CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

022501Orig1s000

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

OFFICE OF CLINICAL PHARMACOLOGY REVIEW

NDA: 22-501	Submission Date(s): 04/20/2010 (Resubmission) 03/26/2009; 12/23/2009 (Original)
Brand Name	Lo Loestrin Fe®
Generic Name	WC3016 (norethindrone acetate, NA 1 mg and ethinyl estradiol, EE 10 µg tablets, ethinyl estradiol 10 µg tablets and ferrous fumarate tablets)
Reviewer	Sandhya Apparaju, Ph.D.
Team Leader	Myong Jin Kim, Pharm.D.
OCP Division	Division of Clinical Pharmacology III (DCP3)
OND Division	Division of Reproductive and Urologic products
Sponsor	Warner Chilcott
Submission Type	NDA Resubmission
Formulation; Strength(s)	Oral tablets; 1 mg /10 µg NA/EE tablets and 10 µg EE alone tablets
Indication	Prevention of pregnancy

Table of Contents

1 Executive Summary

The original NDA for WC3016 tablets for prevention of pregnancy (NDA 22-501) was submitted on March 26, 2009. The subject of the NDA is a low dose oral contraceptive consisting of 10 µg of EE and 1 mg of NA (WC3016 1/10 tablets) taken once daily for 24 days, followed by two daily doses of 10 µg of EE (WC3016 EE10 tablets) and ferrous fumarate tablets (75 mg) for 2 days during a 28-day regimen. Three Clinical Pharmacology studies and one phase 3 safety and efficacy trial were conducted in support of this NDA.

An optional intra-divisional Clinical Pharmacology briefing was held for this NDA on November 16, 2009. NDA was found acceptable from a Clinical Pharmacology perspective provided an agreement could be reached with the sponsor pertaining to labeling language [refer to Clinical Pharmacology review in DARRTS signed on 11/27/2009].

During the first review cycle the NDA received a complete response action (letter dated January 26, 2010) due to pending CMC issues (deficiencies identified during inspections of the drug substance manufacturing facility and a control testing laboratory). Satisfactory resolution of these deficiencies was required before the application could be approved. Labeling was not finalized at the time of complete response action.

With this NDA resubmission (submitted 04/20/2010), sponsor intends to address the unresolved deficiencies noted in the first cycle. In addition, draft labeling that incorporates edits recommended by the Division during the first review cycle has also been included for review.

Labeling review: On December 23, 2009 during the first NDA review cycle, sponsor submitted revised draft labeling and additional information in response to labeling comments sent by the Division via e-mail on December 15, 2009. The sponsor had at the time accepted most of the recommended labeling changes including Clinical Pharmacology changes to Drug Interactions (7.0), Use in Specific Populations (8.0), and Clinical Pharmacology (12.0). In addition, the sponsor provided further justification to support a labeling statement pertaining to metabolic conversion of NA to EE within this section.

Following review of the sponsor's December 23, 2009 response to labeling edits, additional labeling comments were sent to the sponsor with the second round of labeling edits in January 2010. In the NDA resubmission, sponsor has adequately addressed pending labeling comments. In addition, Minor revisions to the Clinical Pharmacology sections of the proposed draft labeling were recommended during the review of the resubmitted labeling and were accepted by the sponsor. There are no pending Clinical Pharmacology issues with regard to the proposed labeling.

1.1 Recommendation

NDA 22-501 is acceptable from a Clinical Pharmacology perspective.

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

/s/

SANDHYA K APPARAJU
10/07/2010

MYONG JIN KIM
10/12/2010

OFFICE OF CLINICAL PHARMACOLOGY REVIEW

NDA: 22-501	Submission Date: 03/26/2009
Brand Name	(b) (4)
Generic Name	Norethindrone acetate (NA) & Ethinyl Estradiol (EE) tablets, and Ferrous Fumarate tablets
Reviewer	Sandhya Apparaju, Ph.D.
Team Leader	Myong Jin Kim, Pharm.D.
OCP Division	Division of Clinical Pharmacology 3
OND Division	Division of Reproductive and Urologic Products
Sponsor	Warner Chilcott, LLC
Relevant IND(s)	73,510
Submission Type; Code	Original NDA
Formulation; Strength(s)	Oral immediate release tablets; 1 mg NA + 10 µg EE, 10 µg EE, Ferrous Fumarate 75 mg
Indication	Prevention of Pregnancy

An optional intra-division level OCP briefing was held for NDA 22-501 on Monday, 16 November, 2009 from 1- 2 PM in WO Bldg 51 Conference Room 3200. Attendees included Dr's. Hae Young Ahn, Myong Jin Kim, Ron Orleans, Darrell Abernathy, Hyunjin Kim, LaiMing Lee, Jee Eun Lee, Chongwoo Yu and Sandhya Apparaju.

Table of Contents

1 Executive Summary

1.1 Recommendation

NDA 22-501 is acceptable from a Clinical Pharmacology perspective, provided an agreement can be reached with the sponsor pertaining to labeling language.

1.2 Phase IV Commitments

None.

1.3 Summary of Important Clinical Pharmacology and Biopharmaceutics Findings

Warner Chilcott has submitted a new drug application (NDA) for (b) (4) (b) (4). (b) (4) (or WC3016) is a low dose oral contraceptive consisting of a new dose and new regimen of the combination of norethindrone acetate (NA) and ethinyl estradiol (EE). The combination of 10 µg of EE and 1 mg of NA (WC3016 1/10 tablets) is taken once daily for 24 days, followed by two daily doses of 10 µg of EE (WC3016 EE10 tablets) and ferrous fumarate tablets (75 mg) for 2 days during a 28-day regimen.

Three Loestrin NA/EE combination contraceptive products are currently approved in U.S. (see regulatory history further below in the QBR). These vary in the amounts of active ingredients (NA: 1 mg-1.5 mg; EE: 20 – 30 µg) and in the total active treatment duration (21 days vs. 24 days). (b) (4) or WC3016 was formulated to investigate if the dose of estrogen could be further reduced while still retaining the efficacy of the higher dose products. The dose of EE was reduced to 10 µg and the 24-day treatment with active hormone previously shown to be safe and effective for Loestrin 24 Fe, was extended by adding 2 days of EE 10 mcg alone.

Three Clinical Pharmacology Phase 1 studies and one Phase 3 safety and efficacy trial were conducted in support of this NDA. Results from the Clinical Pharmacology studies are summarized:

<u>Pharmacokinetics</u>:

EE: Following once-daily administration of (b) (4) tablets, the mean Cmax and AUCτ values for EE were 72 ± 22 pg/mL and 633 ± 235 pg.h/mL, respectively on day 24. Accumulation based on Cmax and AUCτ of EE was 1.4- & 1.6-fold, respectively. Steady-state was achieved by day 13 on average.

NE: The mean Cmax and AUCτ values for norethindrone (NE) on day 24 were 13803 ± 4279 pg/mL and 84375 ± 31220 pg.h/mL, respectively.

Following once-daily administration of NA 1 mg as part of WC3016-1/10 tablets, ~ 1.8-fold and 2.4-fold accumulation of NE was observed for C_{max} and AUCτ respectively. NE concentrations more than doubled by Day 24 due to both accumulation and increased concentrations of sex-hormone binding globulin (SHBG) induced by EE. Steady-state was achieved for NE by day 13 on average.

Relative bioavailability:

WC3016 1/10 tablets: Compared to a hydroalcoholic solution of NA/EE, the Cmax of EE and NE from the 1/10 tablets were lower by ~ 23 % and 42 %, respectively, while the AUC values were comparable. The 90 % C.I. surrounding the treatment mean ratios for AUCs were within 80-125 %.
EE10 tablets: The Cmax and AUC of EE from the 10 µg EE tablet were bioequivalent to that of the solution formulation of EE. The 90 % C.I. surrounding the treatment mean ratios were within 80-125%.

Food Effect:

WC3016-1/10 tablets:
When tablets were dosed under fed conditions [high calorie, high fat meal], the mean Cmax value for EE was reduced by ~ 23 %. The AUC values for EE remained relatively unchanged when dosed with food. The 90 % CI for AUC was within the 80-125 % range.
When WC3016-1/10 tablets were dosed under fed conditions, the mean Cmax value for NE was unchanged, while the AUC increased ~ by 24 % relative to fasted conditions. The 90 % C.I. surrounding the treatment mean ratios of the AUC parameters fell outside the 80-125 % range.

EE10 tablets:
When EE 10µg tablet was administered under fed conditions, the C_{max} was reduced by ~ 31 %, while the AUC parameters remained relatively unchanged compared to dosing under fasting conditions.

The Phase 3 clinical efficacy and safety trial for [redacted] (b) (4) was conducted without regard to meals. Therefore, it is acceptable to administer [redacted] (b) (4) with or without meals.

2 Question-Based Review

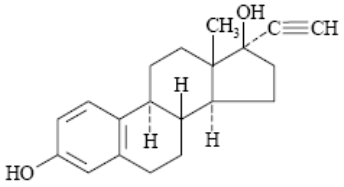
2.1 General Attributes

What pertinent regulatory background or history contributes to the current assessment of the clinical pharmacology and biopharmaceutics of this drug?

- Warner Chilcott has submitted a new drug application for [redacted] (b) (4) a low dose oral contraceptive consisting of a new dose and new regimen of the combination of NA and EE.
- Three versions of Loestrin Fe that contain NA/EE have been previously approved (since 1973):
    - NDA 17-354 Loestrin Fe 1 mg/20 µg NA/EE tablets, USP and Ferrous Fumarate (75 mg) tablets
    - NDA 17-355 Loestrin Fe 1.5 mg /30 µg NA/EE tablets, USP and Ferrous Fumarate (75 mg) tablets.
    - NDA 21-871 Loestrin 24 Fe 1 mg /20 µg NA/EE tablets, USP and Ferrous Fumarate (75 mg) tablets
- [redacted] (b) (4) or WC3016 was formulated to investigate if the dose of estrogen could be further reduced while still retaining the efficacy of the higher dose products. The dose of EE was reduced to 10 µg and the 24-day treatment with active hormone previously shown to be safe and effective for Loestrin 24 Fe, was extended by adding 2 days of EE 10 mcg alone.

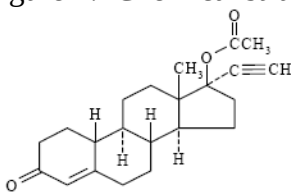
2.1.1. What are the highlights of the chemistry and physical-chemical properties of the drug substance and the formulation of the drug product as they relate to clinical pharmacology and biopharmaceutics review?

- The chemical structures of the two active components are shown:



Ethinyl Estradiol [19-Norpregna-1,3,5(10)-trien-20-yne-3,17-diol, (17α)-]

Figure 1: Chemical structure of Ethinyl Estradiol (EE)



Norethindrone Acetate [19-Norpregn-4-en-20-yn-3-one, 17-(acetyloxy)-, (17α)-]

Figure 2: Chemical structure of Norethindrone Acetate (NA)

- Molecular Weights: 340.46 (NA) and 296.40 (EE)
- Molecular Formulae: $C_{22}H_{28}O_3$ (NA) and $C_{20}H_{24}O_2$ (EE)

- Drug product information:

- The combination tablet containing 1 mg NA and 10 mcg EE has the following inactive ingredients: mannitol, microcrystalline cellulose, FD&C Blue No. 1 Aluminum Lake, sodium starch glycolate, magnesium stearate, povidone, vitamin E and lactose monohydrate.
- The 10 µg EE tablets contain the following inactive ingredients: mannitol, microcrystalline cellulose, sodium starch glycolate, magnesium stearate, povidone, vitamin E and lactose monohydrate.
- Each ferrous fumarate 75 mg tablet contains mannitol, povidone, microcrystalline cellulose, sodium starch glycolate, magnesium stearate, sucralose and spearmint flavor. The ferrous fumarate tablets do not serve any therapeutic purpose.

2.1.2. What are the proposed mechanism(s) of action and therapeutic indication(s)?

- (b) (4) is indicated for the prevention of pregnancy in women (b) (4) (b) (4)

- Combination oral contraceptives act by suppression of gonadotropins. Although the primary mechanism of this action is inhibition of ovulation, other alterations include changes in the cervical mucus (which increase the difficulty of sperm entry into the uterus) and the endometrium (which reduce the likelihood of implantation).

2.1.3. What are the proposed dosage(s) and route(s) of administration?

- The formulation is administered via the oral route. The dosage of (b) (4) is one tablet containing NA and EE daily for 24 consecutive days, followed by one tablet containing EE daily for 2 consecutive days, followed by one tablet containing ferrous fumarate daily for 2 consecutive days.

2.2 General Clinical Pharmacology

2.2.1 What are the design features of the clinical pharmacology and clinical studies used to support dosing or claims?

Three Phase 1 Clinical Pharmacology studies and a Phase 3 safety and efficacy trial were conducted in support of this new formulation:

- Study RR-00108/ Protocol PR-14206: A study to characterize the bioavailability of EE and Norethindrone (NE) following multiple-dose administration of WC3016 tablets in healthy female volunteers. This was a single center, single-treatment, multiple-dose, bioavailability characterization study in N = 18 healthy female subjects (ages 18-35 years). Data from 15 subjects is included as pre-dose concentrations of NE or EE were found prior to first dose in 3 subjects.

- Study RR-09207/ Protocol PR-14006: A study to assess the bioavailability of EE and NE following oral administration of a WC3016 1/10 tablet (fasted) as compared to both a WC3016 tablet (fed) and an EE/NA solution (fasted) in healthy female volunteers. This was a single center, randomized, balanced, single-dose, 3-treatment. 3-period, 6-sequence crossover study in N =24 females.

- Study RR09007/ Protocol PR-14106.0: A study to assess the bioavailability of EE following oral administration of a WC3016 EE10 tablet (fasted) as compared to both a WC3016 EE10 tablet (fed) and a EE solution (fasted) in healthy female volunteers. This was a single-center, randomized, balanced, single-dose, 3-treatment, 3-period, 6-sequence, crossover study in N = 24 healthy female subjects (18-35 years).

- Study PR-05806 (Phase 3): An Open-Label Study of the Safety and Efficacy of a New Low Dose Oral Contraceptive Containing NA and EE. This was an open-label, uncontrolled, multicenter study that enrolled approximately 1,600 heterosexually active women aged 18 to 45 years and at risk of becoming pregnant, who were assigned to take WC3016 daily for thirteen 28-day cycles of treatment *[see clinical review by Dr. Ron Orleans for a discussion of the safety and efficacy outcomes]*.

2.2.2 What is the basis for selecting the response endpoints (i.e., clinical or surrogate endpoints) or biomarkers (collectively called pharmacodynamics (PD)) and how are they measured in clinical pharmacology and clinical studies?

- Pregnancy rate was the primary outcome measure in Phase 3 and is an appropriate endpoint for evaluating the efficacy of a contraceptive product.
- The primary efficacy endpoint in the Phase 3 efficacy and safety study was the incidence of pregnancy, based on the Pearl Index (PI) in the group of women 35 years of age or less based on all at-risk cycles where no other method of birth control was used.
- In addition, the PI for all subjects, regardless of age and based on all at-risk cycles where no other method of birth control was used, was also determined. The 95% confidence intervals for the Pearl Indices and life-table estimates of a subject becoming pregnant were also presented.

2.2.3 Are the active moieties in the plasma (or other biological fluid) appropriately identified and measured to assess pharmacokinetic parameters?

- Yes. Plasma samples were analyzed for EE and NE by (b) (4) (b) (4) using a validated gas chromatographic method with mass spectrometric detection (GC/MS). The validation report and study assay reports were reviewed and found to demonstrate suitability of the assay for determination of EE and NE in human plasma.

2.2.4 Pharmacokinetics

2.2.4.1 What are the single dose and multiple dose PK parameters?

- Study RR-00108/ Protocol PR-14206 was a single center, single-treatment, multiple-dose, bioavailability characterization study that evaluated the single dose and multiple dose pharmacokinetics of NE and EE from the proposed formulation in healthy female volunteers (N = 18; ages 18-35 years); PK data from 3 subjects was excluded by sponsor per protocol as these individuals had unexplained pre-dose concentrations of the analytes that may suggest use of other oral contraceptive products.

- Treatments:
  1 tablet containing 1 mg NE and 10 mcg EE per day on days 1-24
  1 tablet containing 10 mcg EE per day on days 25-26

- PK sampling was done on days 1, 24 and 26 at pre-dose, and at 0.33, 0.67, 1, 1.33, 1.67, 2, 2.5, 3, 4, 6, 9, 12, 16, 24 hours post-dose. Additional samples were obtained just prior to receiving doses 5, 9, 13, 17, and 21 for assessment of steady-state. Blood samples for determination of serum sex-hormone binding globulin (SHBG) concentrations were collected prior to dosing on study day 1 and 24 hours after receiving doses 1, 4, 8, 12, 16, 20, 24 and 26.

- Analytical methodology: Plasma EE and NE concentrations were determined at (b) (4) using a validated GC/MS method. The lower limits of quantitation were 2.5 pg/ml and 25 pg/ml for EE and NE, respectively. SHBG levels in serum samples were determined using a commercially available immunoassay kit (IRMAZEN co SHBG, Zen Tech sa, Belgium). All results were reported as nmol/L. Assay was valid over a range of 10-250 nmol/L. The accuracy and precision data for calibration standards and QCs was acceptable (within 15 %).

- Pharmacokinetic methods: PK parameters were determined for EE and NE on days 1, 24 and 26 using non-compartmental methods.

EE Pharmacokinetics:

- Following once-daily administration of 10 µg EE tablets for 24 days (as part of WC3016-1/10 24-tablet regimen), accumulation ratios based on Cmax and AUCτ of EE were 1.4- and 1.6-fold, respectively on day 24, compared to single dose data on day 1. Steady-state for EE was achieved on average by day 13 based on visual assessment of mean data. Tukey's multiple comparison testing conducted by the sponsor suggests that the trough levels were not significantly different after the second dose of the drug.

- Accumulation of EE was not observed on day 26 (after two days of dosing with EE10 alone) relative to day 1 (when it was administered as part of the combination NA/EE1/10 tablet). This was because the EE exposure on day 26 was lower by ~37 % compared to day 24 (last day of combination 1/10 tablet). Sponsor notes that absence of a contribution from the metabolic conversion of NE to EE after day 24 might be the reason for lower EE systemic exposure on day 26.

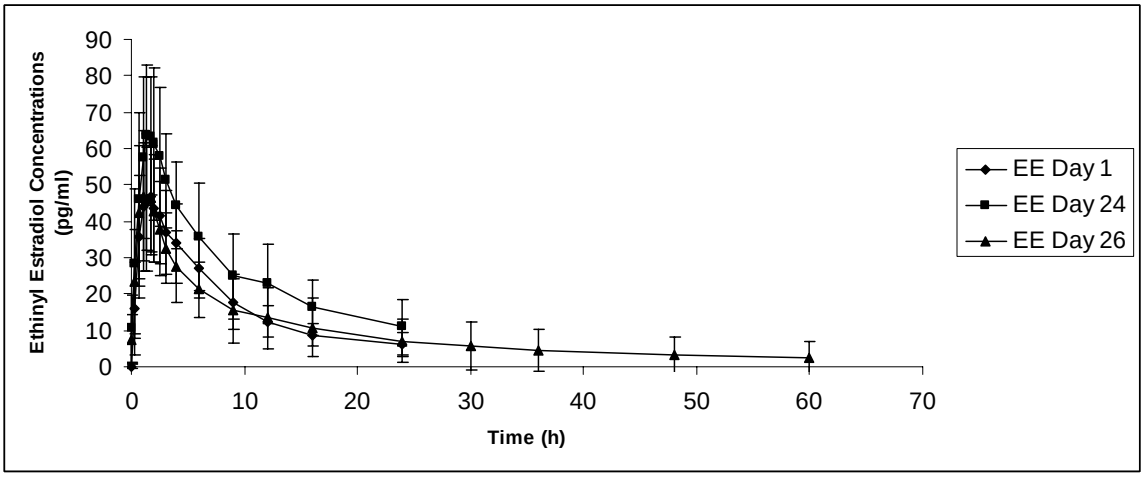


Figure 3: Mean (SD) plasma concentration-time profiles of EE from WC3016 tablets in healthy female volunteers on days 1, 24 and 26.

Table 1: Pharmacokinetic parameters of EE from WC3016 1/10 tablets

EE	**Day 1 (NA/EE 1/10 tablets)**	**Day 24 (NA/EE 1/10 tablets)**	**Day 26 (EE10 tablets)**
T_{max} (h)]	1.33 [1 -4]	1.33 [0.33 - 2.0]	1.33 [1-12]
C_{max} (pg/ml)	51.72 (14.3) [27.8 %]	72.08 (21.65) [30 %]	49.67 (20.1) [40 %]
AUC_{τ} (pg.h/ml)	404 (121) [30 %]	633 (235) [37 %]	395 (198) [50 %]
C_{min} (pg h/ml)	-	9.78 (7.96) [81.42 %]	6.69 (5.76) [86.1 %]
C_{avg} (pg.h/ml)	-	26.38 (9.82) [37.25 %]	16.48 (8.27) [50.2 %]
$T_{1/2}$ (h)	-	-	18.4 (9) [48.9 %]
Accumulation Ratio R_{AUC}	-	1.57	0.97
Values reported are Mean (SD) [% CV]; for Tmax, mean [range] are reported. N =15			

Norethindrone pharmacokinetics:

- Following once-daily administration of NE 1 mg as part of WC3016-1/10 tablets, ~ 1.8-fold and 2.4-fold accumulation of NE was observed on day 24 for C_{max} and AUCτ respectively, relative to single dose data on day 1. Based on visual

assessment of trough levels steady-state was achieved for NE by day 13 on average. Tukey's multiple comparison testing was conducted by sponsor for steady-state assessment and data in general shows that the trough levels were not significantly different among doses after day 5. Serum SHBG concentrations doubled by day 24 [Fig 5]. Norethindrone concentrations more than doubled by day 24 due to both accumulation and increased SHBG concentration.

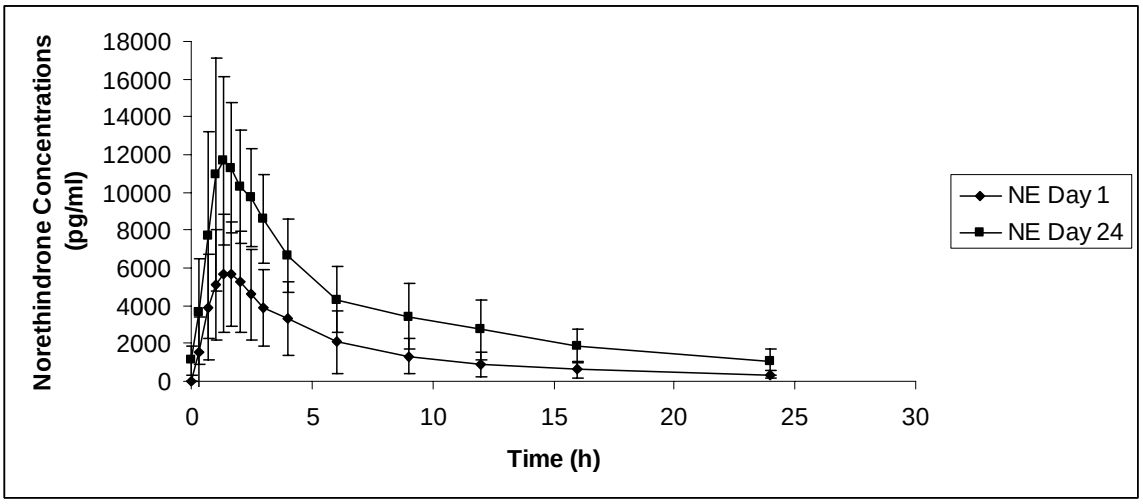


Figure 4: Mean (SD) plasma concentration-time profiles of NE from WC 3016 tablets on days 1 and 24.

Table 2: Plasma NE pharmacokinetics in healthy female subjects on days 1 & 24.

NE	Day 1	Day 24
T_{max} (h)	1.67 [1.33-6.0]	1. 33 [1.0-2.5]
C_{max} (pg/ml)	7683 (1959) [25.5 %]	13803 (4279) [31 %]
AUCτ (pg.h/ml)	37100 (15667) [42 %]	84375 (31220) [37 %]
$T_{1/2}$ (h)	7.89 (2.31) [29 %]	8.86 (2.79) [31.5 %]
Accumulation (R_{AUC})	-	2.4
Values reported are mean (SD) [% CV]; Median [range] are reported for Tmax; N =15		

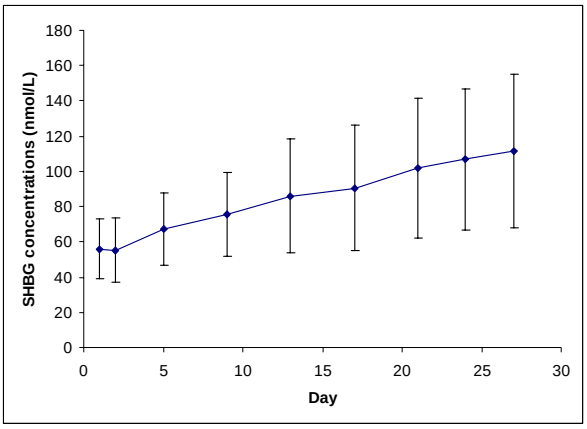


Figure 5: Average SHBG concentrations (pre-dose) during once-daily administration of WC3016 1/10 tablets in healthy female volunteers (N = 15)

2.2.4.2 What are the characteristics of drug absorption?

- NA and EE are rapidly absorbed from (b) (4) tablets. Maximum plasma concentrations of NE and EE occur approximately 1 to 2 hours post-dose. Absolute bioavailability is reported to be approximately 64% for NE and 55% for EE.
- When dosed as a WC3016 1/10 tablet, compared to a solution of the drugs the Cmax of EE and NE were lower but the AUC values were comparable. The EE alone 10 mcg tablets were bioequivalent to the EE solution.
- For the WC3016 1/10 tablet, concomitant food intake reduced the Cmax of EE by 23 %, but the AUC was unchanged. Food did not affect the Cmax of NE but increased AUC by ~ 24 %. When EE 10 µg alone tablet was administered under fed conditions, the Cmax was reduced by ~ 31 % relative to dosing under fasted conditions, but the AUC was relatively unaffected.
- Phase 3 clinical trial for (b) (4) was done without regard to food. Hence it is acceptable to dose (b) (4) with or without food.

2.2.4.3 What are the characteristics of drug distribution?

- Volume of distribution of NE and EE ranges from 2 to 4 L/kg. Plasma protein binding of both steroids is extensive (>95%); NE binds to both albumin and SHBG, whereas EE binds to albumin. Although EE does not bind to SHBG, it induces SHBG synthesis. SHBG concentrations doubled following 24 days of dosing with (b) (4) combination tablets.

2.2.4.4 What are the characteristics of drug metabolism?

- NE undergoes extensive biotransformation, primarily via reduction, followed by sulfate and glucuronide conjugation. The majority of metabolites in the circulation are sulfates, with glucuronides accounting for most of the urinary metabolites.
- EE is also extensively metabolized, both by oxidation and by conjugation with sulfate and glucuronide. Sulfates are the major circulating conjugates of EE and glucuronides predominate in urine. The primary oxidative metabolite is 2-hydroxy ethinyl estradiol, formed by the CYP3A4 isoform of cytochrome P450. Part of the first-pass metabolism of EE is believed to occur in gastrointestinal mucosa. EE may undergo enterohepatic circulation.

2.2.4.5 What are the characteristics of drug excretion?

- NE and EE are excreted in both urine and feces, primarily as metabolites. Plasma clearance values for NE and EE are similar (approximately 0.4 L/hr/kg). Elimination half-lives of NE and EE following administration of 1 mg NA/10 µg EE tablets are approximately 9 hours and 18 hours, respectively.

2.3 Intrinsic Factors

Renal Impairment:

- The effect of renal disease on the disposition of NE and EE after (b) (4) administration has not been evaluated.

In premenopausal women with chronic renal failure undergoing peritoneal dialysis who received multiple doses of an oral contraceptive containing EE and NE, plasma EE concentrations were higher and NE concentrations were unchanged compared to concentrations in premenopausal women with normal renal function (information from the labeling).

Hepatic Impairment:

- The effect of hepatic disease on the disposition of NE and EE after (b) (4) (b) (4) administration has not been evaluated. However, EE and NE may be poorly metabolized in patients with impaired liver function.

2.4 Extrinsic Factors

Drug-drug interactions

- No specific drug-drug interaction studies were conducted for (b) (4)

Changes in contraceptive effectiveness associated with co-administration of other products:

- Drugs or herbal products that induce such enzymes may decrease the plasma concentrations of contraceptive hormones, and may decrease the effectiveness of hormonal contraceptives or increase breakthrough bleeding. Some drugs or herbal products that may decrease the effectiveness of hormonal contraceptives include: barbiturates, bosentan, carbamazepine, felbamate, griseofulvin, oxcarbazepine, phenytoin, rifampin, St. John's wort, topiramate.

- HIV protease inhibitors: Significant changes (increase or decrease) in the plasma levels of the estrogen and progestin have been noted in some cases of co-administration of HIV protease inhibitors.

- Antibiotics: There have been reports of pregnancy while taking hormonal contraceptives and antibiotics, but clinical pharmacokinetic studies have not shown consistent effects of antibiotics on plasma concentrations of synthetic steroids.

Increase in plasma levels of estradiol associated with co-administered drugs:

- Co-administration of atorvastatin and certain combination oral contraceptives containing ethinyl estradiol increase AUC values for ethinyl estradiol by approximately 20%. Ascorbic acid and acetaminophen may increase plasma ethinyl estradiol levels, possibly by inhibition of conjugation. CYP3A4 inhibitors such as itraconazole or ketoconazole may increase plasma hormone levels.

Changes in plasma levels of co-administered drugs:

- Combination OCs have been shown to significantly decrease plasma concentrations of lamotrigine likely due to induction of lamotrigine glucuronidation. This may reduce seizure control; therefore, dosage adjustments of lamotrigine may be necessary. Decreased plasma concentrations of acetaminophen and increased clearance of temazepam, salicylic acid, morphine and clofibric acid, due to induction of conjugation have been noted when these drugs were administered with combination oral contraceptives.
- Combination hormonal contraceptives containing some synthetic estrogens (e.g., ethinyl estradiol) may inhibit the metabolism of other compounds. Increased plasma concentrations of cyclosporine, prednisolone, and theophylline have been reported with concomitant administration of combination oral contraceptives.

2.5 General Biopharmaceutics

2.5.1 What is the 1) relative bioavailability of the proposed WC3016 1/10 tablets (vs. solution) and 2) effect of food on the proposed WC3016 1/10 formulation?

- The relative bioavailability and food-effect of the NA/EE 1/10 tablets compared to a NA/EE 1/10 solution was evaluated in study # RR09207. This was a single

center, randomized, balanced, single-dose, 3-treatment, 3-period, 6-sequence crossover study in ~ N= 24 healthy female, non-smoking subjects ages 18-35 years inclusive;

- Subjects received 3 treatments in a cross over manner in one of the three periods (6 possible sequences ABC, ACB, BCA, BAC, CAB, CBA). Each drug treatment was separated by a washout of 28 days. In the fed group, subjects received a high-fat, high-calorie breakfast which was consumed over 25-30 minutes and drug was administered within 5 minutes of completion.

    - Treatment A: One WC3016-1/10 Tablet containing 1 mg NA and 10 µg EE /fasted; 240 ml water
    - Treatment B: One WC3016-1/10 Tablet containing 1 mg NA and 10 µg EE /fed; 240 ml water
    - Treatment C: 120 ml solution containing 1 mg NA and 10 µg EE /fasted; 120 ml water

Ethinyl Estradiol:

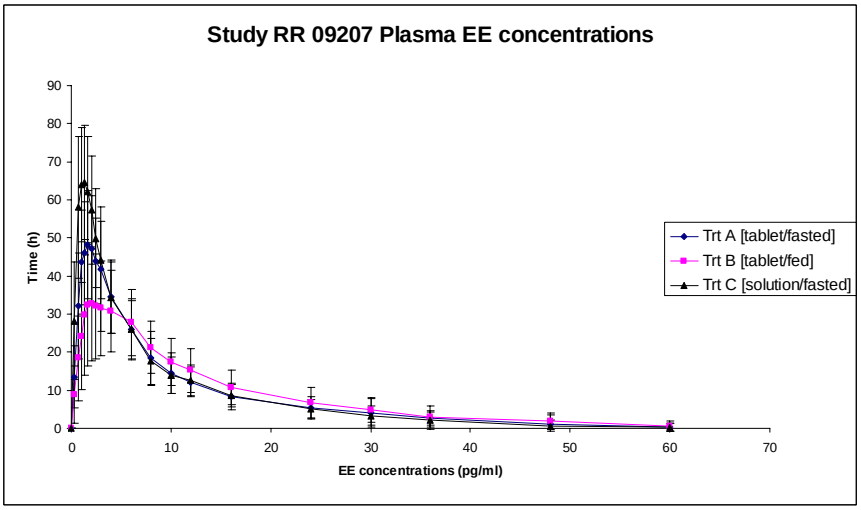


Figure 6: Plasma concentration-time profiles of EE after single doses of WC3016 tablets or solution [A: 1/10 tablet/fasted; B: 1/10 tablet/fed; C: 1/10 solution]

Table 3: Single dose plasma pharmacokinetics of EE

EE PK Study RR09207	Trt A [Tablet/fasted] n =19-22*	Trt B [Tablet/fed] N=18-22*	Trt C [Solution/fasted] N = 21-22*
C_{max} (pg/ml)	53.1 ± 15.5	41.3 ± 12.1	67.7 ± 14.9
T_{max} (h)	1.33 [1.0-4.0]	2.5 [0.67-6.0]	1.33 [0.67-1.67]
AUC_{tldc} (pg.h/ml)	476.1 ± 167.5	491.4 ± 200.1	488.2 ± 161.2
AUC_{inf} (pg.h/ml)	551 ± 216	586.5 ± 228.4	558.6 ± 191.7

$T_{1/2}$ (h)	16.48 ± 13.59	16.2 ± 8.24	13.46 ± 7.27
Values indicate Mean ± SD; Tmax: Median [Range] * Terminal elimination rate constant couldn't be estimated from all individuals and hence T1/2 and AUCinf couldn't be computed from all 22 subjects.			

Relative bioavailability of EE from WC3016 1/10 tablets:

- Compared to a solution of EE, the rate of absorption from the tablet was slower as evidenced by a smaller Cmax value and a wider Tmax range. The extent of EE absorption was not significantly different between the two formulations.
- Statistical comparison using the average bioequivalence approach for the geometric means of test (Trt A) vs. reference (Trt C) confirms that the AUC is comparable as the 90 % confidence interval for the geometric mean ratios of test/reference are within the 80-125 % range.

Table 4: Statistical results for EE - Relative bioavailability of tablets vs. solution

EE PK Parameter	Ratio (Tablet/Solution)	90 % CI
C_{max}	77.63	73.11 – 82.43
$AUC_{0\text{-}tldc}$	96.14	91.11 – 101.46
AUC_{inf}	97.37	91.31 – 103.82

Food-effect on EE from the WC3016 1/10 tablets:

- When WC3016-1/10 tablets were dosed with food, the mean Cmax was reduced by 23 %. Tmax was prolonged when dosed with food. However, the AUC values for EE remained unchanged when dosed with food.
- The 90 % CI for EE AUC remained within the 80-125 % range. Thus it appears that the rate of EE absorption was affected by food but not the extent of absorption.

Table 5: Statistical results for EE- Food effect on bioavailability

EE PK Parameter	Ratio (Fed/Fasted)	90 % CI
C_{max}	77.28	68.83 – 86.77
$AUC_{0\text{-}tldc}$	101.99	96.65 – 107.62
AUC_{inf}	103.11	97.72 – 108.81

Norethindrone:

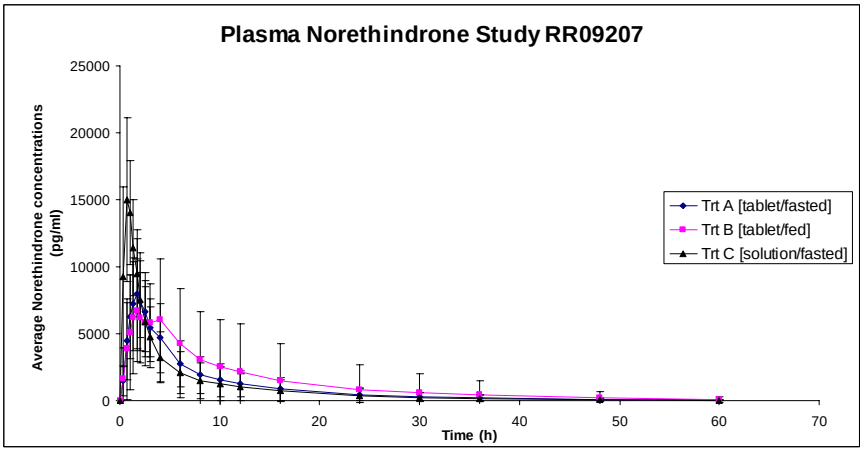


Figure 7: Plasma NE concentration-time profiles following single doses of the tablets or solution

Table 6: Pharmacokinetics of NE after single oral doses of WC3016 tablets

NE PK Study RR09207	Trt A [Tablet/fasted] n =21-22*	Trt B [Tablet/fed] N=22	Trt C [Suspension/fasted] N = 22
C_{max} (pg/ml)	9540 ± 3780	9870 ± 4520	15900 ± 5880
T_{max} (h)	1.67 [0.7 – 4.0]	1.67 [0.67 – 6.0]	0.72 [0.67-1.33]
AUC_{tldc} (pg.h/ml)	56140 ± 32420	80400 ± 97080	57550 ± 38860
AUC_{inf} (pg.h/ml)	58690 ± 33130	82120 ± 100700	58400 ± 39720
$T_{1/2}$ (h)	9.62 ± 2.57	9.78 ± 2.46	9.56 ± 2.62
Values indicate Mean ± SD; Tmax: Median [Range] * Terminal elimination rate constant couldn't be estimated from all individuals and hence T1/2 and AUCinf couldn't be computed from all 22 subjects.			

Relative bioavailability of NE from the WC3016 1/10 tablets:

- The mean Cmax of NE was reduced and Tmax was delayed when dosed as a tablet (vs. a solution).
- The extent of NE absorption (AUC) was however not different as suggested by the 90 % confidence intervals surrounding the treatment ratios that were contained within the 80-125 % range.

Table 7: Statistical results for NE- Relative bioavailability assessment

NE PK Parameter	Ratio (Tablet/Solution)	90 % CI
C_{max}	58.42	53.34 – 64.00
$AUC_{0\text{-}tldc}$	100.37	94.61 – 106.48
AUC_{inf}	99.98	94.10 – 106.23

Food effect on norethindrone PK from WC3016 1/10 tablets:

- When WC3016-1/10 tablets were dosed with food, the mean Cmax and Tmax values for NE remained unchanged; however the AUC was increased by ~24 %. The 90 % confidence intervals surrounding the treatment mean ratios of the AUC parameters fell outside the 80-125 % bioequivalence range.

- Individual subjects varied in the magnitude and direction of food-effect on norethindrone Cmax. Relative to Cmax of norethindrone under fasting conditions, when dosed with food, 9 individuals demonstrated an increase in Cmax (ranging 1.14- 3.0 fold), 9 had a decrease in Cmax (ranging 0.46 – 0.84) and in 4 the Cmax remained relatively unchanged. The increase in AUC of NE that was demonstrated in presence of food was however, more consistently observed among individuals.

Table 8: Statistical results for NE- Food effect assessment

NE PK Parameter	Ratio (Fed/Fasted)	90 % CI
C_{max}	100.32	82.72 – 121.65
$AUC_{0\text{-}tldc}$	123.82	112.36 – 136.46
AUC_{inf}	124.16	112.17 – 137.43

2.5.2. What is the 1) relative bioavailability of the proposed EE 10 µg tablet (vs. solution) and 2) effect of food on the proposed EE 10 µg formulation?

- The relative bioavailability and food-effect of the proposed EE 10 µg tablets were assessed in study # RR09007. Subjects received the following three treatments in a crossover manner:

  A: EE 10 mcg tablet under fasted conditions
  B: EE 10 mcg tablet under fed conditions
  C: EE 10 mcg hydroalcoholic solution

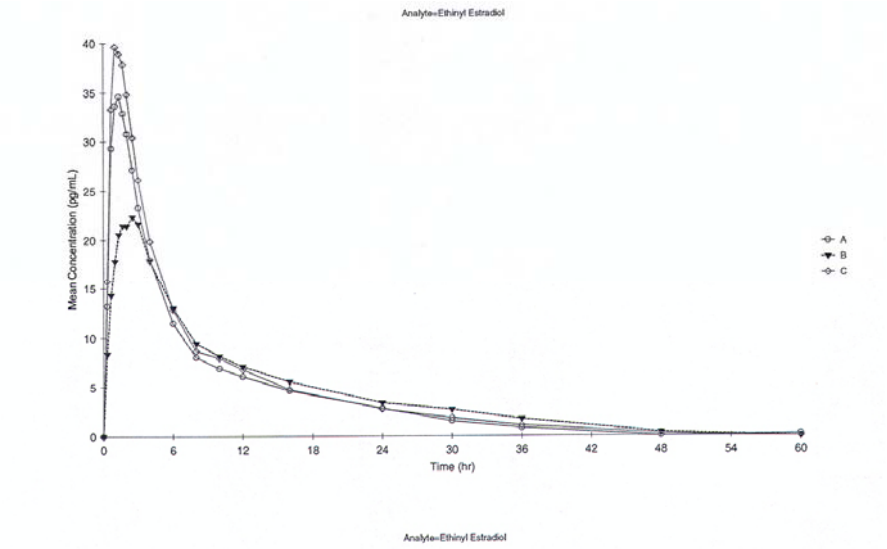


Figure 8: Plasma EE concentration-time profiles in the three treatment groups following single doses of EE 10 µg tablets or solution.

Table 9: Pharmacokinetics of EE from single oral doses of 10 µg EE tablets:

EE PK Study RR09007	**T_{max} (h)**	**C_{max} (pg/mL)**	**AUC_{last} (pg.h/mL)**	**AUC_{inf} (pg.h/mL)**	**T1/2 (h)**
A; Tablet -fasted	1.33 [0.67-2.0]	36.8 ± 11.2	246 ± 95	302 ± 117	12 ± 4
B; Tablet -fed	2.25 [0.67-3.0]	26.4 ± 11.7	252 ± 93	336 ± 118	18 ± 14
C; Solution	1.33 [0.67-2.0]	41.5 ± 11.1	272 ± 103	330 ± 125	13 ± 6

Relative bioavailability of 10 µg EE tablets vs. a solution of EE (A vs. C.):

- When EE was administered as a tablet, relative to a hydroalcoholic solution of the drug, the Cmax and AUC of EE were reduced by ~10 %; however the 90 % confidence intervals surrounding the geometric mean ratios were contained within the bioequivalence limits of 80-125 %.

Table 10: Statistical results for EE- Relative bioavailability of the 10 ug EE tablets

EE 10 µg PK Parameters	Ratio (Tablet/Solution)	90 % CI
Cmax	88.16	81.91 – 94.89
AUC0-tldc	90.86	86.56 – 95.37
AUCinf	92.67	86.55 – 99.24

Food-effect on EE PK from the 10 µg EE tablets (A vs. B):

- When EE 10 mcg tablet was administered under fed conditions, the C_{max} was reduced by ~ 31 % relative to dosing under fasted conditions. While the AUC_{tldc} values were comparable, the AUC_{inf} value under fed conditions was somewhat higher (~ 12 %) under fed conditions, with the upper bound of the 90 % C.I. surrounding the treatment mean ratio exceeding 125 %.

Table 11: Statistical results for EE- Food effect on 10 µg EE tablets

EE 10µg PK Parameter	Ratio (Fed/Fasted)	90 % CI
C_{max}	68.6	58.57 – 80.35
$AUC_{0\text{-}tldc}$	102.25	96.35 – 108.52
AUC_{inf}	112.54	98.52 – 128.55

Overall conclusions: EE 10 µg tablets and solution were bioequivalent. A food-effect on EE Cmax was observed (reduced by ~ 31 %) but food-effect on AUC was small.

2.6 Analytical

- Plasma samples were analyzed for EE and NE by [redacted] (b) (4) using a validated gas chromatographic method with mass spectrometric detection (GC/MS). The validation report and study assay reports were reviewed and found to demonstrate suitability of the assay for determination of EE and NE in human plasma.
- The analytes were extracted from plasma into toluene, followed by several clean-up steps. After extraction, the samples were derivatized in two steps in order to obtain suitable derivatives for gas chromatography. After derivatization, 1-2 ul of the derivatized samples were injected into the GC/MS system. GC/MS measurements were performed in the chemical ionization mode (negative ions) using ammonia as reagent gas.

Validation: The validation samples were extracted and analyzed in 11 runs.

Table 12: Validation results for the assay of EE and NE by GC/MS method

Validation Parameters	EE	NE
Matrix	Plasma	Plasma
Standard curve range; R^2	0.25 – 250 pg/mL; R^2 = 0.99572	25.0 to 25000 pg/mL R^2 = 0.99593
LLOQ	0.25 pg/mL	25 pg/mL

Accuracy (% bias) [EE QCs: 7.5, 30, 200 pg/mL; NE QCs: 75, 2500 and 20000 pg/mL]	Intra-run: 1.61 to 13.53 % Inter-run: 1.2 to 6.54 %	Intra-run: -1.08 to 2.62 % Inter-run: -2.59 to 2.32 %
Precision (% CV) [EE QCs: 7.5, 30, 200 pg/mL; NE QCs: 75, 2500 and 20000 pg/mL]	Intra-run: 2.06 to 4.17 % Inter-run: 5.61 to 6.94 %	Intra-run: 3.65 to 6.58 % Inter-run: 5.53 to 8.16 %
Extraction Recovery	81.1 % - 96.5 %	75.8 % to 106 %
Dilution linearity	2-fold dilution: Accuracy: 11 % Precision: 1.52 % 4-fold dilution: Accuracy: 8.97 % Precision: 1.99 %	2-fold dilution: Accuracy: 10.71 % Precision: 1.72 % 4-fold dilution: Accuracy: 9.66 % Precision: 1.21 %
Stability	acceptable sample stability under various conditions; stable after 3 freeze/thaw cycles	acceptable sample stability under various conditions; stable after 3 freeze/thaw cycles
Selectivity	No significant interfering peaks for either analyte or the internal standard	No significant interfering peaks for either analyte or the internal standard

3 Detailed Labeling Recommendations

(b) (4)

5 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

(b) (4)

[redacted]

[redacted]

[redacted]

[redacted]

4 Appendix

OCP Filing Memo

Office of Clinical Pharmacology *New Drug Application Filing and Review Form*			
General Information About the Submission			
	Information		Information
NDA Number	**22-501**	**Brand Name**	(b) (4) [redacted]
OCP Division	**DCP3**	**Generic Name**	**Norethindrone Acetate and Ethinyl Estradiol (EE) tablets; EE tablets and Ferrous Fumarate tablets**
Medical Division	**DRUP**	**Drug Class**	**Hormonal Contraceptives**
OCP Reviewer	**Sandhya Apparaju, Ph.D.**	**Indication(s)**	**Prevention of Pregnancy**

OCP Team Leader	**Myong Jin Kim, Pharm.D.**	**Dosage Form**	**Tablets**
		Dosing Regimen	**28-day regimen; combination tablets taken once daily for 24 days followed by a daily dose of EE for 2 days and then ferrous fumarate for 2 d**
Date of Submission	**03/26/2009**	**Route of Administration**	**Oral**
Estimated Due Date of OCP Review	**11/20/2009**	**Sponsor**	**Warner Chilcott**
PDUFA Due Date	**01/26/2009**	**Priority Classification**	**Standard**
Division Due Date	**11/20/2009**	**Related IND and NDA**	**73,510 and 21-871**

Clinical Pharmacology and Biopharmaceutics Information

	"X" if included at filing	**Number of studies submitted**	**Number of studies reviewed**	**Critical Comments If any**
STUDY TYPE				
Table of Contents present and sufficient to locate reports, tables, data, etc.	**X**			
Tabular Listing of All Human Studies	**X**			
HPK Summary	**X**			
Labeling	**X**			
Reference Bioanalytical and Analytical Methods	**X**			
I. Clinical Pharmacology				
Mass balance:				
Isozyme characterization:				
Blood/plasma ratio:				
Plasma protein binding:				
Pharmacokinetics (e.g., Phase I) -	**X**			
Healthy Volunteers-				
single dose:	X			
multiple dose:	X	1		**PR 14206**
Patients-				
single dose:				
multiple dose:				
Dose proportionality -				
fasting / non-fasting single dose:				
fasting / non-fasting multiple dose:				
Drug-drug interaction studies -				
In-vivo effects on primary drug:				

In-vivo effects of primary drug:				
In-vitro:				
Subpopulation studies -				
ethnicity:				
gender:				
pediatrics:				
geriatrics:				
renal impairment:				
hepatic impairment:				
PD:				
Phase 2:				
Phase 3:				
PK/PD:				
Phase 1 and/or 2, proof of concept:				
Phase 3 clinical trial:				
Population Analyses -				
Data rich:				
Data sparse:				
II. Biopharmaceutics				
Absolute bioavailability:				
Relative bioavailability -	**X**	**2**		
solution as reference:	X			**PR-14006 and PR-14106**
alternate formulation as reference:				
Bioequivalence studies -				
traditional design; single / multi dose:				
replicate design; single / multi dose:				
Food-drug interaction studies:	**X**			**PR-14006 and PR-14106**
Dissolution:				
(IVIVC):				
Bio-wavier request based on BCS				
BCS class				
III. Other CPB Studies				
Genotype/phenotype studies:				
Chronopharmacokinetics				
Pediatric development plan				(b) (4)
Literature References				
Total Number of Studies		**3**		
Filability and QBR comments				

	"X" if yes	Comments
Application filable ?	**X**	Reasons if the application is not filable (or an attachment if applicable) For example, is clinical formulation the same as the to-be-marketed one?
Comments sent to firm ?		
QBR questions (key issues to be considered)	**Single dose and multiple dose pharmacokinetics** **Food-Effect**	
Other comments or information not included above	**Clinical vs. To-be-marketed formulations are identical.**	
Primary reviewer Signature and Date		
Secondary reviewer Signature and Date		

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22501	ORIG-1	WARNER CHILCOTT CO INC	(b) (4)

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

/s/

SANDHYA K APPARAJU
11/20/2009

MYONG JIN KIM
11/27/2009

Office of Clinical Pharmacology

New Drug Application Filing and Review Form

General Information About the Submission

	Information		Information
NDA Number	**22-501**	**Brand Name**	(b) (4)
OCP Division	**DCP3**	**Generic Name**	**Norethindrone Acetate and Ethinyl Estradiol (EE) tablets; EE tablets and Ferrous Fumarate tablets**
Medical Division	**DRUP**	**Drug Class**	**Hormonal Contraceptives**
OCP Reviewer	**Sandhya Apparaju, Ph.D.**	**Indication(s)**	**Prevention of Pregnancy**
OCP Team Leader	**Myong Jin Kim, Pharm.D.**	**Dosage Form**	**Tablets**
		Dosing Regimen	**28-day regimen; combination tablets taken once daily for 24 days followed by a daily dose of EE for 2 days and then ferrous fumarate for 2 d**
Date of Submission	**03/26/2009**	**Route of Administration**	**Oral**
Estimated Due Date of OCP Review	**11/20/2009**	**Sponsor**	**Warner Chilcott**
PDUFA Due Date	**01/26/2009**	**Priority Classification**	**Standard**
Division Due Date	**11/20/2009**	**Related IND and NDA**	**73,510 and 21-871**

Clinical Pharmacology and Biopharmaceutics Information

	"X" if included at filing	Number of studies submitted	Number of studies reviewed	Critical Comments If any
STUDY TYPE				
Table of Contents present and sufficient to locate reports, tables, data, etc.	**X**			
Tabular Listing of All Human Studies	**X**			
HPK Summary	**X**			
Labeling	**X**			
Reference Bioanalytical and Analytical Methods	**X**			
I. Clinical Pharmacology				
Mass balance:				
Isozyme characterization:				
Blood/plasma ratio:				
Plasma protein binding:				
Pharmacokinetics (e.g., Phase I) -	**X**			
Healthy Volunteers-				
single dose:	X			
multiple dose:	X	1		**PR 14206**
Patients-				
single dose:				
multiple dose:				
Dose proportionality -				
fasting / non-fasting single dose:				
fasting / non-fasting multiple dose:				
Drug-drug interaction studies -				
In-vivo effects on primary drug:				
In-vivo effects of primary drug:				
In-vitro:				
Subpopulation studies -				
ethnicity:				
gender:				
pediatrics:				
geriatrics:				
renal impairment:				

hepatic impairment:				
PD:				
Phase 2:				
Phase 3:				
PK/PD:				
Phase 1 and/or 2, proof of concept:				
Phase 3 clinical trial:				
Population Analyses -				
Data rich:				
Data sparse:				
II. Biopharmaceutics				
Absolute bioavailability:				
Relative bioavailability -	**X**	**2**		
solution as reference:	X			**PR-14006 and PR-14106**
alternate formulation as reference:				
Bioequivalence studies -				
traditional design; single / multi dose:				
replicate design; single / multi dose:				
Food-drug interaction studies:	**X**			**PR-14006 and PR-14106**
Dissolution:				
(IVIVC):				
Bio-wavier request based on BCS				
BCS class				
III. Other CPB Studies				
Genotype/phenotype studies:				
Chronopharmacokinetics				
Pediatric development plan				(b) (4)
Literature References				
Total Number of Studies		**3**		

Filability and QBR comments		
	"X" if yes	**Comments**
Application filable ?	**X**	Reasons if the application is not filable (or an attachment if applicable) For example, is clinical formulation the same as the to-be-marketed one?
Comments sent to firm ?		
QBR questions (key issues to be considered)	**Single dose and multiple dose pharmacokinetics** **Food-Effect**	
Other comments or information not included above	**Clinical vs. To-be-marketed formulations are identical.**	
Primary reviewer Signature and Date		
Secondary reviewer Signature and Date		

Filing Memo

Clinical Pharmacology and Biopharmaceutics Review

NDA: 22-501
Compound: Norethindrone acetate (NA) and Ethinyl Estradiol (EE) (b) (4)
Sponsor: Warner Chilcott

Date: 04/14/2009
Reviewer: Sandhya Apparaju, Ph.D.

Background: Warner Chilcott has submitted a new drug application for (b) (4) (norethindrone acetate and ethinyl estradiol tablets, ethinyl estradiol tablets and ferrous fumarate tablets). (b) (4) (or WC3016) is a low dose oral contraceptive consisting of a new dose and new regimen of the combination of NA and EE. The combination of 10 mcg of EE and 1 mg of NA (or WC3016 1/10 tablets) is taken daily for 24 days followed by a daily dose of 10 mcg of EE (or WC3016 EE10 tablets) for 2 days and then ferrous fumarate tablets (75 mg) for 2 days during a 28-day regimen. The dose may be taken without regard to meals (per draft labeling).

- The sponsor has conducted 3 Clinical Pharmacology and one clinical efficacy & safety trials in support of this NDA:

Protocol Number (Report Number)	Study Objectives	Study Design and Type of Control	Test Product(s); Dosage Regimen; Administration Route	Number of Subjects	Healthy Subjects or Diagnosis of Subjects	Duration of Treatment
Phase 1 Bioavailability and Pharmacokinetic Studies						
PR-14006 (RR-09207)	Assess the comparative EE and NE bioavailability of WC3016-1/10 tablet versus an EE/NA solution/ suspension. Assess the effect of food on EE and NE bioavailability of WC3016-1/10 tablet.	Single-center, randomized, balanced, single-dose, 3-treatment, 3-period, 6-sequence crossover study	WC3016-1/10 tablet; Hydroalcoholic EE solution/NA suspension; Single oral dose	24	Healthy female subjects	2 days
PR-14106 (RR-09007)	Assess the comparative EE bioavailability of WC3016 EE10 tablet versus an EE solution. Assess the effect of food on EE bioavailability of WC3016 EE10 tablet.	Single-center, randomized, balanced, single-dose, 3-treatment, 3-period, 6-sequence crossover study	WC3016 EE10 tablet (10 mcg EE) Hydroalcoholic solution containing 10 mcg EE Single oral dose	24	Healthy female subjects	2 days

Protocol Number (Report Number)	Study Objectives	Study Design and Type of Control	Test Product(s); Dosage Regimen; Administration Route	Number of Subjects	Healthy Subjects or Diagnosis of Subjects	Duration of Treatment
PR-14206 (RR-00108)	Characterize the plasma EE and NE pharmacokinetic profiles and SHBG concentrations following WC3016 administration.	Single-center, single-treatment, multiple-dose	WC3016-1/10 tablet; WC3016 EE10 tablet One WC3016-1/10 tablet x 24 days, one WC3016 EE10 tablet x 2 days. Oral	18	Healthy female subjects	26 days
Phase 3 Efficacy and Safety Study						
PR-05806 (RR-03108)	Assess the efficacy of WC3016 in the prevention of pregnancy. Assess the incidence of IB; assess the safety and tolerability of WC3016.	Multicenter, open-label, uncontrolled study	One WC3016-1/10 tablet x 24 days, one WC3016 EE10 tablet x 2 days, one inactive tablet x 2 days. Oral	1660	Healthy, hetero-sexually active, female subjects	Thirteen 28-day cycles (1 year)

EE: ethinyl estradiol NA: norethindrone acetate NE: norethindrone
SHBG: sex hormone binding globulin IB: intracyclic bleeding
WC3016-1/10: 1 mg NA/ 10 mcg EE tablet WC3106 EE10: 10 mcg EE tablet

The rate of norethindrone and ethinyl estradiol absorption from (b) (4) tablets containing the combination of 1 mg norethindrone acetate and 10 mcg ethinyl estradiol is slower than that from a norethindrone suspension/ethinyl estradiol solution, but the extent of absorption is equivalent. Administration of (b) (4) combination tablets with a high fat meal decreases the rate but not the extent of ethinyl estradiol absorption. The rate of norethindrone absorption is not affected, but the extent of norethindrone absorption is increased by 24% when (b) (4) combination tablets are administered with a high fat meal.

Ethinyl estradiol bioavailability from (b) (4) tablets containing 10 mcg ethinyl estradiol alone is equivalent to that from an ethinyl estradiol solution. Administration of (b) (4) ethinyl estradiol alone tablets with a high fat meal decreases the rate but not the extent of ethinyl estradiol absorption.

The plasma norethindrone and ethinyl estradiol pharmacokinetic profiles and serum sex hormone binding globulin (SHBG) concentrations following multiple-dose administration of (b) (4) were characterized in 15 healthy female volunteers.

Table 3. Summary of Norethindrone (NE) and Ethinyl Estradiol (EE) Pharmacokinetic Parameter Values Following Oral Administration of [redacted] to Healthy Female Volunteers (n=15)

Regimen	Study Day		Arithmetic Mean[a] (%CV) by Pharmacokinetic Parameter				
		Analyte	Cmax	tmax	AUC0–24h	Cmin	Cavg
Single Dose [redacted] combination tablet[c]	1	NE	7360 (21)	1.7 (1.3–6.0)	33280 (33)	--	--
		EE	50.9 (27)	1.3 (1.0-6.0)	389.9 (27)	--	--
		SHBG	--	--	--	54.8 (33) [b]	--
Multiple Dose [redacted] ethinyl estradiol alone tablet[d] x 24 days	24	NE	13900 (34)	1.3 (0.7–3.0)	84160 (41)	917 (84)	3510 (41)
		EE	71.3 (33)	1.3 (0.3–2.0)	621.3 (41)	10.0 (92)	25.9 (41)
		SHBG	--	--	--	109 (38)	--
Multiple Dose [redacted] ethinyl estradiol alone tablet[d] x 2 days	26	EE	49.9 (34)	1.3 (0.7–3.0)	403.6 (50)	--	--

Cmax = Maximum plasma concentration (pg/mL); tmax = Time of Cmax (h); AUC0–24h = Area under plasma concentration versus time curve from 0 to 24 hours (pg·h/mL); Cmin = Minimum plasma concentration (pg/mL); Cavg = Average plasma concentration = AUC0–24h/24 (pg/mL)
%CV = Coefficient of Variation (%); SHBG = Sex hormone binding globulin (nmol/L)
[a] The median (range) is reported for tmax
[b] The Cmin concentration reported for SHBG is the pre-dose concentration
[c] [redacted] combination tablets contain 1 mg norethindrone acetate and 10 mcg ethinyl estradiol
[d] [redacted] ethinyl estradiol alone tablets contain 10 mcg ethinyl estradiol

Ethinyl estradiol and norethindrone Cmax values increase by a factor of 1.4 and 1.9, respectively, following 24 days administration of [redacted] combination tablets as compared to single-dose administration. Ethinyl estradiol and norethindrone AUC0–24h values increase by a factor of 1.6 and 2.5, respectively, following 24 days administration of [redacted] combination tablets as compared to single-dose administration. Norethindrone concentrations more than double by Day 24 due to both accumulation and increased SHBG concentration. Steady state with respect to ethinyl estradiol and norethindrone is reached by Day 5 and Day 13, respectively.

The extent of ethinyl estradiol absorption is 35% lower on Day 26 after administration of the [redacted] ethinyl estradiol alone tablet for 2 days as compared to the 24-day value (after 24 days administration of the [redacted] combination tablets). Norethindrone acetate is partially metabolized to ethinyl estradiol, so ethinyl estradiol concentration is lower on Days 25 and 26 when there is no contribution from norethindrone acetate in the study treatment.

SHBG concentrations double following 24 dosing with [redacted] combination tablets; steady-state with respect to SHBG is reached after 9 days.

- The clinical vs. commercial formulations of [redacted] (b) (4) are identical.
- Study reports and associated electronic datasets for the three phase I studies are included in the NDA submission.
- Bioanalytical method validation and assay reports for the GC/MS analysis of NE and EE in human plasma are included in the submission.
- Labeling is submitted in the new physician's labeling rule (PLR) format.
- There are no filing comments or information requests to the sponsor at this time.

Recommendation:

The Office of Clinical Pharmacology/Division of Clinical Pharmacology 3 find that the Human Pharmacokinetics and Bioavailability section for NDA 22-501 is fileable.

_____ _____

Sandhya Apparaju, Ph.D. Date

_____ _____

Myong Jin Kim, Pharm.D., Team Leader Date

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

/s/

Sandhya Apparaju
5/11/2009 09:33:01 AM
BIOPHARMACEUTICS

Myong-Jin Kim
5/11/2009 08:57:17 PM
BIOPHARMACEUTICS