CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

022573Orig1s000

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

OFFICE OF CLINICAL PHARMACOLOGY REVIEW

NDA: 022573	Submission Dates: 11/26/09; 04/28/10; 06/5/10; 12/16/10, 12/21/10
Brand Name	TRADENAME
Generic Name	Norethindrone and Ethinyl Estradiol chewable tablets and ferrous fumarate chewable tablets
Reviewer	Christian Grimstein, Ph.D.
Team Leader	Myong-Jin Kim, Pharm.D.
OCP Division	Division of Clinical Pharmacology 3
OND Division	Division of Reproductive and Urologic Products (DRUP)
Sponsor	Warner Chilcott Company, LLC.
Submission Type	Original/505(b)(1)
Formulation and Strength	Chewable tablets, Cycle Days 1-24: EE 0.025 mg + NE 0.8 mg; Cycle Days 25-28: ferrous fumarate (placebo)
Indication	Prevention of pregnancy

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1 Executive Summary

The Clinical Pharmacology review of NDA 022573 (DARRTS, 09/01/2010) stated that the NDA 022573 was acceptable provided that an agreement is reached between the sponsor and the Division regarding the language in the package insert labeling. The agreement on the language in the package insert labeling between the sponsor and the Division was reached on 12/21/2010. The highlights of the prescribing information and Clinical Pharmacology relevant sections of the final agreed upon package insert labeling are included in Section 2 of this addendum.

1.1 Recommendation

The Division of Clinical Pharmacology 3, Office of Clinical Pharmacology finds the NDA 022573 acceptable.

8 pages of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

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

/s/

CHRISTIAN GRIMSTEIN
12/21/2010

MYONG JIN KIM
12/22/2010

CLINICAL PHARMACOLOGY REVIEW

NDA:	022573
Type/Category:	Original/505(b)(1)
Brand Name:	TRADENAME
Generic Name:	Norethindrone (NE) and Ethinyl Estradiol (EE) chewable tablets and ferrous fumarate tablets
Relevant IND:	76629
Indication:	Prevention of pregnancy
Dosage Form:	Tablet
Route of Administration:	Oral
Dosing Regimen and Strength:	Once daily 2 phasic (plus placebo phase), 28 day, Cycle Days 1-24: EE 0.025 mg + NE 0.8 mg Cycle Days 25-28: ferrous fumarate (placebo)
Sponsor:	Warner-Chilcott Company, LLC.
OCP Division:	Division of Clinical Pharmacology 3
OND Division:	Division of Reproductive and Urologic Products (DRUP)
Submission Dates:	November 26, 2009, April 28, 2010, June 5, 2010
Reviewer:	Christian Grimstein, Ph.D.
Team Leader:	Myong-Jin Kim, Pharm.D.

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1. Executive Summary

1.1. Recommendation

NDA 022573 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 TRADENAME, a fixed dose combination of 0.8 mg norethindrone (NE) and 0.025 mg ethinyl estradiol (EE). TRADENAME is an oral contraceptive consisting of a new dose and new regimen of the combination of NE and EE, with the proposed indication for the prevention of pregnancy. The TRADENAME tablets are to be taken chewed without water once daily for 24 days, followed by 4 daily doses of ferrous fumarate tablets (75mg) to complete the 28-day regimen.

Four Clinical Pharmacology Phase 1 Studies, 1 Phase 1 safety study, and 1 Phase 3 safety and efficacy study were submitted in support of this NDA. Four Clinical Pharmacology studies include a relative bioavailability study (PR-00807), two multiple dose pharmacokinetics (PK) studies (PR-03808 and PR-00707), and a food effect study (PR-00907). Study PR-00707 does not support the NDA since the drug administration differs from what is proposed in the label. However, the study was reviewed to obtain additional biopharmaceutic information of NE/EE.

The food effect study and relative bioavailability study comparing administration of NE/EE tablet with water vs. without water are reviewed to decide whether the proposed label language regarding food and water intake is acceptable. According to the proposed label language, the TRADENAME tablet is to be taken chewed without regards to food and water.

Results from Clinical Pharmacology studies are summarized:

Pharmacokinetics:

Ethinyl Estradiol: The mean (SD) Cmax and AUC0-24 values for EE following single dose administration (oral, chewed without water) of TRADENAME tablet were 147 (37.1) pg/mL and 902.8 (162.0) pg*h/mL, respectively. Following once-daily administration (oral, chewed without water) of TRADENAME tablet for 24 days, the mean (SD) Cmax and AUCτ values for EE were 168 (41.8) pg/mL and 1400 (449.1) pg*h/mL, respectively on day 24. The median Tmax (range)

following single dose administration was 1.13 h (0.67-2.00) and following once-daily administration for 24 days, median Tmax (range) was 1.00 h (0.33-2.00) on day 24. Accumulation ratios based on Cmax and AUC0-τ of EE were 1.1 and 1.5-fold, respectively. Steady-state for EE was achieved on average by day 9.

Norethindrone: The mean Cmax and AUC0-24 (SD) values for NE following single dose administration (oral, chewed without water) of TRADENAME tablet were 9840 (3520) pg/mL and 41680 (19570) pg*h/mL, respectively. Following once-daily administration (oral, chewed) of TRADENAME tablet for 24 days, the mean (SD) Cmax and AUCτ values for NE were 22200 (6620) pg/mL and 141200 (45230) pg*h/mL, respectively on day 24. Tmax median (range) following single dose administration was 1.05 h (0.67-3.00) and following once-daily administration for 24 days, Tmax median (range) was 1.33 h (0.67-6.00) on day 24. Accumulation ratios based on Cmax and AUCτ of NE were 2.3 and 3.6-fold, respectively. Trough concentrations of NE following a daily administration of TRADENAME continued to increase through to day 21.

Relative Bioavailability:

Formulation effect

The relative bioavailability of NE/EE was assessed in Study PR-00807. Compared to a (b) (4) solution of NE/EE (0.8mg NE/0.025mg EE), when the tablet was chewed without water, Cmax values of EE and NE were 53% higher and 15% lower, respectively. The 90% confidence interval (CI) surrounding the mean ratios for Cmax of EE and NE were outside 80-125%.

Compared to the (b) (4) solution of NE/EE, when the tablet was chewed without water, AUC values of EE and NE were increased by 32% and 3%, respectively. The 90 % CI surrounding the treatment mean ratios for AUCs were outside 80-125 % regarding EE and inside 80-125% regarding NE.

Water effect

When a TRADENAME tablet was chewed and taken with 45ml of water, compared to chewed and taken without water, the absorption rate for EE was decreased. It remained unchanged for NE. Cmax values of EE and NE were reduced by 13 % and 4%, respectively. The 90% CI surrounding the treatment mean ratios for Cmax were outside 80-125% regarding EE and inside 80-125% regarding NE.

The extent of absorption for EE and NE, determined as AUC, did not change when NE/EE was chewed and swallowed with water compared to chewed and swallowed without water.

Food effect

Administration of TRADENAME tablets with food decreased the EE and NE absorption rates. Cmax of EE and NE were 39% and 47 % lower under fed

conditions. Administration with food did not affect the extent of EE absorption but increased the extent of NE absorption by 10-14%. Under fed conditions, the AUC ratio of EE was within 80-125% range but outside this range for NE.

2. Question Based Review

2.1. General Attributes

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

Warner Chilcott has submitted an NDA under Section 505(b)(1) of the Food, Drug and Cosmetic Act for a fixed dose combination of 0.8 mg NE and 0.025 mg EE chewable tablets and ferrous fumarate tablets. NE/EE is an oral contraceptive consisting of a new dose and new regimen of the combination of NE and EE.

Another chewable tablet with similar drug combination is currently approved in the U.S. Femcon® Fe (NDA 021490; 0.4 mg NE and 0.035 mg EE; Warner Chilcott, LLC) is also indicated for prevention of pregnancy and is to be taken once-daily for 21 days followed by one tablet of ferrous fumarate once daily for seven days. Femcon® Fe can be swallowed whole or chewed with water (8 ounces) and taken without regards to food. There are more than five other products with NE/EE combination approved for the same indication. These products contain 0.035 mg or 0.05 mg EE and either 0.5 mg or 1.0 mg NE.

Other products containing a combination of NE and EE are Ovcon-35 (NDA 017716) and Ovcon-50 (NDA 017576) (Warner-Chilcott, LLC). Ovcon-35 contains 0.4 mg NE and 0.035 mg EE, Ovcon-50 contains 1.0 mg NE and 0.05 mg EE.

2.1.2. What is the chemical structure and the formulation of the drug product?

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)-] MW 296.4

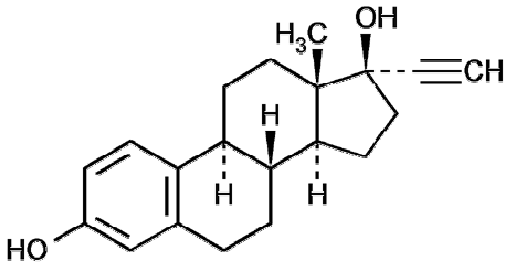

Figure 1: Chemical structure of Ethinyl Estradiol

- Norethindrone [17-hydroxy-19-nor-17α -pregn-4-en-20-yn-3-one]; MW 298.42

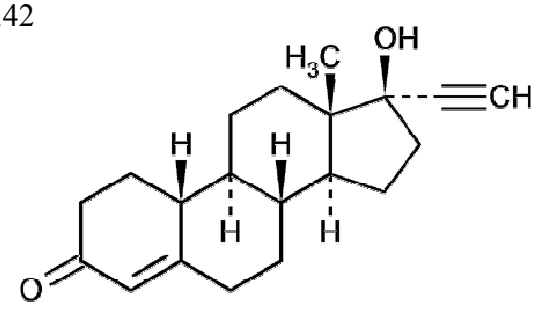

Figure 2: Chemical structure of Norethindrone

- Drug product information

    - The combination tablet is light green and contains 0.8 mg NE and 0.025 mg EE and the following inactive ingredients: D&C Yellow No. 10 aluminum lake, FD&C Blue No. 1 aluminum lake, FD&C Yellow No. 6 aluminum lake, lactose monohydrate, magnesium stearate, mannitol, microcrystalline cellulose, povidone, sodium starch glycolate, spearmint flavor, sucralose and vitamin E.

    - Each brown, round tablet contains ferrous fumarate (75mg), magnesium stearate, mannitol, microcrystalline cellulose, povidone, sodium starch glycolate, spearmint flavor and sucralose. The ferrous fumarate tablets do not serve any therapeutic purpose.

2.1.3. What are the proposed mechanism of action and therapeutic indication?

The proposed indication of TRADENAME is the prevention of pregnancy in women who elect to use oral contraceptives as a method of contraception.

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).

2.1.4. What are the proposed dosages and routes of administration?

The dosage of NE/EE consists of a single light green tablet containing NE and EE to be taken consecutively for 24 days, followed by one brown non-hormonal (placebo) tablet containing ferrous fumarate daily for 4 consecutive days. Both tablets are to be taken chewed without regards to water and food.

2.1.5. What drugs (substances, products) indicated for the same indication are approved in the US?

There are multiple combination oral contraceptives (COC) approved containing EE and progesterone derivatives for the prevention of pregnancy. COC products representing the range of EE and NE available are: Femcon Fe chewable tablets (EE 0.035 mg/NE 0.4 mg, NDA 021490), Ovcon-50 (EE 0.05 mg/NE 1.0 mg (NDA 017576)), Ovcon-35 (EE 0.035 mg NE 0.4 mg (NDA 017716)) and Loestrin 24 FE (EE0.02 mg/norethindrone acetate 1.0 mg, NDA 021871).

2.2. General Clinical Pharmacology

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

Four Phase 1 Clinical Pharmacology studies, one Phase 1 clinical safety study and one Phase 3 clinical safety and efficacy study were submitted in support of this application:

- Study PR00807/ Report RR-07607: A study to assess the bioavailability of EE and NE following oral administration of a NE/EE tablet chewed and swallowed without water as compared to both a NE/EE tablet chewed and swallowed with 45 ml of water and an EE/NE suspension/solution. This was a single-center, randomized, balanced, single-dose, 3-treatment, 3-period, 6-sequence, crossover study in N = 30 healthy female subjects (ages 19-35 years). Data from 26 subjects was evaluable for PK analysis.
- Study PR-00907/ Report RR 09407: A study to assess the effect of food on EE and NE bioavailability following oral administration (chewed and swallowed without water) of NE/EE tablet (fasted) as compared to NE/EE tablet (fed) in healthy female subjects (ages 18-35). This was a single center, randomized, balanced, single-dose, 2-treatment, 2-period, 2-sequence, crossover, food effect study in N=18 subjects. Data from 13 subjects was evaluable for PK analysis.

- Study PR-03808/Report RR-00509: A study to characterize bioavailability of EE and NE as well as sex hormone binding globulin (SHBG) serum concentrations following multiple-dose administration of NE/EE tablets. This was a single-center, single-treatment, multiple-dose study in N=18 healthy female subjects (ages 19-33). All subjects received one NE/EE tablet per day for 24 days after an initial overnight fast; the tablet was chewed and swallowed without water. Data from 17 subjects was evaluable for PK analysis.
- Study PR-00707/ Report RR-03409: A study to characterize the EE and NE bioavailability and SHBG concentrations following multiple-dose administration of NE/EE tablets. This was a single-center, single-treatment, multiple-dose study in N= 18 healthy female subjects (ages 20-32 years). All subjects received one NE/EE tablet per day for 24 days after an initial overnight fast; the tablet was swallowed whole and followed with 240 mL water. Data from 16 subjects was evaluable for PK analysis.
- Study PR-00207/Report RR-03009: An open-label, historical controlled, multicenter study to evaluate efficacy and safety of a new dose/new regimen oral contraceptive containing EE and NE. Approximately 1,600 heterosexually active women aged 18 to 45 years and at risk of becoming pregnant were enrolled. They were assigned to take NE/EE daily for thirteen 28-day cycles of treatment *[see clinical review by Dr. Gerald Willett regarding safety and efficacy evaluation]*.
- Study PR10107/Report RR-00309: A study to determine the oral irritation potential of NE/EE tablets following use over a 24 day treatment period. This was a single-center, open-label, uncontrolled study in N=54 healthy female subjects (ages 18-44). 52 subjects completed the study. All subjects received one NE/EE tablet per day for 24 days. The tablet was chewed without regards to water and taken with or without food *[see clinical review by Dr. Gerald Willett regarding safety evaluation]*.

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

The primary outcome measure in the Phase 3 efficacy and safety study was pregnancy rate. This is an adequate response endpoint. The pregnancy rate was assessed using the Pearl-Index (defined as the number of pregnancies per 100 woman-years of treatment) and life-table methods.

The primary efficacy analysis was based on the PI in the group of women 35 years of age or less, including all at-risk cycles during which no other method of birth control had been used.

The PI was also computed for all subjects regardless of age, including all at risk cycles during which no other method of birth control had been used.

2.2.3. Are the active moieties in plasma or serum appropriately identified and measured to assess pharmacokinetic parameters?

Yes. Plasma samples were analyzed for EE and NE by (b) (4) using a validated gas chromatographic method with mass spectrometric detection (GC/MS). In addition, SHBG concentrations were determined in human serum using an immunoradiometric assay (IRMA). The concentrations measured for the various active moieties were within assay range. The validation reports and study assay reports were reviewed and found to demonstrate suitability of the assay for determination of EE, NE and SHBG.

2.2.4. Pharmacokinetics

2.2.4.1. What are the single and multiple dose PK parameters in healthy premenopausal women?

Study PR-03808/Report RR-00509 was a single center, single-treatment, multiple dose, bioavailability study that evaluated the single dose and multiple dose PK of NE and EE from the proposed formulation in healthy female subjects (N=18, ages 19-33).

Treatment: 1 tablet containing 0.8 mg NE and 0.025 mg EE per day on days 1-24, taken chewed without water.

PK sampling to determine NE and EE plasma concentration was performed on days 1 and 24 at pre-dose, and at 0.33, 0.67, 1, 1.33, 1.67, 2, 2.5, 3, 4, 6, 8, 10, 12, 16, and 24 hours post-dose. Further, on day 24, sampling was also performed 30, 36, 48 and 60 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 SHBG concentrations were collected prior to dosing on study day 1 and 24 hours after receiving doses 1, 4, 8, 12, 16, 20, and 24.

EE Pharmacokinetics:
Following once-daily administration of 0.025 mg EE for 24 days (as part of NE/EE-24-tablet regimen), accumulation ratios based on Cmax and AUC0-τ of EE were 1.1 and 1.5-fold, respectively on day 24, compared to single dose data on day 1. Based on visual assessment of trough concentrations steady-state was achieved for EE by day 9 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.

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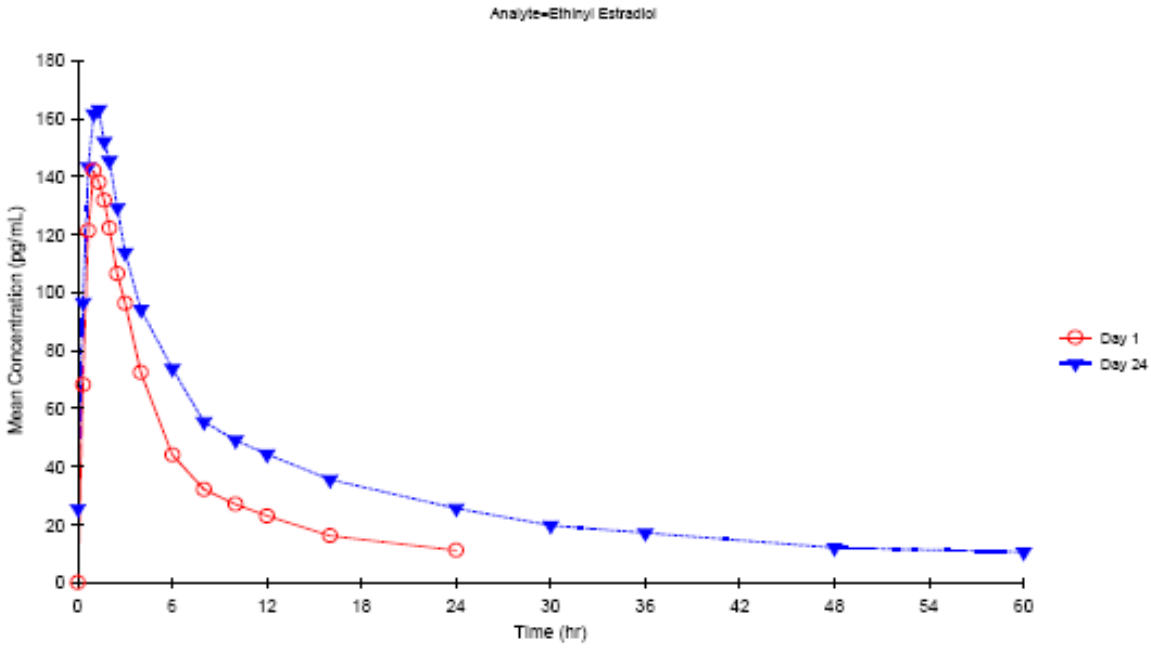


Figure 3: Mean plasma EE concentration-time profiles after the administration of NE/EE tablets on Days 1 and 24 (n = 17).

Table 1: Pharmacokinetic parameters of EE in healthy female subjects on days 1 & 24.

	Arithmetic mean parameters (%CV)			
Regimen NE/EE tablet	Cmax (pg/mL)	Tmax (h)	AUC 0–24h (pg*h/mL)	t½ (h)
Day 1 (Single Dose) N=17	147 (25)	1.2 (27)	903 (18)	
Day 24 (Multiple Dose) N=17	168 (25)	1.2 (35)	1400 (32)	17.1

NE pharmacokinetics:

Following once-daily administration of 0.8 mg NE for 24 days (as part of NE/EE-24-tablet regimen), accumulation ratios based on Cmax and AUC0-τ of NE were 2.3 and 3.6-fold, respectively on day 24, compared to single dose data on day 1. Based on visual assessment of trough concentrations predose concentrations for NE continue to increase through to day 21.

Serum SHBG concentration more than doubled by day 24 [Fig.5]. This is to be expected, as it is extensively reported that EE induces the synthesis of SHBG. NE concentrations more than doubled by day 24 due to both, accumulation and increased SHBG concentration.

Figure 4: Mean plasma NE concentration-time profiles after the administration of NE/EE tablets on Days 1 and 24 (n = 17).

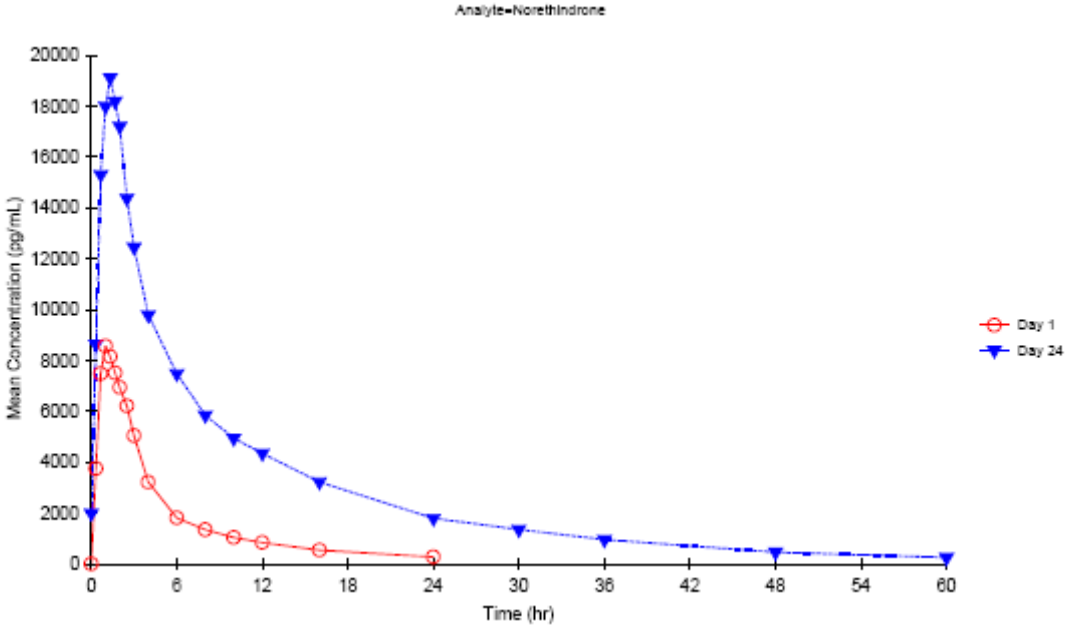
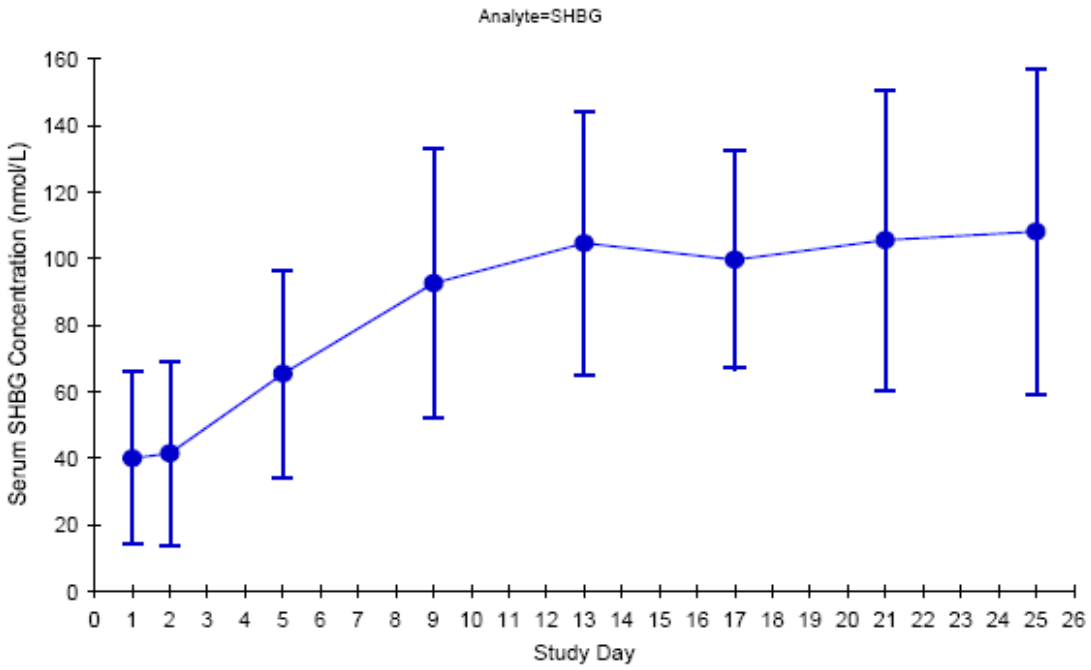


Table 2: Pharmacokinetic parameters of NE in healthy female subjects on days 1 and 24 (n=17).

	Arithmetic mean parameters (%CV)			
Regimen NE/EE tablet	Cmax (pg/mL)	Tmax (h)	AUC 0–24h (pg*h/mL)	t½ (h)
Day 1 (Single Dose) N=17	9840 (36)	1.44 (49)	41680 (47)	
Day 24 (Multiple Dose) N=17	22200 (30)	1.64 (76)	141200 (32)	10.8

Figure 5: Average SHBG concentrations (pre-dose) during once-daily administration of NE/EE tablets in healthy female subjects (N = 17). Error bars represent one standard deviation.



2.2.4.2. What are the characteristics of drug absorption?

NE and EE were rapidly absorbed from NE/EE tablets when chewed without water. Maximum plasma concentrations of NE and EE occurred approximately 1 to 2 hours post-dose. Absolute bioavailability was not evaluated under this NDA but according to the literature it is approximately 64% for NE and 55% for EE.

Both the rate and extent of EE absorption were higher for NE/EE tablets chewed without water than for the EE/NE solution/suspension. Cmax was increased by ~50% and AUC ~30%. Cmax of NE for NE/EE tablets chewed without water was decreased by ~15%, but the extent of NE absorption was not affected as compared to the EE/NE solution/suspension.

Administration of NE/EE tablets chewed with water compared to chewed without water decreased EE Cmax by ~13% but did not affect the extent of EE absorption. With respect to NE, NE/EE tablets chewed with 45 ml water are bioequivalent to NE/EE tablets chewed without water.

Food Effect:

Administration of NE/EE tablets with food decreased Cmax of EE by ~39% and Cmax of NE by ~47%. Administration with food did not affect the extent of EE absorption but increased the extent of NE absorption by 10-14%.

Phase 3 clinical trial for NE/EE was done without regard to food and tablets were taken chewed without water. Hence it is acceptable to dose NE/EE with or without food and chewed without water.

2.2.4.3. What are the characteristics of drug distribution?

According to the literature, NE is 36% bound to SHBG and 61% bound to albumin. EE is not bound to SHBG but is highly (98.5%) bound to albumin. Volume of distribution of NE and EE ranges from 2 to 4 L/kg. Although EE does not bind to SHBG, it induces SHBG synthesis. SHBG concentrations more than doubled following 24 days of dosing with NE/EE tablets (Study PR-03808).

2.2.4.4. What are the characteristics of drug metabolism?

According to the literature, 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. A small amount of NE is metabolically converted to EE.

It is stated in the literature, that EE is 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. NE and EE are excreted in both urine and feces, primarily as metabolites.

2.2.4.5. What are the characteristics of drug excretion?

According to the literature, 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 0.8 mg NE/0.025 mg EE tablets (TRADENAME) are approximately 11 hours and 17 hours, respectively.

2.3. Intrinsic Factors

2.3.1. Renal Impairment

The effects of renal impairment on the PK of NE/EE have not been studied. 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.

2.3.2. Hepatic Impairment

The effects of hepatic impairment on the PK of NE/EE have not been studied. However, EE and NE may be poorly metabolized in patients with impaired liver function.

2.4. Extrinsic Factors

2.4.1. What are the drug-drug interactions?

No specific drug-drug interaction studies were conducted with TRADENAME.

Changes in contraceptive effectiveness associated with co-administration of other products:
If a woman on hormonal contraceptives takes a drug or herbal product that induces enzymes, including CYP3A4, that metabolize contraceptive hormones, counsel her to use additional contraception or a different method of contraception. 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 and non-nucleoside reverse transcriptase inhibitors:
Significant changes (increase and decrease) in the plasma levels of the estrogen and progestin have been noted in some cases of co-administration of anti-HIV protease inhibitors or with non-nucleoside transcriptase 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.

Consult the labeling of all concurrently-used drugs to obtain further information about interactions with hormonal contraceptives or the potential for enzyme alterations.

Increase in Plasma Levels of Estradiol Associated with Co-Administered Drugs:
Co-administration of atorvastatin and certain COCs 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:
COCs containing some synthetic estrogens (e.g., ethinyl estradiol) may inhibit the metabolism of other compounds. COCs 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. Consult the labeling of the concurrently-used drug to obtain further information about interactions with COCs or the potential for enzyme alterations.

2.5. General Biopharmaceutics

2.5.1. What is the relative bioavailability of the proposed NE/EE tablets (vs. solution)?

The relative bioavailability of NE/EE tablets taken chewed without water compared to taken chewed with water or a NE/EE 0.8 mg/0.025 mg solution was evaluated in study PR 00807.
This was a single-center, randomized, balanced, single-dose, 3-treatment, 3-period, 6-sequence crossover, relative bioavailability study which was conducted in 30 healthy, normal, female subjects. The subjects had a median (range) age of 23 (19–35) years, a median (range) weight of 63.5 (44–85) kg, and a median (range) height of 163.5 (148–181) cm. Twenty-nine subjects were Caucasian and one was Asian. The subjects were randomly assigned to receive the following 3 treatments in each of 3 treatment periods (6 possible sequences):

- TREATMENT A: NE/EE tablet administered orally, chewed, without water.
- TREATMENT B: NE/EE tablet administered orally, chewed, and followed with 45 mL of water.
- TREATMENT C: A (b) (4) solution/suspension containing EE 0.025 mg/NE 0.8 mg administered orally and followed with water; total volume administered was 45 mL.

Ethinyl Estradiol

Figure 8: Plasma concentration-time profiles of EE after single doses of NE/EE tablets or solution (n=26). [A: NE/EE tablet/chewed w/o water; B: NE/EE tablet/chewed with water; C: 0.8 mg/0.025 mg solution]

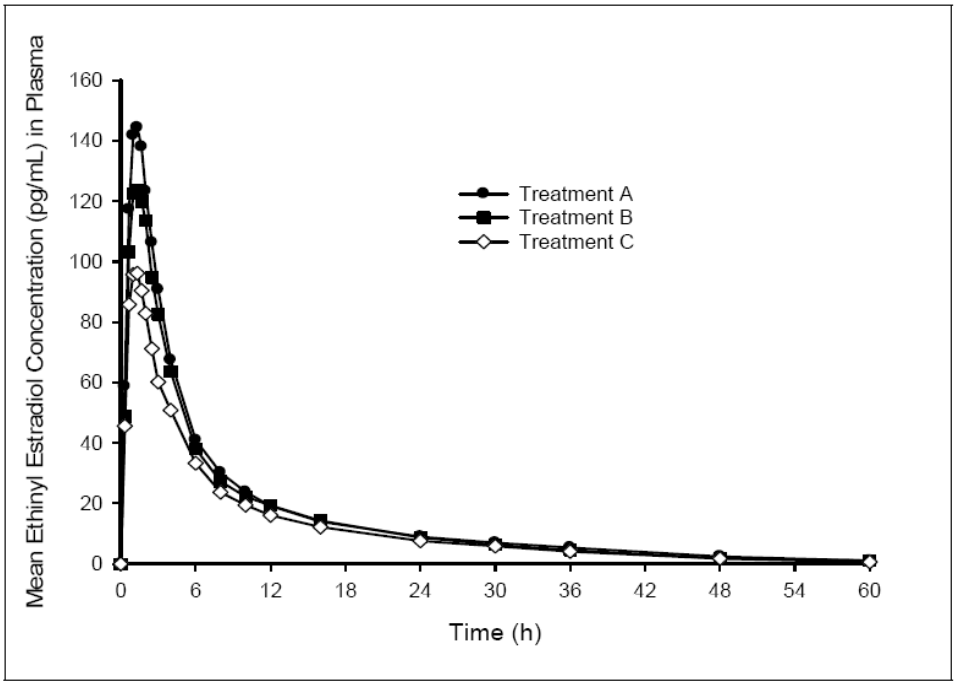


Table 6: Single dose plasma pharmacokinetics parameter of EE (n=26)

Parameter	Least Squares [Median{Range}] Formulation Effect: Treatment A (Test)	Formulation Effect: Treatment C (Reference)	Ratio (%) (Test:Reference)	90% Confidence Interval
Cmax (pg/mL)	148	96.6	153.6	135.41-174.24
AUC0-tdlc (pg*h/mL)	929	703	132.1	122.69-142.23
AUCinf (pg*h/mL)	999	773	129.3	119.81-139.46
tmax (h)	[1.33 (0.67-2)]	[1.33 (0.67-4)]	/	/
Parameter	Water Effect: Treatment B (Test)	Water Effect: Treatment A (Reference)	Ratio (%) (Test:Reference)	90% Confidence Interval
Cmax (pg/mL)	128	148	86.6	76.45-98.00
AUC0-tdlc (pg*h/mL)	880	929	94.7	88.06-101.85
AUCinf (pg*h/mL)	973	999	97.3	90.31-104.88
tmax (h)	[1.33 (1-3)]	[1.33 (0.67-2)]	/	/

Treatment A: NE/EE tablet administered orally, chewed, without water.
Treatment B: NE/EE tablet administered orally, chewed, and followed with 45 mL of water.

Treatment C: A [redacted] (b) (4) solution/suspension containing EE 0.025 mg/NE 0.8 mg administered orally and followed with water; total volume administered was 45 mL.

Relative bioavailability of EE from NE/EE tablets:

Formulation effect

Both the rate and extent of EE absorption were higher for NE/EE tablets chewed without water (Treatment A) than for the NE/EE solution/suspension (Treatment C).

Statistical comparison using the average bioequivalence approach for the least square means of test (Treatment A) vs. reference (Treatment C) reveals that the AUC is not comparable, as the 90% confidence interval for the least square mean ratios of test/reference are not within the 80-125% range.

Water effect

Administration of NE/EE tablets chewed with water (Treatment B) decreased EE absorption rate by 13% but did not affect the extent of EE absorption compared to administration of NE/EE tablets chewed without water (Treatment A). Statistical comparison using the average bioequivalence approach for the least square means of test (Treatment B) vs. reference (Treatment A) reveals that the AUC is comparable, as the 90% confidence interval for the least square mean ratios of test/reference are within the 80-125% range.

Norethindrone

Figure 9: Plasma concentration-time profiles of NE after single doses of NE/EE tablets or solution (n=26). [A: NE/EE tablet/chewed w/o water; B: NE/EE tablet/chewed with water; C: NE/EE solution]

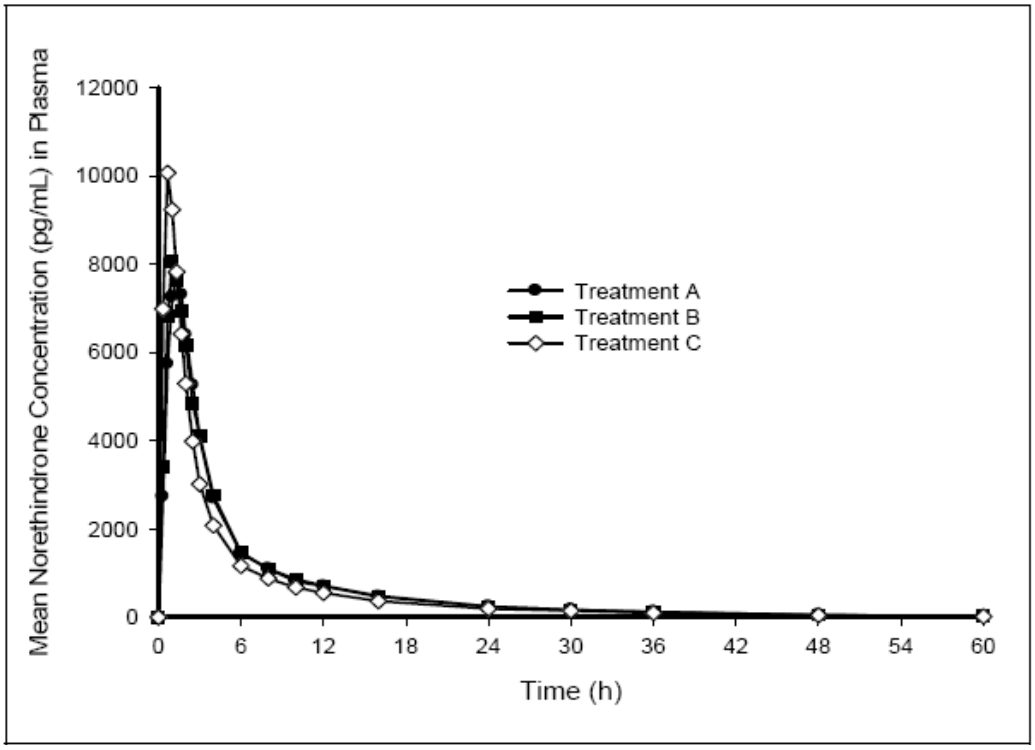


Table 7: Single dose plasma pharmacokinetics parameter of NE (n=26)

Parameter	Least Squares [Median{Range}] Formulation Effect: Treatment A (Test)	Treatment C (Reference)	Ratio (%) (Test:Reference)	90% Confidence Interval
Cmax (pg/mL)	7953	9362	84.95	72.91-98.98
AUC0-tdlc (pg*h/mL)	34800	33702	103.26	94.47-112.87
AUCinf (pg*h/mL)	35480	34394	103.16	94.52-112.58
tmax (h)	[1.33 (0.67-3)]	[0.67 (0.67-3)]	/	/
Parameter	Water Effect: Treatment B (Test)	Treatment A (Reference)	Ratio (%) (Test:Reference)	90% Confidence Interval
Cmax (pg/mL)	7610	7953	95.68	82.31-111.22
AUC0-tdlc (pg*h/mL)	35256	34800	101.31	92.81-110.59
AUCinf (pg*h/mL)	36113	35480	101.79	93.39-110.94
tmax (h)	[1 (0.67-3)]	[1.33 (0.67-3)]	/	/

Treatment A: NE/EE tablet administered orally, chewed, without water.
Treatment B: NE/EE tablet administered orally, chewed, and followed with 45 mL of water.
Treatment C: A [redacted] (b) (4) solution/suspension containing EE 0.025 mg/NE 0.8 mg administered orally and followed with water; total volume administered was 45 mL.

Relative bioavailability of NE from NE/EE tablets:

Formulation effect
The rate of NE absorption for NE/EE tablets chewed without water (Treatment A) was decreased, but the extent of NE absorption was not affected as compared to the EE/NE solution/suspension (Treatment C). Statistical comparison using the average bioequivalence approach for the least square means of test (Treatment A) vs. reference (Treatment C) reveals that the AUC is comparable, as the 90% confidence interval for the least square mean ratios of test/reference are within the 80-125% range.

Water effect
With respect to NE, NE/EE tablets chewed with water (Treatment B) are bioequivalent to NE/EE tablets chewed without water (Treatment A). Statistical comparison using the average bioequivalence approach for the least square means of test (Treatment B) vs. reference (Treatment A) reveals that the AUC is comparable, as the 90% confidence interval for the least square mean ratios of test/reference are within the 80-125% range.

Conclusion:
(b) (4)
AUC and Cmax of NE as well as AUC of EE met the bioequivalence criteria (80-125%) when comparing NE/EE tablet taken chewed with water vs. chewed without water. However, the decrease in Cmax (-13%) of EE when taken with water compared to taken without water was noted. This decrease may be considered clinically not significant given that the more profound effect of food on Cmax of EE has no relevance in the administration instruction (see section 2.5.2).
(b) (4)
Therefore, we recommend taking TRADENAME tablets chewed without water.

2.5.2. What is the effect of food on the proposed NE/EE tablets?

The food-effect of the NE/EE tablets was evaluated in study PR 00907/ RR09407. This was a single-center, randomized, balanced, single-dose, 2-treatment, 2-period, 2-sequence, crossover study. Subjects received one NE/EE tablet in each treatment period; the tablet was chewed and swallowed without water. There was a 28-day washout period between treatments. Subjects randomized to the Fasted treatment did not receive food for at least 4 hours post-dose and subjects randomized to the Fed treatment received their tablet within 5 minutes of having consumed a high-fat, high-calorie test meal. Water was allowed ad libitum except 1 hour prior to dosing and 1 hour after treatment administration.

Eighteen subjects were enrolled in the study. PK data from 13 subjects were available since 5 subjects did not complete the study. The 18 subjects enrolled in the study had a median (range) age of 27 (18–35) years, a median (range) weight of 62.8 (51.0–72.8) kg, and a median (range) height of 165.3 (155.5–174.0) cm. All subjects were female. There were 9 subjects (50%) who were Non-Hispanic/Latino-White, 8 subjects (44%) who were Hispanic/Latino-White, and 1 subject (6%) who was Non-Hispanic/Latino-Black.

Ethinyl Estradiol

Figure 10: Plasma concentration-time profiles of EE after single doses of NE/EE tablets (n=13) [A: Fed; B; Fasted].

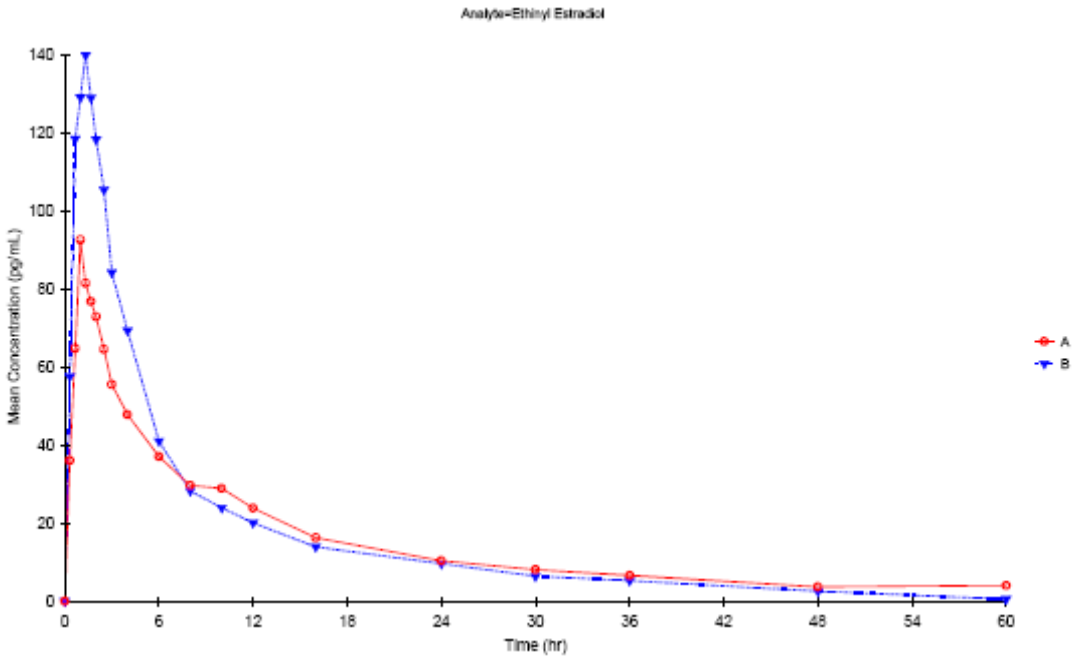


Table 8: Single dose plasma pharmacokinetics of EE (n=13)

Parameter	Geometric Mean [Median (Range)]			
	NE/EE tablet, FED	NE/EE tablet, FASTED	Ratio (%) (FED:FASTED)	90% Confidence Interval
Cmax (pg/mL)	87.5	142	60.98	50.43-73.73
AUC0-tdlc (pg*h/mL)	860.6	934	91.98	84.50-100.12
AUCinf (pg*h/mL)	938.9	1025	92.38	84.55-100.93
tmax (h)	[1.33 (1-2)]	[1.33 (0.67-1.67)]	/	/

Food-effect on EE from NE/EE tablets

When NE/EE tablets were administered with food, mean Cmax of EE was reduced by ~39%. Median Tmax values as well as the AUC for EE remained unchanged when dosed with food.
The 90% CI for EE AUC remained within the 80-125% range. Therefore it appears that the rate of EE absorption was affected by food but not the extent of absorption.

Norethindrone

Figure 11: Plasma concentration-time profiles of NE after single doses of NE/EE tablets (n=13) [A: Fed; B; Fasted].

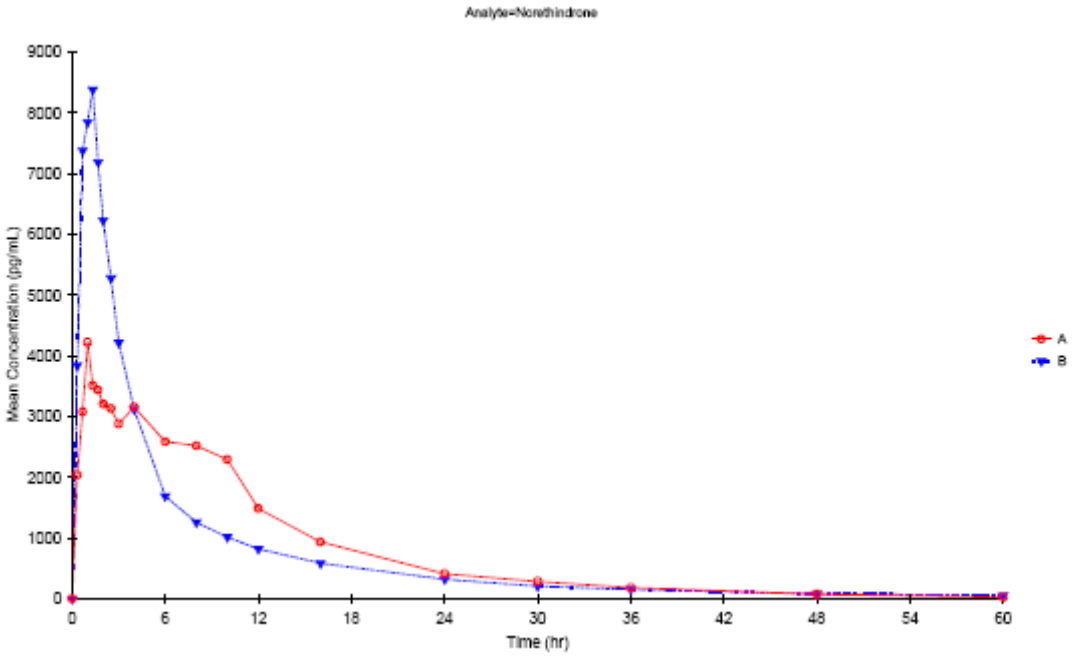


Table 9: Single dose plasma pharmacokinetics of NE (n=13)

Parameter	Geometric Mean [Median (Range)]			
	NE/EE tablet, FED	NE/EE tablet, FASTED	Ratio (%) (FED:FASTED)	90% Confidence Interval
Cmax (pg/mL)	4760	8830	53.46	42.59-67.12
AUC0-tdlc (pg*h/mL)	45810	40460	113.6	99.06-130.28
AUCinf (pg*h/mL)	46460	42430	109.58	92.12-130.34
tmax (h)	[1.33 (0.67-8)]	[1.33 (0.67-1.67)]	/	/

Food-effect on NE from NE/EE tablets

When NE/EE tablets were administered with food, mean Cmax of NE was reduced by ~47% indicating an effect of food on the absorption rate of NE. Tmax values for NE were not affected by food. However, the AUC was increased by ~10-14% when tablets were taken with food and the 90% CI surrounding the treatment mean ratios of the AUC parameters fell outside the 80-125% bioequivalence range.

Conclusion

(b) (4)

Given the fact that the absence of food effect is not established due to the change of Cmax of both EE and NE as well as AUC0-tdlc of NE (i.e., failure to meet the 90% CI under fed condition) the data should be reflected in the labeling. However, it appears that this should not affect the food intake instructions. The Phase 3 study was done without regards to meals and therefore the results of the Phase 3 efficacy and safety studies support the administration of NE/EE regardless of food intake. No special recommendation concerning food intake is considered to be necessary.

2.5.3. How is the proposed to-be-marketed formulation linked to the clinical service formulation?

The sponsor stated that the unit-dose composition and manufacturing process of the to-be-marketed formulation (Table 10) is identical to that of the clinical study formulation.

Table 10: Composition of NE/EE tablets:

	Formulation WC3026-5C	
Component	mg/tablet	% w/w
Ethinyl estradiol USP*	0.025	(b) (4)
Povidone USP	(b) (4	(b) (4
Vitamin E USP	(b) (4	
Lactose monohydrate NF,	(b) (4	
Norethindrone USP	0.80	
Mannitol USP	(b) (4)	(b) (4
Mannitol USP		
Microcrystalline cellulose, NF	(b) (4	
FD&C Yellow No. 6 aluminum lake		
FD&C Blue No. 1 aluminum lake		
D&C Yellow No. 10 aluminum lake		
Spearmint flavor	(b) (4	
Sodium starch glycolate		
Sucralose		
Magnesium stearate		
Total	70.00	

(b) (4)

2.6. Analytical Section

2.6.1. How are parent drug and other relevant analytes identified and what are the analytical methods used to measure them in plasma?

Plasma samples were analyzed for EE and NE by (b) (4) using a validated gas chromatographic method with mass spectrometric detection (GC/MS). The validation report (CR-04507) and study assay reports were reviewed and found to demonstrate suitability of the assay for determination of EE and NE in human plasma.

(b) (4)

The SHBG assay is an immunoradiometric assay (IRMA) based on coated tubes with monoclonal antibodies directed against distinct epitopes of the SHBG molecule. Two capture antibodies are coated on the inner wall of the tubes; SHBG

of the calibration standard samples, quality control samples or study samples is captured by these antibodies. Addition of a third antibody labeled with 125iodine completes the system, allowing the formation of a bridge between the coated antibodies and the labeled antibody. After washing, the remaining radioactivity bound to the tubes is directly related to the concentration of the SHBG in the samples.

Precision and accuracy of QC samples in the validation assay as well as the bioanalytical assays performed are within the 15% range of nominal values. The GC/MS assay used to determine EE and NE and the immunoradiometric assay used to determine SHBG in plasma are acceptable (Table 11, 12).

Table 11: Validation results for the assay of EE and NE by GC/MS method

Validation Parameters	EE	NE
Matrix	Plasma	Plasma
Standard curve range; R2	2.5 – 250 pg/mL; R2 = 0.99572	25.0 to 25000 pg/mL R2 = 0.99593
LLOQ	2.5 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

Table 12: QC analysis results for EE, NE and SHBG

Study #	PR-00807		PR-00907		PR-03808			PR-00707		
Method	GC/MS		GC/MS		GC/MS			GC/MS		
	EE	NE	EE	NE	EE	NE	SHBG	EE	NE	SHBG
Accuracy (% bias) [EE QCs: 7.5, 30, 200 pg/mL; NE QCs: 75, 2500 and 20000 pg/mL SHBG QCs: 20, 75.9 (79.7 in study PR00707),200 nmol/mL]	-5.5-3.47	-6.79-3.07	-7.1- (-4.8)	-4.2-2.7	0.88-3.84	-1.11-0.81	1.73-1.69	-4.7-1.4	-9.2-1.7	-10.8-(-3.13)
Precision (% CV) [EE QCs: 7.5, 30, 200 pg/mL; NE QCs: 75, 2500 and 20000 pg/mL SHBG QCs: 20, 75.9 (79.7 in study PR00707), 200 nmol/mL]	6.81-10.49	5.88-11.05	5.2-6.3	4.7-8.5	4.44-10.79	4.77-5.75	2.18-5.98	6.9-10.1	5.2-12.4	2.46-5.25

3. Detailed Labeling Recommendations

Additions are shown underlined and deletions are shown by double-strikethroughs.

Highlights of prescribing information:

5 WARNINGS AND PRECAUTIONS

5.16 Liver Function

(b) (4)

7 DRUG INTERACTIONS

7.1 Changes in Contraceptive Effectiveness Associated with Co-Administration of Other Products

(b) (4)

If a woman on hormonal contraceptives takes a drug or herbal product that induces enzymes, including CYP3A4, that metabolize contraceptive hormones, counsel her to use additional contraception or a different method of contraception. 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 and non-nucleoside reverse transcriptase 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 or with non-nucleoside reverse transcriptase 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.

Consult the labeling of all concurrently-used drugs to obtain further information about interactions with hormonal contraceptives or the potential for enzyme alterations.

7.2 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.

7.3 Changes in Plasma Levels of Co-Administered Drugs

(b) (4)

COCs containing some synthetic estrogens (e.g., ethinyl estradiol) may inhibit the metabolism of other compounds. COCs 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. Consult the labeling of the concurrently-used drug to obtain further information about interactions with COCs or the potential for enzyme alterations.

8 USE IN SPECIFIC POPULATIONS

8.7 Hepatic Impairment

(b) (4)

No studies have been conducted to evaluate the effect of hepatic disease on the disposition of [TRADENAME]. However, steroid hormones may be poorly metabolized in patients with impaired liver function. Acute or chronic disturbances of liver function may necessitate the discontinuation of COC use until markers of liver function return to normal. [*see Contraindications (4) and Warnings and Precautions (5.16)*].

12 CLINICAL PHARMACOLOGY

12.1 Absorption

The plasma norethindrone and ethinyl estradiol pharmacokinetics following single- and multiple-dose administrations of [TRADENAME] in 17 healthy female subjects are provided in Table 3.

Following multiple-dose administration of [TRADENAME], mean maximum concentrations of norethindrone and ethinyl estradiol were increased by 126% and 14%, respectively, as compared to single-dose administration. Mean norethindrone and ethinyl estradiol exposures (AUC values) were increased by 239% and 55% respectively, as compared to single-dose administration of [TRADENAME].

Mean sex hormone binding globulin (SHBG) concentrations were increased by 170% from baseline (40.0 pg/mL) to 108 pg/mL at steady-state.

12.3 Pharmacokinetics

Table 3. Pharmacokinetic Parameter Values Following Single and Multiple Dose Administration of [TRADENAME]

EE = ethinyl estradiol; NE = norethindrone; SHBG = Sex hormone binding globulin; %CV = coefficient of variation; Cmax = maximum plasma concentration (pg/mL); Cmin = SHGB concentration at predose (Day 1) or 24 hours after dose 24 (Day 24); units are pg/L; tmax = time of the maximum measured plasma concentration (h); AUC0–24h = area under the plasma concentration versus time curve from time 0 to 24h, (pg·h/mL); t½ = apparent elimination half life (h)

[a] The harmonic mean for t½ is presented

Effect of Food: TRADENAME may be administered with or without food. A single-dose administration of [TRADENAME] with food decreased the maximum concentration of norethindrone by 47% and increased the extent of absorption by 10-14% and decreased the maximum concentration of ethinyl estradiol by 39% but not the extent of absorption.

(b) (4)

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	**22573**	**Brand Name**	**Pending**
OCP Division	**DCP3**	**Generic Name**	**Norethindrone/ethinyl estradiol**
Medical Division	**DRUP**	**Drug Class**	**Hormone**
OCP Reviewer	**Christian Grimstein, Ph.D**	**Indication(s)**	**Prevention of Pregnancy**
OCP Team Leader	**Myong Jin Kim, Pharm. D.**	**Dosage Form**	**Tablet**
		Dosing Regimen	**1 tablet daily for 28 consecutive days, the last 4 days, the tablet only contains (non-hormonal placebo) 75mg ferrous fumarate**

Date of Submission	**11/26/09**	**Route of Administration**	**Oral**
Estimated Due Date of OCP Review	**07/26/10**	**Sponsor**	**Warner Chilcott**
PDUFA Due Date	**09/26/10**	**Priority Classification**	**Standard**
Division Due Date			

<u>Clin. Pharm. and Biopharm. Information</u>

	"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) -				
***Healthy Volunteers*-**				
single dose:				
multiple dose:	**X**	**2**		**PR03808, PR00707**
***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 -				

solution as reference:	**X**	**1**		**PR00807**
alternate formulation as reference:				
Bioequivalence studies -				
traditional design; single / multi dose:				
replicate design; single / multi dose:				
Food-drug interaction studies:	**X**	**1**		**PR00907**
Dissolution:				
(IVIVC):				
Bio-wavier request based on BCS				
BCS class				
III. Other CPB Studies				
Genotype/phenotype studies:				
Chronopharmacokinetics				
Pediatric development plan				
Literature References		**4**		**References to support ADME**
Total Number of Studies		**8**		
Filability and QBR comments				
	"X" if yes	**Comments**		
Application filable?	**X**			
Comments sent to firm?				

QBR questions (key issues to be considered)	
Other comments or information not included above	
Primary reviewer Signature and Date	
Secondary reviewer Signature and Date	

A.1. Individual Study Review
A.1.1. Study PR-00807

Study to Assess the Relative Bioavailability of Ethinyl Estradiol and Norethindrone following Oral Administration of NE/EE Tablets in Healthy Female Volunteers

Protocol No: PR-00807
Phase: 1
Principal Investigator: Dennis Morrison, DO
Clinical Study Center: Bio-Kinetic Clinical Applications, Inc, 1816 W Mount Vernon Street, Springfield, MO 65802
Clinical Study Dates: June 23, 2007 – August 25, 2007
Analytical Study Facility: (b) (4)
Analytical study Date: 10/31/07

OBJECTIVE
The primary objective is to assess the relative bioavailability of EE and NE following oral administration of NE/EE tablets as compared to an EE/NE solution/suspension and to assess the effect of a small volume of water on EE and NE bioavailability following oral administration of a single NE/EE tablet.

STUDY ENDPOINTS
Pharmacokinetic parameters including C_{max}, T_{max}, $AUC_{t\text{-}tldc}$, AUC_{inf}, k_{el} and $t_{1/2}$ were determined.

STUDY DESIGN, TREATMENT, AND SUBJECTS
The study is a single-center, randomized, balanced, single-dose, 3-treatment, 3-period, 6-sequence crossover, relative bioavailability study. 30 female subjects were enrolled in the study and 27 subjects completed the study.
The subjects had a median (range) age of 23 (19–35) years, a median (range) weight of 63.5 (44–85) kg, and a median (range) height of 163.5 (148–181) cm. Twenty-nine subjects were Caucasian and 1 was Asian. One subject was discontinued for a positive drug screen result; one subject withdrew consent after Period 1; and one subject was discontinued because of an AE that was not treatment related.

The subjects were randomly assigned to receive the following 3 treatments in each of 3 treatment periods (6 possible sequences):

TREATMENT A: NE/EE tablet administered orally, chewed, without water.
TREATMENT B: NE/EE tablet administered orally, chewed, and followed with 45 mL of water.
TREATMENT C: A (b) (4) solution/suspension containing EE 0.025 mg/NE 0.8 mg administered orally and followed with water; total volume administered was 45 mL.

The following investigational product was administered either with or without water or dissolved/suspended in a (b) (4) solution:

WC3026 tablets, 25 mcg EE and 0.8 mg NE	
Package description	Blister card contained 24 light-green, round active tablets and 4 pale lilac round inactive tablets; **ONLY THE LIGHT-GREEN ACTIVE TABLETS WERE ADMINISTERED**
Dosage form description	Active WC3026 tablets are round, light-green, flat-faced, beveled-edged tablets; tablets have a slight spearmint odor. Each tablet contains 25 mcg ethinyl estradiol (EE) and 0.8 mg norethindrone (NE).
Dose per time unit	25 mcg EE and 0.8 mg NE
Cumulative maximal dosage	75 mcg EE and 2.4 mg NE

The EE/NE solution/suspension to be administered for TREATMENT C was prepared by a pharmacist at the study site within 4 hours of dosing.

Treatments were administered following an overnight fast of at least 10 hours and subjects did not receive food for at least 4 hours post-dose. Fourteen days after receiving treatment in Period 1, subjects returned to the clinic for the second treatment in Period 2 and 14 days after receiving treatment in Period 2 subjects returned to the clinic for the third treatment in Period 3.

Inclusion criteria:

- Healthy female subjects, of any race who have not taken any form a medication within the 14 days prior to dosing.
- Aged 18–35 years inclusive.
- Subjects weighing at least 45 kg (99 lbs) who are within 15% of their ideal weight according to the 1983 Metropolitan Height and Weight Tables.

Exclusion criteria:

- History or presence of alcoholism or drug abuse within the past year.
- Hypersensitivity or idiosyncratic reaction to estrogens, progestogens or other hormonal agents.
- History of jaundice with previous use of oral contraceptives.
- History of liver tumors.
- Tobacco or nicotine use in any form during the previous three months.
- Subjects who are pregnant or lactating.
- Subjects who are sexually active or not either surgically sterilized bilateral tubal ligation, (6 months minimum), practicing a non-heterosexual lifestyle, or using one of the following acceptable methods of birth control:
    - Barrier method (condom, diaphragm) with spermicide for at least 7 days prior to the first dose and throughout the study
    - Non-hormonal IUD in place for at least 3 months.

- Subjects who have used any substances known to be strong inhibitors of cytochrome P450 (CYP) enzymes (such as cimetidine, fluoxetine, quinidine, erythromycin, fluconazole, and ketoconazole) or any substances known to be strong inducers of CYP enzymes (such as barbiturates, carbamazepine, glucocorticoids, phenytoin and rifampin) within 28 days of study start.

FORMULATION

- Active substance : EE/NE
- Dose: 0.025mg EE/0.8mg NE
- Formulation: tablet
- Batch designation: For the active tablets used in the study: 80157F. The bulk tablet lot number was 80157T. The formulation number was WC3026.
- Producer: Warner Chilcott (US), LLC., Rockaway, NJ 07866, USA

For treatment C, the tablet was suspended in 25ml (b) (4) solution and then taken with 20ml water (total volume of liquid administered: 45ml).

The lot number for the active tablets used in the study was 80157F (bulk tablet lot number was 80157T); the formulation number was WC3026.

PHARMACOKINETIC EVALUATION

Blood sampling

PK samples were collected at pre-dose (0 hour) and 0.33, 0.67, 1, 1.33, 1.67, 2, 2.5, 3, 4, 6, 8, 10, 12, 16, 24, 30, and 36 hours post-treatment while subjects remained in the clinic. Subjects returned to the clinic for collection of additional blood samples at 48 and 60 hours post-treatment. There was a 14-day period between the dosing of each study period. Blood samples for EE/NE analysis were collected into Vacutainers containing lithium heparin. Blood samples were collected by direct venipuncture.

Concomitant Therapy

The subjects listed in Text Table 8 reported medication use over the course of the study. According to the sponsor, it is not expected that this medication use interfered with the outcomes of the study.

Text Table 8. Use of Concomitant Medication Over Course of Study; PR-00807

Subject	Period	Medication	Formulation	Dose	Regimen	Indication	Start Date	End Date
5	3	Cold Pack/Cloth	N/A	N/A	Once	Headache	07/21/07	07/21/07
20	1,2,3	Intrauterine Device	N/A	N/A	N/A	Contraception	02/01/07	Continuous
25	Pre-study	Vitamins	Capsule	N/A	Once daily	Supplement	01/01/04	01/06/07

N/A = Not applicable

Source data: Appendix 16.2.6

Other restrictions

- The consumption of alcohol- or xanthine-containing beverages and food was prohibited for 24 hours before each dose and throughout the blood sampling periods.
- Grapefruit-containing beverages and foods were prohibited for 10 days before dosing and throughout the blood sampling periods.
- Subjects were prohibited from smoking for the duration of the study.

Bioanalytical method

Plasma samples were analyzed for EE and NE by (b) (4) using a validated gas (b) (4)

Sensitivity: Sensitivity was determined during validation prior to the analysis of study samples. The upper and lower quantification limits for EE were 2.50 and 200 pg/mL, respectively; the upper and lower quantification limits for NE were 25.0 and 20,000 pg/mL, respectively. Dilution integrity was demonstrated up to a 4-fold dilution for both EE and NE.

Precision: Precision of the calibration standards and quality control (QC) samples during sample analysis was expressed as the percent coefficient of variation (%CV). For EE the %CV ranged from 3.81% to 9.10% for calibration standards and 6.81% to 10.49% for QCs. For NE the %CV ranged from 3.58% to 9.49% for calibration standards and 5.88% to 11.05% for QCs.

Accuracy: Accuracy during sample analysis was expressed as percent difference from theoretical (bias). For EE the bias ranged from -8.13% to 5.99% for calibration standards and -5.50% to 3.47% for QCs. For NE the bias ranged from -10.40% to 6.55% for calibration standards and -6.79% to 3.07% for QCs.

Linearity: Linearity during sample analysis was described as the mean correlation coefficient of the standard curves. For EE this was 0.99253, for NE it was 0.99181.

Specificity: There were no significant chromatographic peaks detected at mass transitions and expected retention times of the analytes or their internal standards which would interfere with quantification.

Recovery: Recovery was determined prior to the analysis of the study samples, during assay validation. Mean recovery of EE at 7.50, 30.0 and 200 pg/mL was 81.1, 68.7 and 96.5%, respectively. Mean recovery of NE at 75.0, 2500 and 20,000 pg/mL was 75.8, 75.8 and 106%, respectively.

Stability: The stability of NE and EE in frozen human plasma had already been demonstrated; EE is stable in human plasma at room temperature for 94 hours and stable for 97 days at -20ºC. NE is stable in human plasma at room temperature for 144 hours and stable for 3 years at -20ºC. Both analytes have been shown to be stable during 3 freeze-thaw cycles.

Reviewers comment: *All acceptance criteria were in compliance with the Bioanalytical Method Validation Guidance and were met.*

DATA ANALYSIS

Pharmacokinetic Analysis

The pharmacokinetic analysis for EE and NE was performed using WinNonlin Professional Edition, version 5.1 (Pharsight Corporation, Mountain View, CA). PK parameters C_{max}, T_{max},

$AUC_{t\text{-}tldc}$, AUC_{inf}, k_{el} and $t_{1/2}$ were determined. The nominal sampling times were used for all samples. There were 9 samples drawn before or after the scheduled times, but these deviations were not significant.
The mean concentration-time plots were created with Sigma Plot 8/0 (SPSS Science, Chicago, IL). The noncompartmental Model 200 with extravascular input was used to obtain the pharmacokinetic parameters for NE and EE.

PHARMACOKINETIC RESULTS

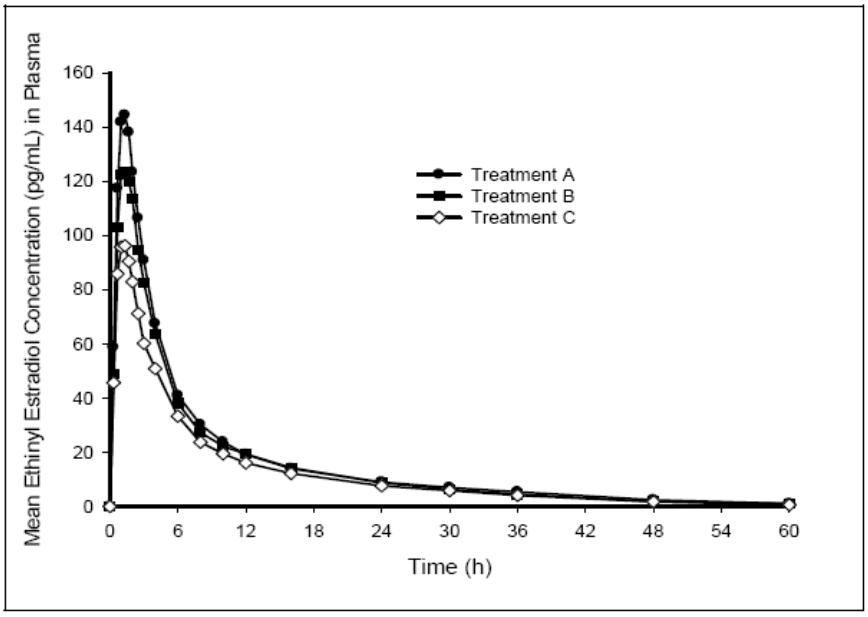
The pharmacokinetic data from 26 subjects were assessable; for one subject NE concentrations could not be determined for analytical reasons so this subject was excluded from pharmacokinetic analysis.

Ethinyl estradiol

Mean plasma EE concentration versus time curves following administration of treatment A, B or C is presented in Figures 1 and 2. Mean pharmacokinetic parameters of these treatments are summarized in Table 4.

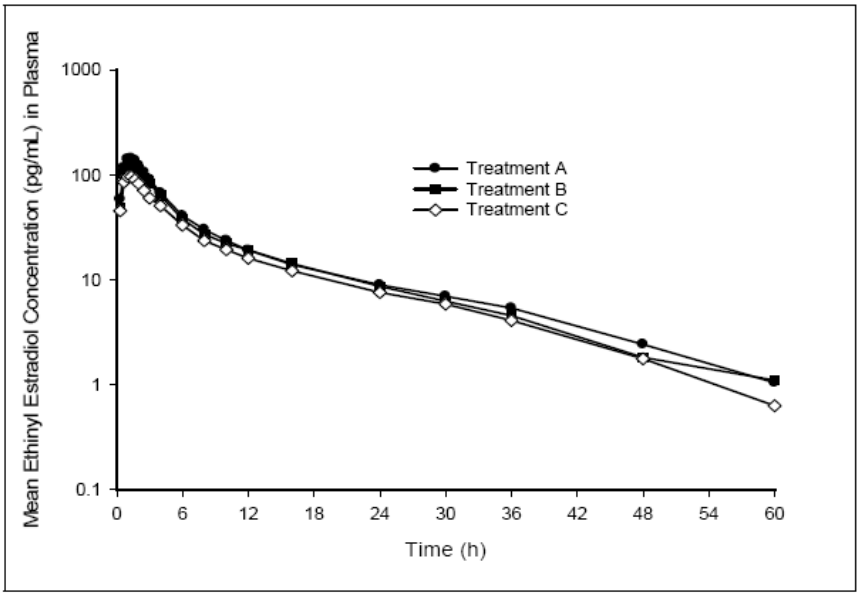
Following administration of 0.025 mg EE and 0.8 mg NE either as a NE/EE tablet with 45 mL water (Treatment B) or without water (Treatment A) or dissolved/suspended in a (b) (4) solution (Treatment C), plasma EE concentrations increased rapidly until Cmax was reached at 1.33 h (1-3), 1.33 h (0.67-2), and 1.33 h (0.67-4) [median(range)], respectively, followed by a loglinear decrease over the remainder of the treatment period (Figures 1 and 2).

Figure 1. Mean Plasma Ethinyl Estradiol Concentration Versus Time Curves (Linear Scale) Following Administration of WC3026 tablets without water (Treatment A), with water (Treatment B) or a Solution/Suspension containing 25 mcg EE/0.8 mg NE (Treatment C) to Healthy Female Volunteers; PR-00807 (n=26)



Source data: Table 2, Table 3 and Table 4

Figure 2. Mean Plasma Ethinyl Estradiol Concentration Versus Time Curves (Log Scale) Following Administration of WC3026 tablets without water (Treatment A), with water (Treatment B) or a Solution/Suspension containing 25 mcg EE/0.8 mg NE (Treatment C) to Healthy Female Volunteers; PR-00807 (n=26)



Source data: The log of plasma ethinyl estradiol concentrations presented in Table 2, Table 3, and Table 4

Text Table 4. Ethinyl Estradiol Pharmacokinetic Parameter Values Following Administration of Treatments A, B, and C to Healthy Female Volunteers; PR-00807 (n=26)

	Least Squares [Median (Range)]			
	Formulation Effect			
Parameter	Treatment A (Test)	Treatment C (Reference)	Ratio (%) (Test : Reference)	90% Confidence Interval
Cmax	148	96.6	153.60	135.41–174.24
AUC0–tldc	929	703	132.10	122.69–142.23
AUCinf	999	773	129.26	119.81–139.46
tmax	[1.33 (0.67–2)]	[1.33 (0.67–4)]	-	-
	Water Effect			
Parameter	Treatment B (Test)	Treatment A (Reference)	Ratio (%) (Test : Reference)	90% Confidence Interval
Cmax	128	148	86.56	76.45–98.00
AUC0–tldc	880	929	94.70	88.06–101.85
AUCinf	973	999	97.33	90.31–104.88
tmax	[1.33 (1–3)]	[1.33 (0.67–2)]	-	-

	Arithmetic Mean (%CV) [Harmonic Mean]		
	Treatment A	Treatment B	Treatment C
Cmax	151 (22.3)	132 (28.1)	105 (37.8)
tmax	1.28 (22.9)	1.40 (33.8)	1.59 (64.2)
AUC0–tldc	980 (24.1)	890 (26.8)	741 (29.1)
AUCinf	1050 (22.8)	977 (24.3)	812 (28.0)
kel	0.054 (30.0)	0.057 (34.3)	0.058 (34.0)
t½	[12.7]	[12.2]	[11.9]

Cmax = Maximum drug concentration (pg/mL); AUC0–tldc = Area under the drug concentration versus time curve from time 0 to the tldc, time of last determinable concentration (pg·h/mL); AUCinf = Area under the drug concentration versus time curve from time 0 to infinity. AUCinf is calculated as the sum of AUC0–tldc plus the ratio of the last measurable drug concentration to the elimination rate constant (pg·h/mL); tmax = time of the maximum measured drug concentration (h); kel = Apparent first-order terminal elimination rate constant calculated from a semi-log plot of the plasma concentration versus time curve; t½ = Apparent first-order terminal elimination half-life, calculated as 0.693/kel

Treatment A: WC3026 tablet chewed without water
Treatment B: WC3026 tablet chewed and followed with 45 mL water
Treatment C: A hydroalcoholic solution/suspension containing EE 25 mcg/NE 0.8 mg administered orally and followed with water; total volume administered was 45 mL.

Source data: Table 8, Table 9, and Table 10

Formulation effect comparison (Treatment A (Test) vs Treatment C (Reference)) on EE bioavailability

Reviewer's comment:

The rate of EE absorption was increased when EE was administered in a NE/EE tablet as compared to the EE/NE solution/suspension; the mean Cmax value was over 50% higher with the Test treatment as compared to the Reference treatment. Tmax values were not significantly affected by formulation. The extent of EE absorption was also increased following administration of NE/EE tablets without water as compared to the EE/NE solution/suspension; mean AUC values were approximately 30% higher for the Test treatment as compared to the Reference treatment (Table 4).

Water effect comparison (Treatment B (Test) vs Treatment A (Reference)) on EE bioavailability

Reviewer's comment:

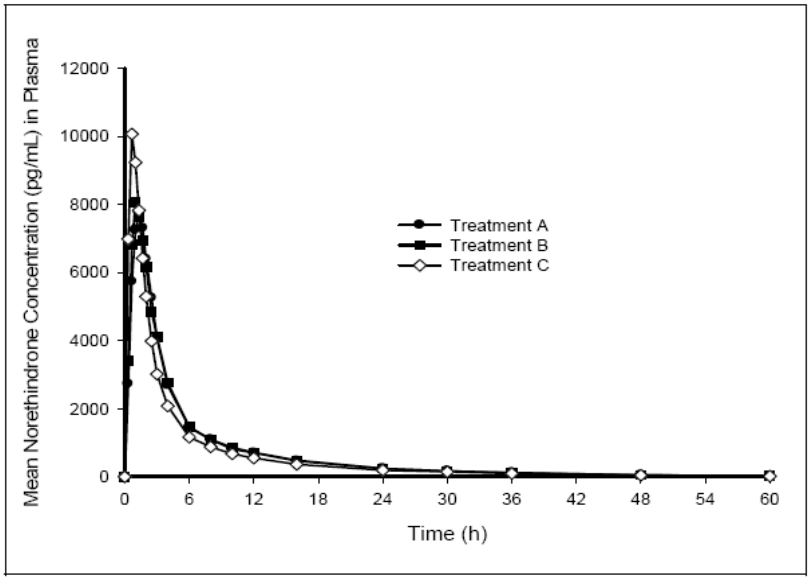
When NE/EE tablets were administered with water the rate of EE absorption was slightly decreased; the mean Cmax value was about 13% lower for the tablet taken with water and the 90% confidence intervals for EE Cmax were outside the 80.00% to 125.00% bioequivalence limits. The extent of EE absorption, however, was not affected by the administration of water with the NE/EE tablets; the confidence intervals around the ratios for EE AUC values were inside the 80.00% to 125.00% bioequivalence limits (Table 4).

Norethindrone

Mean plasma norethindrone concentrations versus time curves following administration of treatment A, B or C are presented in Figure 3 and 4. Mean pharmacokinetic parameters of these treatments are summarized in Table 5.

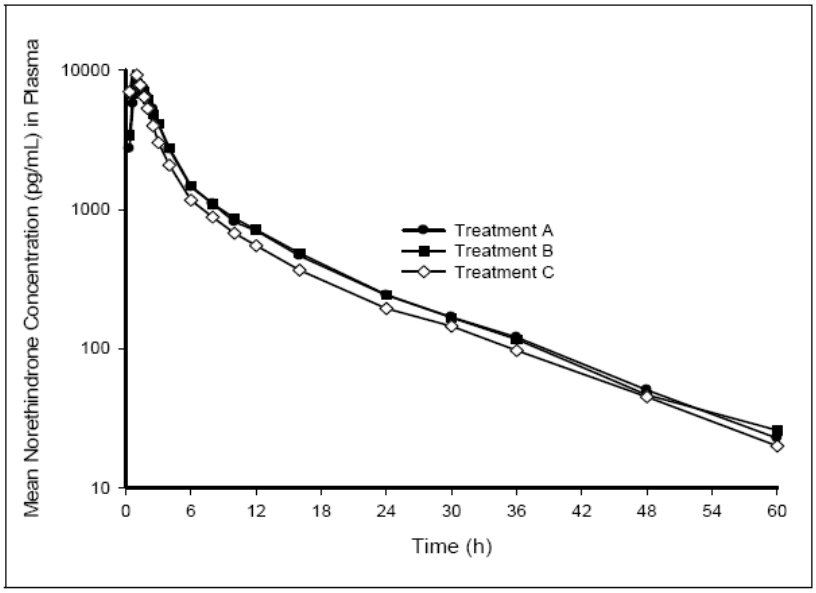
Following administration of 0.025mg EE and 0.8 mg NE either as a NE/EE tablet with 45 mL water (Treatment B) or without water (Treatment A) or dissolved/suspended in a (b) (4) solution (Treatment C), plasma NE concentrations increased rapidly until Cmax was reached at 1 h (0.67-3), 1.33 h (0.67-3) and 0.67 h (0.67-3) [median (range)], respectively, followed by a loglinear decrease over the remainder of the treatment period (Figures 3 and 4).

Figure 3. Mean Plasma Norethindrone Concentration Versus Time Curves (Linear Scale) Following Administration of WC3026 tablets without water (Treatment A), with water (Treatment B) or a Solution/Suspension containing 25 mcg EE/0.8 mg NE (Treatment C) to Healthy Female Volunteers; PR-00807 (n=26)



Source data: Table 5, Table 6, and Table 7

Figure 4. Mean Plasma Norethindrone Concentration Versus Time Curves (Log Scale) Following Administration of WC3026 tablets without water (Treatment A), with water (Treatment B) or a Solution/Suspension containing 25 mcg EE/0.8 mg NE (Treatment C) to Healthy Female Volunteers; PR-00807 (n=26)



Source data: The log of plasma norethindrone concentrations presented in Table 5, Table 6, and Table 7

Text Table 5. Norethindrone Pharmacokinetic Parameter Values Following Administration of Treatments A, B, and C to Healthy Female Volunteers; PR-00807 (n=26)

	Least Squares Mean [Median (Range)]			
	Formulation Effect			
Parameter	Treatment A (Test)	Treatment C (Reference)	Ratio (%) (Test : Reference)	90% Confidence Interval
Cmax	7953	9362	84.95	72.91–98.98
AUC0–tldc	34800	33702	103.26	94.47–112.87
AUCinf	35480	34394	103.16	94.52–112.58
tmax	[1.33 (0.67–3)]	[0.67 (0.67–3)]	-	-
	Water Effect			
Parameter	Treatment B (Test)	Treatment A (Reference)	Ratio (%) (Test : Reference)	90% Confidence Interval
Cmax	7610	7953	95.68	82.31–111.22
AUC0–tldc	35256	34800	101.31	92.81–110.59
AUCinf	36113	35480	101.79	93.39–110.94
tmax	[1 (0.67–3)]	[1.33 (0.67–3)]	-	-

	Arithmetic Mean (%CV) [Harmonic Mean]		
	Treatment A	Treatment B	Treatment C
Cmax	8550 (41.4)	8450 (38.1)	10400 (39.9)
tmax	1.38 (41.1)	1.26 (44.8)	0.89 (54.0)
AUC0–tldc	38588 (40.0)	39430 (41.5)	36017 (31.7)
AUCinf	39264 (39.5)	40258 (40.7)	36720 (31.3)
kel	0.079 (33.4)	0.078 (36.6)	0.075 (37.9)
t½	[8.7]	[8.8]	[9.3]

See Text Table 4 for definitions and abbreviations
Source data: Table 12, Table 13, and Table 14

Formulation effect comparison (Treatment A (Test) vs Treatment C (Reference)) on NE bioavailability

Reviewer's comment:

A decreased rate of NE absorption from the NE/EE tablet as compared to the EE/NE (b) (4) *solution/suspension was reflected in a 15% decrease in the mean NE Cmax and increased tmax*

values. The extent of NE absorption, however, was equivalent between the tablet and the EE/NE solution/suspension; the 90% confidence intervals about the NE AUC ratio were within the 80% to 125% bioequivalence limits (Table 5).

Water Effect Comparison (Treatment B (Test) vs Treatment A (Reference)) on NE bioavailability

Reviewer's comment:

Both the rate and extent of NE absorption were bioequivalent between the NE/EE tablet chewed with water as compared to the tablet chewed without water; the 90% confidence intervals for NE Cmax and AUC were within the 80% to 125% bioequivalence limits (Table 5).

Analytical Issues

No data values were reported missing due to blood samples not being collected. There were 68 concentrations not reported due to analytical issues (Table 6). Due to the difficulties encountered in the NE analysis of samples from Subject 26 this subject was excluded from the pharmacokinetic analysis.

Text Table 6. Missing data due to analytical issues; PR-00807

Subject	Time (h)	Period	Treatment	Analyte	Reason
8	36	1	C	EE	(1)
15	36	1	A	NE	(1)
20	Predose	2	C	EE	(1)
20	Predose	1	A	NE	(1)
20	Predose	2	C	NE	(1)
20	Predose	3	B	NE	(1)
26	All (60 samples)	1, 2, 3	B, A, C	NE	(2)
26	0.67	2	A	EE	(1)
26	16	2	A	EE	(1)

(1) Result from reanalyzed sample(s) did not confirm original results; no result reported
(2) An interfering signal in the norethindrone chromatogram could not be separated from the analyte; no result could be reported

STATISTICAL ANALYSIS

Descriptive statistics (arithmetic mean, standard deviation and %CV) were calculated for EE and NE concentrations at each time point for the 3 treatments. Descriptive statistics (geometric mean, arithmetic mean, standard deviation and %CV) were also calculated for all pharmacokinetic parameters. Additionally, the harmonic mean was calculated for t½ and the median value was determined for tmax.

The bioavailability measures of the Test and Reference treatments were compared using the average bioequivalence approach. Analyses of variance (ANOVA) were performed on the log-transformed pharmacokinetic parameters AUC_{0-tldc}, AUC_{inf}, and C_{max}. The ANOVA model included sequence, formulation and period as fixed effects and subject nested within sequence as a random effect. Sequence was tested using subject nested within sequence as the error term. A 10% level of significance was used to test the sequence effect. Each analysis of variance included calculation of least-squares means, differences between adjusted formulation means and the standard error associated with these differences. Statistical analyses were conducted using the appropriate SAS® procedure.

Consistent with the two one-sided test for bioequivalence, 90% confidence intervals for the exponential of the difference between drug formulation least-squares means (LSM) were calculated for the parameters AUC_{0-tldc}, AUC_{inf} and C_{max} using log-transformed data. The confidence intervals were expressed as a percentage relative to the LSM of the Reference formulation. The treatments were defined as bioequivalent if the 90% confidence interval for the exponential of the difference between treatment LSM for the parameters C_{max}, AUC_{0-tldc}, and AUC_{inf} were between 80 and 125%.

CONCLUSION
NE/EE tablets administered with (45 mL) or without water or 0.025mg EE/0.8mg NE administered in a (b) (4) solution/suspension were generally well tolerated.
Both the rate and extent of EE absorption were higher for NE/EE tablets chewed without water than for the EE/NE solution/suspension. The rate of NE absorption for NE/EE tablets chewed without water was slightly decreased, but the extent of NE absorption was not affected as compared to the EE/NE solution/suspension.
Administration of NE/EE tablets chewed with water decreased EE absorption rate but did not affect the extent of EE absorption. With respect to NE, NE/EE tablets chewed with water are bioequivalent to NE/EE tablets chewed without water.

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A.1.2. Study PR-00907.1

A Study to Determine the Effect of Food on Ethinyl Estradiol and Norethindrone Bioavailability Following Oral Administration of a NE/EE Tablet in Healthy Female Volunteers

Protocol No: PR-00907.1
Phase: 1
Principal Investigator: Frederick A Bieberdorf, MD, CPI
Clinical Study Center: CEDRA Clinical Research, LLC
8501 North MoPac Expressway Suite 200, Austin, Texas 78759
Clinical Study Dates: Sept.29, 2007 – Oct. 29, 2007
Analytical Study Facility: (b) (4)

Analytical Study Dates: 08/04/08

OBJECTIVE
To assess the effect of food on ethinyl estradiol and norethindrone bioavailability following oral administration of a single NE/EE chewable tablet.

STUDY ENDPOINTS
Pharmacokinetic parameters including C_{max}, T_{max}, $AUC_{t\text{-}tldc}$, AUC_{inf}, k_{el} and $t_{1/2}$ were determined.

STUDY DESIGN, TREATMENT, AND SUBJECTS
This was a single-center, randomized, balanced, single-dose, 2-treatment, 2-period, 2-sequence, crossover study. Thirteen of the 18 subjects completed the study.

Subjects received one NE/EE tablet in each treatment period; the tablet was chewed and swallowed without water. All subjects were fasted for at least 10 hours prior to treatment. Subjects randomized to the Fasted treatment did not receive food for at least 4 hours post-dose and subjects randomized to the Fed treatment received their tablet within 5 minutes of having consumed a high-fat, high-calorie test meal. Water was allowed ad libitum except 1 hour prior to dosing and 1 hour after treatment administration. There was a 28-day washout period between treatments. Subjects attended the clinic on the evening prior to dosing and fasted overnight. The treatments were administered after pre-dose clinical assessments were completed.

The 18 subjects enrolled in the study had a median (range) age of 27 (18–35) years, a median (range) weight of 62.8 (51.0–72.8) kg, and a median (range) height of 165.3 (155.5–174.0) cm. All subjects were female. There were 9 subjects (50%) who were Non-Hispanic/Latino-White, 8 subjects (44%) who were Hispanic/Latino-White, and 1 subject (6%) who was Non-Hispanic/Latino-Black.

Inclusion criteria:

- Healthy female subjects of any race who had not taken any form of medication within the 14 days prior to dosing.
- Aged 18–35 years inclusive.
- Weighed at least 45 kg (99 lbs) and were within 15% of their ideal weight as defined by the 1983 Metropolitan Life Assurance Tables.

Exclusion criteria:

- Had a history or presence of alcoholism or drug abuse within the past year.
- Had hypersensitivity or idiosyncratic reaction to estrogens, progestogens or other hormonal agents.
- Had a history of jaundice with previous use of oral contraceptives.
- Had a history of liver tumors.
- Had used tobacco or nicotine in any form during the previous three months.
- Were pregnant or lactating.
- Were sexually active and not either surgically sterilized (bilateral tubal ligation; 6 months minimum), practicing a non-heterosexual lifestyle, or using one of the following acceptable methods of birth control:
    - Barrier method (condom, diaphragm) with spermicide for at least 7 days prior to the first dose and throughout the study
    - Non-hormonal IUD in place for at least 3 months.
- Had used any substances known to be strong inhibitors of cytochrome P450 (CYP) enzymes (such as cimetidine, fluoxetine, quinidine, erythromycin, fluconazole, and ketoconazole) or any substances known to be strong inducers of CYP enzymes (such as barbiturates, carbamazepine, glucocorticoids, phenytoin and rifampin) within 28 days of study start.

FORMULATION

The following product, a single NE/EE tablet (0.8 mg norethindrone [NE] and 0.025mg ethinyl estradiol [EE]) was administered in either the fed or the fasted state:

Dosage form description	Active WC3026 tablets are round, light-green, flat-faced, beveled-edged tablets; tablets have a slight spearmint odor. Each tablet contains 0.8 mg norethindrone (NE) and 25 mcg ethinyl estradiol (EE).
Package description	Blister card containing 24 light-green, round active tablets and 4 pale lilac round inactive tablets; **ONLY THE LIGHT-GREEN ACTIVE TABLETS WERE ADMINISTERED**
Dose per time unit	One active WC3026 tablet (0.8 mg NE and 25 mcg EE)
Cumulative dosage	Two active WC3026 tablets (1.6 mg NE and 50 mcg EE)

The tablet was chewed and swallowed without water. The investigational product (Batch #80157F) was manufactured in March 07, 2007 by Warner Chilcott Company, LLC. The formulation number was WC3026.

Treatment was administered following either:

- an overnight fast of at least 10 hours (Reference; Fasted), or

- an overnight fast (of at least 10 hours) and within 5 minutes of having consumed a high fat, high calorie, test meal consumed over a 25–30-minute period (Test; Fed).

PHARMACOKINETIC EVALUATION

Blood sampling

Blood samples were collected pre-treatment (0 hours) and at 0.33, 0.67, 1, 1.33, 1.67, 2, 2.5, 3, 4, 6, 8, 10, 12, 16, 24, 30, 36, 48 and 60 hours post-treatment. Blood samples were collected into Vacutainers containing lithium heparin. Blood samples were collected by direct venipuncture.

Concomitant Therapy

Concomitant medication was not allowed 14 days preceding the study and during the study. Strong CYP enzyme inhibitors or inducers as well as other contraceptives were not allowed within 28 days of study start. However, one subject received a single dose of acetaminophen as a result of an adverse event (Table 9). The same subject withdrew consent following the AE of headache in Period 1. Collected samples from this subject were not included in the PK analysis.

Text Table 9. Use of Concomitant Medication Over Course of Study; Study PR-00907

Subject	Visit	Medication	Formulation	Dose [a]	Regimen	Indication	Start Date and Time	Stop Date and Time
306	2	Acetamino-phen	Tablet	1000 mg	One dose	Headache	9/29/2007 20:00	9/29/2007 20:00

[a] Medication was administered orally

Source data: Appendix 16.2.2.4

Bioanalytical method

The bioanalytical method is reviewed under individual study review for study PR-00807 (Section A.1.1)

DATA ANALYSIS

Pharmacokinetic Analysis

EE and NE non-compartmental pharmacokinetic parameters from the 13 subjects who completed the study were calculated following single-dose administration of NE/EE tablet in the fed and fasted states. Individual subject data and descriptive statistics were inspected for trends likely to be of clinical relevance.

PHARMACOKINETIC RESULTS

Thirteen (13) of the 18 subjects completed the study and the pharmacokinetic data from 13 subjects were evaluable. Five (5) subjects did not complete the study and the partial sample sets from these 5 subjects were not analyzed. Withdrawal of study participation was due to non-compliance (1 patient), consent withdrawal due to personal reasons (3 patients) and adverse events (headache, 1 patient).

A summary of the EE pharmacokinetic values and statistical evaluation is presented in Table 6.

Text Table 6. Ethinyl Estradiol Pharmacokinetic Parameter Values following Administration of WC3026 Tablet under Fed (Treatment A) and Fasted (Treatment B) Conditions to Healthy Female Volunteers; Study PR-00907 (n=13)

Parameter	Geometric Mean [Median (Range)]		Ratio (Test : Ref)	90% Confidence Interval
	WC3026 Tablet FED, Treatment A (Test)	WC3026 Tablet FASTED, Treatment B (Reference)		
Cmax	87.5	142	60.98%	50.43-73.73
AUC0-tldc	860.6	934.0	91.98%	84.50-100.12
AUCinf	938.9	1025	92.38%	84.55-100.93
Tmax	[1.33 (1.00-2.00)]	[1.33 (0.67-1.67)]	-	-
	Arithmetic Mean (%CV) [Harmonic Mean]			
Cmax	96.2 (48)	146 (23)		
Tmax	1.28 (26)	1.18 (22)		
AUC0-tldc	886.5 (26)	951.0 (20)		
AUCinf	963.6 (24)	1042 (19)		
kel	0.0446 (27)	0.0492 (29)		
t½	[15.53]	[14.09]		

Cmax = Maximum plasma concentration (pg/mL)
AUC0-tldc = Area under the plasma concentration versus time curve from time 0 to the tldc, time of last determinable concentration (pg•h/mL)
AUCinf = Area under the plasma concentration versus time curve from time 0 to infinity. AUCinf is calculated as the sum of AUC0-tldc plus the ratio of the last measurable plasma concentration to the elimination rate constant (pg•h/mL)
tmax = time of the maximum measured plasma concentration (h)
kel = Apparent first-order terminal elimination rate constant calculated from a semi-log plot of the plasma concentration versus time curve (1/h)
t½ = Apparent first-order terminal elimination half-life, calculated as 0.693/kel (h)
Source data: Table 14.2.2.1, Table 14.2.2.2, and Table 14.2.4.1

When NE/EE tablets were administered with a high fat meal mean EE Cmax decreased by 39% indicating a decreased EE absorption rate. However, the extent of EE absorption was unchanged; the 90% confidence intervals for EE AUC0–tldc and AUCinf were within the 80.00% to 125.00% bioequivalence limits.

A summary of the NE pharmacokinetic values and statistical evaluation is presented in Table 7.

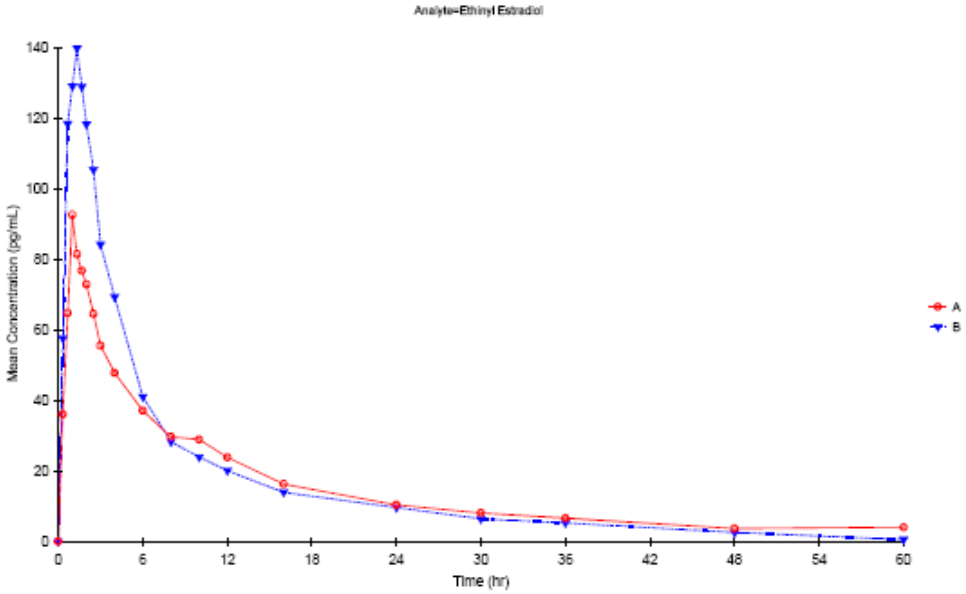
Text Table 7. Norethindrone Pharmacokinetic Parameter Values following Administration of WC3026 Tablet under Fed (Treatment A) and Fasted (Treatment B) Conditions to Healthy Female Volunteers; Study PR-00907 (n=13)

Parameter	Geometric Mean [Median (Range)]		Ratio (Test : Ref)	90% Confidence Interval
	WC3026 Tablet FED, Treatment A (Test)	WC3026 Tablet FASTED, Treatment B (Reference)		
C_{max}	4760	8830	53.46%	42.59-67.12
$AUC_{(0-tldc)}$	45810	40460	113.60%	99.06-130.28
AUC_{inf}	46460	42430	109.58%	92.12-130.34
t_{max}	[1.33 (0.67 - 8.00)]	[1.33 (0.67 - 1.67)]	-	-
	Arithmetic Mean (%CV) [Harmonic Mean]			
C_{max}	5190 (50)	9090 (24)		
t_{max}	2.54 (90)	1.18 (25)		
$AUC_{(0-tldc)}$	47350 (27)	44590 (50)		
AUC_{inf}	47970 (26)	49210 (71)		
kel	0.0746 (14)	0.0783 (31)		
t½	[9.29]	[8.86]		

See Text Table 6 for definitions of terms.
Source data: Table 14.2.2.3, Table 14.2.2.4, and Table 14.2.4.2

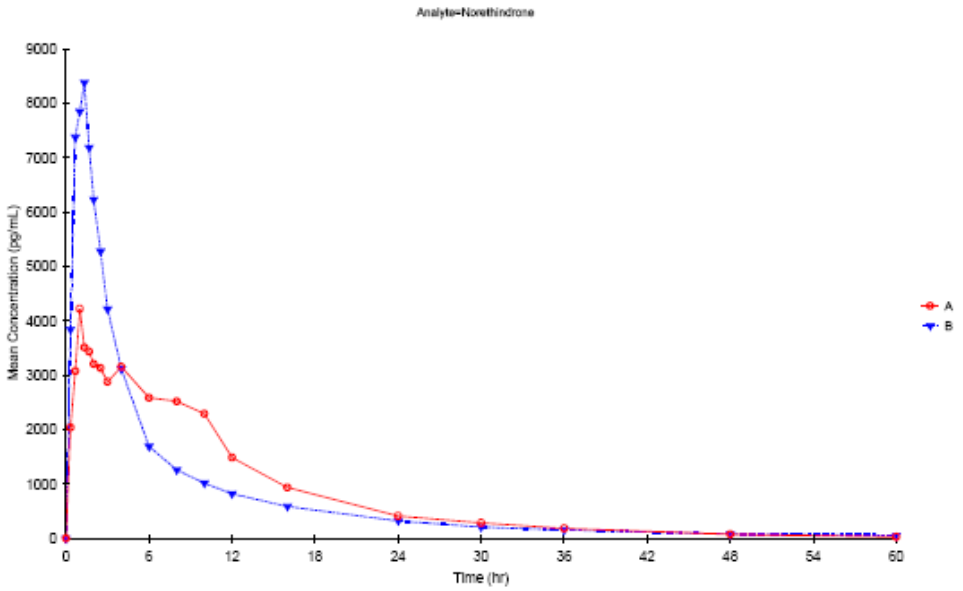
When NE/EE tablets were administered with a high fat meal, mean NE Cmax decreased by 47% indicating a decreased NE absorption rate. However, the extent of NE absorption, as reflected by NE AUC0–tldc and AUCinf values, was increased by 10–14%.

Figure 1: Mean Plasma Ethinyl Estradiol Concentration versus Time Curves Following Administration of a NE/EE Tablet under Fed (Test, Treatment A) and Fasted (Reference, Treatment B) Conditions to Healthy Female Subjects (n=13).



Reviewer's comment: *The arithmetic mean Cmax and AUC0-tldc values under fasted conditions in this study (146pg/mL and 951pg*h/mL) appear to be comparable to those obtained in Study PR00807 (151pg/mL and 980pg*h/mL) under fasted conditions using the same formulation (NE/EE) chewed without water.*

Figure 2: Mean Plasma Norethindrone Concentration versus Time Curves Following Administration of a NE/EE Tablet under Fed (Test, Treatment A) and Fasted (Reference, Treatment B) Conditions to Healthy Female Subjects (n=13)



Reviewer's comment: *The arithmetic mean Cmax and AUC0-tldc values under fasted conditions in this study (9090pg/mL and 44590pg*h/mL) appear to be comparable to those obtained in Study PR00807 (8550pg/mL and 38588pg*h/mL) under fasted conditions using the same formulation (NE/EE) chewed without water.*

STATISTICAL ANALYSIS

The data from all 13 subjects who completed the study were analyzed. Descriptive statistics (ie, geometric mean, arithmetic mean, standard deviation, and relative standard deviation) were calculated for all pharmacokinetic parameters. Additionally, the harmonic mean was calculated for t½ and the median was reported for tmax.

Analyses of variance (ANOVA) was performed on the log-transformed pharmacokinetic parameters AUC0-tldc, AUCinf, and Cmax. The ANOVA model included sequence, treatment, and period as fixed effects and subject nested within sequence as a random effect. Sequence was tested using subject nested within sequence as the error term. A 10% level of significance was used to test the sequence effect. Each analysis of variance included calculation of least-squares means, differences between adjusted treatment means, and the standard error associated with these differences. Statistical analyses were conducted using the appropriate SAS® procedure. The 90% confidence intervals for the difference between treatment least-squares means (LSM) was calculated for the parameters AUC0-tldc, AUCinf, and Cmax using log-transformed data. The confidence intervals were expressed as a percentage relative to the LSM of the reference formulation.

Five (5) subjects did not complete the study; the partial sample sets from these 5 subjects were not analyzed. Only the samples from the 13 subjects who completed the study were analyzed; the data on all 13 subjects who completed the study was evaluable. No data values were reported missing due to blood samples not being collected for subjects included in the pharmacokinetic analysis. There were no missing data as a result of analytical problems.

CONCLUSION

NE/EE tablets administered in either the fed or fasted states were generally well tolerated.

Administration of NE/EE tablets with food decreased the EE and NE absorption rates. Administration with food did not affect the extent of EE absorption but increased the extent of NE absorption by 10%. With respect to Study 00207 (Phase 3 safety and efficacy study), no specific recommendations regarding food intake are necessary.

A.1.3. Study PR03808

A Study to Characterize the Bioavailability of Ethinyl Estradiol and Norethindrone following Multiple-Dose Administration of NE/EE Tablets in Healthy Female Volunteers

Protocol No: PR03808
Phase: 1
Principal Investigator: Mark T Leibowitz, MD
Clinical Study Center: CEDRA Clinical Research, LLC; 8501 North Mopac Expressway, Suite 200, Austin, Texas 78759
Clinical Study Dates: 19 February 2009 – 16 March 2009 (first subjects dosed – last blood sample collected)
Analytical Study Facility: (b) (4)
Analytical Study Dates: 04/08/09 (SHBG), 05/12/09 (NE/EE)

OBJECTIVE

To characterize the plasma EE and NE pharmacokinetic profiles and SHBG concentrations following multiple-dose administration of NE/EE tablets to healthy female volunteers under fasting conditions.

STUDY ENDPOINTS

Pharmacokinetic parameter Cmax, AUC0-24, Tmax, AUC0-tau, t1/2, fluctuation of NE and EE and Cmin of SHBG were determined.

STUDY DESIGN, TREATMENT, AND SUBJECTS

This single-center, single-treatment, multiple-dose, bioavailability characterization study was conducted under medical supervision. All subjects received one NE/EE tablet per day for 24 days with an overnight fast prior day 1 and day 24; each tablet contained 0.8 mg NE and 0.025mg EE. The tablet was chewed prior to swallowing and was not followed with water. Subjects received Dose 1 during Week 1 of their menstrual cycle.

The 18 female subjects enrolled in the study had a median (range) age of 26 (19–33) years, a median (range) weight of 64.4 (47.6–77.0) kg, and a median (range) height of 164.0 (142.5–179.5) cm. There were 10 subjects (approximately 56%) who were White, of which 7 (approximately 39%) were Hispanic/Latino and 3 (approximately 17%) were Non-Hispanic/Latino. Additionally, 7 (approximately 39%) subjects were Non-Hispanic/Latino Black and 1 (approximately 6%) subject was Non-Hispanic/Latino Asian.

Inclusion criteria:

- Healthy female subjects, of any race who had not taken any form of medication within the 14 days prior to dosing.
- Aged 18–35 years inclusive.
- Subjects weighing at least 45 kg (99 lbs) who were within 15% of their ideal weight according to the 1983 Metropolitan Height and Weight Tables.
- Subjects who had regular menstrual cycles defined as a usual length of 21−35 days and a variability of ± 3 days (subjects who were recently post partum or post abortion must have had at least 2 normal cycles).

Exclusion criteria:

- History or presence of alcoholism or drug abuse within the past year.
- Hypersensitivity or idiosyncratic reaction to estrogens, progestogens or other hormonal agents.
- History of jaundice with previous use of oral contraceptives.
- History of liver tumors.
- Tobacco or nicotine use in any form during the previous three months.
- Subjects who were pregnant or lactating.
- Subjects who had used any substances known to be strong inhibitors of cytochrome P450 (CYP) enzymes (such as cimetidine, fluoxetine, quinidine, erythromycin, fluconazole, and ketoconazole) or any substances known to be strong inducers of CYP enzymes (such as barbiturates, carbamazepine, glucocorticoids, phenytoin and rifampin) within 28 days of study start.

FORMULATION

A single NE/EE tablet (0.8 mg NE and 0.025 mg EE) was orally administered per day for 24 days (Table1). Each treatment was administered following an overnight fast (at least 10 hours), and subjects did not consume food for 4 hours following the treatment. The tablets were chewed prior to swallowing and were not followed with water. The tablets (Batch 80537F) were manufactured September 21, 2007 by Warner Chilcott Company, LLC, Fajardo, Puerto Rico. The formulation number was WC3026.

Table 1:

Test Treatment, WC3026	
Package description	Blister card contained 24 light-green, round active tablets and 4 pale lilac round inactive tablets; **ONLY THE LIGHT-GREEN ACTIVE TABLETS WERE ADMINISTERED**
Dosage form description	The active WC3026 tablets were round, light-green, flat-faced, beveled-edged tablets; tablets had a slight spearmint odor. Each tablet contained 0.8 mg norethindrone (NE) and 25 mcg ethinyl estradiol (EE).
Dose per time unit	One active WC3026 tablet (0.8 mg NE and 25 mcg EE)
Cumulative maximal dosage	Twenty-four (24) active WC3026 tablets (19.2 mg NE and 600 mcg EE)

PHARMACOKINETIC EVALUATION

Blood sampling

Blood samples for determination of NE/EE concentrations were collected at predose and at the following times after Dose 1: 0.33, 0.67, 1, 1.33, 1.67, 2, 2.5, 3, 4, 6, 8, 10, 12, 16, and 24 hours.

Additional blood samples for determination of NE and EE concentrations were collected 24 hours after receiving Doses 4, 8, 12, 16, and 20, i.e., just prior to receiving Doses 5, 9, 13, 17, and 21.

Blood samples for determination of plasma NE/EE concentrations were collected at pre-Dose 24 and at the following times after Dose 24: 0.33, 0.67, 1, 1.33, 1.67, 2, 2.5, 3, 4, 6, 8, 10, 12, 16, 24, 30, 36, 48, and 60 hours.

Blood samples for determination of serum SHBG concentrations were collected prior to dosing on study Day 1 and 24 hours after receiving Doses 1, 4, 8, 12, 16, 20, and 24.

Blood samples were collected by direct venipuncture.

Concomitant Therapy

Concomitant medication was not allowed 14 days preceding the study and during the study. Strong CYP enzyme inhibitors or inducers as well as other contraceptives were not allowed within 28 days of study start. Subjects were asked not to take any other oral contraceptives containing estrogens or any form of hormone therapy by any route for the 28 days prior to dosing and throughout the entire study. Subjects could not have received medroxyprogesterone acetate contraceptive injection (eg, Depo-Provera®) for the year prior to dosing.

Table 10 presents concomitant medication taken by subjects during the study. According to the sponsor it was not expected that this medication use interfered with the outcomes of the study.

Text Table 10. Concomitant Medication; Study PR-03808

Subject	Timing	Medication	Formulation	Dose	Regimen	Indication	Start Date and Time	Stop Date and Time
106	Predose	Acetaminophen	Tab/Cap	500 mg [a]	PRN	Tension Headache	01/22/2009 1030	01/22/2009 1030
109	Day 14	Imodium A-D	Tab/Cap	4 mg [a]	PRN	Diarrhea	03/04/2009 1300	03/04/2009 1300
109	Day 14	Imodium A-D	Tab/Cap	2 mg [a]	PRN	Diarrhea	03/04/2009 1500	03/04/2009 1700
109	Day 14	Preparation H Medicated Wipes	Wipe	1 App [b]	PRN	Hemorrhoids	03/04/2009 1500	03/04/2009 2200
109	Day 15	Lidocaine 4% Anorectal Cream	Cream	1 App [b]	PRN	Hemorrhoids	03/05/2009 1730	03/06/2009 1230

[a] Medication was administered orally
[b] Medication was administered topically

Source data: Appendix 16.2.2.4

Other restrictions

- The consumption of alcohol- or xanthine-containing beverages and food was prohibited for 24 hours before each dose and throughout the blood sampling periods.
- Grapefruit-containing beverages and foods were prohibited for 10 days before dosing and throughout the blood sampling periods.
- Subjects were prohibited from smoking for the duration of the study.

Bioanalytical method

The bioanalytical method used to determine NE and EE concentration is reviewed under individual study review for study PR-00807 (Section A.1.1)

SHBG

For the determination of SHBG in serum samples, a commercially available immunoassay kit was used (IRMAZEN co SHBG, Zen Tech sa, Belgium); the kit contained all the reagents needed to calibrate, assay, and quality control the analysis. The SHBG test was an immunoradiometric assay (IRMA) based on coated tubes with monoclonal antibodies directed against distinct epitopes of the SHBG molecule. Two capture antibodies are coated on the inner wall of the tubes; SHBG of the calibration standard samples, quality control samples, or study samples is captured by these antibodies. Addition of a third antibody labeled with 125iodine completes the system, allowing the formation of a bridge between the coated antibodies and the labeled antibody. After washing, the remaining radioactivity bound to the tubes is directly related to the concentration of the SHBG in the samples.

Sensitivity: The analytical range of the method as quoted by the kit manufacturer was 10.0-250 nmol/L.

Precision: Precision of the calibration standards and quality control (QC) samples during sample analysis was expressed as the percent coefficient of variation (%CV). For SHBG, the %CV ranged from 0.000% to 3.83% for calibration standards and 2.18% to 5.98% for QCs.

Accuracy: Accuracy of the calibration standards and quality control (QC) samples during sample analysis was expressed as the percent difference from theoretical (inaccuracy). For SHBG, the inaccuracy ranged from -2.09% to 0.876% for calibration standards and -1.73% to 1.69% for QCs.

DATA ANALYSIS

Pharmacokinetics

NE and EE noncompartmental pharmacokinetic parameters were calculated following multiple-dose administration of NE/EE tablets for 24 consecutive days. Steady state with respect to NE, EE, and SHBG was determined by visual assessment. Individual subject data and descriptive statistics were inspected for trends likely to be of clinical relevance.

PHARMACOKINETIC RESULTS

All 18 subjects completed the study and 17 were evaluable for pharmacokinetic analysis. One subject had a quantifiable EE predose concentration on Day 1 of the study and was excluded from all pharmacokinetic and statistical analyses per protocol.

A summary of the NE and EE pharmacokinetic values is presented in Synopsis Table 1.

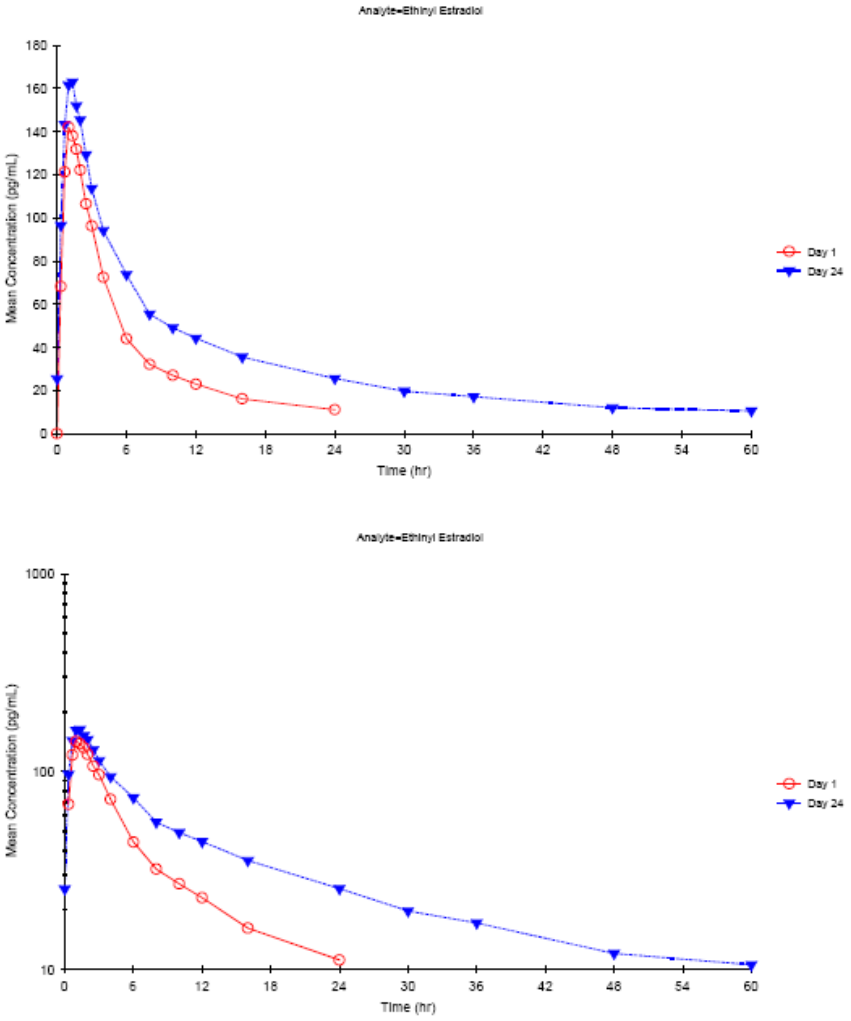
Synopsis Table 1. Summary of NE, EE, and SHBG Pharmacokinetic Parameter Values Following Administration of One WC3026 Tablet (0.8 mg NE and 25 mcg EE) on Days 1 through 24 to Healthy Female Volunteers (n = 17); Study PR-03808

Analyte	Parameter	Arithmetic Mean (%CV) [Median (Range)] {Harmonic Mean}	
		Day 1	Day 24
NE	Cmax	9840 (36)	22200 (30)
	Cmin	--	1820 (40)
	Cavg	--	5880 (32)
	AUC0-24	41680 (47)	--
	tmax	[1.05 (0.67 – 3.00)]	[1.33 (0.67 - 6.00)]
	AUC0-τ	--	141200 (32)
	t½	--	{10.8}
	Fluctuation	--	356 (27)
	R	--	3.6 (27)
EE	Cmax	147 (25)	168 (25)
	Cmin	--	23.4 (58)
	Cavg	--	58.4 (32)
	AUC0-24	902.8 (18)	--
	tmax	[1.13 (0.67 – 2.00)]	[1.00 (0.33 – 2.00)]
	AUC0-τ	--	1400 (32)
	t½	--	{17.1}
	Fluctuation	--	260 (27)
	R	--	1.5 (21)
SHBG	Cmin*	40 (65)	108 (45)

Cmax = Maximum plasma concentration (pg/mL)
Cmin = Minimum, post-Cmax plasma concentration during the 24 hours which follow dose administration (pg/mL)
Cavg = Average plasma concentration = AUC0-τ / 24, (pg/mL)
AUC0-24 = Area under the plasma concentration versus time curve from time 0 to 24 hours (pg-h/mL)
AUC0-τ = The area under the plasma concentration versus time curve, from time 0 to tau (τ), the dosing interval (24 hours) (pg-h/mL)
tmax = time of the maximum measured plasma concentration (h)
t½ = Apparent first-order terminal elimination half-life, calculated as 0.693/kel
Fluctuation = 100 x ((Cmax – Cmin) / Cavg) (%)
R = Accumulation factor = AUC0-τ / AUC0-24
SHBG = Sex hormone binding globulin (concentrations in nmol/L)
* Day 1 is the predose SHBG concentration; Day 24 is the SHBG concentration 24 hours after Dose 24.
Source data: Report RR-00509.0; Tables 14.2.1.7 and 14.2.2.1 through 14.2.2.4

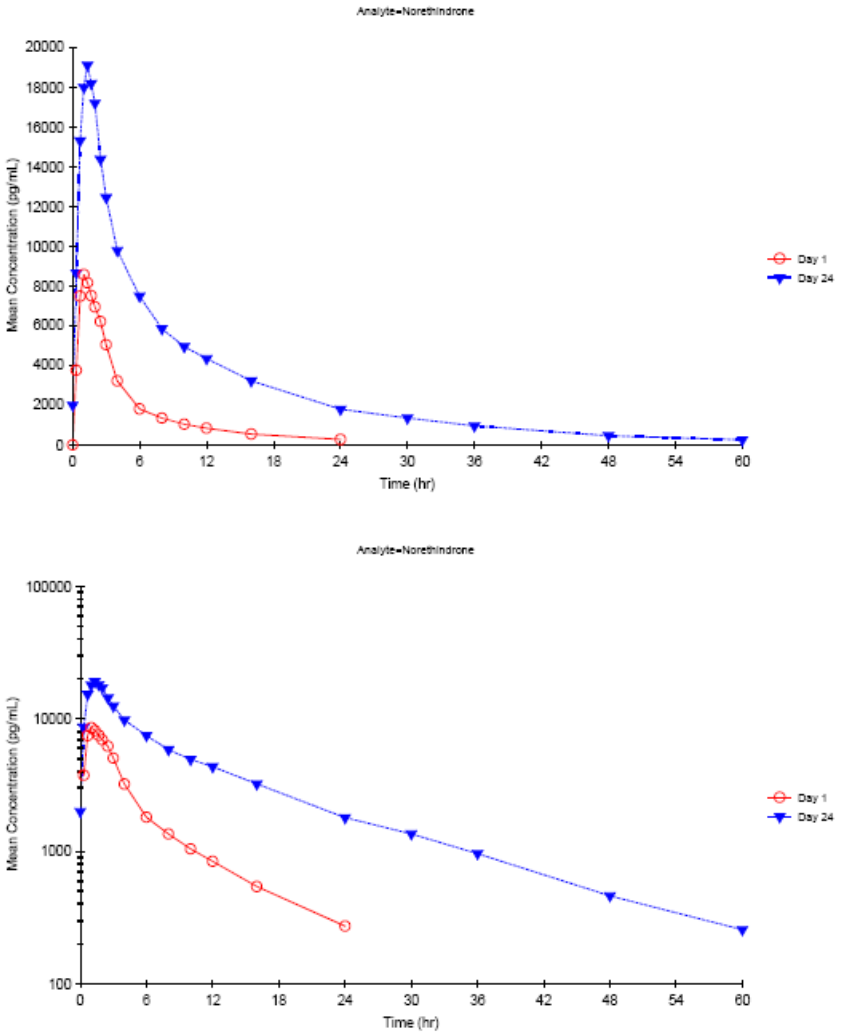
Mean concentration-time data are shown in Synopsis Figures 1 and 2.

Synopsis Figure 1. Mean Ethinyl Estradiol Concentration-Time Plots after the Administration of WC3026 on Days 1 and 24 (n = 17); Study PR-03808



Source data: Report RR-00509.0; 14.4.1

Synopsis Figure 2. Mean Norethindrone Concentration-Time Plots after the Administration of WC3026 on Days 1 and 24 (n = 17); Study PR-03808



Source data: Report RR-00509.0; 14.4.2

NE and EE Cmax concentrations increased by a factor of 2.3 and 1.1, respectively, following 24 days administration of NE/EE tablets as compared to single-dose administration. NE and EE AUC0–τ values increased by a factor of 3.6 and 1.5, respectively, following 24 days administration of NE/EE tablets as compared to single-dose administration. NE accumulation estimated from the elimination rate constant (1.3) was significantly less than that calculated from AUC0–τ/AUC0–24 (3.6), as increases to SHBG concentrations contribute to NE accumulation. During the dosing interval, there was a 356% fluctuation about the average concentration (Cavg), 5880 pg/mL.

EE accumulation, however, was consistent with that calculated from the elimination rate constant (1.6). During the dosing interval, there was a 260% fluctuation about the average concentration (Cavg), 58.4 pg/mL. Based on visual assessment of trough levels steady-state was achieved for EE by day 9 on average (Figure 3). 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. Based on visual assessment of trough levels pre-dose concentrations for NE continue to increase through to day 21 (Figure 4). 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 9.

Figure 3: Plasma EE concentrations prior to and following NE/EE tablets (mean±1SD; n=17).

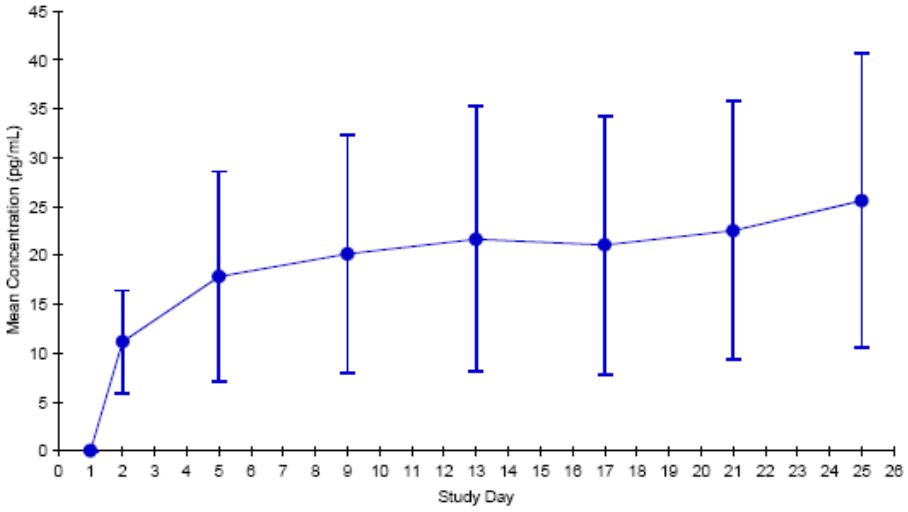
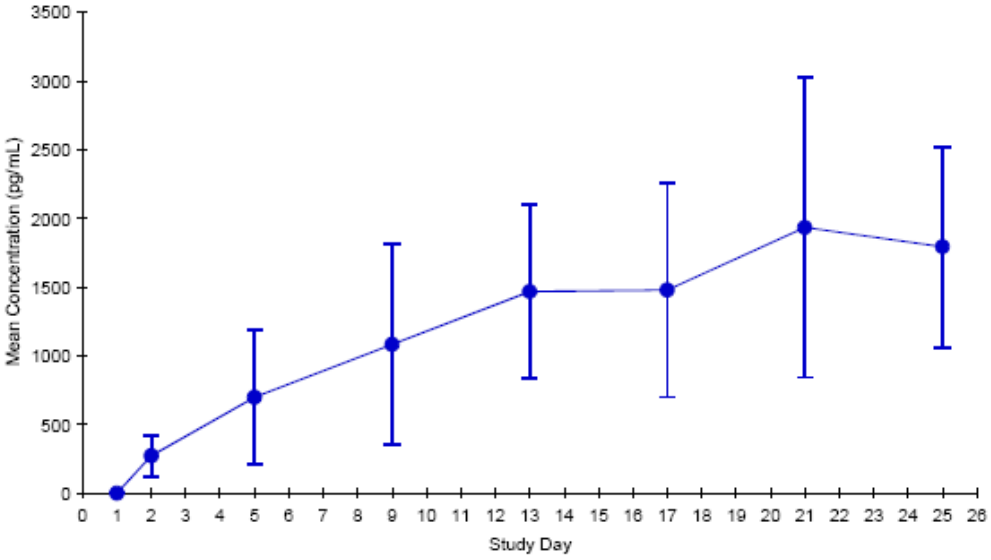


Figure 4: Plasma NE concentrations prior to and following NE/EE tablets (mean±1SD; n=17)



Mean SHBG concentrations more than doubled (170% increase) from predose to Day 24 (24 hours after Dose 24) (Table7)). This is to be expected, as it is extensively reported that EE induces the synthesis of SHBG.

Text Table 7. Mean SHBG concentrations Following Administration of One WC3026 Tablet (0.8 mg NE and 25 mcg EE) on Days 1 through 24 to Healthy Female Volunteers (n = 17); Study PR-03808

Study Day	Mean SHBG concentration (nmol/L)	CV (%)
1	40.0	65
2	41.5	66
5	65.4	48
9	92.6	44
13	105	38
17	99.7	33
21	106	43
25	108	45

Source data: Table 14.2.1.7

CONCLUSION

Norethindrone and EE exposure increased by factors of 3.6 and 1.5, respectively, following multiple-dose administration of NE/EE tablets as compared to single-dose administration of NE/EE tablets chewed without water. Steady state with respect to EE was reached approximately by Day 9, NE concentrations continue to increase until day 21.

A.1.3. Study PR00707

A Study to Characterize the Bioavailability of Ethinyl Estradiol and Norethindrone following Multiple-Dose Administration of NE/EE Tablets in Healthy Female Volunteers

Protocol No: PR00707
Phase: 1
Principal Investigator: Frederick A Bieberdorf, MD, CPI
Clinical Study Center: CEDRA Clinical Research, LLC; 8501 North Mopac Expressway, Suite 200, Austin, Texas 78759
Clinical Study Dates: 24 July 2008 – 18 August 2008
Analytical Study Facility: (b) (4)
Analytical Study Dates: 10/16/08 (SHBG), 12/01/08 (NE/EE)

OBJECTIVE

To characterize the plasma EE and NE pharmacokinetic profiles and SHBG concentrations following multiple-dose administration of NE/EE tablets to healthy female volunteers under fasting conditions.

STUDY ENDPOINTS

Pharmacokinetic parameters to determine bioavailability (i.e. Cmax, AUC0-24, Tmax, AUC0-tau, t1/2, fluctuation of NE and EE and Cmin of SHBG)

STUDY DESIGN, TREATMENT, AND SUBJECTS

This was a single-center, single-treatment, multiple-dose, bioavailability characterization study was conducted under medical supervision.

The 18 subjects enrolled in the study had a median (range) age of 26 (20–32) years, a median (range) weight of 61.2 (46.0–71.0) kg, and a median (range) height of 163.0 (142.5–178.0) cm. There were 15 subjects who were White (approximately 83%), of which 9 subjects (50%) were Hispanic/Latino and 6 (approximately 33%) who were Non-Hispanic/Latino. Additionally, 3 subjects (approximately 17%) were Black (Non-Hispanic/Latino).
All subjects received one NE/EE tablet per day for 24 days with an overnight fast prior day 1 and day 24 and subjects did not consume food for 4 hours following the treatment. The tablets were swallowed and followed with 240 mL water. Each tablet contained 0.8 mg NE and 0.025 mg EE. Seventeen subjects completed the study; one subject was withdrawn from the study due to the adverse event of rash.

Inclusion criteria

- Healthy female subjects, of any race who had not taken any form of medication within the 14 days prior to dosing.
- Aged 18–35 years inclusive.
- Subjects who weighed at least 45 kg (99 lbs) and who were within 15% of their ideal weight according to the 1983 Metropolitan Height and Weight Tables.
- Subjects who had a history of regular menstrual periods defined as a usual length of 21−35 days and a variability of ± 3 days (subjects who were recently post partum or post abortion must have had at least 2 normal cycles).

Exclusion criteria

- History or presence of alcoholism or drug abuse within the past year.
- Hypersensitivity or idiosyncratic reaction to estrogens, progestogens or other hormonal agents.
- History of jaundice with previous use of oral contraceptives.
- History of liver tumors.
- Tobacco or nicotine use in any form during the previous three months.
- Subjects who are pregnant or lactating.
- Subjects who are sexually active and not either surgically sterilized (bilateral tubal ligation; 6 months minimum), practicing a non-heterosexual lifestyle, or using one of the following acceptable methods of birth control:
    - a. Barrier method (condom, diaphragm) with spermicide for at least 7 days prior to the first dose and throughout the study
    - Non-hormonal IUD in place for at least 3 months.
- Subjects who have used any substances known to be strong inhibitors of cytochrome P450 (CYP) enzymes (such as cimetidine, fluoxetine, quinidine, erythromycin, fluconazole, and ketoconazole) or any substances known to be strong inducers of CYP enzymes (such as barbiturates, carbamazepine, glucocorticoids, phenytoin and rifampin) within 28 days of study start.

FORMULATION

The following investigational product was administered orally, one tablet per day for 24 days:

Treatment, WC3026 tablet	
Package description	Blister card containing 24 light-green, round active tablets and 4 pale lilac round inactive tablets; **ONLY THE LIGHT-GREEN ACTIVE TABLETS WERE ADMINISTERED**
Dosage form description	The active WC3026 tablets were round, light-green, flat-faced, beveled-edged tablets; tablets had a slight spearmint odor. Each tablet contained 0.8 mg NE and 25 mcg EE
Dose per time unit	One active WC3026 tablet (0.8 mg NE and 25 mcg EE)
Cumulative dosage	Twenty-four (24) active WC3026 tablets (19.2 mg NE and 600 mcg EE)

Blister cards were provided each containing 24 light-green, round active tablets and 4 pale lilac round inactive (placebo) tablets; each light-green tablet contained 0.8 mg NE and 0.025 mg EE. The pale lilac tablets did not contain active ingredient and were not be administered.

PHARMACOKINETIC EVALUATION

Blood sampling

Blood samples were collected predose and at 0.33, 0.67, 1, 1.33, 1.67, 2, 2.5, 3, 4, 6, 8, 10, 12, 16, and 24 hours post-treatment on day 1. Additional blood samples for determination of NE and EE concentrations were collected 24 hours after receiving Doses 4, 8, 12, 16, and 20. A pre-dose blood sample was taken before administration of Dose 24. Subsequent blood samples were collected at 0.33, 0.67, 1, 1.33, 1.67, 2, 2.5, 3, 4, 6, 8, 10, 12, 16, 24, 30, 36, 48 and 60 hours post dose 24.
Blood samples for determination of serum SHBG concentrations were collected prior to dosing on study Day 1 and 24 hours after receiving Doses 1, 4, 8, 12, 16, 20, and 24.

Concomitant therapy

Subjects were asked not to take medication (including over-the-counter products) for the 14 days preceding the study and throughout the entire study. This prohibition included vitamin supplements and herbal remedies e.g., St John's Wort.

Subjects were asked not to use any substances known to be strong inhibitors of CYP enzymes or any substances known to be strong inducers of CYP enzymes within 28 days of study start. Subjects were asked not to take any other oral contraceptives containing estrogens or any form of hormone therapy by any route for the 28 days prior to dosing and throughout the entire study. No subject was permitted to have received medroxyprogesterone acetate contraceptive injection (eg, Depo-Provera) for the year prior to dosing.

Table1 shows concomitant medication used in the study PR-00707

Subject	Period	Medication	Formulation	Dose	Regimen	Indication	Start Date and Time	Stop Date and Time
114	1	Ibuprofen	Tab/Cap	800 mg [a]	QD	Dysmenorrhea	6/21/2008 [b]	6/25/2008 [b]
114	1	Acetaminophen	Tab/Cap	1000 mg [a]	Once	Headache/ Abdominal cramping	7/25/2008 01:13	7/25/2008 01:13
114	1	Acetaminophen	Tab/Cap	500 mg [a]	PRN	Headache	7/25/2008 13:00	7/27/2008 21:00
114	1	Acetaminophen	Tab/Cap	500 mg [a]	Once	Headache	8/3/2008 18:00	8/3/2008 18:00
114	1	Acetaminophen	Tab/Cap	500 mg [a]	Once	Headache	8/5/2008 01:16	8/5/2008 01:16
114	1	Calamine lotion	Liquid	1 App [c]	PRN	Rash	8/7/2008 07:30	8/25/2008 [b]
115	1	Ibuprofen	Tab/Cap	600 mg [a]	PRN	Tension headache	07/09/2008 20:30	07/09/2008 20:30
118	1	Multi Vitamin	Tab/Cap	1 Tab [a]	QD	Nutritional Supplement	07/08/2008 09:00	07/09/2008 09:00

[a] Medication was administered orally
[b] Exact time is unknown
[c] Medication was administered topically

Other restrictions

- The consumption of alcohol- or xanthine-containing beverages and food was prohibited for 24 hours before each dose and throughout the blood sampling periods.
- Grapefruit-containing beverages and foods were prohibited for 10 days before dosing and throughout the blood sampling periods.
- Subjects were prohibited from smoking for the duration of the study.

Bioanalytical methods

The bioanalytical method to determine NE and EE concentration is reviewed under individual study review for study PR-00807 (Section A.1.1).

SHBG

For the determination of SHBG in serum samples, a commercially available immunoassay kit was used (IRMAZEN co SHBG, Zen Tech sa, Belgium); the kit contained all the reagents needed to calibrate, assay, and quality control the analysis.

Sensitivity: The analytical range of the method as quoted by the kit manufacturer was 10.0-250 nmol/L.

Precision: Precision of the calibration standards and QC samples during sample analysis was expressed as the %CV. For SHBG, the %CV ranged from 0.000% to 1.99% for calibration standards and 2.46% to 5.25% for QCs.

Accuracy: Accuracy of the calibration standards and QC samples during sample analysis was expressed as the percent difference from theoretical (inaccuracy). For SHBG the inaccuracy ranged from -3.17% to 3.09% for calibration standards and -10.8% to -3.13% for QCs.

DATA ANALYSIS
Pharmacokinetics

Seventeen subjects completed the study; the pharmacokinetic data from 16 subjects were evaluable. One subject was excluded from the summary statistics and pharmacokinetic evaluation (per protocol), as this subject had measurable concentrations of EE at predose.

No value of AUCinf, kel, or t½ was reported for cases that did not exhibit a terminal log-linear phase in the concentration versus time profile.

Descriptive statistics (arithmetic mean, standard deviation, relative standard deviation, maximum, and minimum) were reported for NE, EE, and SHBG concentrations at all time-points. Concentrations below the limit of quantitation were reported as zero (0.00) for the purpose of calculating descriptive statistics.

Actual sample collection times were used in the calculation of NE and EE pharmacokinetic parameters; nominal sample collection times were used for calculation of summary statistics for NE, EE, and SHBG concentrations.

Pre-dose (trough) concentrations of NE, EE, and SHBG on study Days 1, 2, 5, 9, 13, 17, and 21 and 24 hours after Dose 24 were analyzed using Tukey's multiple comparison test to determine if steady-state conditions have been achieved for each analyte.

PHARMACOKINETIC RESULTS

Following administration of a NE/EE tablet on Days 1 and 24 in the fasted state, plasma NE and EE concentrations increased rapidly until Cmax was reached at [median(range)] 1.69 h (1-8) and 1.33 h (1-2.5), respectively on day 1 as well as 1.67 h (0.67-4) and 1.33 (1-6), respectively on day 24, followed by a log-linear decrease over the remainder of the treatment period.

Synopsis Table 1. Summary of NE, EE and SHBG Pharmacokinetic Parameter Values Following Administration of One WC3026 Tablet (0.8 mg NE and 25 mcg EE) on Days 1 through 24 to Healthy Female Volunteers (n = 16); Study PR-00707

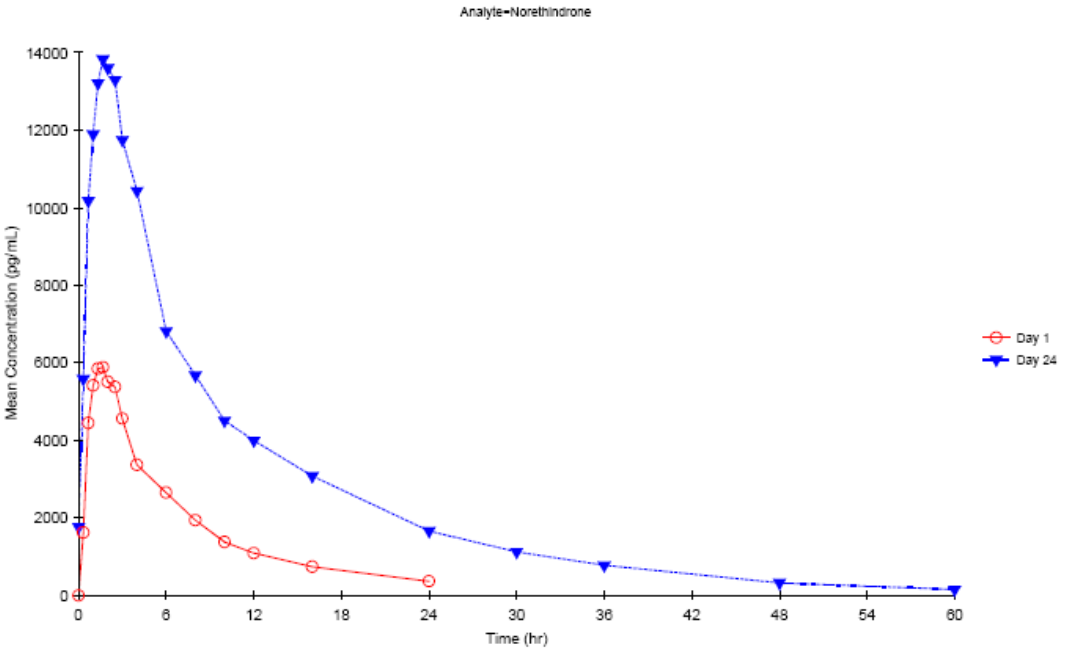
Analyte	Parameter	Arithmetic Mean (%CV) [Median (Range)] {Harmonic mean}	
		Day 1	Day 24
NE	Cmax	7550 (36)	16500 (18)
	Cmin	--	1630 (48)
	Cavg	--	5270 (38)
	AUC0-24	42850 (50)	--
	tmax	[1.69 (1.00 - 8.00)]	[1.67 (0.67 - 4.00)]
	AUC0-τ	--	126400 (38)
	t½	--	{10.2}
	Fluctuation	--	305 (25)
	R	--	3.3 (39)
EE	Cmax	99.3 (30)	136 (34)
	Cmin	--	17.1 (42)
	Cavg	--	44.4 (31)
	AUC0-24	666.2 (33)	--
	tmax	[1.33 (1.00 - 2.50)]	[1.33 (1.00 - 6.00)]
	AUC0-τ	--	1067 (31)
	t½	--	{17.9}
	Fluctuation	--	270 (21)
	R	--	1.6 (14)
SHBG	Cmin*	61.4 (43)	134 (26)

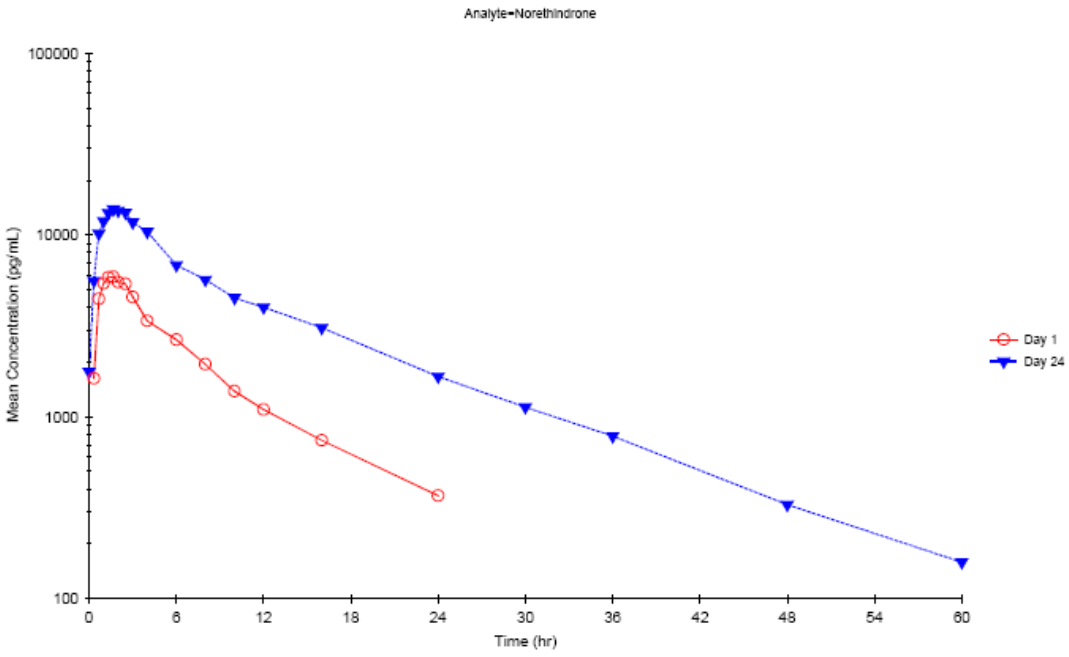
Cmax = Maximum plasma concentration (pg/mL)
Cmin = Minimum, post-Cmax plasma concentration during the 24 hours which follow dose administration (pg/mL)
Cavg = Average plasma concentration = AUC0−τ/24 (pg/mL)
AUC0-24 = Area under the plasma concentration versus time curve from time 0 to 24 hours (pg-h/mL)
AUC0-τ = The area under the plasma concentration versus time curve, from time 0 to tau (τ), the dosing interval (24 hours) (pg-h/mL)
tmax = time of the maximum measured plasma concentration (h)
t½ = Apparent first-order terminal elimination half-life, calculated as 0.693/kel
R = Accumulation factor = AUC0-τ / AUC0-24
Fluctuation = 100 x ((Cmax – Cmin) / Cavg) (%)
SHBG = Sex hormone binding globulin (concentrations in nmol/L)
*Day 1 is the predose SHBG concentration; Day 24 is the SHBG concentration 24 hours after Dose 24.
Source data: RR-03408; Tables 14.2.2.1 through 14.2.2.4

EE Cmax and AUC0–τ values increased by a factor of 1.4 and 1.6, respectively, following 24 days administration of NE/EE tablets as compared to single-dose administration. EE accumulation is consistent with that estimated from the elimination rate constant (1.7). During the dosing interval, there was a 270% fluctuation about the average concentration (Cavg), 44.4 pg/mL.

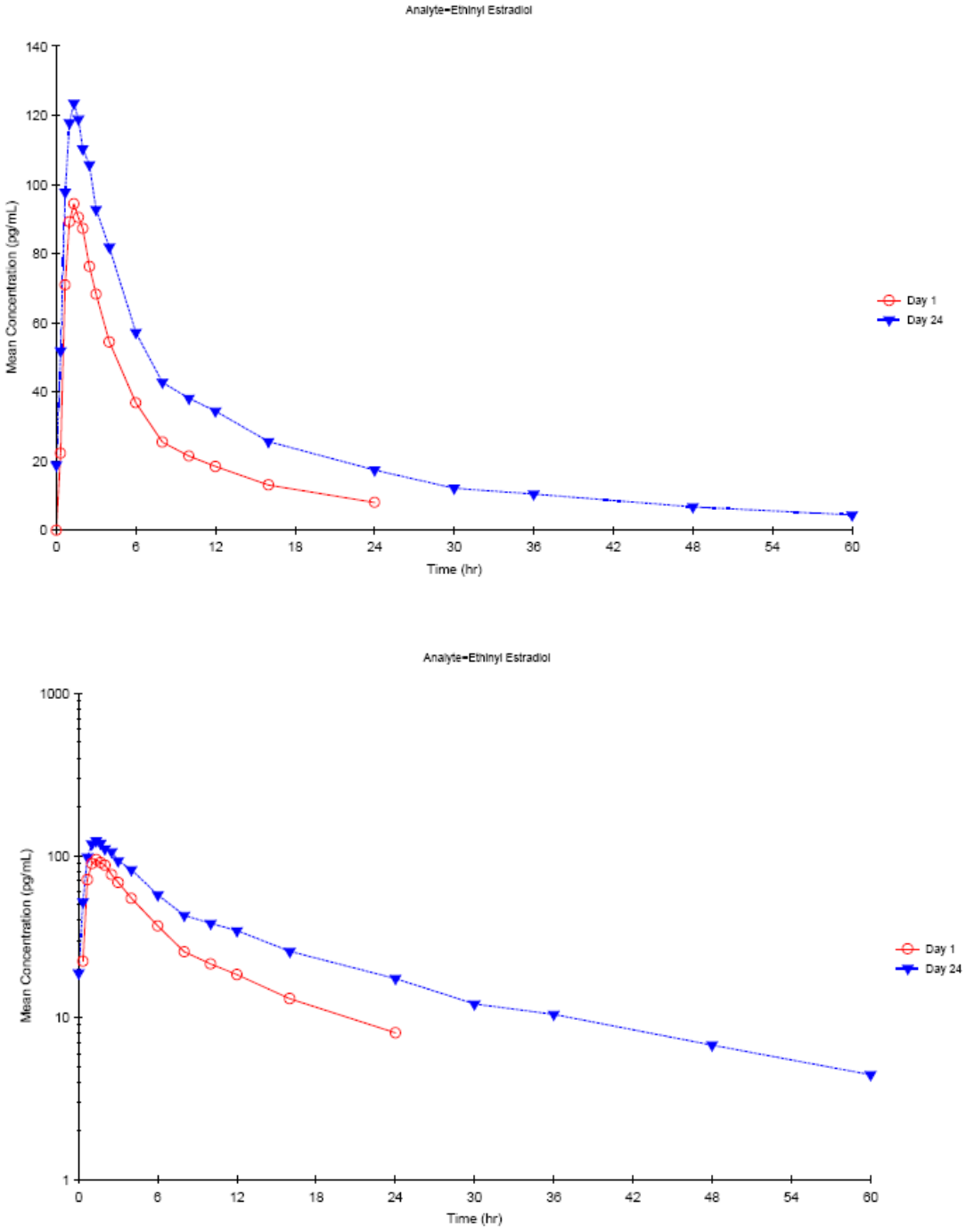
NE Cmax and AUC0–τ values increased by a factor of 2.2 and 3.3, respectively, following 24 days administration of NE/EE tablets as compared to single-dose administration. NE accumulation estimated from the elimination rate constant (1.3) was significantly less than that calculated from AUC0–τ/AUC0–24 as increases to SHBG concentrations further contribute to NE accumulation. During the dosing interval, there was a 305% fluctuation about the average concentration (Cavg), 5270 pg/mL.

Synopsis Figure 1. Mean Norethindrone Concentration-Time Plots after the Administration of a WC3026 Tablet on Days 1 and 24 (n = 16); Study PR-00707





Synopsis Figure 2. Mean Ethinyl Estradiol Concentration-Time Plots after the Administration of a WC3026 Tablet on Days 1 and 24 (n = 16); Study PR-00707



Based on visual assessment of trough levels steady-state was achieved for EE by day 13 on average (Figure 3). 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. Based on visual assessment of trough levels, pre-dose concentrations for NE continue to increase through to day 21 (Figure 4). 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 13.

Figure3: Plasma EE concentrations prior to and following multiple-dose administration of NE/EE tablets (mean±1SD; n=16)

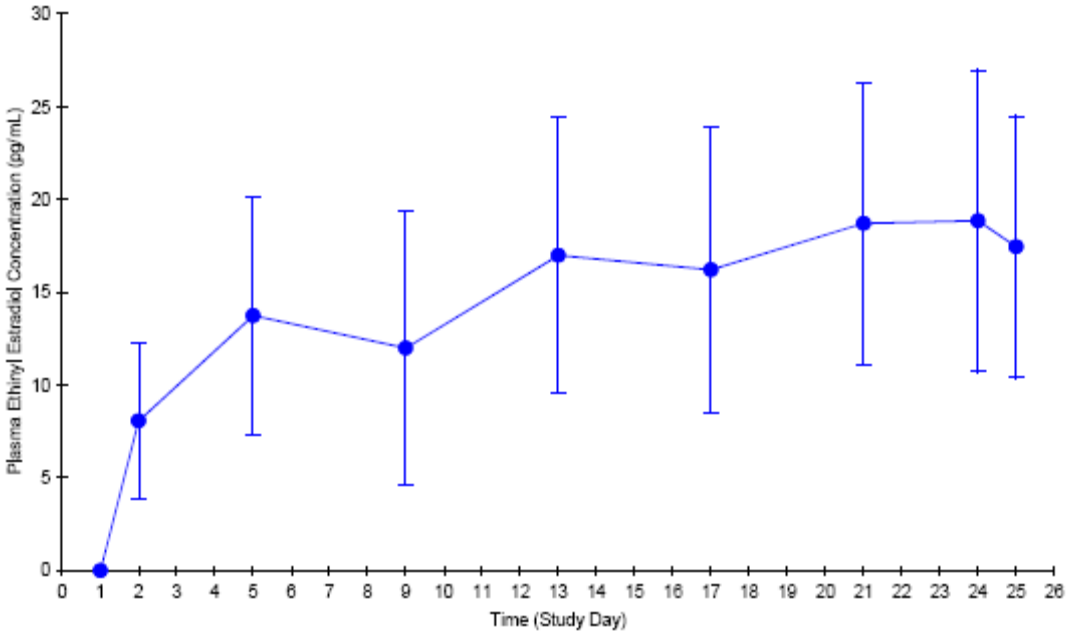
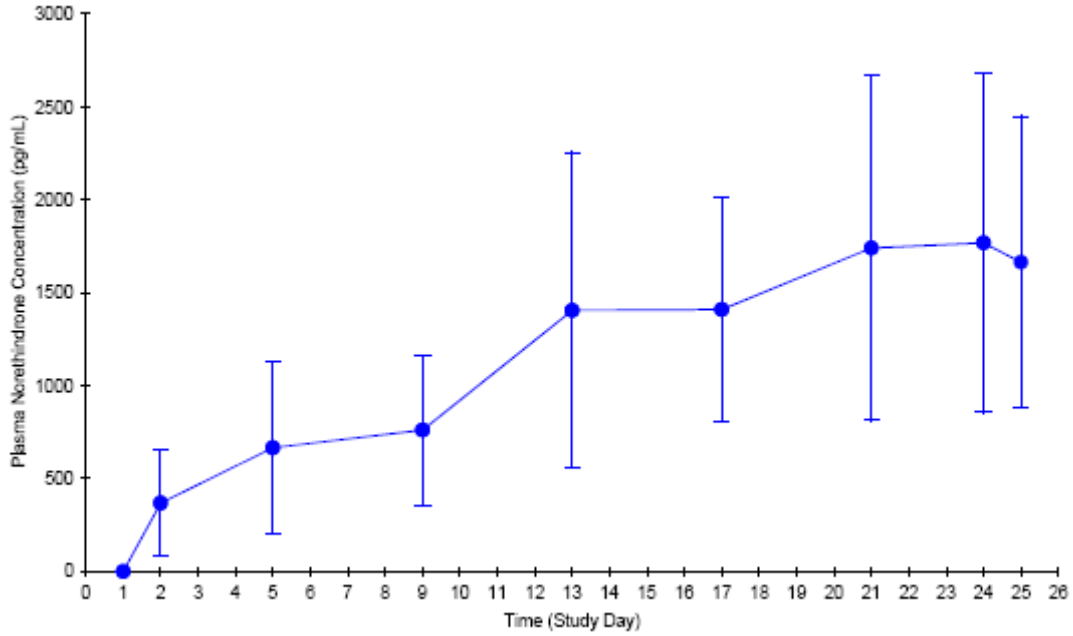


Figure4: Plasma NE concentrations prior to and following multiple-dose administration of NE/EE tablets (mean±1SD; n=16)



Text Table 7. Mean SHBG concentrations Following Administration of One WC3026 Tablet (0.8 mg NE and 25 mcg EE) on Days 1 through 24 to Healthy Female Volunteers (n = 16); Study PR-00707

Study Day	Mean SHBG concentration (nmol/L)	CV (%)
1	61.4	43
2	63.7	42
5	94.1	34
9	121	32
13	139	25
17	142	28
21	142	27
25	134	26

Source data: Table 14.2.1.7

Mean SHBG concentrations more than doubled (118% increase) from pre-dose to Day 25 (24 hours after Dose 24). This is to be expected, as it is extensively reported that EE induces the synthesis of SHBG. Steady state with respect to SHBG according to Tukey's test was reached by Day 13.

CONCLUSION

NE and EE total exposure increased by factors of 3.3 and 1.6, respectively, following multiple-dose administration of NE/EE tablets as compared to single-dose administration of NE/EE tablets. As determined by visual assessment, steady state with respect to EE was reached on average by Day 13 and pre-dose concentrations for NE continue to increase through to day 21.

The mean SHBG concentration more than doubled from pre-dose to Day 24; steady state with respect to SHBG was reached by Day 13.

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22573	ORIG-1	WARNER CHILCOTT INC	(b) (4) (norethindrone and ethinyl estradiol tablets, chewable and ferrous fumarate tablets)

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/s/

CHRISTIAN GRIMSTEIN
09/01/2010

MYONG JIN KIM
09/01/2010

BIOPHARMACEUTICS REVIEW Office of New Drugs Quality Assessment			
Application No.:	NDA 22-573-**Addendum**	**Reviewer:** Sandra Suarez Sharp, Ph.D	
Division:	DRUP		
Sponsor:	Warner Chilcott	**Team Leader:** Angelica Dorantes, Ph.D .	
Trade Name:	(b) (4)	**Supervisor:** Patrick J. Marroum, Ph.D	
Generic Name:	Norethindrone 0.8 mg + ethinyl estradiol 0.025 mg, chewable + ferrous fumarate 75 mg tablet	**Date Assigned:**	Dec 17, 2009
Indication:	Prevention of pregnancy	**Date of Review:**	Aug 30, 2010
Formulation	Chewable Tablet		
Route of Administration	Oral		

SUBMISSIONS REVIEWED IN THIS DOCUMENT			
Submission date	**CDER Stamp Date**	**Date of informal/Formal Consult**	**PDUFA DATE**
Aug 25, 2010	Aug 25, 2010	Aug 25, 2010	Sep 24, 2010
Type of Submission:	Original NDA		
Type of Consult:	Dissolution method and specifications/**Addendum**		

REVIEW SUMMARY:

Ovcon® 50 (norethindrone and ethinyl estradiol tablets, USP or WC3026 tablet) was approved by the Agency for the prevention of pregnancy in women who elect to use an oral contraceptive (NDA 17-576). The sponsor, Warner Chilcott is seeking approval of (b) (4). (b) (4) is an oral contraceptive consisting of a new dose and new regimen of the combination of norethindrone (NE) and ethinyl estradiol (EE). The combination of 0.8 mg of NE and 0.025 mg of EE is to be taken daily for 24 days followed by one daily ferrous fumarate tablet for 4 days to facilitate ease of drug administration via a 28-day regimen.

This review is an addendum to the biopharmaceutics review entered in DARRTS on Jul 29, 2010. The biopharmaceutics review for the original submission entered in DARRTS on Jul 29, 2010 made the following recommendations:

1. The proposed dissolution method for the norethindrone (NE)/ethinyl estradiol (EE) tablets (0.025M sodium acetate with 0.15% of sodium dodecyl sulphate buffer, pH 5, (b) (4), 75 rpm) will be acceptable as interim since the data you presented indicate that the method is not discriminating. It appears that considering different method conditions such as lower paddle speed (i.e. 50 rpm), lower concentration of surfactant and different surfactant will result in a more robust and discriminating method. You will have one year after the expedition of this letter to submit data supporting a more discriminating dissolution method for EE/NE tablets.

2. In addition, the proposed dissolution specifications for both EE/NE tablets and Ferrous Fumarate tablets are too permissive. The following dissolution specification is recommended for EE/NE tablets as interim until you submit a more discriminating dissolution method:

Specification (Q)
(b) (4) (Q) of the labeled amount of each active is dissolved in (b) (4)

This recommendation is based on mean dissolution values from clinical drug product release and drug product stability testing. Please revise the specifications accordingly.

3. The following dissolution specification is recommended for the Ferrous Fumarate Tablets based on mean dissolution values from clinical drug product release and drug product stability testing:

Specification (Q)
(b) (4) (Q) of ferrous fumarate is dissolved in 30 min.

Please revise the specifications accordingly

The above recommendations were discussed in a teleconference with the sponsor on Aug 19, 2010. The following agreements were reached and are officially accepted by the sponsor in the present submission:

- The sponsor agreed upon developing a more discriminating dissolution method and to submit the results within a year of expedition of the request.
- The following dissolution specification was agreed upon for EE/NE tablets as interim until the sponsor submits a more discriminating dissolution method:

Specification (Q)
(b) (4) (Q) of the labeled amount of each active is dissolved in 20 min.

- The following dissolution specification was agreed upon for the Ferrous Fumarate Tablets:

Specification (Q)
(b) (4) (Q) of ferrous fumarate is dissolved in 30 min.

RECOMMENDATION:

The ONDQA/biopharmaceutics team has reviewed the submission to NDA 22-573(000) received on Aug 25, 2010. There are no comments to the sponsor at this time. The following dissolution method and specification (as interim) have been agreed upon for the norethindrone (NE)/ethinyl estradiol (EE) tablets:

Dosage Form	USP Apparatus	Speed (rpm)	Medium	Volume (mL)	Specification (Q)
Chewable tablet	II (Paddle)	75	0.025M sodium acetate buffer containing 0.15% of sodium dodecyl sulphate, pH 5.0 ± 0.05, 37 ± 0.5°C	500	(b) (4) (Q) of the labeled amount of each active is dissolved in 20 min.

In addition, the following dissolution method and specification have been agreed upon for the Ferrous Fumarate tablets:

Dosage Form	USP Apparatus	Speed (rpm)	Medium	Volume (mL)	Specification (Q)
Chewable tablet	II (Paddle)	75	0.1N HCl containing 0.5% sodium lauryl sulfate,, 37 ± 0.5°C	900	(b) (4) (Q) of ferrous fumarate is dissolved in 30 min..

Sandra Suarez Sharp, Ph. D.
Biopharmaceutics Reviewer
Office of New Drugs Quality Assessment

Patrick J. Marroum, Ph. D.
Biopharmaceutics Supervisor
Office of New Drugs Quality Assessment

cc: RMcKnight, ADorantes, Dchristner, JChang

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22573	ORIG-1	WARNER CHILCOTT INC	(b) (4) (norethindrone and ethinyl estradiol tablets, chewable and ferrous fumarate tablets)

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/s/

SANDRA SUAREZ
08/31/2010

PATRICK J MARROUM
08/31/2010

BIOPHARMACEUTICS REVIEW Office of New Drugs Quality Assessment			
Application No.:	NDA 22-573	**Reviewer:** Sandra Suarez Sharp, Ph.D	
Division:	DRUP		
Sponsor:	Warner Chilcott	**Team Leader:** Angelica Dorantes, Ph.D .	
Trade Name:	(b) (4)	**Supervisor:** Patrick J. Marroum, Ph.D	
Generic Name:	Norethindrone 0.8 mg + ethinyl estradiol 0.025 mg, chewable + ferrous fumarate 75 mg tablet	**Date Assigned:**	Dec 17, 2009
Indication:	Prevention of pregnancy	**Date of Review:**	Jul 18, 2010
Formulation	Chewable Tablet		
Route of Administration	Oral		

SUBMISSIONS REVIEWED IN THIS DOCUMENT			
Submission date	**CDER Stamp Date**	**Date of informal/Formal Consult**	**PDUFA DATE**
Nov 25, 2009 May 20, 2010	Nov 26, 2009	Dec 17, 2009	Sep 24, 2010
Type of Submission:	Original NDA		
Type of Consult:	Dissolution method and specifications		

REVIEW SUMMARY:

Ovcon® 50 (norethindrone and ethinyl estradiol tablets, USP or WC3026 tablet) was approved by the Agency for the prevention of pregnancy in women who elect to use an oral contraceptive (NDA 17-576).

The sponsor, Warner Chilcott is seeking approval of (b) (4). (b) (4) is an oral contraceptive consisting of a new dose and new regimen of the combination of norethindrone (NE) and ethinyl estradiol (EE). The combination of 0.8 mg of NE and 0.025 mg of EE is to be taken daily for 24 days followed by one daily ferrous fumarate tablet for 4 days to facilitate ease of drug administration via a 28-day regimen.

This review focuses on the acceptability of the dissolution method and specifications for (b) (4). Two dissolution methods have been used for the dissolution testing of NE/EE tablets. The following method (b) (4) was used to perform the dissolution testing (release and stability) of all batches of NE/EE tablets manufactured in support of this application:

(b) (4)

The following method (b) (4) is an alternate dissolution method that has been used to test selected batches of NE/EE tablets in order to evaluate the similarity of dissolution profiles obtained for NE/EE tablets using both methods:

(b) (4)

The dissolution method and specifications for the ferrous fumarate chewable tablets are as follows:

Dosage Form	USP Apparatus	Speed (rpm)	Medium	Volume (mL)	Specification (Q)
Chewable tablet	II (Paddle)	75	0.1N HCl containing 0.5% sodium lauryl sulfate,, 37 ± 0.5°C	900	No less than (b) (4) (Q) of ferrous fumarate is dissolved in (b) (4)

The approved USP dissolution method (0.1N HCl containing 0.09% sodium lauryl sulfate; 600 mL; 75 rpm) for NE/EE tablet is different from that for the product under investigation. The approved USP dissolution method (0.1N HCl containing 0.5% sodium lauryl sulfate; 900 mL) for ferrous fumarate tablet is the same as that for the product under investigation. According to the USP monograph for ferrous fumarate, not less than 75% (Q) of ferrous fumarate is dissolved in 45 min.

The method development results demonstrated that the sponsor's proposed method is not discriminating. In addition, the alternate method is not acceptable since it seems to be less discriminating that the original one (b) (4). This reviewer recommends different dissolution acceptance criteria for both EE/NE and ferrous fumarate components of (b) (4) Tablets.

RECOMMENDATION:

The ONDQA/biopharmaceutics team has reviewed NDA 22-573(000) submitted on Nov 25, 2009 and May 20, 2010. The proposed dissolution method for EE/NE tablets and dissolution specifications for (b) (4) tablets are not acceptable. The following comments should be conveyed to the sponsor:

1. The proposed dissolution method for the norethindrone (NE)/ethinyl estradiol (EE) tablets (0.025M sodium acetate with 0.15% of sodium dodecyl sulphate buffer, pH 5, (b) (4), 75 rpm) will be acceptable as interim since the data you presented indicate that the method is not discriminating. It appears that considering different method conditions such as lower paddle speed (i.e. 50 rpm), lower concentration of surfactant and different surfactant will result in a more robust and discriminating method. You will have one year after the expedition of this letter to submit data supporting a more discriminating dissolution method for EE/NE tablets.

2. In addition, the proposed dissolution specifications for both EE/NE tablets and Ferrous Fumarate tablets are too permissive. The following dissolution specification is recommended for EE/NE tablets as interim until you submit a more discriminating dissolution method:

Specification (Q)
(b) (4) (Q) of the

labeled amount of each active is dissolved in [redacted]

This recommendation is based on mean dissolution values from clinical drug product release and drug product stability testing. Please revise the specifications accordingly.

3. The following dissolution specification is recommended for the Ferrous Fumarate Tablets based on mean dissolution values from clinical drug product release and drug product stability testing:

Specification (Q)
[redacted] (Q) of ferrous fumarate is dissolved in 30 min.

Please revise the specifications accordingly

Sandra Suarez Sharp, Ph. D.
Biopharmaceutics Reviewer
Office of New Drugs Quality Assessment

Patrick J. Marroum, Ph. D.
Biopharmaceutics Supervisor
Office of New Drugs Quality Assessment

cc: NDA 22-573, RMcKnight, ADorantes, Dchristner, JChang

Background

Ovcon® 50 (norethindrone and ethinyl estradiol tablets, USP) was approved by the Agency for the prevention of pregnancy in women who elect to use an oral contraceptive (NDA 17-576); the approved Ovcon 50 regimen includes the administration of 21 active tablets each containing the combination of 1 mg NE and 0.05 mg EE. Femcon® Fe (NDA 21-490) is an oral contraceptive containing 21-days of active therapy and was approved by the Agency in 2003 as a chewable tablet. Femcon® Fe contains 0.4 mg of norethindrone (NE) and 35 mcg of ethinyl estradiol (EE), and 7-days of inactive tablets containing 75 mg of ferrous fumarate.

The sponsor, Warner Chilcott is seeking approval of [redacted]. [redacted] is an oral contraceptive consisting of a new dose and new regimen of the combination of norethindrone (NE) and ethinyl estradiol (EE). The combination of 0.8 mg of NE and 0.025 mg of EE is to be taken daily for 24 days followed by one daily ferrous fumarate tablet for 4 days to facilitate ease of drug administration via a 28-day regimen.

In support of this NDA the sponsor included the results of total of five studies: clinical data from a Phase 3 safety and contraceptive efficacy study as well as a Phase 1 oral safety study. It also includes results from three Phase 1 BA and PK studies conducted to assess the BA of EE and NE following a single tablet administration, the food effect following a single tablet administration, and the NE and EE pharmacokinetic profiles and sex hormone binding globulin (SHBG) concentrations following multiple doses of

NE/EE. The BA/BE studies are being reviewed by OCP. This review focuses on the acceptability of the dissolution method and specifications for (b) (4).

Chemistry

Drug Product

WC3026 tablets are light-green, round, flat-faced, bevel-edged tablets debossed with "WC" on one side and "483" on the other side. Tablet 1 summarizes the components and composition for WC3026 tablets.

Table 1. Tablet Formulation for WC3026-5C Tablets (Norethindrone/Ethinyl Estradiol 0.8 mg/25 µg, Chewable)

Component	Specification #	mg/tablet	%w/w	kg/batch[1]
EE (b) (4)	WC3016-8T	(b) (4)		(b) (4)
Norethindrone, USP	RM-10001	0.80		
Mannitol, USP (b) (4)	RM-10020			(b) (4)
Mannitol, USP	RM-10019			
Microcrystalline Cellulose, NF (b) (4)	000A326			
FD&C Yellow # 6 Aluminum Lake	RM-10014			
FD&C Blue # 1 Aluminum Lake	RM-10015			
D&C Yellow # 10 Aluminum Lake	RM-10005			
Spearmint Flavor (b) (4)	RM-10009			
Sodium Starch Glycolate, NF	RM-10003			
Sucralose, NF	RM-10008			
Magnesium Stearate, NF	RM-10018			
Total	-	70.00	(b) (4)	

The ferrous fumarate tablets are round, flat-faced, bevel-edged, brown tablets debossed with "WC" on one side and "624" on the other side. Tablet 2 summarizes the components and composition for these tablets.

Table 2. Tablet Formulation for Ferrous Fumarate Tablets, Formulation # WC3026-10P

Component	Specification #	Mg/tablet	%w/w	kg/batch[1]
Ferrous Fumarate, USP	C03A075	75.0		(b) (4)
Mannitol, USP (b) (4)	RM-10020			(b) (4)
Povidone, USP	343A003			
Microcrystalline Cellulose, NF (b) (4)	356A003			
Sodium Starch Glycolate, NF	RM-10003			
Magnesium Stearate, NF	RM-10018			
Sucralose, NF	RM-10008			
Spearmint Flavor (b) (4)	RM-10009			
Total	-	125.0		(b) (4)
(b) (4)				

Dissolution Method

NE/EE Tablets

The following method (b) (4) was used to perform the dissolution testing (release and stability) of all batches of NE/EE tablets manufactured in support of this application:

(b) (4)

It is noted that the approved USP dissolution method (0.1N HCl containing 0.09% sodium lauryl sulfate; 600 mL; 75 rpm) for NE/EE tablet is different from that for the product under investigation.

Dissolution Method Development for NE/EE Tablets

Investigations were conducted in order to evaluate the effect of different dissolution parameters on the dissolution behavior of NE and EE in WC3026-5C tablets (0.8 mg norethindrone/25 µg ethinyl estradiol). The parameters investigated were pH of dissolution medium, type of surfactant ((b) (4)), concentration of surfactant, paddle rotational speed and volume of dissolution medium.

Effect of pH

The effect of pH was evaluated by conducting dissolution testing at pH values in the range of (b) (4), using the dissolution media detailed in Table 3. Testing was performed using WC3026-5C tablets from lot 80157T. The test 1 parameters are the same as those stated for dissolution testing in the current USP monograph for NE and EE tablets; therefore, the sponsor states that test 1 was used as a control to evaluate the equivalence of the USP dissolution parameters to those used in tests 2, 8, 9 and 10.

Table 3. Evaluation of the Effect of pH (PD.EIP.204-1)

(b) (4)

The NE and EE dissolution profiles obtained are presented in Figure 1 and Figure 2, respectively.

Figure 1. Effect of pH on the Dissolution of NE, WC3026 Active Tablets, Batch 80157T

Figure 2. Effect of pH on the Dissolution of EE, WC3026-5C Tablets, Batch 80157T

According to the sponsor, the USP 32 monograph for tablets containing NE and EE requires dissolution testing using a medium composed of 0.1N hydrochloric acid containing 0.09% sodium lauryl sulphate (SLS). (b) (4)

(b) (4)

(b) (4)

Reviewer Comments

The sponsor reported f2 values comparing every method against the approved USP method. (b) (4)

Effect of Type of Surfactant

(b) (4)

(b) (4)

Reviewer's Comments

The validity of testing for f2 is questionable (b) (4)

(b) (4)

Effect of Paddle Speed

The effect of altering the paddle speed in the range of (b) (4) rpm was evaluated (see Table 6). Testing was performed using WC3026-5C tablets from lot 80157T. The dissolution profiles obtained are shown in Figure 5.

(b) (4)

According to the sponsor, since no significant difference between the NE and EE dissolution profiles obtained with rotation speeds in the range of (b) (4) rpm was determined (f2 factors > 50, the (b) (4) paddle speed (75 rpm) was selected.

Reviewer's Comments

(b) (4)

It is clear that the objective of the dissolution method development was to select a method that was similar to the one approved in the USP rather than the development of the most discriminating one. Therefore, the sponsor will be informed that the proposed dissolution method is not adequate since it is not the most discriminating one.

Alternate Dissolution Method Proposed by Sponsor

The following method (b) (4)) is an alternate dissolution method that has been used to test selected batches of NE/EE tablets in order to evaluate the similarity of dissolution profiles obtained for NE/EE tablets using both methods:

(b) (4)

(b) (4)

Reviewer's Remarks

This dissolution method seems to be even less discriminating than method (b) (4) *and therefore is not acceptable.*

Ferrous Fumarate Dissolution Method

The dissolution method and specifications for the ferrous fumarate chewable tablets are as follows:

Dosage Form	USP Apparatus	Speed (rpm)	Medium	Volume (mL)	Specification (Q)
Chewable tablet	II (Paddle)	75	0.1N HCl containing 0.5% sodium lauryl sulfate,, 37 ± 0.5°C	900	(b) (4) (Q) of ferrous fumarate is dissolved in (b) (4).

The approved USP dissolution method (0.1N HCl containing 0.5% sodium lauryl sulfate; 900 mL) for ferrous fumarate tablet is the same as that for the product under investigation. According to the USP monograph for ferrous fumarate, not less than 75% (Q) of ferrous fumarate is dissolved in 45 min.

Dissolution Method Validation for NE/EE

Table 7 summarizes the results of the analytical method validation for dissolution.

Table 7. Validation information for NE/EE Dissolution Method

Test	Acceptance Criteria	Results
Accuracy / Recovery – NE	At each concentration: 1. Mean recovery: 97.0% – 103.0% 2. RSD ≤ 3.0%	Level / 1. Mean Recovery / 2. RSD 50% / 99.1% / 0.3% 100% / 98.2% / 0.8% 150% / 97.8% / 0.9%
Accuracy / Recovery – EE	At each concentration: 1. Mean recovery: 97.0% – 103.0% 2. RSD ≤ 3.0%	Level / 1. Mean Recovery / 2. RSD 50% / 99.3% / 0.1% 100% / 98.9% / 0.8% 150% / 98.5% / 1.1%
Linearity – NE	1. $R^2 \geq 0.990$ 2. y-intercept ≤ 2% of 100% response 3. Response factor at each concentration is 98% – 102% of response factor at 100%	1. $R^2 = 0.999$ 2. y-intercept = 2% 3. Response factors: Level / % of response factor at 100% 50% / 102% 75% / 100% 125% / 98% 150% / 100%
Linearity – EE	1. $R^2 \geq 0.990$ 2. y- intercept ≤ 2% of 100% response 3. Response factor at each concentration is 98% – 102% of response factor at 100%	1. $R^2 = 1.000$ 2. y-intercept = 2% 3. Response factors: Level / % of response factor at 100% 50% / 102% 75% / 100% 125% / 99% 150% / 100%
Injection Repeatability	1. RSD (n=10) ≤ 2.0%	1. RSD: NE = 0.2%, EE = 0.2%
Analysis Repeatability	1. Results comply with specification (Q = (b) (4)) 2. RSD (n=6; 30 min) ≤ 10%	1. Each individual tablet (n=12) at 30 min.: NE ≥ (b) (4), EE ≥ 2. RSD: NE = 2.0%, EE = 1.5%
Intermediate Precision	1. Relative difference between means (30 min) ≤ 10% 2. Repeatability requirements are met (Q = (b) (4), RSD (n=6; 30 min) ≤ 10%)	1. Relative difference between means: NE = 0.1%, EE = 0.6% 2. Each individual tablet (n=6) at 30 min.: NE (b) (4), EE RSD: NE = 1.9%, EE = 1.1%
Range	1. Combine complying data from linearity, accuracy and precision	1. Validated concentration range: NE = 0.796 µg/mL – 2.388 µg/mL (50% – 149%) EE = 0.0249 µg/mL – 0.0746 µg/mL (50% – 149%)
Specificity / Selectivity	1. No visible interfering peaks	1. No visible interfering peaks

Test	Acceptance Criteria	Results
Accuracy– NE	At each concentration: 1. Mean recovery: 97.0% – 103.0% 2. RSD ≤ 3.0%	Level / 1. Mean Recovery / 2. RSD 50% / 99.8% / 0.2% 55% / 100.1% / 0.5% 100% / 98.2% / 0.5% 150% / 98.1% / 0.1%
Accuracy– EE	At each concentration: 1. Mean recovery: 97.0% – 103.0% 2. RSD ≤ 3.0%	Level / 1. Mean Recovery / 2. RSD 55% / 100.2% / 0.3% 100% / 98.1% / 0.8% 150% / 98.5% / 0.1%
Recovery – NE	1. Record result 2. Calculate the relative difference from the mean amount dissolved at the previous sampling point.	Time (mins) / 1. Mean % LC / 2. RSD 10 / 94.3% / n/a 20 / 100.1% / -6.2% 30 / 101.8% / -1.7% 60 / 103.9% / -2.1% 90 / 104.8% / -0.9% 120 / 105.1% / - 0.3%
Recovery – EE	1. Record result 2. Calculate the relative difference from the mean amount dissolved at the previous sampling point.	Time (mins) / 1. Mean % LC / 2. RSD 10 / 103.1% / n/a 20 / 106.1% / -2.9% 30 / 106.2% / -0.1% 60 / 107.4% / -1.1% 90 / 106.5% / 0.8% 120 / 107.2% / -0.7%
Linearity – NE	1. $R^2 \geq 0.990$ 2. y-intercept ≤ 2% of 100% response 3. Response factor at each concentration is 97% – 103% of response factor at 100%	1. $R^2 = 1.000$ 2. y-intercept = 2% 3. Response factors: Level / % of response factor at 100% 50% / 101% 75% / 101% 125% / 99% 150% / 99%
Linearity – EE	1. $R^2 \geq 0.990$ 2. y- intercept ≤ 2% of 100% response 3. Response factor at each concentration is 97% – 103% of response factor at 100%	1. $R^2 = 1.000$ 2. y-intercept = 2% 3. Response factors: Level / % of response factor at 100% 50% / 102% 75% / 101% 125% / 100% 150% / 99%
Injection Repeatability	1. RSD (n=10) ≤ 2.0%	1. RSD NE = 0.2% EE = 0.4%

Test	Acceptance Criteria	Results
Analysis Repeatability	For the 55%, 100% and 150% accuracy preparations: 1. RSD (n=9) ≤ 3.0%	1. RSD NE = 1.1% EE = 1.1%
Intermediate Precision	For each solution: 1. Relative difference between results ≤ 3.0%	1. Relative difference between results: NE = 100%-1 = 1.8% NE = 100%-2 = 1.7% NE = 100%-3 = 1.7% EE = 100%-1 = 2.5% EE = 100%-2 = 2.7% EE = 100%-3 = 2.4%
	2. Accuracy requirements are met	2. Sample / % Recovery / %RSD NE 100%-1 / 101.7% / NE 100%-2 / 100.8% / 0.5% NE 100%-3 / 100.9% / EE 100%-1 / 102.7% / EE 100%-2 / 101.9% / 0.5% EE 100%-3 / 101.8% /
Range	1. Combine complying data from linearity, accuracy and precision	1. Validated concentration range: NE = 0.815320 µg/mL – 2.445959 µg/mL (50% – 150%) EE = 0.027554 µg/mL – 0.075106 µg/mL (55% – 150%)
Specificity / Selectivity	1. No visible interfering peaks	1. No visible interfering peaks
Robustness – Solution Stability	1. Relative difference from initial result ≤ 3.0%	1. Sample solutions are stable for up to 1 day when stored under ambient conditions. Working standards are stable for up to 1 day when stored under ambient conditions. Intermediate standard solutions are stable for up to 5 days when stored under ambient conditions.
Robustness – Filter Qualification	1. Relative difference between result from filtered and centrifuged samples ≤ 3.0%	1. Mean (n=3) relative difference between results from filtered and centrifuged samples *NE = 0.6%, EE = 1.2% *The chromatography of the NE peaks obtained from the filtered samples was unsuitable, therefore, filtration of samples is not recommended.

Reviewer's Comments

The sponsor provided enough information to support the validity of the analytical method for determining the dissolution of NE/EE Tablets.

Dissolution Specifications

EE/NE Tablets

Table 8 summarizes the development batches of EE/NE tablets. Tables 9 and 10 summarize the results of the dissolution profiles for EE and NE, respectively from release through stability testing (25ºC/60% RH).

Table 8. List of Development Batches of WC3026 Active Tablets

Lot Number	Date of Manufacture	Batch Size	Batch Purpose
80537T	27 Sep 07	(b) (4)	Clinical/stability studies
80547T	21 Sep 07		Clinical/stability studies
80278T	09 Jul 08		Alternative API supplier/stability studies
80019T	05 Feb 09		Commercial scale/market image/stability studies
80157T	07 Mar 07		Clinical/stability studies

Table 9. Dissolution Profiles of Release and Long-Term Stability Samples of Development Batches of WC3026 Active Tablets (% of EE Label Claim Dissolved at Specified Sampling Month)

Table 10. Dissolution Profiles of Release and Long-Term Stability Samples of Clinical Batches of WC3026 Active Tablets (% of NE Label Claim Dissolved at Specified Sampling Month)

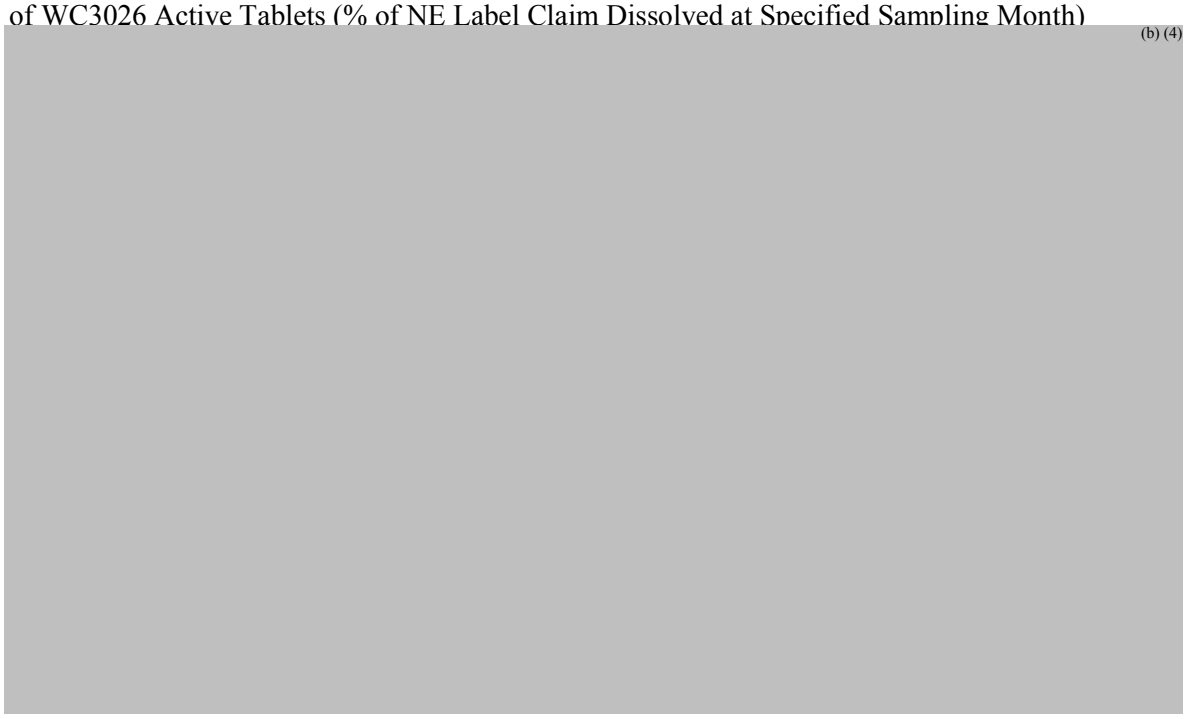
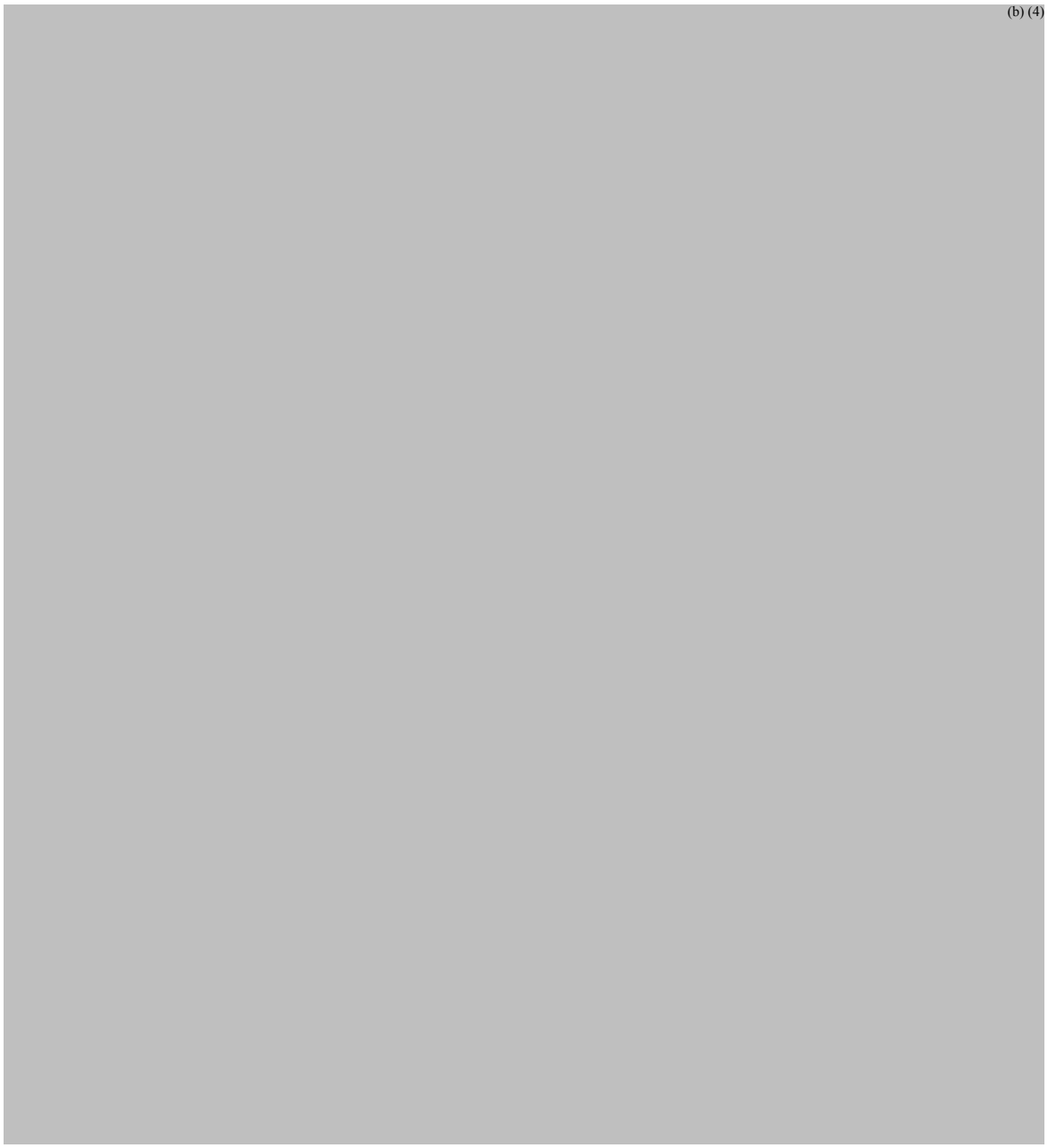


Figure 6 and 7 show the average dissolution profiles available for long-term (25ºC/60% RH) stability samples of each development batch for NE and EE, respectively.



Averaged EE and NE dissolution profiles for the clinical and NDA study batches of WC3026 active tablets (Lots 80157T, 80537T and 80547T) were similar as demonstrated by similarity factor (f_2) values which were greater than 50 for all batches compared (ranging from (b) (4) for EE and from (b) (4) for NE).

The market image batch of WC3026 active tablets (Lot 80019T) (b) (4) using tooling debossed with 'WC' on one side and '483' on the other side. All other tablets in the evaluation (b) (4) using non-debossed tooling of the same shape and dimensions. The dissolution profiles for this batch are similar to those for the non-market image batches; similarity values were greater than 50 for all batches compared (ranging from (b) (4) for EE and from (b) (4) for NE).

Reviewer's Comments

The dissolution method does not seem to have discriminatory power. In addition, it is clear that the proposed dissolution specifications are not appropriate for this product (b) (4)*. Therefore, the following dissolution specification are recommended for the NE/EE component of* (b) (4) *as interim until a more discriminating method is proposed:*

Specification (Q)
(b) (4) (Q) of the labeled amount of each active is dissolved in (b) (4).

Dissolution Specifications for Ferrous Fumarate Tablets

The sponsor's proposed dissolution specification for ferrous fumarate tablets is as follows:

Specification (Q)
(b) (4) (Q) of ferrous fumarate is dissolved in (b) (4).

The batches of ferrous fumarate tablets manufactured in support of this application are listed in Table 11. The dissolution data for each batch of finished product listed is shown in Figure 8.

Table 11. Batch Analysis for Ferrous Fumarate Tablet

Lot Number	Date of Manufacture	Batch Size	Ferrous Fumarate Manufacturer	Ferrous Fumarate Manufacturer Lot No. (Warner Chilcott Lot No.)	Use
80507T	02 Aug 07	(b) (4)		135868 (F027663)	Stability studies
80577T	17 Sep 07			135868 (F027663)	Stability studies
80587T	17 Sep 07			135868 (F027663)	Stability studies
80018T	30 Jan 08			136045 (F027766)	Market image/ stability studies
80038T	31 Jan 08			136045 (F027766)	Scale-up/stability studies

(b) (4)

Reviewer's Comments

The dissolution specification for Ferrous Fumarate Tablets is very permissive (b) (4) *. This reviewer recommends tighten the specification as follows:*

Specification (Q)
(b) (4) (Q) of ferrous fumarate is dissolved in 30 min.

These proposed specifications are also met for stability batches ((b) (4) ; see table below).

(b) (4)

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22573	ORIG-1	WARNER CHILCOTT INC	(b) (4) (norethindrone and ethinyl estradiol tablets, chewable and ferrous fumarate tablets)

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

/s/

SANDRA SUAREZ
07/29/2010

PATRICK J MARROUM
07/29/2010

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING CHECKLIST FOR A NEW NDA/BLA

NDA Number: 22573 **Applicant: Warner Chilcott** **Stamp Date: 11/26/09**

Drug Name: Norethindrone/Ethinyl estradiol **NDA/BLA Type: Original**

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

	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			Literature data
Criteria for Assessing Quality of an NDA					
	Data				
3	Are the data sets, as requested during pre-submission discussions, submitted in the appropriate format (e.g. CDISC)?			X	
4	If applicable, are the pharmacogenomic data sets submitted in the appropriate format?			X	
	Studies and Analyses				
5	Has the applicant made an appropriate attempt to determine the reasonable dose individualization strategy for this product (i.e., appropriately designed and analyzed dose-ranging or pivotal studies)?			X	
6	Did the applicant follow the scientific advice provided regarding matters related to dose selection?			X	
7	Are the appropriate exposure-response (for desired and undesired effects) analyses conducted and submitted in a format as described in the Exposure-Response guidance?			X	
8	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	
9	Are the pediatric exclusivity studies adequately designed to demonstrate effectiveness, if the drug is indeed effective?			X	
10	Did the applicant submit all the pediatric exclusivity data, as described in the WR?			X	
11	Is the appropriate pharmacokinetic information submitted?	X			
12	Is there adequate information on the pharmacokinetics and exposure-response in the clinical pharmacology section of the label?	X			
	General				
13	On its face, is the clinical pharmacology and	X			

	biopharmaceutical section of the NDA organized in a manner to allow substantive review to begin?				
14	Is the clinical pharmacology and biopharmaceutical section of the NDA indexed and paginated in a manner to allow substantive review to begin?	X			
15	On its face, is the clinical pharmacology and biopharmaceutical section of the NDA legible so that a substantive review can begin?	X			
16	Are the clinical pharmacology and biopharmaceutical studies of appropriate design and breadth of investigation to meet basic requirements for approvability of this product?	X			
17	Was the translation from another language important or needed for publication?		X		

IS THE CLINICAL PHARMACOLOGY SECTION OF THE APPLICATION FILEABLE? ____Yes____

Review issue: In the Phase 3 safety/efficacy study, the study drug was allowed to be taken with or without water. There is no clear instruction related to drug administration with or without water in the label. Effect of water intake will be a review issue.

Christian Grimstein, Ph.D. 01/06/10

Reviewing Pharmacologist Date

Myong-Jin Kim, Pharm.D. 01/06/10

Team Leader/Supervisor Date

Office of Clinical Pharmacology
New Drug Application Filing and Review Form

General Information About the Submission

	Information		Information
NDA Number	**22573**	**Brand Name**	**Pending**
OCP Division	**DCP3**	**Generic Name**	**Norethindrone/ethinyl estradiol**
Medical Division	**DRUP**	**Drug Class**	**Hormone**
OCP Reviewer	**Christian Grimstein, Ph.D**	**Indication(s)**	**Prevention of Pregnancy**
OCP Team Leader	**Myong Jin Kim, Pharm. D.**	**Dosage Form**	**Tablet**
		Dosing Regimen	**1 tablet daily for 28 consecutive days, the last 4 days, the tablet only contains (non-hormonal placebo) 75mg ferrous fumarate**
Date of Submission	**11/26/09**	**Route of Administration**	**Oral**
Estimated Due Date of OCP Review	**07/26/10**	**Sponsor**	**Warner Chilcott**
PDUFA Due Date	**09/26/10**	**Priority Classification**	**Standard**
Division Due Date			

Clin. Pharm. and Biopharm. 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) -				
Healthy Volunteers-				
single dose:				
multiple dose:	X	2		PR03808, PR00707
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 -				
solution as reference:	X	1		PR00807
alternate formulation as reference:				
Bioequivalence studies -				
traditional design; single / multi dose:				
replicate design; single / multi dose:				
Food-drug interaction studies:	X	1		PR00907
Dissolution:				
(IVIVC):				
Bio-wavier request based on BCS				
BCS class				
III. Other CPB Studies				
Genotype/phenotype studies:				
Chronopharmacokinetics				
Pediatric development plan				
Literature References		4		References to support ADME
Total Number of Studies		8		

Filability and QBR comments

	"X" if yes	**Comments**
Application filable?	**X**	
Comments sent to firm?		
QBR questions (key issues to be considered)		
Other comments or information not included above		
Primary reviewer Signature and Date		
Secondary reviewer Signature and Date		

Filing Memo

Clinical Pharmacology Review

NDA: 22-573
Compound: **Norethindrone (NE), Ethinyl estradiol (EE)**
Sponsor: **Warner Chilcott**
Date: **12/08/09**
Reviewer: Christian Grimstein

Background:
The sponsor developed a new oral contraceptive product, WC3026 chewable tablets, containing a combination of norethindrone (NE) 0.8 mg and ethinyl estradiol (EE) 25 mcg (NE 0.8/EE 25). The indication is prevention of pregnancy. The tablets are taken orally qd over a 24-day period followed by a qd administration over 4 days of 75 mg ferrous fumarate (placebo) to complete the 28 day regimen. The tablets are to be chewed without water. According to the sponsor, it has been shown that extending the duration of active treatment from 21 to 24 days and decreasing the drug-free interval to 4 days can decrease the likelihood of development of a dominant follicle; therefore, a 24/4 regimen will be a more effective contraceptive than a 21/7 regimen. The sponsor also states that overall bleeding, especially withdrawal bleeding can be reduced by using a 24/4 regimen.
The NDA is supported by two clinical pharmacology studies which were conducted to characterize NE and EE bioavailability following (1) the single dose administration of WC3026 tablets with or without water or suspended/dissolved in a (b) (4) solution (PR00807) and (2) the single-dose administration of WC3026 tablets under fasted or fed conditions (food effect study, PR 00907).
Additional studies include characterization of NE and EE bioavailability and sex hormone binding globulin (SHBG) serum concentration determination following multiple doses administration of WC3026 tablets chewed without water (PR 03808) and WC3026 tablets swallowed (unchewed) with 240 ml water (PR00707). However, the sponsor stated that the method of administration used in study PR00707 will not be included in the prescribing information and the preferred administration is chewed without water. Administration in the Phase 3 clinical efficacy/safety trial was chewed. However, no instruction concerning administration with or without water was given.
Additional supporting data include in vitro dissolution studies, bioanalytical assays and literature references related to absorption, distribution, metabolism, and excretion (ADME).

Bioavailability:

Bioavailability of EE and NE to determine the formulation and water intake effect was evaluated in a single center, randomized, balanced, single dose, 3-treatment, 3-period, 6 sequence, crossover, comparative study (study 00807). Healthy female volunteers received a WC3026 tablet chewed without water (Treatment A) or chewed with a small

volume (45ml) of water (Treatment B) or they received a [redacted] (b) (4) suspension/solution containing 0.025mg EE/0.8mg NE followed with water (total volume administered 45ml) (Treatment C). 30 subjects were dosed and 26 were evaluable for PK analysis.

Results provided by the sponsor indicate that both Cmax and AUC values of EE were higher for WC3026 tablets chewed without water than for the EE/NE solution/suspension. The Cmax of NE for WC3026 tablets chewed without water was decreased, but the AUC of NE was not affected as compared to the EE/NE solution/suspension. The 90% confidence intervals of the NE AUC ratio were within the 80% to 125% bioequivalence limits (Table 2).

Synopsis Table 2. Summary of the Statistical Evaluation of EE and NE Pharmacokinetic Values Following Administration of a WC3026 Tablet or an EE/NE Solution/Suspension in Healthy Female Volunteers; Study PR-00807 (n=26)

Ethinyl Estradiol		
Formulation Effect (Treatment A/Treatment C)		
Pharmacokinetic Parameter	Ratio (%)	90% Confidence Interval
Cmax	153.60	135.41–174.24
AUC0–tldc	132.10	122.69–142.23
AUCinf	129.26	119.81–139.46
Norethindrone		
Formulation Effect (Treatment A/Treatment C)		
Pharmacokinetic Parameter	Ratio (%)	90% Confidence Interval
Cmax	84.95	72.91–98.98
AUC0–tldc	103.26	94.47–112.87
AUCinf	103.16	94.52–112.58

Treatment A = WC3026 tablet chewed without water; Treatment C = a hydroalcoholic solution/suspension containing EE 25 mcg/NE 0.8 mg administered orally and followed with water; total volume administered was 45 mL; Cmax = Maximum drug concentration (pg/mL); tmax = Time of Cmax (h); AUC0–tldc = Area under drug concentration versus time curve from 0 to time of last determinable concentration (pg·h/mL); AUCinf = Area under drug concentration versus time curve from 0 to infinity (pg·h/mL).
Source data: Source data: Report RR-07607; Table 4 and Table 5

Administration of WC3026 tablets chewed with water decreased Cmax of EE but did not affect the AUC of EE. With respect to NE, WC3026 tablets chewed with water are bioequivalent to WC3026 tablets chewed without water. The 90% confidence intervals for NE Cmax and AUC were within the 80% to 125% bioequivalence limits (Table 3).

Synopsis Table 3. Summary of the Statistical Evaluation of EE and NE Pharmacokinetic Values Following Administration of a WC3026 Tablet chewed and swallowed with water or without water in Healthy Female Volunteers; Study PR-00807 (n=26)

Ethinyl Estradiol		
Water Effect (Treatment B/Treatment A)		
Cmax	86.56	76.45–98.00
AUC0–tldc	94.70	88.06–101.85
AUCinf	97.33	90.31–104.88
Norethindrone		
Water Effect (Treatment B/Treatment A)		
Pharmacokinetic Parameter	Ratio (%)	90% Confidence Interval
Cmax	95.68	82.31–111.22
AUC0–tldc	101.31	92.81–110.59
AUCinf	101.79	93.39–110.94

Treatment A = WC3026 tablet chewed without water; Treatment B = WC3026 tablet chewed with 45 mL water;
See Synopsis Table 2 for definitions and abbreviations.

The sponsor also evaluated the effect of food on EE and NE bioavailability following oral administration of a single WC3026 chewable (taken without water) tablet in a single-center, randomized, balanced, single-dose, 2-treatment, 2-period, 2-sequence, crossover study (PR00907). 18 subjects were enrolled in the study. The data provided by the sponsor indicates that administration of WC3026 tablets with food decreased the Cmax of EE and NE but did not affect the AUC of EE. However, the AUC of NE was increased slightly (by 10%). The sponsor stated that the food effect is not clinically significant. In the Phase 3 clinical trial (PR-00207) the tablet was to be taken with or without food.

Synopsis Table 1. **Summary of Ethinyl Estradiol and Norethindrone Pharmacokinetic Parameter Values following Administration of a WC3026 Tablet under Fed (Test, Treatment A) and Fasted (Reference. Treatment B) Conditions to Healthy Female Volunteers; Study PR-00907 (n=13)**

Analyte	Parameter	Geometric Mean [Median (Range)]		Ratio (Test : Ref)	90% Confidence Interval
		WC3026 Tablet FED, Treatment A (Test)	WC3026 Tablet FASTED, Treatment B (Reference)		
EE	Cmax	87.5	142	60.98%	50.43 - 73.73
	AUC0-tldc	860.6	934.0	91.98%	84.50 - 100.12
	AUCinf	938.9	1025	92.38%	84.55 - 100.93
	tmax	[1.33 (1.00 – 2.00)]	[1.33 (0.67 – 1.67)]	-	-
NE	Cmax	4760	8830	53.46%	42.59 – 67.12
	AUC0-tldc	45810	40460	113.60%	99.06 - 130.28
	AUCinf	46460	42430	109.58%	92.12 - 130.34
	tmax	[1.33 (0.67 – 8.00)]	[1.33 (0.67 – 1.67)]	-	-

The sponsor also conducted a single-center, single-treatment, multiple-dose, bioavailability characterization study under fasting conditions (PR 03808) which evaluated plasma EE and NE PK profiles and SHBG concentrations. To characterize bioavailability after multiple doses, the sponsor conducted a single-center, single-treatment, multiple-dose study in which 18 subjects were enrolled. As indicated by provided data, NE and EE exposure increased by factors of 3.6 and 1.5, respectively, following multiple-dose administration of WC3026 tablets as compared to single-dose administration of WC3026 tablets chewed without water. According to the sponsor, steady state with respect to NE and EE was reached by Day 9 and Day 5, respectively. The mean SHBG concentration more than doubled from pre-dose to Day 25; steady state with respect to SHBG was reached by Day 9.

Absorption:

Intensive PK plasma sampling was obtained in BA/PK study PR03808 which evaluated bioavailability following multiple dose administration of WC3026 tablets. Tmax of EE and NE after administration of WC3026 tablet after a single administration (chewed without water) (day 1) is 1.05h and 1.13 h, respectively. These values only slightly

change after multiple dosing (day 24) when Tmax of EE and NE is 1.33h and 1.00h, respectively.

For further information on absorption see Bioavailability section.

Distribution, Metabolism, Excretion:

These data are primarily based on literature reports. The sponsor's provided information and conclusions are quoted below. However, the validity is not considered in this filing review.

"Volume of distribution of NE and EE ranges from 2 to 4 L/kg.(Back-1978) Plasma protein binding of both steroids is extensive (>95%); NE binds to both albumin and sex hormone binding globulin (SHBG), whereas EE binds only to albumin. Although EE does not bind to SHBG, it induces SHBG synthesis."

"Norethindrone 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. (Fotherby 1994) A small amount of NE is metabolically converted to EE, such that exposure to EE following administration of 1 mg of norethindrone acetate is equivalent to oral administration of 2.8 mcg EE; therefore 0.8 mg NE would be equivalent to the oral administration of 2.6 mcg EE. Ethinyl estradiol 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. Ethinyl estradiol may undergo enterohepatic circulation. (Goldzieher 1994)"

"Norethindrone and EE are excreted in both urine and feces, primarily as metabolites. (Fotherby 1994, Goldzieher 1994) 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 0.8 mg NE / 0.025 mcg EE tablets are approximately 11 hours and 17 hours, respectively."

Drug-drug interactions:

The sponsor did not perform DDI studies but stated that estrogens are metabolized by CYP3A4 and therefore inhibitors or inducers of CYP3A4 may affect estrogen drug metabolism.

Specific population:

WC3026 is not indicated in children. PK of WC3026 has not been studied in renal impaired, hepatic impaired and geriatric population. The effect on race has not been evaluated either.

Clinical vs. to-be-marketed formulation:

The sponsor stated that the unit-dose composition and manufacturing process of the to-be-marketed formulation (Table1) is identical to that of the clinical study formulation.

Table 1: Composition of WC3026-5C tablets

	Formulation WC3026-5C	
Component	mg/tablet	% w/w
Ethinyl estradiol USP*	0.025	(b) (4)
Povidone USP (b) (4)	(b) (4	
Vitamin E USP (b) (4) *		
Lactose monohydrate NF, (b) (4)		
Norethindrone USP	0.80	
Mannitol USP (b) (4)	(b) (4)	
Mannitol USP		
Microcrystalline cellulose, NF (b) (4)		
FD&C Yellow No. 6 aluminum lake		
FD&C Blue No. 1 aluminum lake		
D&C Yellow No. 10 aluminum lake		
Spearmint flavor ((b) (4))		
Sodium starch glycolate		
Sucralose		
Magnesium stearate		
Total	70.00	
(b) (4)		

Method validation:

A combination method to simultaneous detecting EE and NE in human plasma samples was used. The analytes were derivatized and measured by GC/MS. According to the sponsor lower and upper quantification limits for EE were 2.5 and 250 pg/mL and for NE 25 and 25000 pg/mL. SHBG concentrations were determined in human serum using an immunoradiometric assay (IRMA) kit with a range of 10-250nmol/L. Method validation reports were submitted in the NDA.

Recommendation:

The Office of Clinical Pharmacology/Division of Clinical Pharmacology 3 finds that the Human Pharmacokinetics and Bioavailability section for NDA 22-573 is fileable.

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22573	ORIG-1	WARNER CHILCOTT INC	(b) (4) (norethindrone and ethinyl estradiol tablets, chewable and ferrous fumarate tablets)

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

/s/

CHRISTIAN GRIMSTEIN
02/01/2010

MYONG JIN KIM
02/01/2010

BIOPHARMACEUTICS REVIEW Office of New Drugs Quality Assessment			
Application No.:	NDA 22-573	**Reviewer:** Sandra Suarez Sharp, Ph.D	
Division:	DRUP		
Sponsor:	Warner Chilcott	**Team Leader:** Angelica Dorantes, Ph.D .	
Trade Name:	(b) (4)	**Supervisor:** Patrick J. Marroum, Ph.D	
Generic Name:	Norethindrone 0.8 mg + ethinyl estradiol 0.025 mg, chewable + ferrous fumarate 75 mg tablet	**Date Assigned:**	Dec 17, 2009
Indication:	Prevention of pregnancy	**Date of Review:**	Jan 04, 2010
Formulation	Chewable Tablet		
Route of Administration	Oral		

SUBMISSIONS REVIEWED IN THIS DOCUMENT			
Submission date	**CDER Stamp Date**	**Date of informal/Formal Consult**	**PDUFA DATE**
Nov 25, 2009	Nov 26, 2009	Dec 17, 2009	Sep 24, 2010
Type of Submission:	Original NDA		
Type of Consult:	Dissolution method and specifications---**FILING REVIEW**		

REVIEW SUMMARY:

Ovcon® 50 (norethindrone and ethinyl estradiol tablets, USP) was approved by the Agency for the prevention of pregnancy in women who elect to use an oral contraceptive (NDA 17-576); the approved Ovcon 50 regimen includes the administration of 21 active tablets each containing the combination of 1 mg NE and 0.05 mg EE. Femcon® Fe (NDA 21-490) is an oral contraceptive containing 21-days of active therapy and was approved by the Agency in 2003 as a chewable tablet. Femcon® Fe contains 0.4 mg of norethindrone (NE) and 35 mcg of ethinyl estradiol (EE), and 7-days of inactive tablets containing 75 mg of ferrous fumarate.

The sponsor, Warner Chilcott is seeking approval of (b) (4). (b) (4) is an oral contraceptive consisting of a new dose and new regimen of the combination of norethindrone (NE) and ethinyl estradiol (EE). The combination of 0.8 mg of NE and 0.025 mg of EE is to be taken daily for 24 days followed by one daily ferrous fumarate tablet for 4 days to facilitate ease of drug administration via a 28-day regimen.

In support of this NDA the sponsor included the results of total of five studies: clinical data from a Phase 3 safety and contraceptive efficacy study as well as a Phase 1 oral safety study. It also includes results from three Phase 1 BA and PK studies conducted to assess the BA of EE and NE following a single tablet administration, the food effect following a single tablet administration, and the NE and EE pharmacokinetic profiles and sex hormone binding globulin (SHBG) concentrations following multiple doses of NE/EE.

Two dissolution methods have been used for the dissolution testing of NE/EE tablets. The following method ((b) (4)) was used to perform the dissolution testing (release and stability) of all batches of NE/EE tablets manufactured in support of this application:

(b) (4)

The following method ((b) (4)) is an alternate dissolution method that has been used to test selected batches of NE/EE tablets in order to evaluate the similarity of dissolution profiles obtained for NE/EE tablets using both methods:

(b) (4)

According to the sponsor, a lack of reproducibility for the system suitability due to non-compliance with the standard verification requirements was encountered during routine use of dissolution method (b) (4). In an effort to obtain a more robust method, a new dissolution method was developed and validated. This new method (DP-10630) retained the same HPLC and dissolution test parameters as in (b) (4)

The dissolution method and specifications for the ferrous fumarate chewable tablets are as follows:

Dosage Form	USP Apparatus	Speed (rpm)	Medium	Volume (mL)	Specification (Q)
Chewable tablet	II (Paddle)	75	0.1N HCl containing 0.5% sodium lauryl sulfate,, 37 ± 0.5°C	900	(b) (4) (Q) of ferrous fumarate is dissolved in (b) (4)

The approved USP dissolution method (0.1N HCl containing 0.09% sodium lauryl sulfate; 600 mL; 75 rpm) for NE/EE tablet is different from that for the product under investigation. The approved USP dissolution method (0.1N HCl containing 0.5% sodium lauryl sulfate; 900 mL) for ferrous fumarate tablet is the same as that for the product under investigation. According to the USP monograph for ferrous fumarate, not less than 75% (Q) of ferrous fumarate is dissolved in 45 min.

The biopharmaceutics review for this NDA will focus on the acceptability of the proposed

dissolution methods and specifications.

RECOMMENDATION:

The ONDQA/biopharmaceutics team has reviewed NDA 22-573(000) for filing purposes. We found this NDA filable from biopharmaceutics perspective. The following comment should be conveyed to the sponsor as part of the 74-day letter:

1. The proposed dissolution method for the norethindrone/ethinyl estradiol tablets (0.025M sodium acetate with 0.15% of sodium dodecyl sulphate buffer, pH 5, (b) (4) L, 75 rpm) is different from that established in the USP monograph for this product. Submit a report of your dissolution method development and validation for Norethindrone/Ethinyl Estradiol Chewable Tablets. These data should also include tabulated values of individual and mean % dissolved under the conditions tested.

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cc: NDA 22-573, TBoui, ADorantes, Dchristner, JChang

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22573	ORIG-1	WARNER CHILCOTT INC	(b) (4) (norethindrone and ethinyl estradiol tablets, chewable and ferrous fumarate tablets)

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/s/

SANDRA SUAREZ
01/12/2010

PATRICK J MARROUM
01/13/2010