CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

203667Orig1s000

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

OFFICE OF CLINICAL PHARMACOLOGY REVIEW ADDENDUM

NDA #	203667
Submission Dates	July 9, 2012; May 3, 2013
Brand Name	None proposed
Generic Name	Norethindrone acetate (NA) and ethinyl estradiol (EE) chewable tablets and ferrous fumarate tablets
Strength and Formulation; Regimen	One chewable tablet (active) containing 1 mg NA and 0.020 mg EE taken daily for 24 days followed by one tablet containing 75 mg ferrous fumarate (inactive) taken for 4 days as a part of the 28-day regimen
Sponsor	Warner Chilcott
Proposed Indication	Prevention of pregnancy
Submission Type	Original NDA; standard review
Relevant NDA	021871 (Loestrin® 24 Fe tablets)
Clinical Pharmacology Reviewer	LaiMing Lee, PhD
Team Leader	Myong-Jin Kim, PharmD
OCP Division	Division of Clinical Pharmacology-3
OND Division	Division of Reproductive and Urologic Products

1 Executive Summary

The Clinical Pharmacology review of NDA 203667 (DARRTS, April 9, 2013) stated that NDA 203667 was acceptable provided that an agreement is reached between the Applicant and the Division regarding the language in the package insert labeling. The final agreement was reached on May 3, 2013 and there are no pending issues from the Office of Clinical Pharmacology. 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 NDA 203667 acceptable.

2 Final Agreed Upon Package Insert Labeling

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

---

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

/s/

LAI M LEE
05/03/2013

MYONG JIN KIM
05/03/2013

OFFICE OF CLINICAL PHARMACOLOGY REVIEW

NDA #	203667
Submission Dates	July 9, 2012; January 28, 2013; February 15, 2013
Brand Name	None proposed
Generic Name	Norethindrone acetate (NA) and ethinyl estradiol (EE) chewable tablets and ferrous fumarate tablets
Strength and Formulation; Regimen	One chewable tablet (active) containing 1 mg NA and 0.020 mg EE taken daily for 24 days followed by one tablet containing 75 mg ferrous fumarate (inactive) taken for 4 days as a part of the 28-day regimen
Sponsor	Warner Chilcott
Proposed Indication	Prevention of pregnancy
Submission Type	Original NDA; standard review
Relevant NDA	021871 (Loestrin® 24 Fe tablets)
Clinical Pharmacology Reviewer	LaiMing Lee, PhD
Team Leader	Myong-Jin Kim, PharmD
OCP Division	Division of Clinical Pharmacology-3
OND Division	Division of Reproductive and Urologic Products

A roundtable discussion was held on April 3, 2013 in lieu of a formal OCP Briefing and was attended by Edward D. Bashaw, Hae-Young Ahn, Myong-Jin Kim, Christina Chang, and Michiyo Yamazaki.

TABLE OF CONTENTS

1 EXECUTIVE SUMMARY

Warner Chilcott is seeking approval of WC3040, norethindrone acetate (NA) and ethinyl estradiol (EE) chewable tablets and ferrous fumarate (Fe) tablets (same components, composition, doses, and dosing regimen of Loestrin® 24 Fe), for the prevention of pregnancy. Warner Chilcott received approval of Loestrin® 24 Fe on February 17, 2006 under NDA 021871. The difference between the new product WC3040 (also referred to as WC3040-1F tablets) and approved Loestrin® 24 Fe is the method of use. The NA and EE tablets in the new product may be chewed and swallowed or swallowed whole compared to the NA and EE tablets in the Loestrin® 24 Fe product that are swallowed whole. The proposed product consists of 24 white active tablets containing 1 mg NA and 0.02 mg EE taken daily for 24 days (may be chewed and swallowed or swallowed whole) and 4 brown inactive tablets containing 75 mg Fe, and may be administered without regard to meals. With the exception of tablet debossing and insignificant manufacturing changes, the to-be-marketed NA and EE tablets are the same as the NA and EE tablets of Loestrin® 24 Fe.

The sponsor submitted 3 clinical studies to NDA 203667: one bioequivalence (BE) study PR-08507 comparing the bioavailability (BA) of norethindrone (NE) and EE tablets chewed prior to swallowing and NE and EE tablets from Loestrin® 24 Fe Tablet swallowed; one safety study PR-10007 evaluating the oral irritation potential of chewing NE and EE tablets; and one relative BA study PR-07411 comparing development formulation WC3040-2F to Loestrin® 24 Fe and food effect on WC3040-2F.

The sponsor is seeking approval of this product with a new method of administration based upon the BE study PR-08507 and oral safety study PR-10007. This NDA review will focus on the pivotal BE study.

The clinical portion of Study PR-08507 was conducted at Cedra Clinical Research, Austin, TX. The bioanalytical laboratory was (b) (4) . The approvability of this NDA is dependent upon the results of Study PR-08507; therefore, an inspection of the clinical and bioanalytical sites was requested to the Office of Scientific Investigations (OSI).

1.1 Recommendations

The Division of Clinical Pharmacology-3/Office of Clinical Pharmacology (DCP-3 /OCP) has reviewed NDA 203667 for NA (1 mg) and EE (0.02 mg) chewable tablets and Fe (75 mg) tablets submitted to the Agency on July 9, 2012. We have found this NDA acceptable from a Clinical Pharmacology perspective provided that an agreement is reached between the sponsor and the Division regarding the labeling language.

1.2 Phase IV Commitments

None

1.3 Summary of Clinical Pharmacology and Biopharmaceutics Findings

Bioequivalence of Loestrin 24 Fe (swallow method) and WC3040 tablets (chew and swallow method)

The sponsor demonstrated BE for both active moieties (NE and EE) following a single dose administration of NA and EE tablets chewed and swallowed or swallowed as whole in a randomized, two-way, two treatment crossover study in 40 healthy female subjects.

During the audit of the bioanalytical site (Pivotal BE study, PR-08507), OSI identified a number of issues with samples from four subjects; the sponsor has rectified the issues and submitted a new study report for the pivotal BE study in 35 subjects.

For NE, the geometric mean ratio (90% CI) for Cmax, AUC_{0-t}, and AUC_{0-inf} were 1.04 (96-112%) , 1.03 (98-107%), and 1.02 (97-107%). For EE, the geometric mean ratio (90% CI) for Cmax, AUC_{0-t}, and AUC_{0-inf} were 1.04 (99-108%) , 1.02 (98-106%), and 0.97 (91-104%). The point estimates are near unity and the 90% CI are within the BE acceptance criteria of 80-125%. Therefore, NA and EE tablets from NDA 203667 and NDA 021871 are found to be BE.

PK characteristics

The following table is the PK parameters of **NE** following a single dose of NA (1 mg) and EE (0.020 mg) tablets (chewed and swallowed) in healthy female subjects (N=35) (data from study PR-08507).

PK parameter*	NA and EE tablets (chewed and swallowed)
Cmax (pg/mL)	10200 (36)
Tmax (hr)	1.28 (45)
AUC_{0-tldc} (pg hr/mL)	48620 (40)
AUC_{0-inf} (pg hr/mL)	49250 (40)
Kel (1/hr)	0.0807 (23)
$T_{1/2}$ (hr)	8.58

* arithmetic mean (CV%)

AUC_{0-tldc} : area under the plasma concentration-time curve from time 0 to time of last determinable concentration, calculated by the linear trapezoidal method

The following table is the PK parameters of **EE** following a single dose of NA and EE tablets (chewed and swallowed) in healthy female subjects (N=35) (data from study PR-08507).

PK parameter*	NA and EE chewable tablets (chewed and swallowed)
Cmax (pg/mL)	84.7 (24)
Tmax (hr)	1.51 (26)
AUC_{0-tldc} (pg hr/mL)	677.5 (33)
AUC_{0-inf} (pg hr/mL)	741.6 (33)
Kel (1/hr)	0.0716 (53)
$T_{1/2}$ (hr)	9.68

* arithmetic mean (CV%)

AUC_{0-tldc} : area under the plasma concentration-time curve from time 0 to time of last determinable concentration, calculated by the linear trapezoidal method

The clinical portion of Study PR-08507 was conducted at Cedra Clinical Research, Austin, TX. During an inspection of the clinical site from October 1 to 6, 2008, no issues were identified. Division of Scientific Investigations (DSI) (currently referred to as OSI) concluded that the clinical data were acceptable for review (see DSI report DARRTS March 31, 2009).

2 QUESTION-BASED REVIEW

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

Warner Chilcott received approval of Loestrin® 24 Fe on February 17, 2006 under NDA 021871. Loestrin 24 Fe tablets consists of 24 white active tablets containing 1 mg NA and 0.02 mg EE taken daily for 24 days (swallowed) and 4 brown inactive tablets containing 75 mg Fe. Loestrin 24 Fe may be administered without regard to meals.

Warner Chilcott is seeking approval of NA and EE chewable tablets, and Fe tablets (same components, composition, doses, and dosing regimen of Loestrin® 24 Fe) for the prevention of pregnancy. The difference between the new product WC3040 (also referred to as WC3040-1F tablets) and approved Loestrin® 24 Fe is the method of use. The NA and EE tablets in the new product may be chewed and swallowed or swallowed whole compared to the NA and EE tablets in the Loestrin® 24 Fe product that are swallowed whole.

The difference between the new product WC3040 (also referred to as WC3040-1F tablets) and approved Loestrin® 24 Fe is the method of use. The NA and EE tablets in the new product may be chewed and swallowed or swallowed whole compared to the NA and EE tablets in the Loestrin® 24 Fe product that are swallowed whole.

The sponsor originally sought approval of NA and EE chewable tablets and Fe tablets under NDA 022365. The application was submitted on May 20, 2008, but it was withdrawn for business reasons on January 12, 2009. The application was resubmitted under the same NDA number on September 12, 2010 and withdrawn for a second time on November 15, 2010. The clinical portion of Study PR-08507 was conducted at Cedra Clinical Research, Austin, TX. During an inspection of the clinical site from October 1 to 6, 2008, no issues were identified. Division of Scientific Investigations (DSI) (currently referred to as DSI) concluded that the clinical data were acceptable for review (see report DARRTS March 31, 2009). The bioanalytical laboratory was (b) (4) . An OSI inspection of the bioanalytical site was not conducted prior to the current application because the original application was withdrawn shortly before the initiation of the inspection.

The basis of approval will be dependent upon BE study PR-08507 (linking the new method of administration (chew and swallow) to the former method of administration (swallow) used in the original Phase 3 studies for the approval of NDA 021871) and oral safety study PR-10007. Because the approvability of this NDA is dependent upon the results of Study PR-08507, an inspection of the bioanalytical site was requested.

During an audit of the bioanalytical site from November 5 to 9, 2012, OSI identified a number of issues with samples from four subjects (#206, 207, 229 and 230) (see DARRTS December 4, 2012). An INFORMATION REQUEST letter was issued to

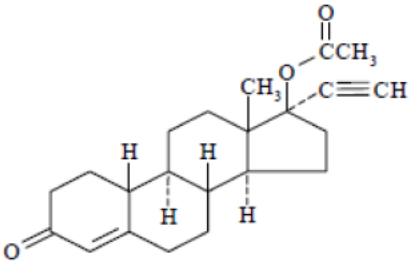
Warner Chilcott (see DARRTS January 15, 2013) outlining the findings identified by OSI and requests from the DCP-3/OCP to address the issues.

The sponsor rectified the OSI issues by removing the data from Subjects 206 and 207 from the study analysis and replaced the original data for Subjects 229 and 230 with the recalculated data from (b) (4). The sponsor submitted an amended study report for the pivotal BE study on February 16, 2013. Due to OSI findings, out of 37 subjects, BE assessment was conducted in 35 subjects.

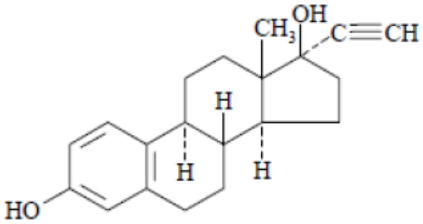
2.2 GENERAL ATTRIBUTES OF THE DRUG

2.2.1 What are the highlights of the chemistry and physical-chemical properties of the drug substance and the formulation of the drug product?

NA has a chemical name of [19-norpreg-4-en-20-yn-3-one,17-(acetyloxy)-,(17α)] with an empirical formula of $C_{22}H_{28}O_3$ and a molecular weight of 340.5.



EE has a chemical name of [19-norpregna-1,3,5(10)-trien-20-yne-3,17-diol,(17α)-] with an empirical formula of $C_{20}H_{248}O_2$ and a molecular weight of 296.4.



The chewable tablet will be debossed with "535" and is referred to as formulation WC3040-1F by the sponsor. The table below summarizes the components and composition of the to-be-marketed formulation.

	Formulation WC3040-1F	
Component	mg/tablet	% w/w
Norethindrone acetate	1.00	1.37
Ethinyl estradiol	0.02	0.03
Acacia (b) (4)	(b) (4)	
Lactose monohydrate		
Magnesium stearate		
Starch		
Confectioner's sugar		
Talc (b) (4)		
Total	73.00	100.00

2.2.2 What are the proposed mechanism of action and therapeutic indication?

The sponsor is seeking approval to market NA and EE chewable tablets and Fe tablets for the prevention of pregnancy. As a monophasic combination oral contraceptive, NA and EE tablets acts by suppressing gonadotropins to inhibit ovulation and altering changes in the cervical mucus (thereby increasing the difficulty of sperm entry into the uterus) and the endometrium (thereby reducing the likelihood of implantation). The Fe tablets are inactive tablets and serve as "reminder tablets".

2.2.3 What are the proposed dosages and routes of administration?

The sponsor is seeking approval of a 28-day monophasic combination oral contraceptive. The white active tablet containing 1 mg NA and 0.02 mg EE would be taken daily (chewed) for 24 days with 8 oz of liquid followed by a brown inactive 75 mg Fe tablet taken daily for 4 days. The proposed label states with liquid; however, the subjects in study PR-08507 were administered the product with water at ambient temperature. Therefore, the label should specify take with water, not any liquid.

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

NA, a progestin, is approved for use in combination with EE, a semi-synthetic estrogen, for the prevention of pregnancy and as a single entity for the treatment of secondary amenorrhea, endometriosis, and abnormal uterine bleeding such as Aygestin®. EE is approved and used in many formulations for the prevention of pregnancy such as Ortho Evra® and NuvaRing®. There are numerous products approved for the prevention of pregnancy including Loestrin 24 Fe, the one referenced in this NDA.

2.3 GENERAL CLINICAL PHARMACOLOGY

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

The clinical program for this NDA included one BE study (Study PR-08507) and one oral irritation study (Study PR-10007). The BE study was a single-center, randomized, single dose, two-period, two treatment, crossover study. Forty subjects were enrolled (35 subjects in the PK analysis) to take NA and EE tablets (chewed and swallowed) and NA and EE tablets (swallowed).

No new safety or efficacy study was conducted for this product as the sponsor is relying on the previous Phase 3 study of Loestrin 24 Fe swallow tablets for the demonstration of safety and efficacy.

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

For BE study PR-08507, PK parameters and statistical analyses for NE and EE after both treatments - chewed and swallowed or swallowed whole - were reported for the purpose of demonstrating bioequivalence between the two different routes of administration.

2.3.3 Are the active moieties in the plasma and clinically relevant tissues appropriately identified and measured to assess pharmacokinetic parameters and exposure response relationships?

NA, the acetate salt of NE, is rapidly deacetylated to NE after oral administration. NE and EE are the active moieties that are relevant for the assessment of BE. Plasma concentrations, PK parameters and statistical analyses of NE and EE from both treatments are reported for the purpose of BE determination.

2. 4 EXPOSURE-RESPONSE

2.4.1 Does the exposure-response (dose-response, concentration-response) relationship support evidence of effectiveness?

In this NDA, no new safety and efficacy studies were conducted. The sponsor is relying on the Phase 3 studies used to approve Loestrin® 24 Fe and is bridging to the original safety and efficacy data with BE study PR-08507. The proposed doses in the new product are NA 1 mg and EE 0.02 mg chewable tablet and Fe 75 mg tablet, which are the same doses as the approved Loestrin® 24 Fe, the reference product used in the pivotal BE study.

2.4.2 Does this drug prolong QT/QTc interval?

No information is available.

2.5 WHAT ARE THE PK CHARACTERISTICS OF THE DRUG?

2.5.1 What are the single and multiple dose PK parameters of parent drug and relevant metabolites in healthy adults?

The following table is the PK parameters of **NE** following a single dose of NA (1 mg) and EE (0.02 mg) tablets (chewed and swallowed) in healthy female subjects (N=35) (data from study PR-08507).

PK parameter*	NA and EE tablets (chewed and swallowed)
Cmax (pg/mL)	10200 (36)
Tmax (hr)	1.28 (45)
$AUC_{0\text{-tldc}}$ (pg hr/mL)	48620 (40)
$AUC_{0\text{-inf}}$ (pg hr/mL)	49250 (40)
Kel (1/hr)	0.0807 (23)
$T_{1/2}$ (hr)	8.58

* arithmetic mean (CV%)
$AUC_{0\text{-tldc}}$: area under the plasma concentration-time curve from time 0 to time of last determinable concentration, calculated by the linear trapezoidal method

The following table is the PK parameters of **EE** following a single dose of NA and EE tablets (chewed and swallowed) in healthy female subjects (N=35) (data from study PR-08507).

PK parameter*	NA and EE tablets (chewed and swallowed)
Cmax (pg/mL)	84.7 (24)
Tmax (hr)	1.51 (26)
$AUC_{0\text{-tldc}}$ (pg hr/mL)	677.5 (33)
$AUC_{0\text{-inf}}$ (pg hr/mL)	741.6 (33)
Kel (1/hr)	0.0716 (53)
$T_{1/2}$ (hr)	9.68

* arithmetic mean (CV%)
$AUC_{0\text{-tldc}}$: area under the plasma concentration-time curve from time 0 to time of last determinable concentration, calculated by the linear trapezoidal method

No multiple-dose PK parameters for this new method of administration are available.

2.5.2 What are the characteristics of drug absorption?

Following oral administration of NA and EE tablets (chewed and swallowed) in study PR-08507, plasma concentrations of NE increased rapidly with a median (range) Tmax of 1.03 (0.67 to 2.50) and EE also increased rapidly with a median (range) Tmax of 1.33 hr (1 to 2.5) followed by a log-linear decrease.

2.5.3 What are the characteristics of drug distribution?

Based on Loestrin® 24 Fe labeling, volume of distribution of NE and EE ranges from 2 to 4 L/kg. Plasma protein binding is extensive for both NE and EE and is >95%. NE binds to both albumin and sex hormone binding globulin (SHBG). EE binds only to albumin, but induces SHBG synthesis even though it does not bind to SHBG.

2.5.4 Does the mass balance study suggest renal or hepatic as the major route of elimination?

Based on Loestrin 24® Fe labeling, NE and EE are extensively metabolized and both are excreted in urine and feces primarily as metabolites.

2.5.5 What are the characteristics of drug metabolism?

Based on published literature and Loestrin® 24 Fe labeling, the following is known about the metabolism of NE and EE. NE undergoes extensive biotransformation, primarily via reduction, followed by sulfation and glucuronidation. The most important metabolites of NA are isomers of 5α-dihydro-norethindrone and tetrahydro-norethindrone, which are excreted mainly in the urine as sulfate or glucuronide conjugates. 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. Metabolism by CYP3A4 results in the formation of 2-hydroxy ethinyl estradiol.

2.5.6 Is there evidence for enterohepatic recirculation for parent and/or metabolites?

Based on Loestrin® 24 Fe labeling, EE may undergo enterohepatic recirculation.

2.5.7 What are the characteristics of drug excretion in urine?

Based on Loestrin® 24 Fe labeling, both NE and EE are excreted in urine and feces primarily as metabolites. Plasma clearance for NE and EE are approximately 0.4 L/hr/kg. Based on the PK data from study PR-08507, arithmetic mean (SD) elimination half-lives of NE and EE following a single dose of NA 1 mg and EE 0.02 tablet (chewed and swallowed) are approximately 9.0 (2.0) hrs and 12.7 (7.4) hrs, respectively. These values are similar to the values for both NE (8 hrs) and EE (14 hrs) tablets (swallowed whole) from the Loestrin® 24 Fe label.

2.5.8 How do the PK parameters change with time following chronic dosing?

This NDA did not include multiple-dose PK for the new method of administration. Based on Loestrin® 24 Fe labeling, arithmetic mean Cmax of NE and EE increased by 95% and 27%, respectively, following 24 days of NA and EE daily administration compared to a single dose. Arithmetic mean $AUC_{0\text{-}24hr}$ increased by 165% and 51% for NE and EE, respectively, following 24 days of NA and EE daily administration compared to a single dose. Steady-state for NE and EE was reached by Day 17 and Day 13, respectively. The following figures and table are from the Loestrin® 24 Fe label.

Figure 1. Mean Plasma Norethindrone Concentration-Time Profiles Following Single- and Multiple-Dose Oral Administration of Loestrin 24 Fe Tablets to Healthy Female Volunteers under Fasting Condition (n = 17)

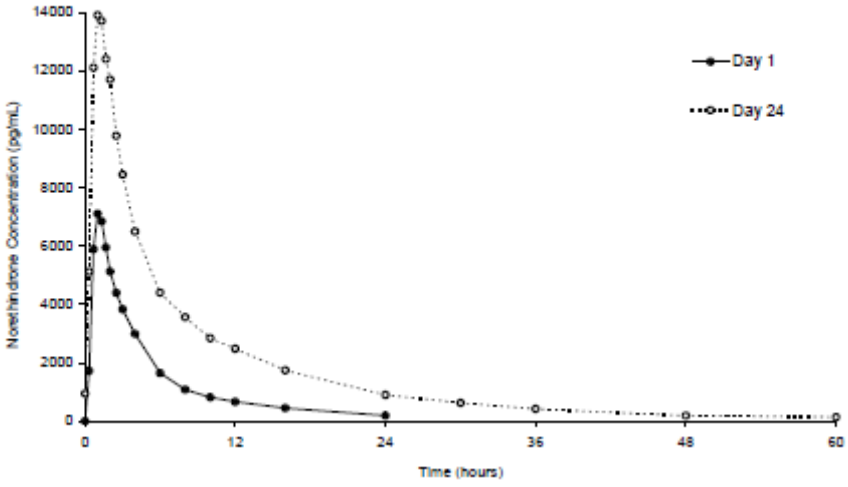


Figure 2. Mean Plasma Ethinyl Estradiol Concentration-Time Profiles Following Single- and Multiple-Dose Oral Administration of Loestrin 24 Fe Tablets to Healthy Female Volunteers under Fasting Condition (n = 17)

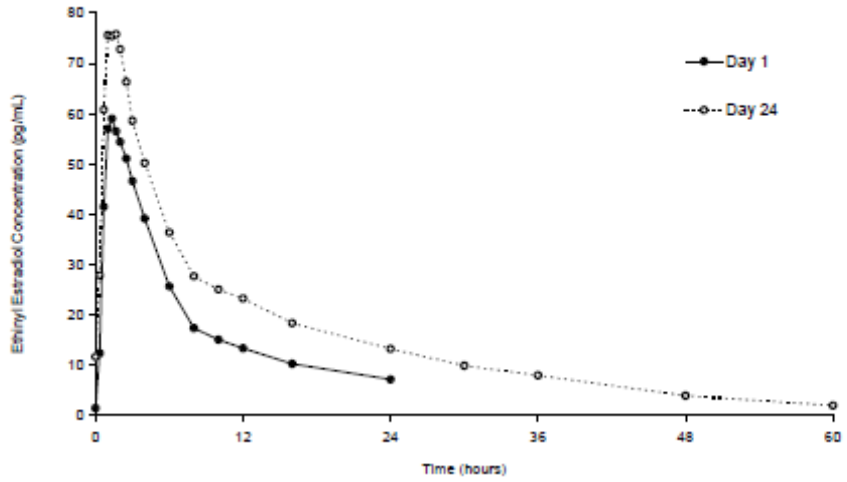


Table 1. Summary of Norethindrone (NE) and Ethinyl Estradiol (EE) Pharmacokinetics Following Single- and Multiple-Dose Oral Administration of Loestrin 24 Fe Tablets to Healthy Female Volunteers under Fasting Condition (n = 17)

Regimen	Analyte	Arithmetic Mean [a] (%CV) by Pharmacokinetic Parameter					
		C_{max} (pg/mL)	t_{max} (hr)	$AUC_{(0-24)}$ (pg/mL•h)	C_{min} (pg/mL)	$t_{½}$ (hr)	C_{avg} (pg/mL)
Day 1 (Single Dose)	NE	8420 (31)	1.0 (0.7–4.0)	33390 (40)	--	--	--
	EE	64.5 (27)	1.3 (0.7–4.0)	465.4 (26)	--	--	--
	SHBG	--	--	--	57.5 (37) [b]	--	--
Day 24 (Multiple Dose)	NE	16400 (26)	1.3 (0.7–4.0)	88160 (30)	880 (51)	8.4	3670 (30)
	EE	81.9 (24)	1.7 (1.0–2.0)	701.3 (28)	11.4 (43)	14.5	29.2 (28)
	SHBG	--	--	--	144 (24)	--	--

2.6 INTRINSIC FACTORS

2.6.1 What intrinsic factors (pregnancy, lactation, age, organ dysfunction, body mass index (BMI)) influence exposure and/or response, and what is the impact of any differences in exposure on efficacy or safety responses?

For this NDA, the sponsor did not conduct studies to evaluate the effect of intrinsic factors on the exposure of NE and EE, or the safety and efficacy response following administration of NA and EE tablets. The following information was obtained from the Loestrin® 24 Fe label.

Pregnancy
Extensive epidemiological studies have revealed no increased risk of birth defects in women who have used oral contraceptives prior to pregnancy. Studies also do not suggest a teratogenic effect, particularly in so far as cardiac anomalies and limb reduction defects are concerned, when taken inadvertently during early pregnancy.

The administration of oral contraceptives to induce withdrawal bleeding should not be used as a test for pregnancy. Oral contraceptives should not be used during pregnancy to treat threatened or habitual abortion.

It is recommended that for any patient who has missed two consecutive periods, pregnancy should be ruled out. If the patient has not adhered to the prescribed schedule, the possibility of pregnancy should be considered at the time of the first missed period. Oral contraceptive use should be discontinued if pregnancy is confirmed.

Lactation
Small amounts of oral contraceptive steroids and/or metabolites have been identified in the milk of nursing mothers and a few adverse effects on the child have been reported, including jaundice and breast enlargement. In addition, combination oral contraceptives given in the postpartum period may interfere with lactation by decreasing the quantity and quality of breast milk. If possible, the nursing mother should be advised not to use combination oral contraceptives but to use other forms of contraception until she has completely weaned her child.

Pediatric
Safety and efficacy of Loestrin 24 Fe have been established in women of reproductive age. Safety and efficacy are expected to be the same in postpubertal adolescents under the age of 16 years and in users age 16 years and older. Use of this product before menarche is not indicated. The current NDA is not subject to the Pediatric Research Equity Act (PREA); therefore, it was not necessary for the FDA's Pediatric Review Committee (PeRC) and the Division of Reproductive and Urologic Products (DRUP) to meet.

Geriatric
This product has not been studied in women over 65 years of age and is not indicated in this population.

Renal Impairment
The effect of renal disease on the disposition of NE and EE after Loestrin 24 Fe administration has not been evaluated. In premenopausal women with chronic renal failure undergoing peritoneal dialysis who received multiple doses of an oral contraceptive containing EE and NE, plasma EE concentrations were higher and NE concentrations were unchanged compared to concentrations in premenopausal women with normal renal function.

Hepatic Impairment
The effect of hepatic disease on the disposition of NE and EE after Loestrin 24 Fe administration has not been evaluated. However, EE and NE may be poorly metabolized in patients with impaired liver function.

BMI
In the proposed label, the sponsor states the following: The safety and efficacy of NE and EE chewable tablets and Fe tablets in women with a BMI >35 kg/m^2 has not been evaluated.

2.7 EXTRINSIC FACTORS

2.7.1 What extrinsic factors influence dose-exposure and/or response and what is the impact of any differences in exposure on response?

No formal studies were conducted to evaluate the effect of extrinsic factors on the exposure of NE and EE by the applicant for this NDA. According to the Loestrin® 24 Fe label, the following are identified under PHARMACOKINETCS: Absorption: Effect of Food and DRUG INTERACTIONS.

Absorption
Effect of Food: Loestrin 24 Fe tablets may be administered without regard to meals. A single-dose administration of Loestrin 24 Fe tablet with food decreased the maximum concentration of norethindrone by 11% and increased the extent of absorption by 27% and decreased the maximum concentration of ethinyl estradiol by 30% but not the extent of absorption.

Changes in contraceptive effectiveness associated with co-administration of other products:
a. Anti-infective agents and anticonvulsants
Contraceptive effectiveness may be reduced when hormonal contraceptives are co-administered with antibiotics, anticonvulsants, and other drugs that increase the metabolism of contraceptive steroids. This could result in unintended pregnancy or breakthrough bleeding. Examples include rifampin, barbiturates, phenylbutazone, phenytoin, carbamazepine, felbamate, oxcarbazepine, topiramate, and griseofulvin.

b. Anti-HIV protease inhibitors
Several of the anti-HIV protease inhibitors have been studied with co-administration of oral combination hormonal contraceptives; significant changes (increase and decrease) in the plasma levels of the estrogen and progestin have been noted in some cases. The safety and efficacy of combination oral contraceptive products may be affected with co-administration of anti-HIV protease inhibitors. Healthcare providers should refer to the label of the individual anti-HIV protease inhibitors for further drug-drug interaction information.

c. Herbal products
Herbal products containing St. John's Wort (hypericum perforatum) may induce hepatic enzymes (cytochrome P450) and p-glycoprotein transporter and may reduce the effectiveness of contraceptive steroids. This may also result in breakthrough bleeding.

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

Changes in plasma levels of co-administered drugs:
Combination hormonal contraceptives containing some synthetic estrogens (e.g., ethinyl estradiol) may inhibit the metabolism of other compounds. Increased plasma concentrations of cyclosporine, prednisolone, and theophylline have been reported with

concomitant administration of combination oral contraceptives. Decreased plasma concentrations of acetaminophen and increased clearance of temazepam, salicylic acid, morphine and clofibric acid, due to induction of conjugation have been noted when these drugs were administered with combination oral contraceptives.

2.8 GENERAL BIOPHARMACEUTICS

2.8.1 How is the proposed to-be-marketed formulation linked to the clinical trial formulation?

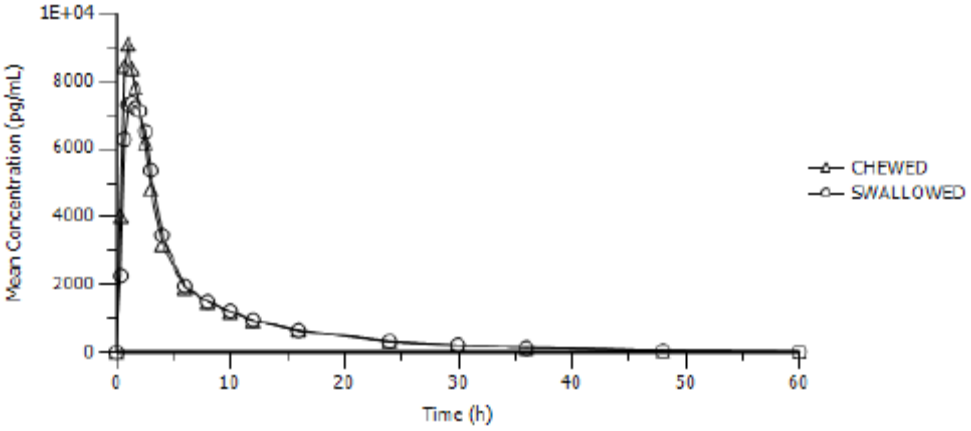
The NA and EE tablets of the proposed product have the same components, composition, doses, and dosing regimen as the NA and EE tablets of Loestrin® 24 Fe. The difference between the new product WC3040 (also referred to as WC3040-1F tablets) and approved Loestrin® 24 Fe is the method of use. The NA and EE tablets in the new product may be chewed and swallowed or swallowed whole compared to the NA and EE tablets in the Loestrin® 24 Fe product that are swallowed whole.

The proposed product consists of 24 white active tablets containing 1 mg NA and 0.02 mg EE taken daily for 24 days (chewed and swallowed) and 4 brown inactive tablets containing 75 mg Fe, and may be administered without regard to meals. With the exception of tablet debossing and insignificant manufacturing changes (as determined by the Chemistry Reviewer Ray Frankewich), the to-be-marketed NA and EE tablets are the same as the NA and EE tablets of Loestrin® 24 Fe. The active tablets are white, round, flat-faced, beveled edged tablets with "WC" debossed on one side and "535" on the other side. The Fe tablets are brown, round, flat-faced, beveledged with "WC" debossed on one side and "624" on the other side.

The sponsor is relying on the Phase 3 studies used to approve Loestrin® 24 Fe and is bridging to the original safety and efficacy data with BE study PR-08507. The basis for approval depends upon demonstrating BE for NE and EE following both methods of administration. The sponsor demonstrated BE for NE and EE in 35 healthy female subjects between the age of 18 and 35 years.

The sponsor demonstrated BE for both active moieties (NE and EE) following a single dose administration of NA and EE tablets chewed and swallowed or swallowed whole in a randomized, two-way, two treatment crossover study. For NE, the geometric mean ratio (90% CI) for Cmax, AUC_{0-t}, and AUC_{0-inf} were 1.04 (96-112%), 1.03 (98-107%), and 1.02 (97-107%). For EE, the geometric mean ratio (90% CI) for Cmax, AUC_{0-t}, and AUC_{0-inf} were 1.04 (99-108%), 1.02 (98-106%), and 0.97 (91-104%). The point estimates are near unity and the 90% CI are within the BE acceptance criteria of 80-125%.

The following figure is the arithmetic mean plasma concentration-time profile of **NE** following a single dose of NA (1 mg) and EE (0.02 mg) tablet chewed and swallowed with 8 oz water or swallowed whole with 8 oz water , N=35 (figure 14.4.2, Study PR-08507).



The following table are the PK parameters of **NE** following a single dose of NA and EE tablets (chewed and swallowed) and NA and EE tablets (swallowed whole) in healthy female subjects (N=35) (data from study PR-08507).

PK parameter*	NA and EE tablets (chewed and swallowed)	NA and EE tablets (swallowed whole)
Cmax (pg/mL)	10200 (36)	9860 (35)
Tmax (hr)	1.28 (45)	1.64 (44)
$AUC_{0\text{-}tldc}$ (pg hr/mL)	48620 (40)	46940 (38)
$AUC_{0\text{-}inf}$ (pg hr/mL)	49250 (40)	48260 (36)
Kel (1/hr)	0.0807 (23)	0.0806 (25)
$T_{1/2}$ (hr)	8.58	8.60

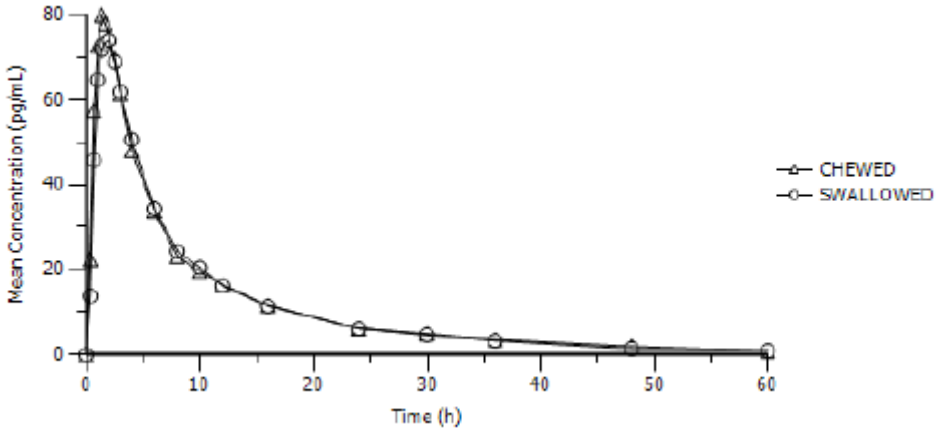
* arithmetic mean (CV%)
$AUC_{0\text{-}tldc}$: area under the plasma concentration-time curve from time 0 to time of last determinable concentration, calculated by the linear trapezoidal method

The following table is the statistical comparison of PK parameters for **NE** following a single dose of NA and EE tablets (chewed and swallowed) and NA and EE tablets (swallowed whole) in healthy female subjects (N=35) (data from study PR-08507).

PK parameter*	NA and EE tablets (chewed and swallowed)	NA and EE tablets (swallowed whole)	Geometric mean ratio (chewed and swallowed: swallowed whole)	90% Confidence Interval
Cmax	9620	9250	1.04	95.9-112.2
$AUC_{0\text{-}tldc}$	44710	43530	1.03	97.9107.3
$AUC_{0\text{-}inf}$	45350	45020	1.02	97.3106.9
Tmax**	1.0 (0.72.5)	1.7 (0.74.0)		

* geometric mean
** median (range)
$AUC_{0\text{-}tldc}$: area under the plasma concentration-time curve from time 0 to time of last determinable concentration, calculated by the linear trapezoidal method

The following figure is the arithmetic mean plasma concentration-time profile of **EE** following a single dose of NA (1 mg) and EE (0.020 mg) tablet chewed and swallowed with 8 oz water or swallowed whole with 8 oz water, N=35 (figure 14.4.1, Study PR-08507).



The following table are the PK parameters of **EE** following a single dose of NA and EE tablets (chewed and swallowed) and NA and EE tablets (swallowed whole) in healthy female subjects (N=35) (data from study PR-08507).

PK parameter*	NA and EE tablets (chewed and swallowed)	NA and EE tablets (swallowed whole)
Cmax (pg/mL)	84.7 (24)	82.0 (24)
Tmax (hr)	1.51 (26)	1.63 (33)
$AUC_{0\text{-tldc}}$ (pg hr/mL)	677.5 (33)	665.2 (32)
$AUC_{0\text{-inf}}$ (pg hr/mL)	741.6 (33)	770.8 (29)
Kel (1/hr)	0.0716 (53)	0.0585 (53)
$T_{1/2}$ (hr)	9.68	11.8

* arithmetic mean (CV%)
$AUC_{0\text{-tldc}}$: area under the plasma concentration-time curve from time 0 to time of last determinable concentration, calculated by the linear trapezoidal method

The following table is the statistical comparison of PK parameters for **EE** following a single dose of NA and EE tablets (chewed and swallowed) and NA and EE tablets (swallowed whole) in healthy female subjects (N=35) (data from study PR-08507).

PK parameter*	NA and EE tablets (chewed and swallowed)	NA and EE tablets (swallowed whole)	Geometric mean ratio (chewed and swallowed: swallowed whole)	90% Confidence Interval
Cmax	82.5	79.7	1.04	98.9108.4
$AUC_{0\text{-tldc}}$	645.0	633.6	1.02	97.6106.0
$AUC_{0\text{-inf}}$	703.8	739.1	0.97	91.5103.5
Tmax**	1.3 (1.02.5)	1.7 (0.73.0)		

* geometric mean
** median (range)
$AUC_{0\text{-tldc}}$: area under the plasma concentration-time curve from time 0 to time of last determinable concentration, calculated by the linear trapezoidal method

(b) (4)

2.8.2 What is the effect of food on the BA of the drug from the dosage form? What dosing recommendation should be made, if any, regarding administration of the product in relation to meals or meal types?

Based upon the Loestrin® 24 Fe labeling, tablets may be administered without regard to meals. A single dose administration of Loestrin 24 Fe tablet with food decreased the maximum concentration of NE by 11% and increased the extent of absorption by 27% and decreased the maximum concentration of EE by 30% but not the extent of absorption. No dose adjustment or meal restrictions are recommended. The NA and EE tablets are to be taken without regard to meals.

2.9 ANALYTICAL SECTION

2.9.1 What bioanalytical methods are used to assess drug concentrations? Briefly describe the methods and summarize the assay performance.

The bioanalytical laboratory was (b) (4) (b) (4) Plasma samples were analyzed for NE and EE by using a validated gas chromatographic method with mass spectrometric detection (GC/MS). A combination method for the simultaneous determination of EE and NE in human plasma samples was utilized. For sample work-up, the analytes were extracted from plasma into toluene. Extraction was followed by several clean-up steps, resulting in a final dichloromethane extract. (b) (4)

2.9.2 Which metabolites have been selected for analysis and why?

NE and EE were measured. NE is the active form the acetate salt of NA.

2.9.3 What is the range of the standard curve? How does it relate to the requirements for clinical studies? What curve fitting techniques were used?

The concentration range for the NE standard curve was 25 to 25000 pg/mL (sponsor's table 11 of bioanalytical report, study PR-08507).

Cal. std. nominal conc. [pg/mL]	25.0	50.0	250	1000	5000	12500	22500	25000
Number	29	29	29	28	29	29	29	28
Mean (calc.)	24.6	51.2	258	1030	5060	12300	21700	24200
sd	1.10	4.31	14.1	40.9	232	399	1320	1440
cv (%)	(b) (4)							
bias (%)								

The accuracy and precision for NE quality control samples (sponsor's table 13 of bioanalytical report, study PR-08507).

Nominal QC conc. [pg/mL]	75.0	2500	20000	20000 (DF2)[10]
Number	57	57	56	6
Mean (calc.)	77.7	2620	19800	20100
sd	7.24	145	1340	1040
cv (%)	(b) (4)			
bias (%)				

The concentration range for the EE standard curve was 2.5 to 250 pg/mL (sponsor's table 10 of bioanalytical report, study PR-08507).

Cal. std. nominal conc. [pg/mL]	2.50	5.00	15.0	50.0	75.0	125	225	250
Number	29	28	29	29	28	29	29	28
Mean (calc.)	2.54	4.95	14.2	49.3	74.2	128	230	257
sd	0.0889	0.388	0.905	2.11	3.05	4.58	8.23	10.6
cv (%)	(b) (4)							
Bias (%)								

The accuracy and precision for EE quality control samples (sponsor's table 12 of bioanalytical report, study PR-08507).

Nominal QC conc. [pg/mL]	7.50	30.0	200	200 (DF2)[1]
Number	56	57	57	6
Mean (calc.)	7.27	30.0	208	193
sd	0.810	1.74	9.84	8.54
cv (%)	(b) (4)			
bias (%)				

The following is the statistics on EE and NE regression parameters (sponsor's table 9 of bioanalytical report, study PR-08507).

Analyte	Ethinyl estradiol			Norethindrone		
	Intercept	Slope	r^2	Intercept	Slope	r^2
Number	29	29	29	29	29	29
Mean	-0.00161	0.01743	0.99571	0.00158	0.00034	0.99511
sd	0.01184	0.00109	0.00279	0.00134	0.00002	0.00362
cv (%)	(b) (4)					

2.9.4 What are the lower and upper limits of quantification (LLOQ/ULOQ)? What are the accuracy, precision and selectivity at these limits?

For NE, the lower and upper quantification limits were 25.0 and 25,000 pg/mL, respectively. For EE, the lower and upper quantification limits were 2.50 and 250 pg/mL, respectively.

Summary on the Study Performance		
Parameter	**Ethinyl estradiol**	**Norethindrone**
Calibrated Range	2.50 – 250 pg/mL	25.0 – 25000 pg/mL
Defined LLOQ	2.50 pg/mL	25.0 pg/mL
Overall linearity (mean r^2 of the standard curves)	0.99571	0.99511
Overall accuracy [bias %] (lowest QC sample) (QC 7.50 / 75.0 pg/mL)	-3.06	3.55
Overall precision [cv %] (lowest QC sample) (QC 7.50 / 75.0 pg/mL)	11.15	9.32

The bioanalytical method used for the measurement of NE and EE are acceptable.

3 LABELING RECOMMENDATIONS

Detailed labeling recommendations will be incorporated into DRUP's proposed label.

The Clinical Pharmacology relevant edits to the proposed label include the following:

(1) Under Section 2 Dosage and Administration and Section 17 Patient Counseling Information, replace the word (b) (4) with "water".
(2) Under Section 2 Dosage and Administration and Section 17 Patient Counseling Information, remove (b) (4).
(3) Update Section 7 Drug Interactions to align with current COC labels.
(4) Under Section 12.3 Pharmacokinetics, add the following statement "In a single-dose, two-way crossover clinical study conducted in 35 healthy, non-smoking premenopausal women under fasted condition. Norethindrone acetate and ethinyl estradiol tablet chewed and swallowed was bioequivalent to norethindrone acetate and ethinyl estradiol tablet swallowed whole (Loestrin 24 Fe) based on the exposure (AUC) and peak concentration (Cmax) of norethindrone and ethinyl estradiol." to show that the new method of administration (chewed and swallowed) is bioequivalent to approved method (swallowed whole) for Loestrin 24 Fe.
(5) Under Section 12.3 Pharmacokinetics, remove (b) (4).
(6) Under Section 12.3 Pharmacokinetics, add single-dose PK data and profile for NA and EE tablets chewed and swallowed.

4. Appendix

4.1 Individual Study Review

Study PR-08507 (Report RR-00508.1)

Title: "A study to assess the comparative bioavailability of ethinyl estradiol and norethindrone following oral administration of a WC2061 tablet chewed as compared to a WC2061 tablet intact in healthy female volunteers"

Objectives: To examine the bioavailability of NE and EE following oral administration of NA and EE tablets (chewed and swallowed) and NA and EE tablets (swallowed whole) in healthy female subjects.

Methods: This study was a single center, randomized, balance, single dose, two-treatment, 2-period, 2-sequence, crossover study in healthy young female subjects. The median age of subjects was 25 yrs (range 19 to 35 yrs) and median weight was 60.0 kg (range 49.3 to 80.3). All forty subjects received one white NA 1 mg and EE 0.02 mg tablet (Loestrin 24 Tablet) with 240 mL of water in each of the two treatment periods after an overnight fast of at least 10 hrs. In one treatment period, subjects chewed and swallowed the tablet. In the other treatment period, subjects swallowed the tablet whole. Subjects remained at the clinic for 36 hours after dosing during the blood sampling period and returned to the clinic for the 48 and 60 hr blood draws.

Of the 40 healthy, young women enrolled, 38 completed the study. Of the two subjects who did not complete the study, one subject withdrew consent prior to Period 2 dosing for personal reasons and one subject was withdrawn from the study for protocol non-compliance (a positive serum pregnancy test prior to Period 2 dosing). There were 35 evaluable subjects included in the pharmacokinetic analysis. One subject with quantifiable predose EE and NE concentrations was excluded from the pharmacokinetic evaluation as per protocol, and the EE and NE concentration data for 2 subjects were excluded from evaluation as the bioanalytical run was rejected due to QCs failing to meet specifications (see below: bioanalytical site inspection).

Pharmacokinetic Sampling: Blood samples were collected for determination of EE and NE plasma concentrations 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 hrs post-dosing. The applicant used a validated gas chromatographic method with mass spectrometric detection (GC/MS). The clinical study was conducted at Cedra Clinical Research, LLC, Austin, TX. The bioanalytical laboratory was (b) (4)

Clinical and Bioanalytical Site Inspections
An inspection of the clinical and bioanalytical sites was submitted to the OSI, Division of Bioequivalence and GLP Compliance (DBGLPC) on September 4, 2012 by this reviewer. An inspection of the clinical site CEDRA was conducted from (b) (4) when the product was reviewed at the first submission. According to the OSI report, there were five protocol violations identified, but none had any impact on the study outcomes, and no FORM FDA 483 was issued (see DARRTS March 31, 2008). OSI DBGLPC conducted an audit of the bioanalytical site at (b) (4) under the current NDA submission. The report of the inspection findings is in DARRTS Dec. 14, 2012. A number of issues were identified as follows:

Inspection Issue #1
Inspection Finding and OSI recommendation: Not all of the chromatograms of Quality Control (QC) samples were evaluated consistently in Sequence 3. The Internal Standard (IS) peak areas of 3 of 6 QC samples were less than the demonstrated linear range of their paired analytes. Although rechromatography of extracts confirmed the low IS areas, these chromatograms were used to accept data from Sequence 3 (Subjects 206 and 207). Because the IS peak areas were less than the smallest areas of analytes for which accuracy was demonstrated, under the same conditions, the IS peak areas could not be quantified accurately. The DBGLPC reviewer believes that data from Sequence 3 should have been rejected and the samples from Subjects 206 and 207 should have been reassayed.

Clinical Pharmacology's Request Sent to the Sponsor on January 15, 2013: Reassay the samples from Subjects 206 and 207, and incorporate the data into a revised study report. If sponsor cannot reassay the samples, remove data from Subjects 206 and 207 from the study analysis and submit the revised report.

Sponsor's Response Dated February 15, 2013: The data from Subjects 206 and 207 was removed and the pharmacokinetic analysis was repeated using a new SAS dataset. Study Report RR-00508.0, inclusive of a revised bioanalytical report (CR-00408.1) in Appendix 16.1.11.2, was amended to Study Report RR-00508.1 and is herein provided in Section 5.3.1.2.

Inspection Issue #2
Inspection Finding and OSI recommendation: The Lower Limit of Quantitation (LLOQ, 2.5 pg/mL for ethinyl estradiol and 25 pg/mL for norethindrone) calibrator in Sequence 17 failed to meet the acceptance criteria. The analyst rechromatographed the comparable calibrator extract from Sequence 14, and substituted its values into the Sequence 17 calculations.

Clinical Pharmacology's Request to the Sponsor: Replace the original data for Subjects 229 and 230 with the recalculated data from (b) (4) and provide an amended study report.

Test Treatment
A single Loestrin 24 Tablet (WC2061) containing NA and EE administered orally and chewed and swallowed. Batch #02017F manufactured by Warner Chilcott, Fajardo, Puerto Rico.

Reference Treatment
A single Loestrin 24 Tablet (WC2061) containing NA and EE administered orally and swallowed whole. Batch #02017F manufactured by Warner Chilcott, Fajardo, Puerto Rico.

Results and Reviewer's Comments: The following results are based upon the results of the new report with 2 subjects (#206 and #207) removed from the study analysis and recalculated data from 2 subjects (#229 and #230).

The NA and EE tablets have the same components, composition, doses, and dosing regimen as the NA and EE tablets of Loestrin® 24 Fe. The difference between the new product WC3040 and approved Loestrin® 24 Fe is the method of use. The NA and EE tablets in the new product may be chewed and swallowed or swallowed whole compared to the NA and EE tablets in the Loestrin® 24 Fe product that are swallowed whole.

The sponsor is relying on the Phase 3 studies used to approve Loestrin® 24 Fe and is bridging to the original safety and efficacy data with BE study PR-08507. The basis for approval depends

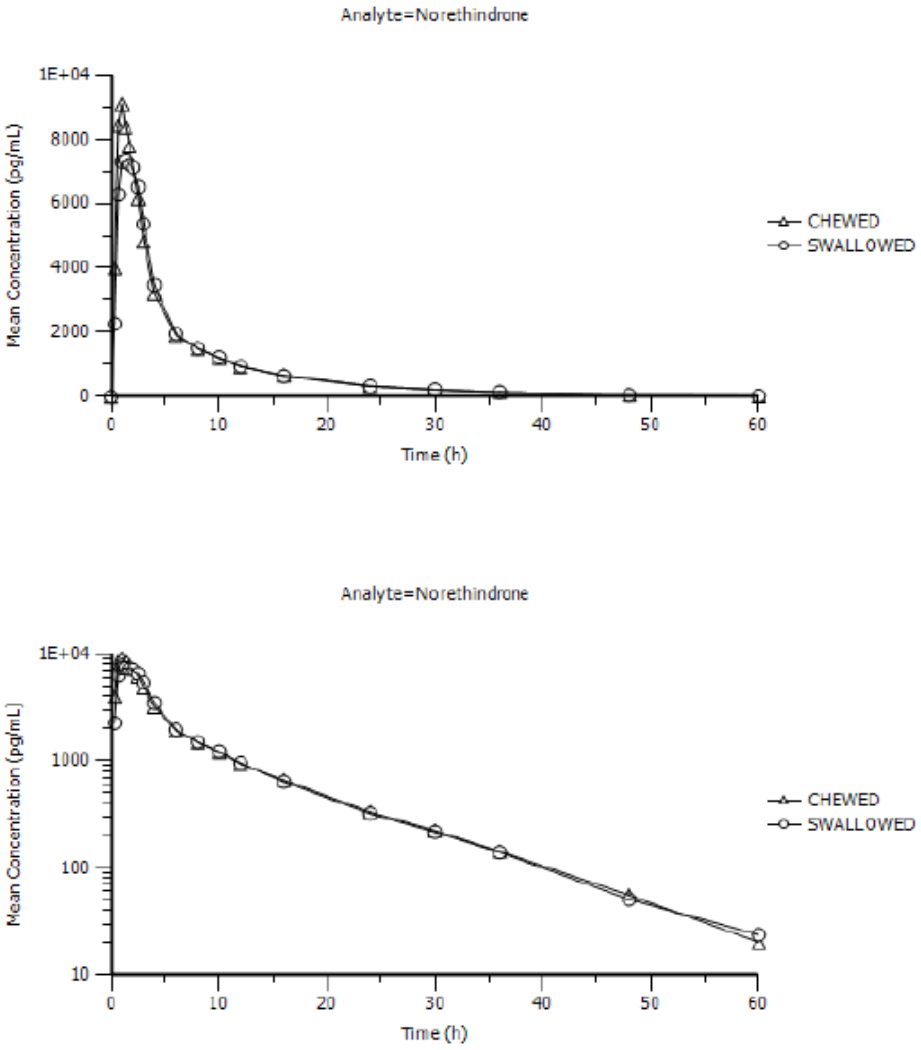
upon demonstrating BE for NE and EE following both methods of administration. The sponsor demonstrated BE for NE and EE in 35 healthy female subjects between the age of 18 and 35 years.

Bioequivalence
The sponsor demonstrated BE for both active moieties (NE and EE) following a single dose administration of NA and EE tablets chewed and swallowed or swallowed whole in a randomized, two-way, two treatment crossover study. For NE, the geometric mean ratio (90% CI) for Cmax, AUC_{0-t}, and AUC_{0-inf} were 1.04 (96-112%), 1.03 (98-107%), and 1.02 (97-107%). For EE, the geometric mean ratio (90% CI) for Cmax, AUC_{0-t}, and AUC_{0-inf} were 1.04 (99-108%), 1.02 (98-106%), and 0.97 (91-104%). The point estimates are near unity and the 90% CI are within the BE acceptance criteria of 80-125%.

Safety
The number of adverse events (AEs) (12 in chewed and swallowed group; 9 in swallowed whole group) and number of subjects (6/39 chewed and swallow group; 6/39 in swallowed whole group) who experienced an AE are similar irrespective of the method of administration.

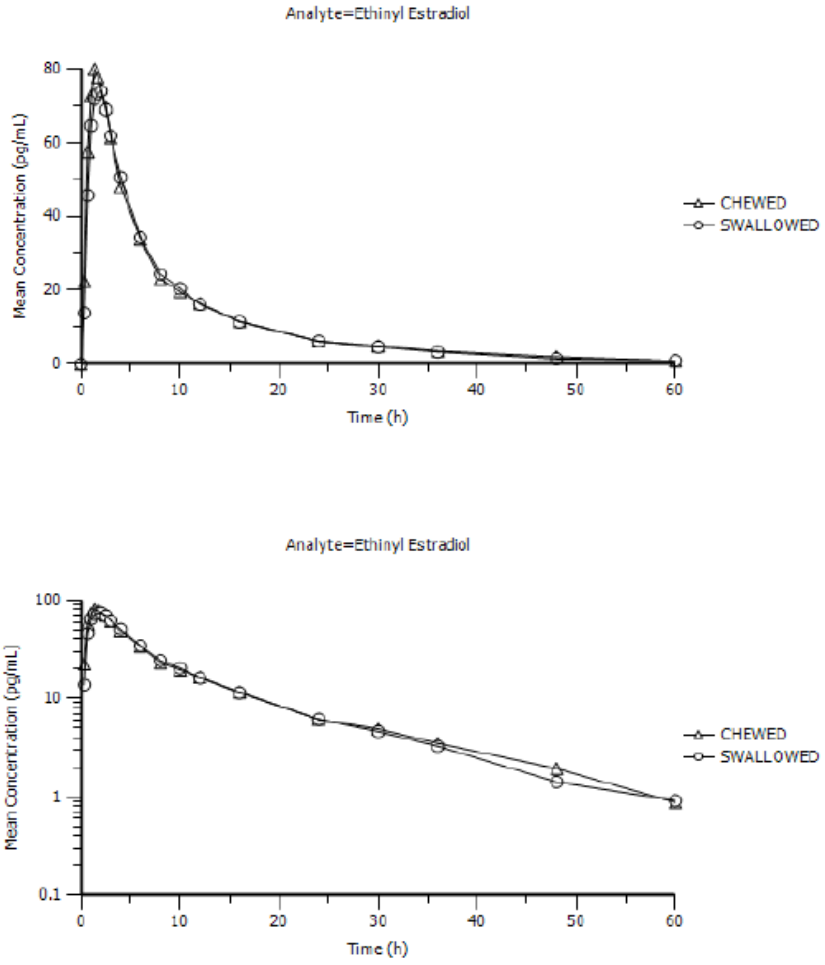
The following figure is the concentration vs. time profile for **NE** following a single dose of NA and EE tablet (chewed and swallowed with 8 oz of water) and a single dose of NA and EE tablet from Loestrin® 24 Fe (swallowed whole with 8 oz of water) (sponsor's figure 14.4.2).

Figure 14.4.2 **Mean Norethindrone Concentration-Time Profiles for Loestrin 24 (Treatment A, Chewed) and Loestrin 24 (Treatment B, Swallowed) on Linear and Semi-Logarithmic Scales**



The following figure is the concentration vs. time profile for **EE** following a single dose of NA and EE tablet (chewed and swallowed with 8 oz of water) and a single dose of NA and EE tablet from Loestrin® 24 Fe (swallowed whole with 8 oz water) (sponsor's figure 14.4.1).

Figure 14.4.1 Mean Ethinyl Estradiol Concentration-Time Profiles for Loestrin 24 (Treatment A, Chewed) and Loestrin 24 (Treatment B, Swallowed) on Linear and Semi-Logarithmic Scales



Text Table 6. Norethindrone Pharmacokinetic Parameter Values Following Administration of Loestrin 24 Tablet Chewed (Treatment A, Test) and Swallowed (Treatment B, Reference) to Healthy Female Volunteers, Study PR-08507 (n=35)

Parameter	Geometric Mean or [Median (Range)]		Ratio (Test : Ref)	90% Confidence Interval
	Loestrin 24 Tablet Chewed, Treatment A (Test)	Loestrin 24 Tablet Swallowed, Treatment B (Reference)		
Cmax	9620	9250	103.72%	95.87 – 112.22
AUC0–tldc	44710	43530	102.52%	97.91 – 107.34
AUCinf	45350	45020	101.99%	97.28 – 106.93
tmax	[1.03 (0.67 – 2.50)]	[1.67 (0.67 – 4.00)]	--	--
	Arithmetic Mean (%CV) or [Harmonic Mean]			
Cmax	10200 (36)	9860 (35)		
tmax	1.28 (45)	1.64 (44)		
AUC0–tldc	48620 (40)	46940 (38)		
AUCinf	49250 (40)	48260 (36)		
kel	0.0807 (23)	0.0806 (25)		
t½	[8.58]	[8.60]		

Text Table 5. Ethinyl Estradiol Pharmacokinetic Parameter Values Following Administration of Loestrin 24 Tablet Chewed (Treatment A, Test) and Swallowed (Treatment B, Reference) to Healthy Female Volunteers, Study PR-08507 (n=35)

Parameter	Geometric Mean or [Median (Range)]		Ratio (Test : Ref)	90% Confidence Interval
	Loestrin 24 ablet Chewed, Treatment A (Test)	Loestrin 24 Tablet Swallowed, Treatment B (Reference)		
Cmax	82.5	79.7	103.55%	98.94 – 108.38
AUC0–tldc	645.0	633.6	101.74%	97.61 – 106.04
AUCinf	703.8	739.1	97.32%	91.49 – 103.52
tmax	[1.33 (1.00 – 2.50)]	[1.67 (0.69 – 3.00)]	--	--
	Arithmetic Mean (%CV) or [Harmonic Mean]			
Cmax	84.7 (24)	82.0 (24)		
tmax	1.51 (26)	1.63 (33)		
AUC0–tldc	677.5 (33)	665.2 (32)		
AUCinf	741.6 (33)	770.8 (29)		
kel	0.0716 (53)	0.0585 (53)		
t½	[9.68]	[11.8]		

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 (pg·h/mL)
tmax = time of the maximum measured plasma concentration (h)
kel = Terminal phase rate constant (1/h)
t½ = Terminal phase half-life (h)
Source data: Table 14.2.2.1, Table 14.2.2.2 and Table 14.2.3.1

14.3 Safety Data Summary Tables

Table 14.3.1 Summary of Adverse Events by Treatment

	Treatment A (N=39)		Treatment B (N=39)	
Number of Treatment-Emergent Adverse Events Reported	12		9	
Number of Subjects Reporting One or More Events (Percent of Subjects)	6 (15%)		6 (15%)	
Adverse Event	**Subject**	**Event**	**Subject**	**Event**
Constipation	0 (0%)	0 (0%)	1 (3%)	1 (11%)
Cystisis	0 (0%)	0 (0%)	1 (3%)	1 (11%)
Dizziness	1 (3%)	1 (8%)	0 (0%)	0 (0%)
Early Menstrual Period	0 (0%)	0 (0%)	2 (5%)	2 (22%)
Emesis	0 (0%)	0 (0%)	1 (3%)	1 (11%)
Feeling hot	1 (3%)	1 (8%)	0 (0%)	0 (0%)
Headache	3 (8%)	3 (25%)	1 (3%)	1 (11%)
Intermittent Emesis	1 (3%)	1 (8%)	0 (0%)	0 (0%)
Menstrual spotting	1 (3%)	1 (8%)	1 (3%)	1 (11%)
Nasal Congestion	0 (0%)	0 (0%)	1 (3%)	1 (11%)
Nausea	4 (10%)	4 (33%)	0 (0%)	0 (0%)
Stomach cramps	0 (0%)	0 (0%)	1 (3%)	1 (11%)
Vasovagal Reaction	1 (3%)	1 (8%)	0 (0%)	0 (0%)

Treatment A: Tablet Chewed and Swallowed
Treatment B: Tablet Swallowed Whole

2 Page(s) has been Withheld in Full as b4 (CCI/TS) immediately following this page

---

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

/s/

LAI M LEE
04/09/2013

MYONG JIN KIM
04/09/2013