of the date of this review, review of the proposed proprietary name by DMEPA is still pending. The pending status has no impact on the CMC recommendation and conclusion on approvability for the NDA since review of the proprietary name is outside CMC purview.

The Chemistry Review for NDA 22-573

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

This NDA has provided sufficient CMC information to assure the identity, strength, purity, and quality of the drug product. The Office of Compliance has made an "Acceptable" site recommendation. The labels have adequate information as required. Therefore, from the CMC perspective, this NDA is recommended for "Approval".

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

None

II. Summary of Chemistry Assessments

A. Description of the Drug Product(s) and Drug Substance(s)

(1) Drug Substance

The drug substances are norethindrone and ethinyl estradiol, which are a synthetic progestin and estrogen, respectively. Both drug substances are monographed in the USP. Norethindrone is manufactured by (b) (4) . Ethinyl estradiol is manufactured by (b) (4) . CMC information for norethindrone and ethinyl estradiol are referenced to their respective DMFs and letters of authorization have been provided from the respective DMF holders. DMFs (b) (4) have been reviewed recently by Drs. P. Jin (06/30/2010), V. S. Prabhu (11/04/2009), and P. Jin (07/07/2010), respectively, and found to be adequate. DMF (b) (4) has recently been reviewed by this reviewer and found to be adequate to support this NDA. In addition to the tests listed in the USP monographs, testing for residual solvents are included in the norethindrone and ethinyl estradiol specifications.

(2) Drug Product

The drug product, norethindrone and ethinyl estradiol chewable tables and ferrous fumarate chewable tablets, is an immediate release chewable tablet formulation containing 0.8 mg norethindrone and 0.025 mg ethinyl estradiol indicated for oral contraceptive. The drug product are blister packed into a blister card containing 24

light green active tablets (designated as WC3026-5C tablets in this review) and 4 brown inactive (placebo) tablets. Each inactive tablet contains 75 mg ferrous fumarate.

(b) (4)

In-process controls for ethinyl estradiol (b) (4) include (b) (4) and ethinyl estradiol assay. In-process controls for WC3026-5C chewable tablets include weight, appearance, hardness, thickness, friability, and content uniformity. The specification for WC3026-5C chewable tablets includes description, identification, uniformity of dosage unit, assay, degradation products, dissolution, (b) (4) , and hardness. Except for the dissolution method for WC3026-5C chewable tablets, the proposed specification is acceptable to ensure product identity, strength, purity, and quality. The acceptance criteria for the tests are acceptable based on their developmental studies, and the analytical methods for the tests are adequately validated. Per the review dated August 31, 2010 by the Biopharm reviewer, Dr. S. Suarez, the dissolution method for NE/EE tablets is acceptable as interim. The sponsor agreed to develop a more discriminating dissolution method and to submit the results within a year of expedition of the request. Stability data based on three registration batches and two additional batches support the proposed expiration dating period, 36-month when stored at 25°C (77°F); excursions permitted to 15 – 30°C (59 – 86°F).

(b) (4)

If the change in the active tablets formulation is implemented, in-process and release data and comparative dissolution data will be reported in Changes-Being-Effected-in-30-Days Supplement. Long-term ICH stability data for the first post-change product batch will be reported in the product annual report.

The request for a categorical exclusion from the preparation of an environmental assessment (EA) under 21 CFR 25.31(b) is acceptable.

B. Description of How the Drug Product is Intended to be Used

The recommended dose for the drug product is 1 active tablet/per day for 24 days and 1 placebo tablet per day for 4 days. The placebo (ferrous fumarate) tablets, which are present to facilitate ease of drug administration via a 28-day regimen, are nonhormonal, and do not serve any therapeutic purpose. The tablets are recommended to be chewed.

C. Basis for Approvability or Not-Approval Recommendation

The applicant has provided sufficient information on the raw material controls, manufacturing process and process controls, and adequate specifications for assuring consistent product quality of the drug substance and drug product. This NDA also has provided sufficient stability information on the drug product to assure identity, strength, purity, and quality of the drug product during the expiration dating period.

All the facilities have acceptable site recommendation.
All labels have the required information.

III. Administrative

A. Reviewer's Signature

See appended electronic signature page

B. Endorsement Block

See appended electronic signature page

C. CC Block

Entered electronically in DARRTS

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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/

JANE L CHANG
09/09/2010

MOO JHONG RHEE
09/09/2010
Chief, Branch IV

Initial Quality Assessment
Branch III
Pre-Marketing Assessment Division II

OND Division:	Division of Reproductive and Urologic Products
NDA:	22-573
Applicant:	Warner Chilcott
Stamp Date:	26-Nov-2009
PDUFA Date:	24-Sep-2010
Trademark:	(b) (4)
Established Name:	Norethindrone and ethinyl estradiol tablets, chewable and ferrous fumarate tablets
Strength	0.8 mg NE and 0.025 mg EE
Dosage Form:	Tablets
Route of Administration:	Oral
Indication:	Prevention of Pregnancy
PAL:	Donna F. Christner, Ph.D.

	YES	NO
ONDQA Fileability:	X	☐
Comments for 74-Day Letter	☐	X

Summary and Critical Issues:

A. Summary

The drug product is a 28-tablet oral contraceptive consisting of 24 chewable active tablets containing norethindrone (NE) 0.8 mg and ethinyl estradiol (EE) 25 µg followed by 4 inert tablets containing ferrous fumarate, 75 mg. The NE/EE tablets are light-green, round, flat-faced, bevel-edged tablets debossed with "WC" on one side and "483" on the other side. The ferrous fumarate tablets are round, flat-faced, beveled-edged, brown tablets debossed with "WC" on one side and "624" on the other side. The drug product is packaged in unit-dose blister (b) (4) .

B. Critical issues for review

(b) (4)

Two different dissolution methods have been developed for the active tablet. (b) (4) *is the proposed regulatory method, while* (b) (4) *is an alternate dissolution method that has been used to test selected batches of drug product in order to evaluate the similarity of dissolution profiles with the two methods. A Technical Report has been included in the*

application. The two dissolution methods will require review by the ONDQA BioPharm reviewer. Sandra Suarez-Sharp, Ph.D. has been assigned.

C. Comments for 74-Day Letter

There are no comments at this time.

D. Recommendation:

This NDA is fileable from a CMC perspective. Jane Chang, Ph.D., has been assigned as the primary reviewer.

_____

Donna F. Christner, Ph.D.

NDA Number: 22-573 **Type: 5** **Established/Proper Name: norethindrone and ethinyl estradiol**

Applicant: Warner Chilcott **Letter Date: 25-Nov-2009** **Stamp Date: 26-Nov-2009**

The following parameters are necessary in order to initiate a full review, i.e., complete enough to review but may have deficiencies. On **initial** overview of the NDA application for filing:

A. GENERAL				
	Parameter	**Yes**	**No**	**Comment**
1.	Is the CMC section organized adequately?	X		
2.	Is the CMC section indexed and paginated (including all PDF files) adequately?	X		
3.	Are all the pages in the CMC section legible?	X		
4.	Has all information requested during the IND phase, and at the pre-NDA meetings been included?	X		

B. FACILITIES*				
	Parameter	**Yes**	**No**	**Comment**
5.	Is a single, comprehensive list of all involved facilities available in one location in the application?	X		
6.	For a naturally-derived API only, are the facilities responsible for critical intermediate or crude API manufacturing, or performing upstream steps, specified in the application? If not, has a justification been provided for this omission? **This question is not applicable for synthesized API.**		X	N/A

7.	Are drug substance manufacturing sites identified on FDA Form 356h or associated continuation sheet? For each site, does the application list: • Name of facility, • Full address of facility including street, city, state, country • FEI number for facility (if previously registered with FDA) • Full name and title, telephone, fax number and email for on-site contact person. • Is the manufacturing responsibility and function identified for each facility?, and • DMF number (if applicable)	X		
8.	Are drug product manufacturing sites are identified on FDA Form 356h or associated continuation sheet. For each site, does the application list: • Name of facility, • Full address of facility including street, city, state, country • FEI number for facility (if previously registered with FDA) • Full name and title, telephone, fax number and email for on-site contact person. • Is the manufacturing responsibility and function identified for each facility?, and • DMF number (if applicable)	X		

9.	Are additional manufacturing, packaging and control/testing laboratory sites are identified on FDA Form 356h or associated continuation sheet. For each site, does the application list: • Name of facility, • Full address of facility including street, city, state, country • FEI number for facility (if previously registered with FDA) • Full name and title, telephone, fax number and email for on-site contact person. • Is the manufacturing responsibility and function identified for each facility?, and • DMF number (if applicable)	X		
10.	Is a statement provided that all facilities are ready for GMP inspection at the time of submission?	X		

* If any information regarding the facilities is omitted, this should be addressed ASAP with the applicant and can be a *potential* filing issue or a *potential* review issue.

C. ENVIRONMENTAL ASSESMENT				
	Parameter	**Yes**	**No**	**Comment**
11.	Has an environmental assessment report or categorical exclusion been provided?	X		Categorical exclusion as per 21 CFR 25.31(b)

D. DRUG SUBSTANCE/ACTIVE PHARMACEUTICAL INGREDIENT (DS/API)				
	Parameter	**Yes**	**No**	**Comment**
12.	Does the section contain a description of the DS manufacturing process?	X		Cross reference to DMFs (b) (4)
13.	Does the section contain identification and controls of critical steps and intermediates of the DS?	X		Cross reference to DMFs (b) (4)
14.	Does the section contain information regarding the characterization of the DS?	X		Cross reference to DMFs (b) (4)
15.	Does the section contain controls for the DS?	X		Cross reference to DMFs (b) (4)
16.	Has stability data and analysis been provided for the drug substance?	X		Cross reference to DMFs (b) (4)
17.	Does the application contain Quality by Design (QbD) information regarding the DS?		X	Not a filing issue
18.	Does the application contain Process Analytical Technology (PAT) information regarding the DS?		X	Not a filing issue

E. DRUG PRODUCT (DP)				
	Parameter	**Yes**	**No**	**Comment**
19.	Is there a description of manufacturing process and methods for DP production through finishing, including formulation, filling, labeling and packaging?	X		
20.	Does the section contain identification and controls of critical steps and intermediates of the DP, including analytical procedures and method validation reports for assay and related substances if applicable?	X		
21.	Is there a batch production record and a proposed master batch record?	X		
22.	Has an investigational formulations section been provided? Is there adequate linkage between the investigational product and the proposed marketed product?	X		
23.	Have any biowaivers been requested?		X	
24.	Does the section contain description of to-be-marketed container/closure system and presentations)?	X		
25.	Does the section contain controls of the final drug product?	X		
26.	Has stability data and analysis been provided to support the requested expiration date?	X		
27.	Does the application contain Quality by Design (QbD) information regarding the DP?		X	Not a filing issue
28.	Does the application contain Process Analytical Technology (PAT) information regarding the DP?		X	Not a filing issue

F. METHODS VALIDATION (MV)				
	Parameter	**Yes**	**No**	**Comment**
29.	Is there a methods validation package?	X		

G. MICROBIOLOGY				
	Parameter	**Yes**	**No**	**Comment**
30.	If appropriate, is a separate microbiological section included assuring sterility of the drug product?		X	N/A

H. MASTER FILES (DMF/MAF)				
	Parameter	**Yes**	**No**	**Comment**
31.	Is information for critical DMF references (i.e., for drug substance and important packaging components for non-solid-oral drug products) complete?	X		See table below

(b) (4) (b) (4)

TYPE		LOA DATE	COMMENTS
II		26-May-2009	ADEQUATE on 06-Jul-2009 by B. Mirzai-Azarm.
II		30-Jun-2008	ADEQUATE on 15-Apr-2009 by G. Sun
II		29-Sep-2008	ADEQUATE on 22-Oct-2009 by V. Prabhu
II		17-Dec-2004	ADEQUATE on 04-Aug-2008 by J. Chang
III		18-Sep-2008	ADEQUATE on 30-Nov-2009 by Y. Tang. See ONDC Policies on Bottles and Blisters*
III		15-Sep-2008	ADEQUATE on 04-Aug-2008 by J. Chang

Policy on the Review of Container Closure Systems for Solid Oral Drug Products (Bottles), 26-Apr-2001
Policy on the Review of Blister Container Closure Systems for Oral Tablets and Hard Gelatin Capsules, 29-May-2002

I. LABELING				
	Parameter	**Yes**	**No**	**Comment**
32.	Has the draft package insert been provided?	X		SPL with DLDE table provided in Section 1.14.1.3
33.	Have the immediate container and carton labels been provided?	X		

J. FILING CONCLUSION				
	Parameter	**Yes**	**No**	**Comment**
34.	**IS THE PRODUCT QUALITY SECTION OF THE APPLICATION FILEABLE?**	X		
35.	If the NDA is not fileable from the product quality perspective, state the reasons and provide **filing** comments to be sent to the Applicant.		X	N/A
36.	Are there any **potential review** issues to be forwarded to the Applicant for the 74-day letter?		X	

{See appended electronic signature page}

Donna F. Christner, Ph.D. Date
Pharmaceutical Assessment Lead
Division of Pre-Marketing Assessment # 2
Office of New Drug Quality Assessment

{See appended electronic signature page}

Moo-Jhong Rhee, Ph.D. Date
Branch Chief
Division of Pre-Marketing Assessment # 2
Office of New Drug Quality Assessment

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/s/

DONNA F CHRISTNER
01/12/2010

MOO JHONG RHEE
01/13/2010
Chief, Branch III