

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**21-871**

**CLINICAL PHARMACOLOGY AND  
BIOPHARMACEUTICS REVIEW(S)**

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**Clinical Pharmacology Review**  
**Division of Clinical Pharmacology 3**

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**NDA:** 21-871

**Brand Name:** Loestrin® 24 Fe

**Generic Name:** Norethindrone Acetate (NETA) and Ethinyl Estradiol (EE) tablets, USP and Ferrous Fumarate tablets

**Sponsor:** Warner Chilcott Company, Inc.

**Relevant IND(s):** 64,817

**Relevant NDA(s):** 17-354, 17-876

**Date(s) of Submission:** April 18, 2005

**Type of Submission:** 3S, Original NDA

**Formulation:** Tablet

**Strength:** NETA 1 mg, EE 20 mcg, Ferrous Fumarate 75 mg

**Indication:** Prevention of Pregnancy

**Reviewer:** Myong-Jin Kim, Pharm.D.

**Team Leader:** Ameeta Parekh, Ph.D.

**OCP Division:** Division of Clinical Pharmacology 3

**OND Division:** Reproductive & Urologic Products

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## 1. Executive Summary

Loestrin® 24 Fe (hereafter called Loestrin) is a new monophasic combination oral contraceptive (COC) containing 1 mg norethindrone acetate (NETA) and 20 mcg ethinyl estradiol (EE). Loestrin provides a dosing regimen consisting of 24 oral contraceptive (OC) tablets and 4 ferrous fumarate tablets. The proposed indication is the prevention of pregnancy in women who elect to use OC as a method of contraception.

Loestrin tablets are the same tablets marketed under approved NDA 17-354 (approval, April 30, 1973) for Loestrin Fe 1/20 and under approved NDA 17-876 (approval, October 1, 1976) for Loestrin 1/20. Loestrin Fe 1/20 and Loestrin 1/20 (1 mg NETA/ 20 mcg EE tablets) differ from Loestrin in that administration is comprised of 21 OC tablets and 7 ferrous fumarate tablets (Loestrin Fe 1/20) or one week of no tablets (Loestrin 1/20). The active tablets and the ferrous fumarate tablets of Loestrin are manufactured at the Warner Chilcott's plant in Fajardo, Puerto Rico under a process identical to that approved under NDA 17-354 and NDA 17-876.

In support of this new NDA, the sponsor submitted the efficacy and safety results of a Phase 3, multi-center, randomized, open-label study (Study PR-03903) of Loestrin and Loestrin Fe 1/20 as the active comparator. In addition, two pharmacokinetic (PK) bioavailability studies consisting of a multiple-dose study (Study PR-01804) and a food effect study (Study PR-01904) were submitted. The sponsor proposed a 24-day regimen of Loestrin to decrease the frequency of spotting in women using this product by extending the duration of active treatment from 21 to 24 days. The results of Study PR-03903 showed that there were 5 pregnancies with Loestrin (Pearl Index, PI, of 1.82, 95% CI, 0.59 - 4.25, where PI is defined as the number of pregnancies per 100 women-years of use). The mean intracyclic bleeding/spotting days (Cycles 2 – 6) for Loestrin and Loestrin Fe 1/20 were 6.31 and 7.31, respectively ( $P = 0.311$ ).

### 1.1 Recommendation

The Office of Clinical Pharmacology / Division of Clinical Pharmacology 3 (OCP/DCP-3) has reviewed NDA 21-871 submitted on April 18, 2005. The overall Human Pharmacokinetic Section is *acceptable*. Labeling comments outlined in the Clinical Pharmacology section and the drug-drug interactions have been accepted by the sponsor.

### 1.2 Phase IV Commitments

None.

### 1.3 Summary of Clinical Pharmacology Findings

Ethinyl estradiol (EE) and norethindrone (NE) were rapidly absorbed following oral administration of Loestrin tablets. The mean  $C_{max}$  values of EE and NE following a single dose administration were 64.5 pg/mL (%CV, 27 %) and 8,420 pg/mL (%CV, 31%), respectively, with a mean  $T_{max}$  of 1.0 – 1.3 hours (range, 0.7 – 4.0 hours).

#### Multiple-dose PK of Loestrin

- Mean  $AUC_{24}$  values of EE and NE were increased by 51% and 164%, respectively, following multiple-dose administration of Loestrin tablets as compared to single-dose administration.

- Mean  $C_{max}$  values of EE and NE were increased by approximately 27% and 95%, respectively, following multiple-dose administration of Loestrin tablets as compared to single-dose administration.
- Sex hormone binding globulin (SHBG) concentrations were increased by 150% following 24 days daily dosing of Loestrin tablets as compared to baseline.

### Effect of Food

- A single-dose administration of Loestrin tablet with food decreased the rate but not the extent of EE absorption, and decreased the rate and increased the extent of NE absorption.
- Following a single dose administration of Loestrin tablet, the mean NE and EE  $C_{max}$  values were 11% and 30% lower, respectively, under the fed condition. The mean NE and EE  $AUC_{last}$  values were 27% and 2% higher, respectively, under the fed condition.

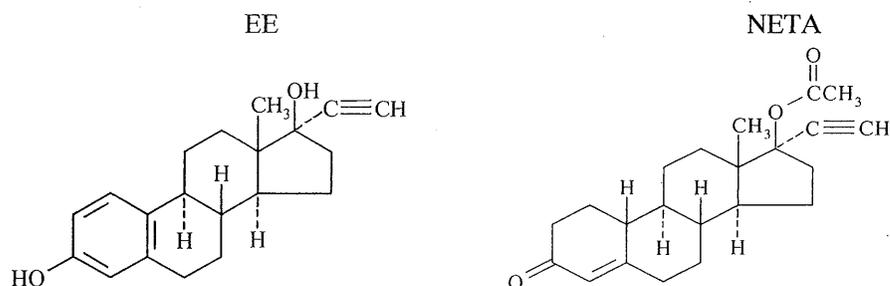
## 2. Question-Based Review

### 2.1 General Attributes

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

#### Physico-chemical properties

- Structural formula:



- Molecular Weight: 340.46 (NETA), 296.40 (EE)
- Molecular Formula:  $C_{22}H_{28}O_3$  (NETA),  $C_{20}H_{24}O_2$  (EE)
- Chemical Name: 19-norpregn-4-en-20-yn-3-one, 17-(acetyloxy)-, (17 $\alpha$ ) (NETA), 19-norpregna-1,3,5(10)-trien-20-yne-3,17-diol, (17 $\alpha$ ) (EE)

### Drug Formulation

The drug formulation of Loestrin tablets is identical to Loestrin 1/20 tablets. Each tablet contains 1 mg NETA and 20 mcg EE.

Component	Theoretical Amount Per Tablet (mg)
Norethindrone Acetate, USP	1.00
Ethinyl Ferrous Fumarate, USP	0.02
Acacia	—
Lactose	—
Magnesium Stearate, NF <sup>1</sup>	—
Starch	—
Confectioner Sugar, NF	—
Talc	—
—	—
—	—
—	—
<b>TOTAL</b>	—

<sup>1</sup> Certified BSE free  
<sup>2</sup> Removed during processing

**What are the proposed indication, dosage and route of administration?**

Loestrin is a new monophasic COC containing 1 mg NETA and 20 mcg EE. Loestrin provides a dosing regimen consisting of 24 OC tablets and 4 ferrous fumarate tablets. Ferrous fumarate tablets are present to facilitate ease of drug administration via a 28-day regimen, are non-hormonal, and do not serve any therapeutic purpose. The proposed indication is the prevention of pregnancy in women who elect to use OC as a method of contraception.

**2.2 General Clinical Pharmacology**

COCs 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).

**What is the effect of food on the rate and extent of EE and NE absorption following a single-dose administration of Loestrin tablet?**

A single-dose administration of Loestrin tablet with food decreased the rate but not the extent of EE absorption, and decreased the rate and increased the extent of NE absorption.

Table 1. PK parameters of NE and EE following a single dose administration of Loestrin tablet under the fed and fasted conditions (n=16).

Analyte	Parameter	Geometric Mean			90% CI
		Fed State (Test)	Fasted State (Reference)	Ratio (Test: Ref)	
NE	C <sub>max</sub> (pg/mL)	7800	8740	89.20	74.5 - 106.8
	AUC <sub>last</sub> (pg/mL*hr)	44920	35350	127.07	109.4 - 147.6
	AUC <sub>inf</sub> (pg/mL*hr)	46020	36540	125.93	108.5 - 146.2
	t <sub>max</sub> (hr)	1.83	1.51	--	--
EE	C <sub>max</sub> (pg/mL)	45.1	64.6	69.82	59.4 - 82.0
	AUC <sub>last</sub> (pg/mL*hr)	508.0	498.2	101.96	94.6 - 109.9
	AUC <sub>inf</sub> (pg/mL*hr)	571.4	548.8	104.12	96.3 - 112.6
	t <sub>max</sub> (hr)	2.50	1.53	--	--

- **EE:** The 90% CIs of the ratios of the geometric means for  $AUC_{last}$  (101.96%) and  $AUC_{inf}$  (104.12%) were within 80 – 125%. The geometric mean for  $C_{max}$  and the lower limit of the 90% CI of the ratio of the geometric mean for  $C_{max}$  (69.82%) were outside of 80 – 125%.
- **NE:** The geometric means for  $AUC_{last}$  (127.07%) and  $AUC_{inf}$  (125.93%), and the upper limits of the 90% CIs were outside of 80 – 125%. The lower limit of the 90% CI of the ratio of the geometric mean for  $C_{max}$  (89.20%) was outside of 80 – 125%.
- Following a single dose administration of Loestrin tablet, the mean NE and EE  $C_{max}$  values were 11% and 30% lower, respectively, under the fed condition. The mean NE and EE  $AUC_{last}$  values were 27% and 2% higher, respectively, under the fed condition.

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

Table 2. PK parameters of EE and NE following single- and multiple-dose oral administration of Loestrin tablets in 17 healthy premenopausal female subjects

Regimen	Analyte	Arithmetic Mean <sup>a</sup> (%CV) by Pharmacokinetic Parameter						
		$C_{max}$	$t_{max}$	$AUC(0-24)$	$t_{1/2}$	$C_{avg}$	$C_{min}$	Fluctuation
Dose 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) <sup>b</sup>	
Dose 24 (Multiple Dose)	NE	16400 (26)	1.3 (0.7-4.0)	88180 (30)	8.4	3670 (30)	880 (51)	441.4 (28)
	EE	81.9 (24)	1.67 (1.0-2.0)	701.3 (28)	14.4	29.2 (28)	11.4 (43)	247.1 (19)
	SHBG	--	--	--	--	--	144 (24)	

$C_{max}$  = pg/mL;  $T_{max}$  = hr;  $AUC_{24}$  = pg/mL\*hr;  $t_{1/2}$  = hr;  $C_{avg}$  =  $AUC_{24}/24$ , pg/mL;  $C_{min}$  = pg/mL; SHBG = nmol/L;  $C_{min}$  for SHBG = pre-dose concentration.

- EE and NE  $AUC_{24}$  values increased by 51% and 164%, respectively, following multiple-dose administration of Loestrin tablets as compared to single-dose administration.
- EE and NE  $C_{max}$  concentrations increased by 27% and 95%, respectively, following multiple-dose administration of Loestrin tablets as compared to single-dose administration.

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Figure 1. Mean plasma EE concentration versus time curves following single- and multiple-dose oral administration of Loestrin tablets in 17 healthy female subjects

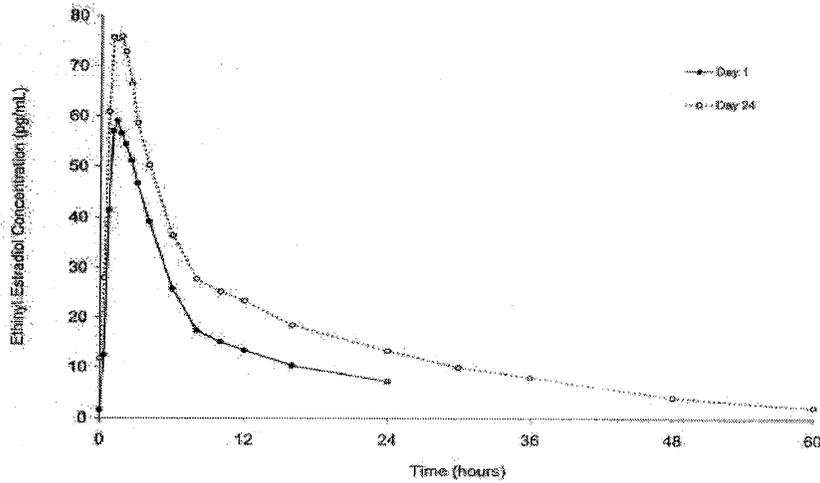
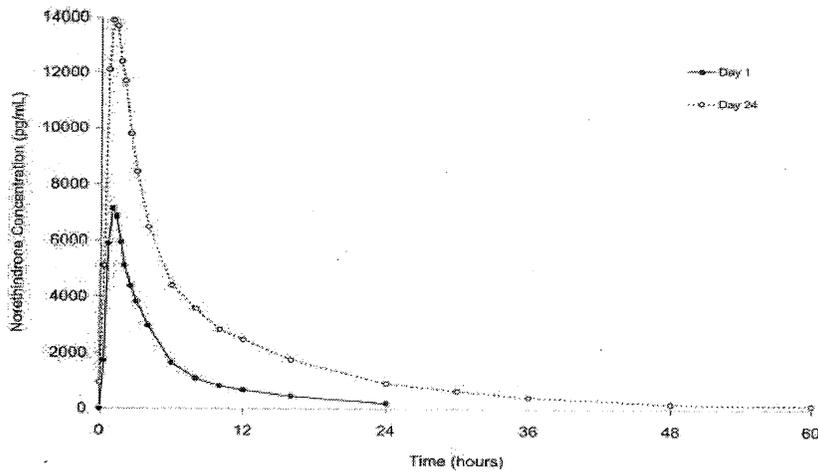


Figure 2. Mean plasma NE concentration versus time curves following single- and multiple-dose oral administration of Loestrin tablets in 17 healthy female subjects



### Sex Hormone Binding Globulin (SHBG):

SHBG concentrations increased during multiple daily doses of Loestrin. Mean SHBG concentrations were increased by 150% from baseline (57.5 nmol/L) to 144 nmol/L on Day 24.

### 2.3 Intrinsic Factors

Not Applicable.

### 2.4 Extrinsic Factors

Not Applicable.

## 2.5 General Biopharmaceutics

### What are the differences between the clinical and the to-be-marketed formulations?

Loestrin clinical study supplies were taken from commercial batches of Loestrin 1/20. Therefore, the clinical trial formulation is identical to the to-be-marketed formulation.

## 2.6 Analytical

Plasma EE and NE concentrations were determined by ~~\_\_\_\_\_~~ using a validated LC/MS-MS with lower limits of quantitation of 50 pg/mL for NE and 2.00 pg/mL for EE. Serum SHBG concentrations were determined by a validated immunoradiometric assay method with a lower limit of quantitation of 5 nmol/L.

	EE	NE	SHBG
Type of Biological Fluid	Plasma	Plasma	Serum
Range of Standard Curve	2.00 – 500 pg/mL	50.0 – 25,000 pg/mL	5.00 – 320 nmol/L
Limit of Detection	2.00 pg/mL	50.0 pgm/mL	5.00 nmol/L
QC Sample Precision	4.55 % to 11.4 %	5.20 % to 14.1 %	7.35 % to 9.63%
QC Sample Accuracy	- 1.40 % to 3.33 %	- 6.61 % to - 5.15 %	0.0547 % to 3.08 %
Linearity	0.9990	0.9984	0.9998
Recovery	79.5 % to 94.9 %	81.0 % to 88.5 %	
Stability	24 hrs at room temperature for 3 freeze-thaw cycles, 29 hrs at 0 - 5°C	24 hrs at room temperature for 3 freeze-thaw cycles, 29 hrs at 0 - 5°C	at least 337 days at - 20°C, 5 freeze-taw cycles

## Dissolution Method and Specification

The sponsor proposed the following dissolution specification of Loestrin tablets based on the specification of already approved Loestrin FE 1/20 and Loestrin 1/20 products:

Dosage Form	Loestrin-24 tablets
Strength	1 mg norethindrone acetate, 20 mcg ethinyl estradiol
Apparatus	
Media	
Volume	
Sampling Time	
Analytical Method	
Number of Tablets	
Specification	
Method	

However, the Division requested the sponsor to re-establish the dissolution specification based on the current batch analysis data (Teleconference Minutes, March 17, 2004). The following dissolution specification of Loestrin tablets was accepted by the sponsor (Teleconference, February 1, 2006):

Dissolution	Meet the requirements of USP <711> Not less than —(Q) in 30 minutes for NA. Not less than —(Q) in 30 minutes for EE
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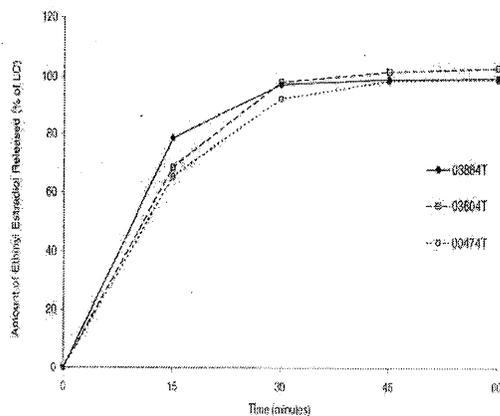
Table 3. Summary of dissolution data of Loestrin (Loestrin 1/20) tablets

Analyte	Loestrin-24 Bulk Tablets Batch Number	Stability Lot Number	Mean Amount Dissolved (%Label Claim) by Sample Time (minutes)			
			15	30	45	60
NETA	00474T	80114F1	65.5 (13.7)	92.0 (7.6)	98.6 (4.0)	99.3 (3.8)
	03604T	80114F2	67.0 (9.4)	94.6 (4.5)	98.6 (1.6)	99.5 (1.5)
	03884T	80114F3	78.0 (6.3)	95.1 (3.1)	96.9 (2.6)	97.0 (2.4)
EE	00474T	80114F1	65.3 (12.7)	92.2 (7.0)	98.3 (3.4)	98.6 (2.9)
	03604T	80114F2	68.4 (7.8)	98.0 (9.1)	101.6 (7.0)	102.7 (8.5)
	03884T	80114F3	78.6 (6.3)	97.2 (3.5)	98.9 (3.1)	99.1 (3.1)

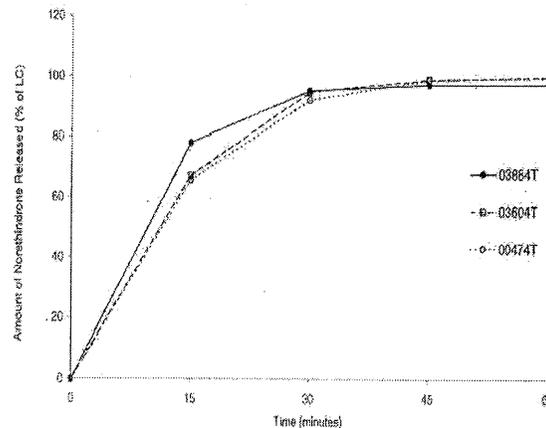
Dissolution Test Parameters: Apparatus 2 (paddle), 75 rpm; 600 mL medium, n=12 tablets

Figure 3. Dissolution Profiles of EE and NE

a) EE



b) NE



### 3. Detailed Labeling Recommendations

#### CLINICAL PHARMACOLOGY

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).

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       Trade Secret / Confidential

✓ Draft Labeling

       Deliberative Process

### **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 ethinyl estradiol increase AUC values for ethinyl estradiol by approximately 20%. Ascorbic acid and acetaminophen may increase plasma ethinyl estradiol levels, possibly by inhibition of conjugation. CYP3A4 inhibitors such as itraconazole or ketoconazole may increase plasma hormone levels.

#### **Changes in plasma levels of co-administered drugs:**

Combination 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.

## **4. Appendices**

### **4.1 Individual Study Reviews**

*Study PR-01804: A Study to Examine the Bioavailability of EE and NE following Multiple-Dose Administration of WC2061 (Loestrin) Tablets, PR-01804.1*

A single-center, multiple-dose, pharmacokinetic study was conducted in 18 healthy non-pregnant female subjects aged 18 – 35 years to characterize the PK profiles of EE and NE, and SHBG concentrations following multiple-dose administration of Loestrin tablets. Subjects received one Loestrin tablet once daily for 24 consecutive days. The first dose of study medication was in the first 7 days of the menstrual cycle. Doses 1 and 24 were administered after a supervised overnight fast. Serial blood samples were collected for plasma EE and NE concentrations during the 24 hours (pre-dose, 0.33, 0.67, 1, 1.33, 1.67, 2, 2.5, 3, 4, 6, 8, 10, 12, 16, and 24 hours) which followed administration of the first dose, at 24 hours after administration of Doses 4, 8, 12, 16, and 20 (Days 5, 9, 13, 17, and 21) and during the 60 hours (pre-dose, 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) which followed administration of the 24<sup>th</sup> dose.

Seventeen subjects completed the study and the PK data from the 17 subjects were evaluable.

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Table 4. PK parameters of EE and NE following single- and multiple-dose oral administration of Loestrin tablets in 17 healthy female subjects

Regimen	Analyte	Arithmetic Mean <sup>a</sup> (%CV) by Pharmacokinetic Parameter						
		C <sub>max</sub>	t <sub>max</sub>	AUC(0-24)	t <sub>1/2</sub>	C <sub>avg</sub>	C <sub>min</sub>	Fluctuation
Dose 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) <sup>b</sup>	--
Dose 24 (Multiple Dose)	NE	16400 (26)	1.3 (0.7-4.0)	88180 (30)	8.4	3670 (30)	880 (51)	441.4 (28)
	EE	81.9 (24)	1.67 (1.0-2.0)	701.3 (28)	14.4	29.2 (28)	11.4 (43)	247.1 (19)
	SHBG	--	--	--	--	--	144 (24)	--

C<sub>max</sub> = pg/mL; T<sub>max</sub> = hr; AUC<sub>24</sub> = pg/mL\*hr; t<sub>1/2</sub> = hr; C<sub>avg</sub> = AUC<sub>24</sub>/24, pg/mL; C<sub>min</sub> = pg/mL; SHBG = nmol/L; C<sub>min</sub> for SHBG = pre-dose concentration.

- EE and NE AUC<sub>24</sub> values increased by a factor of 51% and 164%, respectively, following multiple-dose administration of Loestrin tablets as compared to single-dose administration.
- EE and NE C<sub>max</sub> concentrations increased by a factor of 27% and 95%, respectively, following multiple-dose administration of Loestrin tablets as compared to single-dose administration.

Figure 4. Mean plasma EE concentration versus time curves following single- and multiple-dose oral administration of Loestrin tablets in 17 healthy female subjects

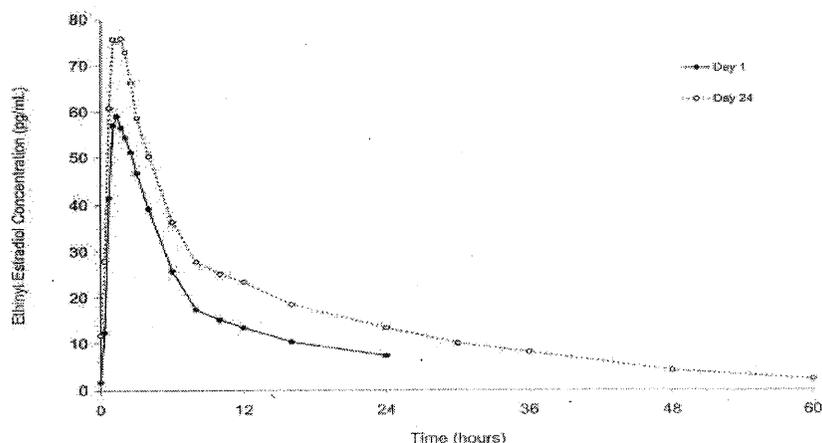


Table 5. Pre-dose mean plasma EE concentrations on Days 1, 2, 5, 9, 13, 17, 21 and 24

Day	Mean (SD) (pg/mL)	Range (pg/mL)
1 (Baseline)	1.51 (5.67)	0 - 23.4
2	7.23 (3.21)	4.47 - 18.5
5	9.27 (2.92)	3.93 - 13.6
9	9.85 (3.48)	3.26 - 14.9
13	11.3 (4.05)	5.90 - 20.3
17	13.1 (6.54)	6.66 - 33.6
21	13.5 (5.75)	6.34 - 25.7
24	11.7 (4.70)	7.79 - 22.4

Figure 5. Mean plasma NE concentration versus time curves following single- and multiple-dose oral administration of Loestrin tablets in 17 healthy female subjects

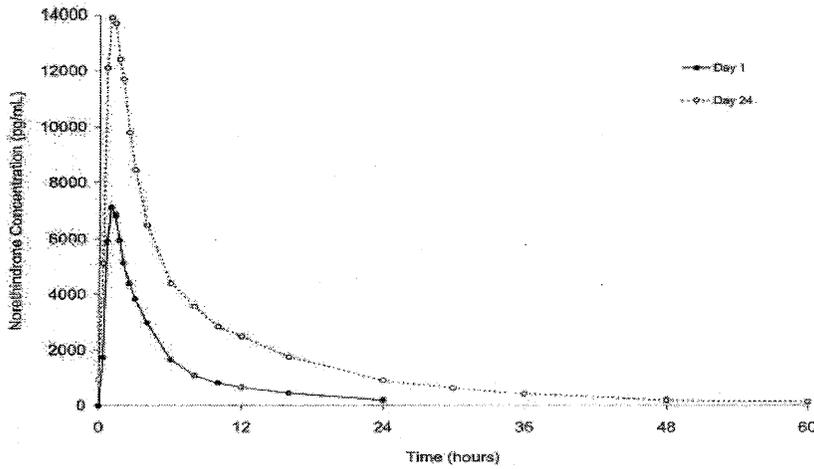


Table 6. Pre-dose mean plasma NE concentrations on Days 1, 2, 5, 9, 13, 17, 21 and 24

Day	Mean (SD) (pg/mL)	Range (pg/mL)
1 (Baseline)	0	0
2	192 (121)	65.9 – 511
5	379 (200)	126 – 897
9	539 (276)	80.5 – 1140
13	723 (331)	314 – 1530
17	963 (712)	233 – 3050
21	883 (420)	347 – 2090
24	942 (457)	228 - 2190

SHBG:

SHBG concentrations increased during multiple daily doses of Loestrin. Mean SHBG concentrations ranged between 57.5 nmol/L on Day 1 to 144 nmol/L on Days 16 and 24.

Study Day (n=17)	Mean (SD) nmol/L	CV%
Baseline (Day 1)	57.5 (21.1)	36.71
1	61.6 (21.7)	35.30
4	83.1 (28.0)	33.71
8	119 (41.9)	35.21
12	137 (50.4)	36.77
16	144 (60.0)	41.54
20	138 (46.3)	33.62
24	144 (34.8)	24.20

- SHBG concentrations increased by 150% from baseline to 144 nmol/L on Day 24.

**Study PR-01904: A Study to Determine the Effect of Food on EE and NE Bioavailability following Oral Administration of a Single Dose of a WC2061 (Loestrin) Tablet in Healthy Female Volunteers, PR-01904.1**

A single-center, randomized, single-dose, crossover study was conducted in 18 healthy non-pregnant female subjects aged 18 – 35 years to evaluate the effect of food on EE and NE bioavailability following oral administration of a Loestrin tablet. Subjects received a single dose of Loestrin tablet following an overnight fast of at least 10 hours and were instructed to fast for additional 4 hours post-dose (fasted). In addition, subjects received a single dose of Loestrin tablet within 5 minutes of having consuming a high-fat, high calorie food over a 30-minute period (fed). There was a wash-out period of 28 days between the two treatments. Blood samples were collected at pre-dose, 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. EE and NE noncompartmental PK parameters were calculated following the test (fed) and reference (fasted) treatments. Analysis of variance (ANOVA) was performed on the log-transformed PK parameters,  $AUC_{last}$ ,  $AUC_{inf}$  and  $C_{max}$ . The 90% CIs for the difference between treatment LSMs were calculated for AUC and  $C_{max}$  using log-transformed data.

Seventeen subjects completed the study. The PK data from 16 subjects were evaluable.

Table 7. PK parameters of NE and EE following a single dose administration of Loestrin tablet under the fed and fasted conditions (n=16).

Analyte	Parameter	Geometric Mean			90% CI
		Fed State (Test)	Fasted State (Reference)	Ratio (Test: Ref)	
NE	$C_{max}$ (pg/mL)	7800	8740	89.20	74.5 - 106.8
	$AUC_{last}$ (pg/mL*hr)	44920	35350	127.07	109.4 - 147.6
	$AUC_{inf}$ (pg/mL*hr)	46020	36540	125.93	108.5 - 146.2
	$t_{max}$ (hr)	1.83	1.51	--	--
EE	$C_{max}$ (pg/mL)	45.1	64.6	69.82	59.4 - 82.0
	$AUC_{last}$ (pg/mL*hr)	508.0	498.2	101.96	94.6 - 109.9
	$AUC_{inf}$ (pg/mL*hr)	571.4	548.8	104.12	96.3 - 112.6
	$t_{max}$ (hr)	2.50	1.53	--	--

- **EE:** The 90% CIs of the ratios of the geometric means for  $AUC_{last}$  (101.96%) and  $AUC_{inf}$  (104.12%) were within 80 – 125%. The geometric mean for  $C_{max}$  and the lower limit of the 90% CI of the ratio of the geometric mean for  $C_{max}$  (69.82%) were outside of 80 – 125%.
- **NE:** The geometric means for  $AUC_{last}$  (127.07%) and  $AUC_{inf}$  (125.93%), and the upper limits of the 90% CIs were outside of 80 – 125%. The lower limit of the 90% CI of the ratio of the geometric mean for  $C_{max}$  (89.20%) was outside of 80 – 125%.
- Following a single dose administration of Loestrin tablet, the mean NE and EE  $C_{max}$  values were 11% and 30% lower, respectively, under the fed condition. The mean NE and EE  $AUC_{last}$  values were 27% and 2% higher, respectively, under the fed condition.
- A single-dose administration of Loestrin tablet with food decreased the rate but not the extent of EE absorption and decreased the rate and increased the extent of NE absorption.

Table 8. PK parameters of EE following a single dose administration of Loestrin tablet under fed and fasted conditions in 16 female subjects

Parameter	Test (Fed)		Reference (Fasted)	
	Arithmetic Mean (SD) (Range)	CV%	Arithmetic Mean (SD) (Range)	CV%
C <sub>max</sub> (pg/mL)	48.4 (18.9) (26.2 – 83.6)	39.05	68.9 (28.1) (38.8 – 153)	40.83
C <sub>last</sub> (pg/mL)	2.88 (0.779) (2.12 – 4.50)	27.09	2.71 (0.637) (2.04 – 3.92)	23.52
AUC <sub>last</sub> (hr*pg/mL)	525.9 (139.9) (280.8 – 824.6)	26.60	510.8 (112.3) (304.7 – 700.7)	21.98
AUC <sub>inf</sub> (hr*pg/mL)	589.7 (148.8) (316.2 – 925.9)	25.24	560.1 (113.2) (375.8 – 759.2)	20.21
T <sub>max</sub> (hr)	2.50 (1.51) (1.33 – 6.00) median of 2.00 hrs	60.38	1.53 (0.56) (0.33 – 3.00) median of 1.33 hrs	36.95
T <sub>1/2</sub> (hr)	15.30 (4.20) (9.81 – 25.75)	27.44	12.70 (2.90) (8.22 – 17.84)	22.84
T <sub>last</sub> (hr)	46.51 (8.63) (36.00 – 60.07)	18.56	39.76 (8.45) (24.00 – 60.00)	21.25

Table 9. PK parameters of NE following a single dose administration of Loestrin tablet under fed and fasted conditions in 16 female subjects

Parameter	Test (Fed)		Reference (Fasted)	
	Arithmetic Mean (SD) (Range)	CV%	Arithmetic Mean (SD) (Range)	CV%
C <sub>max</sub> (pg/mL)	8470 (3,750) (3600 – 19600)	44.22	9040 (2,230) (4500 – 12000)	24.62
C <sub>last</sub> (pg/mL)	92.9 (59.0) (51.0 – 295)	63.46	88.4 (26.5) (59.3 – 155)	29.96
AUC <sub>last</sub> (hr*pg/mL)	49480 (29160) (21360 – 152400)	58.92	36730 (10340) (17920 – 56580)	28.15
AUC <sub>inf</sub> (hr*pg/mL)	50690 (29900) (22110 – 156200)	58.99	37970 (10750) (18840 – 60400)	28.32
T <sub>max</sub> (hr)	1.83 (0.75) (1.33 – 4.00) median of 1.67 hrs	40.82	1.51 (0.86) (0.67 – 3.07) median of 1.17 hrs	57.01
T <sub>1/2</sub> (hr)	9.06 (2.27) (5.71 – 12.38)	25.11	9.20 (3.27) (4.90 – 17.07)	35.57
T <sub>last</sub> (hr)	43.13 (10.10) (30.00 – 60.07)	23.42	36.76 (7.56) (30.00 – 60.05)	20.56

Figure 6. Mean plasma EE concentration versus time following a single dose administration of Loestrin tablet under fed and fasted conditions

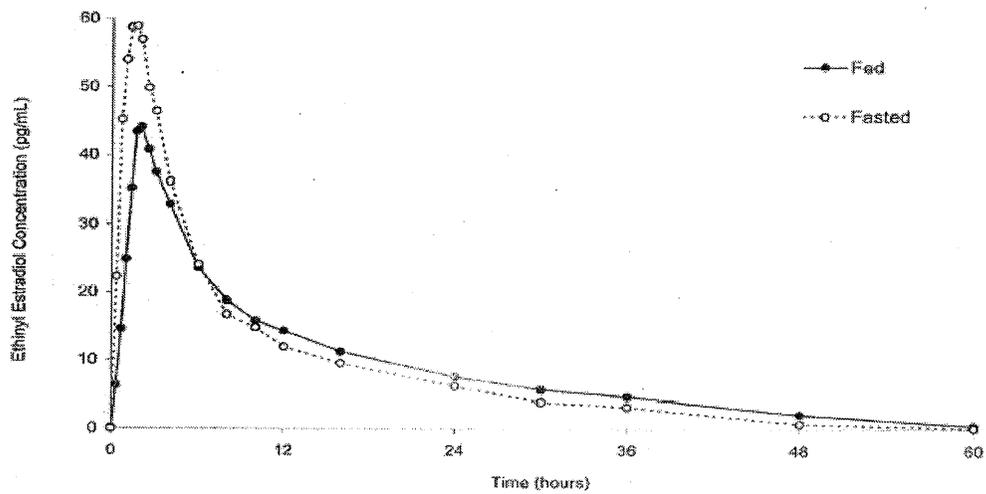
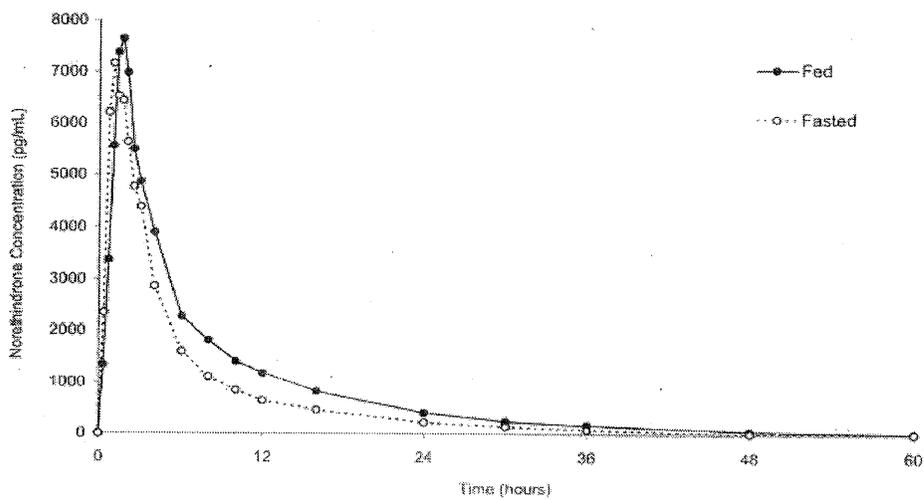


Figure 7. Mean plasma NE concentration versus time following a single dose administration of Loestrin tablet under fed and fasted conditions



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**Office of Clinical Pharmacology and Biopharmaceutics**  
***New Drug Application Filing and Review Form***

General Information About the Submission			
	Information		Information
NDA Number	21-871	Brand Name	Loestrin® 24
OCPB Division (I, II, III)	DPE II	Generic Name	Norethindrone Acetate/Ethinyl Estradiol, and Ferrous Fumarate
Medical Division	DRUDP	Drug Class	Oral Contraceptive
OCPB Reviewer	Myong-Jin Kim	Indication(s)	Prevention of Pregnancy
OCPB Team Leader	Ameeta Parekh	Dosage Form	Tablet
		Dosing Regimen	1 mg/20 mcg/75 mg
Date of Submission	15/April/05	Route of Administration	Oral
Estimated Due Date of OCPB Review		Sponsor	Warner Chilcott
PDUFA Due Date		Priority Classification	S
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
<b>STUDY TYPE</b>				
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			
<b>I. Clinical Pharmacology</b>				
Mass balance:				
Isozyme characterization:				
Blood/plasma ratio:				
Plasma protein binding:				
Pharmacokinetics (e.g., Phase I) -				
Healthy Volunteers-				
single dose:	X	1		
multiple dose:	X	1		
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:	X	1		
Population Analyses -				
Data rich:				

Data sparse:				
<b>II. Biopharmaceutics</b>				
Absolute bioavailability:				
Relative bioavailability -				
solution as reference:				
alternate formulation as reference:				
<b>Bioequivalence studies -</b>				
traditional design; single / multi dose:				
replicate design; single / multi dose:				
Food-drug interaction studies:	X	1		
Dissolution:	X	1		
(IVIVC):				
<b>Bio-wavier request based on BCS</b>				
BCS class				
<b>III. Other CPB Studies</b>				
Genotype/phenotype studies:				
Chronopharmacokinetics				
Pediatric development plan				
Literature References	X			
Total Number of Studies				
<b>Filability and QBR comments</b>				
	"X" if yes	<u>Comments</u>		
Application filable ?	X	Reasons if the application is <u>not</u> filable (or an attachment if applicable) For example, is clinical formulation the same as the to-be-marketed one?		
Comments sent to firm ?		Comments have been sent to firm (or attachment included). FDA letter date if applicable.		
QBR questions (key issues to be considered)				
Other comments or information not included above				
Primary reviewer Signature and Date				
Secondary reviewer Signature and Date				

The Office of Clinical Pharmacology Briefing was held on February 7, 2006. The following people attended the Briefing: Drs. Julie Bullock, Dan Davis, Shirley Murphy, Stephan Ortiz, Ameeta Parekh, Sandra Suarez, and Donny Tran.

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## Filing Memo

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### Clinical Pharmacology and Biopharmaceutics Review

**NDA:** 21-871  
**Compound:** Loestrin® 24 (norethindrone acetate/ethinyl estradiol tablets, USP and ferrous fumarate tablets)  
**Sponsor:** Warner Chilcott  
**Date:** 19/May/2005  
**Reviewer:** Myong-Jin Kim

**Background:**

Loestrin 24 is a new 24-day dosing regimen of the currently marketed Loestrin® Fe 1/20 tablets approved under NDA 17-354. Loestrin contains 1 mg norethindrone acetate/20 mcg ethinyl estradiol tablets, USP and 75 mg ferrous fumarate tablets for prevention of pregnancy.

A study was conducted to characterize the bioavailability of norethindrone and ethinyl estradiol following single- and multiple-dose administration of Loestrin 24 tablets over a 24-day period. In addition, a single-dose food effect study was conducted on Loestrin 24 tablets.

**Study PR-01804:** A single- and multiple-dose PK study to characterize the plasma EE and NE PK profiles and SHBG concentrations following multiple-dose administration of Loestrin 24 tablets to healthy female subjects under fasting conditions.

**Study PR-01904:** A food effect study to evaluate the effect of food on EE and NE bioavailability following oral administration of a single Loestrin 24 tablet.

**Recommendation:**

The Office of Clinical Pharmacology and Biopharmaceutics/Division of Pharmaceutical Evaluation II finds that the Human Pharmacokinetics and Bioavailability section for NDA 21-871 is fileable.

\_\_\_\_\_  
Myong-Jin Kim, Pharm.D.

\_\_\_\_\_  
Date

\_\_\_\_\_  
Ameeta Parekh, Ph.D., Team Leader

\_\_\_\_\_  
Date

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this page is the manifestation of the electronic signature.**  
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/s/

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Myong-Jin Kim  
2/16/2006 09:34:21 AM  
PHARMACOLOGIST

Ameeta Parekh  
2/17/2006 11:11:48 AM  
BIOPHARMACEUTICS

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