CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

204654Orig1s000

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

NDA Number: 204654

Stamp Date: 09/28/2012

Applicant: Warner Chilcott Company, LLC

Drug Name: (b) (4) (norethindrone acetate and ethinyl estradiol chewable tablets, ethinyl estradiol tablets, and ferrous fumarate tablets)

On **initial** review of the NDA/BLA application for filing:

	Content Parameter	Yes	No	N/A	Comment
Criteria for Refusal to File (RTF)					
1	Has the applicant submitted bioequivalence data comparing to-be-marketed product(s) and those used in the pivotal clinical trials?	x			
2	Has the applicant provided metabolism and drug-drug interaction information?			x	new formulation, use the information from the reference product
3	Has the sponsor submitted bioavailability data satisfying the CFR requirements?	x			Pivotal study
4	Did the sponsor submit data to allow the evaluation of the validity of the analytical assay?	x			
5	Has a rationale for dose selection been submitted?			x	
6	Is the clinical pharmacology and biopharmaceutics section of the NDA organized, indexed and paginated in a manner to allow substantive review to begin?	x			
7	Is the clinical pharmacology and biopharmaceutics section of the NDA legible so that a substantive review can begin?	x			
8	Is the electronic submission searchable, does it have appropriate hyperlinks and do the hyperlinks work?	x			
Criteria for Assessing Quality of an NDA (Preliminary Assessment of Quality)					
	Data				
9	Are the data sets, as requested during pre-submission discussions, submitted in the appropriate format (e.g., CDISC)?	x			
10	If applicable, are the pharmacogenomic data sets submitted in the appropriate format?			x	
	Studies and Analyses				
11	Is the appropriate pharmacokinetic information submitted?	x			
12	Has the applicant made an appropriate attempt to determine reasonable dose individualization strategies for this product (i.e., appropriately designed and analyzed dose-ranging or pivotal studies)?			x	

13	Are the appropriate exposure-response (for desired and undesired effects) analyses conducted and submitted as described in the Exposure-Response guidance?			x	
14	Is there an adequate attempt by the applicant to use exposure-response relationships in order to assess the need for dose adjustments for intrinsic/extrinsic factors that might affect the pharmacokinetic or pharmacodynamics?			x	
15	Are the pediatric exclusivity studies adequately designed to demonstrate effectiveness, if the drug is indeed effective?			x	
16	Did the applicant submit all the pediatric exclusivity data, as described in the WR?			x	The Sponsor requests a full pediatric waiver for pre-menarcheal children
17	Is there adequate information on the pharmacokinetics and exposure-response in the clinical pharmacology section of the label?	x			
	General				
18	Are the clinical pharmacology and biopharmaceutics studies of appropriate design and breadth of investigation to meet basic requirements for approvability of this product?	x			
19	Was the translation (of study reports or other study information) from another language needed and provided in this submission?			x	

IS THE CLINICAL PHARMACOLOGY SECTION OF THE APPLICATION FILEABLE? ___Yes___

The following are reviews issues to be conveyed to the sponsor:

The labeling of the new dosing instruction to include volume and type of liquid will be a review issue.

Li Li	10/26/2012
Reviewing Clinical Pharmacologist	Date
Myong Jin Kim	10/26/2012
Team Leader/Supervisor	Date

Filing Memo

Clinical Pharmacology Review

NDA: 204654
Compound: [redacted] (norethindrone acetate and ethinyl estradiol chewable tablets, ethinyl estradiol tablets, and ferrous fumarate tablets)
Sponsor: Warner Chilcott Company, LLC
Date: 10/26/2012
Reviewer: Li Li, Ph.D.

Introduction:
The Sponsor submitted a New Drug Application (NDA) for a combination oral contraceptive (COC) [redacted]
The dose and dosing regimen of [redacted] is

- Cycle Days 1-24: one mint-flavored, chewable tablet containing 1 mg norethindrone acetate (NETA)/10 µg ethinyl estradiol (EE) (referred to as [redacted] 1/10 Tablet)
- Cycle Days 25-26: one 10 µg EE tablet (Referred to as WC3016 EE10 Tablet)
- Cycle Days 27-28: one inactive tablet containing ferrous fumarate

One tablet is to be taken daily for 28 consecutive days.

[redacted] has the same NETA/ EE dose and dosing regimen as the reference product Lo Loestrin Fe (NDA 022501, Warner Chilcott Company, approved on October 21, 2010). The difference is in the mode of administration for tablets in the first 24-day of each cycle. In particular, [redacted] 1/10 tablet can be "chewed" [redacted] whereas WC3016 1/10 tablet in Lo Loestrin Fe should be "swallowed whole". In addition, a [redacted] and spearmint flavor is added to [redacted] 1/10 tablet to enhance the chewability of the formulation. The 10 µg EE tablets and ferrous fumarate tablets in [redacted] are identical to those in Lo Loestrin Fe.

The Sponsor seeks the approval of [redacted] based on the demonstration of bioequivalence (BE) in norethindrone (NE) and EE exposure between [redacted] 1/10 chewable tablets and WC3016 1/10 tablets in Lo Loestrin Fe (Study PR12111).

Clinical Development of [redacted]
This application contains a full report of:

- BE and food effect study (Study PR-12111):
  A Randomized, Single-Dose, Three-Way Crossover Study conducted in healthy female volunteers to
  - assess the BE in NE and EE exposure from [redacted] 1/10 chewable tablets and the approved Lo Loestrin Fe (WC3016 1/10) tablets
  - assess the effect of food on bioavailability of NE and EE from the [redacted] 1/10 chewable tablets
- Food effect study on WC3016 EE10 tablet (Study PR-14106, previously submitted under NDA 022501)
- Single- and multiple-dose study of Lo Loestrin Fe (WC3016 1/10) tablet (Study PR-14206, previously submitted under NDA 022501)
- Oral safety study of [redacted] chewable tablets (Study PR-10007)

Drug Product Formulation:
The [redacted] 1/10 chewable tablet formulation was based on the formulation for the approved WC3016 1/10 tablets. The [redacted] 1/10 chewable tablet formulation has added flavor and [redacted] mannitol. A comparison of the unit-dose composition for the [redacted] 1/10 chewable tablet formulation and the reference product, WC3016 1/10 tablet formulation is provided in **Table 1**.

Table 1: Unit-Dose Composition of [redacted] 1/10 Chewable Tablets and WC3016 1/10 Tablets

	[redacted] 1/10 chewable tablets (Formulation [redacted])		WC3016 1/10 tablets (Formulation WC3016-21C)	
Component	mg/tablet	% w/w	mg/tablet	% w/w
Norethindrone acetate	1.000	[redacted]	1.000	[redacted]
Ethinyl estradiol*	0.010		0.010	
Povidone [redacted]	[redacted]		[redacted]	
Vitamin E [redacted]				
Lactose Monohydrate [redacted]				
Mannitol [redacted]				
Mannitol [redacted]				
Microcrystalline Cellulose [redacted]				
FD&C Blue #1, Aluminum Lake				
Spearmint Flavor [redacted]				
Sucralose				
Sodium Starch Glycolate				
Magnesium Stearate				
Total				

[redacted]

BE Assessment

A single-dose, three way-crossover study was conducted in 42 healthy female volunteers. All subjects received the following 3 treatments:

- Treatment A: WC3016 1/10 tablet administered under fasted conditions
- Treatment B: [redacted] 1/10 chewable tablet administered under fasted conditions
- Treatment C: [redacted] 1/10 chewable tablet administered with a high fat meal

All tablets were administered orally with about 240 mL water following at least a 10-hour fast or following consumption of a standard high fat meal (Treatment C). Blood samples (10 mL) were collected at predose and 0.5, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 12, 16, 24, 36, 48 and 60 hours postdose. Treatment periods were separated by at least 7 days.

Per Sponsor, statistical analysis on PK parameters (i.e., C_{max} and AUC) of NE and EE indicated that the [redacted] chewable 1/10 tablet is bioequivalent to WC3016 1/10 tablet. When [redacted] 1/10 chewable tablets were administered with food, C_{max} values were decreased by 46% for NE and 41% for EE. The extent of NE and EE absorption was not significantly different.

Absorption, Distribution, Metabolism, and Excretion (ADME)

Specific studies describing the ADME of [redacted] were not conducted. The Sponsor is proposing to use the available information of the reference product (i.e., Lo Loestrin Fe).

Drug-Drug Interactions:

No DDI studies were conducted with [redacted]

Specific Populations:

- Pediatric use: No pediatric studies were conducted; the Sponsor requests a full waiver of the requirement for pediatric studies associated with the submission of this NDA
- Geriatric use: No geriatric studies were conducted
- Renal or hepatic impairment: No studies were conducted in patients with renal or hepatic impairments
- Contraindicated for pregnant women

Bioanalytical Method:

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