

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

204654Orig1s000

CHEMISTRY REVIEW(S)

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

OND Division: Division of Reproductive and Urologic Products
NDA: 204654
Applicant: Warner Chilcott
Stamp Date: 27-Sep-2012
PDUFA Date: 26-Jul-2013
Trademark: None provided
Established Name: Norethindrone acetate/Ethinyl estradiol/Ferrous Fumarate
Dosage Form: Tablet
Route of Administration: Oral
Indication: Prevention of pregnancy

CMC Lead: Donna F. Christner, Ph.D.

	YES	NO
ONDQA Fileability:	X	<input type="checkbox"/>
Comments for 74-Day Letter	<input type="checkbox"/>	X

Summary and Critical Issues:

A. Summary

The applicant has provided the following information on the drug product:

- (b) (4) is a 28-tablet oral contraceptive regimen consisting of the following (see Figure 1):
- Twenty-four (b) (4) chewable tablets [norethindrone acetate (NA), 1.0 mg and ethinyl estradiol (EE), 10 µg per tablet].
 - Two WC3016 (b) (4) tablets (EE, 10 µg per tablet).
 - Two ferrous fumarate tablets, containing 75 mg of ferrous fumarate per tablet.
- The formulation for (b) (4) chewable tablets is based on a previously approved formulation, WC3016 (b) (4) in Lo Loestrin (NDA 22-501). The main difference between the two target product profiles was that (b) (4) tablets are intended to be chewable. The WC3016-(b) (4) tablets and the ferrous fumarate tablets are previously approved products in NDA 22-501.

The (b) (4) 1/10 chewable tablet formulation was based on the approved formulation for Lo Loestrin Fe 1 mg NA/10 mcg EE tablets (referred to in the NDA as **WC3016 1/10 tablets** or by its formulation **WC3016 (b) (4) tablets**); a flavor and (b) (4) were added to (b) (4) 1/10 chewable tablets. The WC3016 EE10 tablets are identical to Lo Loestrin Fe 10 mcg EE tablets. Lo Loestrin Fe received approval as an oral contraceptive on October 21, 2010 under NDA 022501.

The drug product is provided in a standard (b) (4) blister pack. The chewable combination tablets are contained in the first 24 wells of the blister pack, while the nonchewable ethinyl estradiol

tablets are contained in blister wells 25-26 and the inert, nonchewable ferrous fumarate tablets are in blister wells 27-28. The blister packaging is the same as used in the approved product under NDA 22501

B. Critical issues for review

All specifications are set based on the approved NDA 22501. Since these are immediate release tablets and the specifications are based on an approved NDA, consultation to ONDQA BioPharm may not be necessary. It is the primary reviewer's decision on whether a BioPharm review is warranted.

The combination tablet has only 6 months of stability data submitted in support of a 12 month expiration dating period. Although 6 months of data are less than what is currently recommended by ONDQA, based on the fact that the formulation is almost identical to an approved formulation except for the addition of sweetener and flavor, the amount of information is deemed adequate to allow review and to determine if 12 months of expiration dating period are appropriate.

C. Comments for 74-Day Letter

No comments to be conveyed at this time.

D. Recommendation:

This NDA is fileable from a CMC perspective. Gene Holbert, Ph.D. is assigned as the primary reviewer.

REGULATORY BRIEFING RECOMMENDATION: Branch level.

Donna F. Christner, Ph.D.

Established/Proper Name:

NDA Number: 204654 Type: 5

Norethindrone acetate and ethinyl estradiol chewable tablets, ethinyl estradiol tablets and ferrous fumarate tablets

Applicant: Warner Chilcott

Letter Date: 27-Sep-2012

Stamp Date: 27-Sep-2012

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.	<p>Are drug substance manufacturing sites identified on FDA Form 356h or associated continuation sheet? For each site, does the application list:</p> <ul style="list-style-type: none"> • 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.	<p>Are drug product manufacturing sites identified on FDA Form 356h or associated continuation sheet. For each site, does the application list:</p> <ul style="list-style-type: none"> • 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.	<p>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:</p> <ul style="list-style-type: none"> • 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(a) because it is a reformulation of an approved product and will substitute directly for the approved product

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		Norethidrone acetate: DMFs (b) (4) and (b) (4) Ethinyl estradiol: DMFs (b) (4) and (b) (4)
13.	Does the section contain identification and controls of critical steps and intermediates of the DS?	X		Norethidrone acetate: DMFs (b) (4) and (b) (4) Ethinyl estradiol: DMFs (b) (4) and (b) (4)
14.	Does the section contain information regarding the characterization of the DS?	X		Norethidrone acetate: DMFs (b) (4) and (b) (4) Ethinyl estradiol: DMFs (b) (4) and (b) (4)
15.	Does the section contain controls for the DS?	X		Norethidrone acetate: DMFs (b) (4) and (b) (4) Ethinyl estradiol: DMFs (b) (4) and (b) (4)
16.	Has stability data and analysis been provided for the drug substance?	X		Norethidrone acetate: DMFs (b) (4) and (b) (4) Ethinyl estradiol: DMFs (b) (4) and (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		Cross reference to NDA 22501
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		12 month expiry requested based on 6 months of data provided.
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		

DMF #	TYPE	HOLDER	ITEM REFERENCED	LOA DATE	COMMENTS
(b) (4)	II	(b) (4)	Norethisterone Acetate	10-Apr-2006	ADEQUATE on 28-Apr-2011. No updates.
	II		Ethinyl estradiol	07-Jun-2012	ADEQUATE on 14-Jun-2012. No updates.
	II		Norethindrone Acetate	07-Jun-2012	ADEQUATE on 10-May-2012. No updates.
	IV		(b) (4) Spearmint Flavor (b) (4)	19-Apr-2010	ADEQUATE on 11-Jun-2010. No updates.
	III		(b) (4)	18-Sep-2008	ADEQUATE on 07-Dec-2009. See ONDC Policies on Bottles and Blisters*
	III		(b) (4)	15-Sep-2008	ADEQUATE on 12-Mar-2010.
	II		Ethinyl estradiol	28-Jul-2011	ADEQUATE on 05-Sep-2012. No updates.
	III		(b) (4)	10-Apr-2012	ADEQUATE on 16-Jun-2011.

*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		
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?			

{See appended electronic signature page}

Donna F. Christner, Ph.D.
 CMC Lead
 Division of New Drug Quality Assessment II
 Office of New Drug Quality Assessment

Date

{See appended electronic signature page}

Moo-Jhong Rhee, Ph.D.
 Chief, Branch IV
 Division of New Drug Quality Assessment II
 Office of New Drug Quality Assessment

Date

Attachment A: Nanotechnology product evaluating questions:

1, This review contains new information added to the table below: _____ Yes; <u> x </u> No Review date: <u>16-Oct-2012</u>
2) Are any nanoscale materials included in this application? (If yes, please proceed to the next questions.) Yes _____; No _____; Maybe (please specify) _____
3 a) What nanomaterial is included in the product? (Examples of this are listed as search terms in Attachment B.) _____
3 b) What is the source of the nanomaterial? _____
4) Is the nanomaterial a reformulation of a previously approved product? Yes _____ No _____
5) What is the nanomaterial functionality? Carrier _____; Excipient _____; Packaging _____ API _____; Other _____
6) Is the nanomaterial soluble (e.g., nanocrystal) or insoluble (e.g., gold nanoparticle) in an aqueous environment? Soluble _____; Insoluble _____
7) Was particle size or size range of the nanomaterial included in the application? Yes _____ (Complete 8); No _____ (go to 9).
8) What is the reported particle size? Mean particle size _____; Size range distribution _____; Other _____
9) Please indicate the reason(s) why the particle size or size range was not provided: _____ _____
10, What other properties of the nanoparticle were reported in the application (See Attachment E)? _____
11) List all methods used to characterize the nanomaterial? _____ _____

Review Notes

The applicant has provided the following information on their drug product. It is highlighted in blue below. The bioavailability studies were performed under IND 73510.

The proposed regimen and daily doses of active ingredients, and consequently the exposure to norethindrone and EE for (b) (4) is the same as the approved regimen for Warner Chilcott's Lo Loestrin® Fe (norethindrone acetate and ethinyl estradiol tablets, ethinyl estradiol tablets and ferrous fumarate tablets) in which all 28 tablets are swallowed. The (b) (4) 1/10 chewable tablet formulation was based on the approved formulation for Lo Loestrin Fe 1 mg NA/10 mcg EE tablets (referred to in the NDA as **WC3016 1/10 tablets** or by its formulation **WC3016 (b) (4) tablets**); a flavor (b) (4) were added to (b) (4) 1/10 chewable tablets. The WC3016 EE10 tablets are identical to Lo Loestrin Fe 10 mcg EE tablets. Lo Loestrin Fe received approval as an oral contraceptive on October 21, 2010 under NDA 022501. Reference is made therefore to NDA 022501 in support of the safety and efficacy of NA and EE in the prevention of pregnancy (see Section 1.4.4 Cross Reference to Other Applications).

The Application provides comparative bioavailability data from Study PR-12111.

DRUG SUBSTANCES

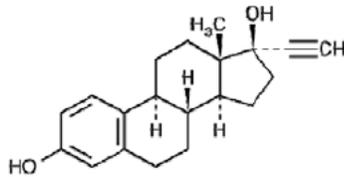
The drug product contains two drug substances: Norethindrone acetate and Ethinyl estradiol. Full information on the drug substances are provided in the following DMFs:

Norethindrone acetate: DMFs (b) (4)
 Ethinyl estradiol: DMFs (b) (4)

The following general information is provided in the NDA.

ETHINYL ESTRADIOL

Ethinyl estradiol is sourced from either (b) (4)
 (b) (4) Full information is provided in the cross-referenced DMFs.



The following tests are performed by Warner Chilcott on Ethinyl estradiol sourced from (b) (4). The testing schedule for the API is also provided below.

Specification		
Test	Specification	Method
Description	Must conform to material description: White to creamy white powder.	Visual Inspection
Identification A	(b) (4)	USP <197K>
Identification B		USP <197U>
Completeness of Solution	The solution is clear and free from undissolved solid.	USP
Melting Range	(b) (4)	USP <741>
Specific Rotation	(b) (4)	USP <781S>
Loss on Drying	NMT (b) (4)	USP <731>
Assay	97.0% to 102.0%	USP
Additional Tests		
Identification (TLC)	The spots of the Sample and Standard should be similar in intensity, size, shape, color, and R _f value.	DS- (b) (4)
Residual Solvent	(b) (4)	USP

Test Plan

Test	Initial Testing Requirements	Re-evaluation Testing Requirements	Reduced Testing Requirements	Supplier Lot Previously Received testing Requirements
Description	(b) (4)			
Identification A				
Identification B				
Completeness of Solution				
Melting Range				
Specific Rotation				
Loss on Drying				
Assay				
Identification (TLC)				
Residual Solvent				

The following tests are performed by Warner Chilcott on Ethinyl estradiol sourced from (b) (4). The testing schedule for the API is also provided below.

Specification

Test	Specification	Method
Description	(b) (4)	Visual Inspection
Identification A		USP <197K>
Identification B		USP <197U>
Completeness of Solution		USP
Melting Range		USP <741>
Specific Rotation		USP <781S>
Loss on Drying		USP <731>
Assay		USP
Residual Solvent		DS (b) (4)
Identification (TLC)		DS (b) (4)

Test Plan

Test	Initial Testing Requirements	Re-evaluation Testing Requirements	Reduced Testing Requirements	Supplier Lot Previously Received testing Requirements
Description	(b) (4)			
Identification A				
Identification B				
Completeness of Solution				
Melting Range				
Specific Rotation				
Loss on Drying				
Assay				
Residual Solvent				
Identification (TLC)				

Comment: Information is adequate to allow review. It should be noted that the impurities and residual solvents (b) (4)

MANUFACTURING

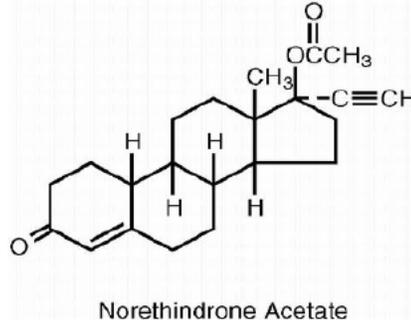
The following sites have manufacturing responsibilities for the Ethinyl Estradiol drug substance.



Comment: EES was submitted on 22-Oct-2012 by Kerri-Ann Jennings.

NORETHINDRONE ACETATE

Norethindrone acetate is sourced from either (b) (4). Full information is provided in the cross-referenced DMFs.



The following tests are performed by Warner Chilcott on Norethindrone acetate sourced from (b) (4). The testing schedule for the API is also provided below.

Specification		
Test	Specification	Method
Description	Must conform to material description: White to creamy white powder.	Visual
Completeness of Solution	The solution prepared for the determination specific rotation is clear and free from undissolved solid.	USP
Identification	(b) (4)	USP <197K>
Specific Rotation	(b) (4)	USP <781S>
Loss on Drying	NMT (b) %	USP <731>
Limit of Ethynyl group	7.13 % to 7.57%	USP
Chromatographic Purity	Test 1 - TLC	USP
	NMT (b) % Individual	
	NMT (b) % Total	
	Test 2 - HPLC	
	NMT (b) % Individual	
	NMT (b) % Total	
Assay	(b) (4) 97.0% to 103.0%	USP or DS (b) (4)

Test	Specification	Method
Additional Tests		
Powder Fineness	(b) (4)	DS (b) (4)
Residual Solvents	(b) (4)	USP

Test Plan

Test	Initial Testing Requirements	Re-evaluation Testing Requirements	Reduced Testing Requirements	Supplier Lot Previously Received testing Requirements
Description	(b) (4)			
Completeness of Solution				
Identification				
Specific Rotation				
Loss on Drying				
Limit of Ethinyl group				
Chromatographic Purity				
Assay (b) (4)				
Powder Fineness				
Residual Solvents				

The following tests are performed by Warner Chilcott on Norethindrone acetate sourced from BSP. The testing schedule for the API is also provided below.

Specification

Test	Specification	Method
Description	(b) (4)	Visual
Completeness of Solution		USP
Identification		USP <197K>
Specific Rotation		USP <781S>
Loss on Drying		USP <731>
Limit of Ethinyl group		USP
Chromatographic Purity		USP
Residual Solvents ³		DS- (b) (4)
Assay (dried basis)		USP or DS (b) (4)
Additional Tests		
Powder Fineness	(b) (4)	DS- (b) (4)

(b) (4)

Test Plan

Test	Initial Testing Requirements	Re-evaluation Testing Requirements	Reduced Testing Requirements	Supplier Lot Previously Received testing Requirements
Description	(b) (4)			
Completeness of Solution				
Identification				
Specific Rotation				
Loss on Drying				
Limit of Ethinyl group				
Chromatographic Purity				
Residual Solvents				
Assay (b) (4)				
Powder				
Fineness				

Comment: Information is adequate to allow review. It should be noted that the impurities and residual solvents are different for each supplier based on the synthetic process.

MANUFACTURING

The following sites have manufacturing responsibilities for the Norethindrone acetate drug substance.

(b) (4)

Comment: EES was submitted on 22-Oct-2012 by Kerri-Ann Jennings.

DRUG PRODUCT

The applicant has provided the following information on the drug product:

- (b) (4) is a 28-tablet oral contraceptive regimen consisting of the following (see Figure 1):
- Twenty-four (b) (4) chewable tablets [norethindrone acetate (NA), 1.0 mg and ethinyl estradiol (EE), 10 µg per tablet].
 - Two WC3016 (b) (4) tablets (EE, 10 µg per tablet).
 - Two ferrous fumarate tablets, containing 75 mg of ferrous fumarate per tablet.

The formulation for (b) (4) chewable tablets is based on a previously approved formulation, WC3016 (b) (4) in Lo Loestrin (NDA 22-501). The main difference between the two target product profiles was that (b) (4) tablets are intended to be chewable. The WC3016-(b) (4) tablets and the ferrous fumarate tablets are previously approved products in NDA 22-501.

The (b) (4) 1/10 chewable tablet formulation was based on the approved formulation for Lo Loestrin Fe 1 mg NA/10 mcg EE tablets (referred to in the NDA as **WC3016 1/10 tablets** or by its formulation **WC3016 (b) (4) tablets**); a flavor and sweetener were added to (b) (4) 1/10 chewable tablets. The WC3016 EE10 tablets are identical to Lo Loestrin Fe 10 mcg EE tablets. Lo Loestrin Fe received approval as an oral contraceptive on October 21, 2010 under NDA 022501.

MANUFACTURING SITES

The following sites have manufacturing responsibilities for the drug product:

Establishment and Contact Information - WC (b) (4)

Facility	Responsibility	Establishment Registration Number	Contact Person	Ready for Inspection	Date of Last FDA Inspection
Warner Chilcott Company, LLC Road 195 (Union Street) Km 1.1 Fajardo, PR 00738-1005	Analytical testing and release of the drug substance and inactive components. Manufacturing, in-process testing, release testing, stability testing and packaging of the drug product	2619635	Elizabeth Sanchez Head of Quality Operations Phone: 787 655-8355 Fax: 787 863-1197 Email: elizabeth.sanchez@wcrx.com	yes	7/22-29/2011
Warner Chilcott UK Limited Old Belfast Road, Millbrook Larne, Northern Ireland BT40 2SH	In-process chemical testing (no manufacturing function), release and stability testing of the drug product	3005206014	Gillian Megaw Head of Quality Operations Phone: 011-44-28-2826 7222 ext 7215 Fax: 011-44-28-2827-9448 Email: gillian.megaw@wcrx.co.uk	yes	11/24/2008
Warner Chilcott (Ireland) Limited Xerox Bus. Campus Bldg B Dundalk, County Louth Ireland	Stability storage and testing	3009402661	David Ussher Senior Manager, Stability Phone: 353 429395900 Email: david.usscher@wcrx.co.uk	yes	6/5-6/2012

(b) (4)

Comment: EES was submitted on 22-Oct-2012 by Kerri-Ann Jennings.

(b) (4) chewable tablets (norethindrone acetate 1.0 mg and ethinyl estradiol, 10 mcg)

The combination tablets have the following formulation:

Table 1: Composition of (b) (4) Chewable Tablets

Component	Quality Standard	Function	Quantity (mg/tablet)
Ethinyl Estradiol	USP	(b) (4)	(b) (4)
Povidone (Plasdone K29/32)	USP		
Vitamin E (DL- α -Tocopherol)	USP		
Lactose Monohydrate, Fast-Flo [®]	NF		
Norethindrone Acetate	USP		
Mannitol (b) (4)	USP		
Mannitol	USP		
Microcrystalline Cellulose (b) (4)	NF		
FD&C Blue #1, Aluminum Lake	FDA Certified		
Spearmint Flavor (b) (4)	In-house		
Sucralose	NF		
Sodium Starch Glycolate	NF		
Magnesium Stearate	NF		
Total			(b) (4)

MANUFACTURING PROCESS

(b) (4)

Figure 2: Process Flow for WC

(b) (4)

(b) (4)

(b) (4)



Comment: Information is adequate to allow review.

SPECIFICATION

The combination tablets are controlled with the following specification:

Specification

Test	Specification	Method	Test Site
Description ¹	Blue, round, flat-faced, bevel-edged tablets, debossed with 'WC' on one side and '537' on the other	Drug Product-24271	WC UK Lame
Identification	HPLC: retention time of the main peaks obtained in the chromatogram for the assay preparation correspond to those obtained for the standard preparation	Drug Product-24271	WC UK Lame
Uniformity of Dosage Units (NA and EE)	Meet the requirements of USP <905> for norethindrone acetate (NA) and ethinyl estradiol (EE)	Drug Product-24269	WC UK Lame
Assay (NA and EE) ¹	Ethinyl estradiol (EE): 88.0 % to 112.0 % of label claim Norethindrone acetate (NA): 90.0 % to 110.0 % of label claim	Drug Product-24271	WC UK Lame
(b) (4)	(b) (4)	Drug Product-24122	WC UK Lame
		Drug Product -24122 Drug Product -24043	WC UK Lame

¹Testing required for release and stability
(b) (4)

Specification (Continued)

Test	Specification	Method	Test Site
Hardness ¹	3.0 kp to 9.0 kp	Drug Product -24146	WC UK Lame
Loss on Drying ¹	Report results	Drug Product -24242	WC UK Lame
Dissolution ¹	Meet the requirements of USP<711>: Not less than (b) (4) (Q) of the NA and EE label claims dissolved in 30 minutes	Drug Product -24044	WC UK Lame
(b) (4) Assay	90.0 % to 110.0 % of theoretical amount	Drug Product -24045	WC UK Lame
(b) (4)	(b) (4)	USP <61>, USP <62>	WC UK Lame

(b) (4)

Comments: Specification is based on that for the approved product in NDA 22501. Since these are immediate release tablets and the specification is based on an approved NDA, consultation to ONDQA BioPharm may not be necessary. It is the primary reviewer's decision on whether a BioPharm review is warranted. Information is adequate to allow review.

WC3016- (b) (4) (ethinyl estradiol 10 mcg)

The ethinyl estradiol tablets have the following formulation:

Table 1: Composition of WC3016-20C Tablets

Component	Quality Standard	Function	Quantity (mg/tablet)
Ethinyl Estradiol	USP	(b) (4)	(b) (4)
Povidone (b) (4)	USP		
Vitamin E (b) (4)	USP		
Lactose Monohydrate, (b) (4)	NF		
Mannitol (b) (4)	USP		
Mannito (b) (4)	USP		
Microcrystalline Cellulose (b) (4)	NF		
Sodium Starch Glycolate	NF		
Magnesium Stearate	NF		
Total			

MANUFACTURING PROCESS



SPECIFICATION

The ethinyl estradiol tablets have the following specification:

Specification

Test	Specification	Method	Test Site
Description ¹	White, hexagonal, flat-faced, bevel-edged tablets, debossed with "WC" on one side and "422" on the other. Use the following images as reference: 	Drug Product - 42	WC Larne, WC Fajardo, WC Dundalk
Identification	HPLC – The retention time of the main peaks obtained in the chromatogram for the Assay preparation correspond to those obtained for the Standard preparation.	Drug Product - 42	WC Larne, WC Fajardo
Assay ¹ (EE)	Ethinyl Estradiol (EE): 88.0% to 112.0% of label claim	Drug Product - 42	WC Larne, WC Fajardo, WC Dundalk
Uniformity of Dosage Units (EE)	Meet the requirements of USP <905>	Drug Product - 43	WC Larne, WC Fajardo
	(b) (4)	Drug Product - 43	WC Larne, WC Fajardo
		Drug Product - 44	WC Larne, WC Fajardo, WC Dundalk

Test	Specification	Method	Test Site
	(b) (4)	Drug Product - 45	WC Larne, WC Fajardo, WC Dundalk
Assay - (b) (4) (b) (4)	90.0% - 110.0% of theoretical amount	Drug Product - 46	WC Larne, WC Fajardo
(b) (4)	(b) (4)	USP <61>, <62>	Scienza Labs ³ , Charles River Labs ³
	(b) (4)		

Comments: Specification is based on that for the approved product in NDA 22501. Information is adequate to allow review.

Ferrous fumarate tablets

The composition of the ferrous fumarate tablets is as follows:

Table 1: Composition of Ferrous Fumarate Tablets

Component	Quality Standard	Function	Quantity (mg/tablet)
Ferrous fumarate	USP	Primary component	(b) (4)
(b) (4)			

MANUFACTURING PROCESS

The applicant has provided the following flow charts for the manufacturing process. Narratives are provided as well.



SPECIFICATION

The specification for the ferrous fumarate tablets is provided below:

Specification

Test	Specification	Method	Test Site
Description ¹	Round, flat-faced, bevel-edged, brown tablets debossed with 'WC' on one side and '624' on the other side. See following images as reference: 	Drug Product - 80	WC Fajardo WC Larnie WC Dundalk
Identification	Test is positive for Iron		WC Fajardo WC Larnie
Uniformity of Dosage Units	Meets the requirements of USP <905>		WC Fajardo WC Larnie
Assay	90.0% to 110.0% of Label Claim		WC Fajardo WC Larnie
Dissolution ¹	Not less than (b)(4)(Q) of label claim of Ferrous Fumarate is dissolved in 30 minutes. Follow the requirements of USP <711>		WC Fajardo WC Larnie WC Dundalk
Hardness ¹	2.5 kp – 6.5 kp		WC Fajardo WC Larnie WC Dundalk
Loss on Drying (LOD) ¹	NMT (b)(4)		WC Fajardo WC Larnie WC Dundalk

Specification (Continued)

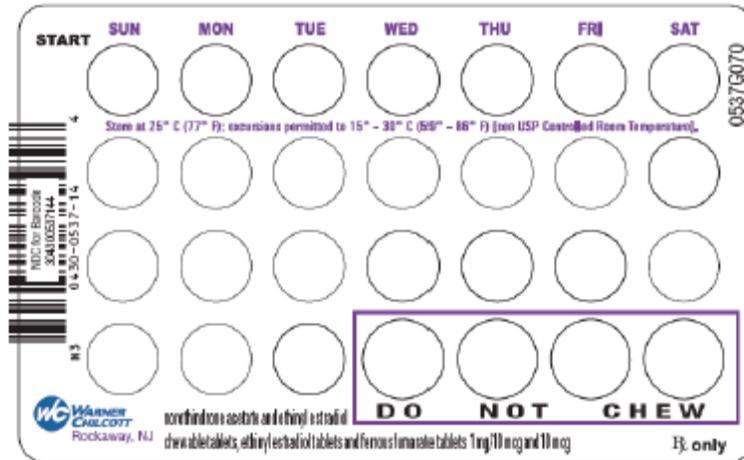
Test	Specification	Method	Test Site
	(b)(4)	USP <61>, <62>	(b)(4)

Comments: Specification is based on that for the approved product in NDA 22501. Information is adequate to allow review.

CONTAINER CLOSURE SYSTEM

The tablets are packaged in the following packaging configuration:

Figure 1: WC3064 Package Configuration



The chewable combination tablets are contained in the first 24 wells of the blister pack, while the nonchewable ethinyl estradiol tablets are contained in blister wells 25-26 and the inert, nonchewable ferrous fumarate tablets are in blister wells 27-28. The blister packaging is the same as used in the approved product under NDA 22501.

STABILITY

The applicant requests 12 months of expiry based on the following expiry determination for the individual tablets:

- 12 months for the combination tablets
- 36 months for the EE tablets
- 48 months for the ferrous fumarate tablets

(b) (4) (chewable combination tablets)

The following stability package was submitted in support of the requested 12 months expiration dating period:

- 3 batches of drug product manufactured using (b) (4) 6 months long term, intermediate and accelerated data
- 3 batches of drug product manufactured using (b) (4) 3 months long term, intermediate and accelerated data
- 1 batch for (b) (4) 3 months long term, intermediate and accelerated data

Comment: Although 6 months of data are less than what is currently recommended by ONDQA, based on the fact that the formulation is almost identical to an approved formulation except for the addition of (b) (4) flavor, and that the applicant requested 12 months of expiration dating period, the amount of information is adequate to allow review.

WC3016 (b) (4) (ethinyl estradiol 10 mcg)

An expiration dating period of 36 months is supported by the following stability package used to support the approved NDA 22501:

- 5 batches of drug product manufactured with (b) (4) Up to 48 months of long term stability data
- 4 batches of drug product manufactured with (b) (4) Up to 18 months of long term stability data.

Comment: The amount of data submitted is adequate for review.

Ferrous fumarate tablets

An expiration dating period of 48 months is supported by the following stability package used to support the approved NDA 22501:

- 8 batches of drug product: Up to 48 months of long term stability data

Comment: The amount of data submitted is adequate for review.

LABELING

The applicant has provided carton/container labels and a Physician's Insert. Information is adequate to allow review.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

DONNA F CHRISTNER
11/29/2012

MOO JHONG RHEE
11/29/2012
Chief, Branch IV

Memorandum

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

Date: 07/23/2013

From: Gene W. Holbert, Ph.D.
Senior Review Chemist, ONDQA
Premarketing Assessment Division II
ONDQA

Through: Moo-Jhong Rhee, Ph.D.
Chief, Branch IV
Premarketing Assessment Division II
ONDQA

To: CMC Review #1 of NDA 204654

Subject: Approval Recommendation

When CMC review #1 was filed, two issues were outstanding, Establishment Evaluation and the final package insert.

On 07/09/2013, the Office of Compliance issued an overall “**Acceptable**” recommendation for all facilities involved in manufacturing and testing of the drug substance and drug product (EER Summary Report, **Attachment 1**).

On 07/23/2013 the final package insert was submitted and the revisions are *satisfactory* from the ONDQA perspective (**Attachment 2**). Final container and carton labels were submitted on 07/15/2013.

Recommendation: This NDA is now recommended for **Approval** from the ONDQA perspective with an expiration dating period of 12 months.

Attachment 1: Establishment Evaluation Report

**FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
SUMMARY REPORT**

Application: NDA 204654/000
Org. Code: 580
Priority: 5
Stamp Date: 28-SEP-2012
PDUFA Date: 28-JUL-2013
Action Goal:
District Goal: 29-MAY-2013

Sponsor: WARNER CHILCOTT
 UNION ST RD 195 KM 1.1
 FAJARDO, PR 00738
Brand Name: (b) (4) norethindroneacetateand ethinyl e
Estab. Name:
Generic Name: (b) (4) norethindroneacetateand ethinyl e
Product Number; Dosage Form; Ingredient; Strengths

001; TABLET (IMMED./COMP. RELEASE), UNCOATED, CHEWABLE;
 NORETHINDRONE ACETATE; 1MG
 001; TABLET (IMMED./COMP. RELEASE), UNCOATED, CHEWABLE;
 ETHINYL ESTRADIOL; 10MCG
 001; TABLET (IMMED./COMP. RELEASE), UNCOATED, CHEWABLE;
 ETHINYL ESTRADIOL; 10MCG
 001; TABLET (IMMED./COMP. RELEASE), UNCOATED, CHEWABLE;
 FERROUS FUMARATE; 75MG

FDA Contacts:	G. HOLBERT	Prod Qual Reviewer		3017961368
	K. JENNINGS	Product Quality PM		3017962919
	P. LUCARELLI	Regulatory Project Mgr	(HFD-580)	3017963961
	D. CHRISTNER	Team Leader		3017961341

Overall Recommendation: ACCEPTABLE on 09-JUL-2013 by M. HEAYN (HFD-320) 3017964753

Establishment: CFN: (b) (4) FEI: (b) (4)
 (b) (4)

DMF No:
Responsibilities: DRUG SUBSTANCE OTHER TESTER
Profile: CONTROL TESTING LABORATORY **OAI Status:** NONE
Last Milestone: OC RECOMMENDATION
Milestone Date: 02-NOV-2012
Decision: ACCEPTABLE
Reason: BASED ON PROFILE

**FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
SUMMARY REPORT**

Establishment: CFN: (b) (4) FEI: (b) (4)
(b) (4)

DMF No: (b) (4) **AADA:** (b) (4)

Responsibilities: DRUG SUBSTANCE MANUFACTURER

Profile: NON-STERILE API BY CHEMICAL SYNTHESIS **OAI Status:** NONE

Last Milestone: OC RECOMMENDATION

Milestone Date: 02-NOV-2012

Decision: ACCEPTABLE

Reason: BASED ON PROFILE

Establishment: CFN: (b) (4) FEI: (b) (4)
(b) (4)

DMF No: (b) (4) **AADA:** (b) (4)

Responsibilities: DRUG SUBSTANCE (b) (4)

Profile: NON-STERILE API BY CHEMICAL SYNTHESIS **OAI Status:** NONE

Last Milestone: OC RECOMMENDATION

Milestone Date: 02-NOV-2012

Decision: ACCEPTABLE

Reason: BASED ON PROFILE

Establishment: CFN: (b) (4) FEI: (b) (4)
(b) (4)

DMF No: (b) (4) **AADA:** (b) (4)

Responsibilities: DRUG SUBSTANCE MANUFACTURER

Profile: NON-STERILE API BY CHEMICAL SYNTHESIS **OAI Status:** NONE

Last Milestone: OC RECOMMENDATION

Milestone Date: 26-JUN-2013

Decision: ACCEPTABLE

Reason: DISTRICT RECOMMENDATION

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

GENE W HOLBERT
07/23/2013

MOO JHONG RHEE
07/23/2013
Chief, Branch IV

NDA 204654

Trade Name

**Norethindrone Acetate and Ethinyl Estradiol
Chewable Tablets, Ethinyl Estradiol Tablets,
and Ferrous Fumarate Tablets
1mg/10mcg and 10mcg**

Warner Chilcott

Gene W. Holbert, Ph.D.

Senior Review Chemist

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

CMC Review for the

Division of Bone, Reproductive and Urologic Products

Table of Contents

Table of Contents	2
Chemistry Review Data Sheet.....	4
The Executive Summary	7
I. Recommendations.....	7
A. Recommendation and Conclusion on Approvability.....	7
B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable.....	7
II. Summary of Chemistry Assessments.....	7
A. Description of the Drug Product(s) and Drug Substance(s).....	7
B. Description of How the Drug Product is Intended to be Used.....	8
C. Basis for Not-Approval Recommendation.....	8
III. Administrative.....	9
A. Reviewer's Signature.....	9
B. Endorsement Block.....	9
C. CC Block.....	9
Chemistry Assessment	10
I. Review of Common Technical Document-Quality (Ctd-Q) Module 3.2: Body of Data.....	10
S DRUG SUBSTANCE [Ethinyl Estradiol, (b) (4)	10
S DRUG SUBSTANCE [Ethinyl Estradiol, (b) (4)].....	15
S DRUG SUBSTANCE [Norethindrone Acetate, (b) (4)].....	19
S DRUG SUBSTANCE [Norethindrone Acetate, (b) (4)	26
P DRUG PRODUCT (b) (4) (Norethindrone Acetate and Ethinyl Estradiol	31
P DRUG PRODUCT (b) (4) Tablets].....	31
P DRUG PRODUCT [WC3016 (b) (4) Tablet].....	92
P DRUG PRODUCT [Ferrous Fumarate Tablets].....	106
A APPENDICES	119
R REGIONAL INFORMATION.....	119
II. Review Of Common Technical Document-Quality (Ctd-Q) Module 1	120



CHEMISTRY REVIEW



A. Labeling & Package Insert.....	120
B. Environmental Assessment or Claim of Categorical Exclusion	127
III. List Of Deficiencies	127
IV. Attachment.....	128

Chemistry Review Data Sheet

1. NDA 204654
2. REVIEW #: 1
3. REVIEW DATE: 22-MAY-2013
4. REVIEWER: Gene W. Holbert, Ph.D.
5. PREVIOUS DOCUMENTS:

Previous DocumentsDocument Date

None

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) ReviewedDocument Date

Original

27-SEPT-2012

Amendment

08-MAY-2013

Amendment

22-MAY-2013

7. NAME & ADDRESS OF APPLICANT:

Name: Warner Chilcott Company, LLC
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) 442-3233

8. DRUG PRODUCT NAME/CODE/TYPE:

- a) Proprietary Name: (b) (4)™
- b) Non-Proprietary Name (USAN): Norethindrone acetate and ethinyl estradiol chewable tablets; ethinyl estradiol tablets; and ferrous fumarate tablets
- c) Code Name/#: (b) (4)
- d) Chem. Type/Submission Priority:

Chemistry Review Data Sheet

- Chem. Type: 5
- Submission Priority: S

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

10. PHARMACOL. CATEGORY: Contraceptive

11. DOSAGE FORM: Tablets and chewable tablets

12. STRENGTH/POTENCY: 1 mg NA/10 mcg EE and 10 mcg EE

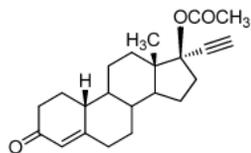
13. ROUTE OF ADMINISTRATION: Oral

14. Rx/OTC DISPENSED: Rx OTC

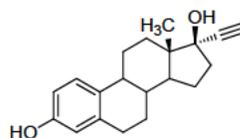
15. [SPOTS \(SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM\)](#):
 SPOTS product – Form Completed

Not a SPOTS product

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



Norethindrone acetate
 Molecular Formula: C₂₂H₂₈O₃
 Molecular Weight: 340.46



Ethinyl estradiol
 Molecular Formula: C₂₀H₂₄O₂
 Molecular Weight: 269.40

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE ¹	STATUS ²	DATE REVIEW COMPLETED	COMMENTS
(b) (4)	II	(b) (4)	Ethinyl estradiol	3	Adequate	08/27/2012 RF Powers	LOA: 07/26/2011
	II		Norethindrone acetate	3	Adequate	04/19/2011 MA Jaigirdar	LOA: 04/10/2006
	II		Ethinyl estradiol	3	Adequate	06/08/2012 SC Dhanesar	LOA: 06/07/2012
	II		Norethindrone acetate	3	Adequate	05/02/2012 RF Powers	LOA: 06/07/2012

Chemistry Review Data Sheet

(b) (4)	III	(b) (4)	(b) (4)	3	Adequate	11/30/2009 Y Tang	LOA: 09/18/2008
	III			3	Adequate	10/25/2012 DN Kline	LOA: 04/10/2012
	III			3, 4	Adequate	09/27/2000 R Lostritto	LOA 09/15/2008
	IV			1	Adequate	11/06/2012 GW Holbert	LOA: 04/19/2010

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
NDA	022501	Lo Loestrin Fe
IND	073510	

18. STATUS:

CONSULTS/CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	N/A		
EES	Pending		
Pharm/Tox	N/A		
Biopharm	N/A		
LNC	N/A		
Methods Validation	N/A		
DMEPA	N/A		
EA	Adequate	02-MAY-2013	GW Holbert
Microbiology	N/A		

The Chemistry Review for NDA 204654

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

The applicant has provided sufficient information to assure the identity, strength, purity, and quality of the drug product.

The Office of Compliance has *not* issued an overall “*Acceptable*” recommendation for the facilities involved in the NDA as of the date of this review.

Labels/labeling issues have *not* yet been resolved.

Therefore, from the ONDQA perspective, this NDA is *not* recommended for approval per 21 CFR 314.125 (b) (1), (13) until the issues delineated above are satisfactorily resolved.

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

Not applicable

II. Summary of Chemistry Assessments

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

(b) (4) consists of three components:

- Twenty-four round, blue (b) (4) chewable tablets [norethindrone acetate (NA), 10 mg and ethinyl estradiol (EE), 10 mcg per tablet]
- Two hexagonal, white WC3016 (b) (4) tablets (EE, 10 mcg per tablet)
- Two round, brown ferrous fumarate tablets containing 75 mg of ferrous fumarate per tablet.

Each blue, chewable tablet also contains the inactive ingredients mannitol, microcrystalline cellulose, FD&C Blue No. 1 Aluminum Lake, sodium starch glycolate, magnesium stearate, povidone, vitamin E, lactose monohydrate, spearmint flavor and sucralose.

Each white tablet also contains the inactive ingredients mannitol, microcrystalline cellulose, sodium starch glycolate, magnesium stearate, povidone, vitamin E and lactose monohydrate.

Executive Summary Section

Each brown tablet contains ferrous fumarate, mannitol, povidone, microcrystalline cellulose, sodium starch glycolate, magnesium stearate, sucralose and spearmint flavor. The ferrous fumarate tablets serve no therapeutic purpose. Ferrous fumarate tablets do not meet the USP monograph criteria for assay or dissolution.

DMEPA found proprietary name (b) (4) to be unacceptable (M. Siahpoushan, 11-JUN-2013).

Norethindrone acetate (NA) and ethinyl estradiol (EE) are synthetic hormones widely used as components of combination oral contraceptives. A USP monograph for the combination of NA and EE has been published. NA and EE used in (b) (4) chewable tablets and WC3016 (b) (4) tablets (EE only) are sourced from (b) (4). Information detailing the manufacture, characterization, quality control, container closure system and stability for the drug substances from each manufacturer are found in drug master files filed with the FDA.

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

Norethindrone acetate and ethinyl estradiol chewable tablets, ethinyl estradiol tablets and ferrous fumarate tablets is indicated for use by women to prevent pregnancy.

Patients are instructed to begin taking norethindrone acetate and ethinyl estradiol chewable tablets, ethinyl estradiol tablets and ferrous fumarate tablets on Day 1 of the menstrual cycle (i.e., the first day of menstrual bleeding). One blue tablet should be taken daily for 24 days, followed by one white tablet daily for two days, followed by one brown tablet daily for two days.

Norethindrone acetate and ethinyl estradiol chewable tablets, ethinyl estradiol tablets and ferrous fumarate tablets must be taken exactly as directed. One tablet is taken orally at the same time every day. The blue tablet (b) (4) chewed before swallowing. If the blue tablet is chewed, the patient should drink a full glass (8 ounces) of liquid immediately after swallowing. The white tablet and the brown tablet are swallowed. Tablets must be taken in the order directed on the blister pack. Tablets should not be skipped or taken at intervals exceeding 24 hours. Norethindrone acetate and ethinyl estradiol chewable tablets, ethinyl estradiol tablets and ferrous fumarate tablets may be administered without regard to meals.

C. Basis for Not-Approval Recommendation

21 CFR 314.125 (b) (6):

- Label/labeling issues are not resolved.

21 CFR 314.125 (b) (13):

Executive Summary Section

- The Office of Compliance has not issued an overall “**Acceptable**” recommendation.

III. Administrative**A. Reviewer’s Signature**

Signed electronically in DARRTS

B. Endorsement Block

Gene W. Holbert, Ph.D./Date: 22-MAY-2013

Moo-Jhong Rhee, Ph.D./Date 17-JUN-2013

C. CC Block

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

GENE W HOLBERT
06/17/2013

MOO JHONG RHEE
06/18/2013
Chief, Branch IV