CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

204426Orig1s000

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

OFFICE OF CLINICAL PHARMACOLOGY REVIEW

NDA: 204426	Submission Dates: 6/21/2012, 9/11/2012, and 9/27/2012
Brand Name:	MINASTRIN 24 Fe
Generic Name:	Norethindrone acetate (NA) / Ethinyl estradiol (EE) / Ferrous fumarate (Fe)
Clinical Pharmacology Primary Reviewer:	Chongwoo Yu, PhD
Clinical Pharmacology Secondary Reviewer:	Myong-Jin Kim, PharmD
OCP Division:	Division of Clinical Pharmacology 3 (DCP-3)
OND Division:	Division of Reproductive and Urologic Products (DRUP)
Sponsor:	Warner Chilcott Company, LLC
Submission Type:	Original / 505(b)(1)
Formulation, Strength, and Dosing Regimen	Capsule, 1 mg NA/20 μg EE for 24 days followed by 75 mg Fe for 4 days (28 day regimen), Daily oral administration
Indication:	Prevention of pregnancy

An Optional Inter-Division Clinical Pharmacology Briefing was held on Wednesday, December 12, 2012. The attendees were as follows: C. Yu, H.Y. Ahn, M-J Kim, L. Lee, H. Kim, L. Li, D. Davis, Y. Pan, and P. Duan.

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1 Executive Summary

The Sponsor submitted a 505(b)(1) new drug application (NDA) to seek approval of MINASTRIN 24 Fe (norethindrone acetate [NA] / ethinyl estradiol [EE] capsule) for prevention of pregnancy. MINASTRIN 24 Fe is a combined oral contraceptive (COC) consisting of one capsule containing 1 mg NA and 20 µg EE taken orally once a day for 24 days followed by one 75 mg ferrous fumarate (Fe) capsule taken orally once a day for 4 days to facilitate a 28 day regimen. The proposed regimen is the same as the approved regimen for Sponsor's Loestrin® 24 Fe (NA/EE tablets and Fe tablets) which received approval as a COC on February 17, 2006 under NDA 021871. (b) (4)

(b) (4)

In this current NDA, the Sponsor submitted 3 Clinical Pharmacology studies including a pivotal bioequivalence (BE) study (Study PR-00810) using Loestrin® 24 as a reference listed drug (RLD) and a food effect study (Study PR-06011). These 2 studies (i.e., Studies PR-00810 and PR-06011) were conducted with the to-be-marketed (TBM) formulation. One additional Clinical Pharmacology study, Study PR-00910 (relative bioavailability [BA] study), was conducted using a non-TBM formulation and it was not reviewed.

For the pivotal BE study (Study PR-00810), a formal consult to the Office of Scientific Investigations (OSI) was made for inspections of the clinical and bioanalytical study sites.

1.1 Recommendation

The Office of Clinical Pharmacology (OCP)/Division of Clinical Pharmacology 3 (DCP-3) has reviewed NDA 204426 submitted on June 21, 2012, September 11, 2012, and September 27, 2012. The overall Clinical Pharmacology information submitted to support this NDA is acceptable provided that a satisfactory agreement is reached regarding the labeling language.

1.2 Post-marketing Requirements or Commitments

None

1.3 Summary of Important Clinical Pharmacology Findings

MINASTRIN 24 Fe provides a 28 day COC regimen as the following:

- One oval, transparent, pale yellow capsule containing 1 mg NA and 20 µg EE once daily for 24 days
- Followed by one oval, opaque, maroon capsule containing 75 mg Fe once daily for 4 days.

Pivotal BE Assessment:
BE between MINASTRIN 24 Fe capsules and Loestrin® 24 Fe tablets was established in a 2-way crossover study (Study PR-00810) in 38 healthy, non-smoking, premenopausal females following a single dose administration under a fasting condition. For both norethindrone (NE) and EE, the 90% confidence intervals (CI) were within the BE limits of 80.00-125.00% for AUC_{tldc}, AUC_{nf}, and C_{max} (Tables 1 and 2).

Table 1: Summary of BE Analysis Results of NE PK Parameters Following a Single Dose of a MINASTRIN 24 Fe Capsule (Test) or a WC2061 Tablet (Reference) (Study PR-00810; N=38)

Parameter	Geometric Mean		LSM Ratio x 100 (Test/Reference)	90% CI
	Test	Reference		
$AUC_{0\text{-}tldc}$ (pg·hr/mL)	38711	42500	91.1	87.4-94.9
AUC_{inf} (pg·hr/mL)	39399	43128	91.4	87.6-95.3
C_{max} (pg/mL)	8588	8014	107.2	100.0-114.9

Test: One MINASTRIN 24 Fe capsule (1 mg NA / 20 µg EE; Formulation: WC3042-05)
Reference: One Loestrin® 24 Fe tablet (1 mg NA / 20 µg EE; Formulation: WC2061)
LSM: Least-square means

Table 2: Summary of BE Analysis Results of EE PK Parameters Following a Single Dose of a MINASTRIN 24 Fe Capsule (Test) or a WC2061 Tablet (Reference) (Study PR-00810; N=38)

Parameter	Geometric Mean		LSM Ratio x 100 (Test/Reference)	90% CI
	Test	Reference		
$AUC_{0\text{-}tldc}$ (pg·hr/mL)	503.2	520.5	96.7	92.1-101.6
AUC_{inf} (pg·hr/mL)[a]	576.7	580.4	99.4	94.2-104.8
C_{max} (pg/mL)	59.1	64.5	91.7	86.8-97.0

Test: One MINASTRIN 24 Fe capsule (1 mg NA / 20 µg EE; Formulation: WC3042-05)
Reference: One Loestrin® 24 Fe tablet (1 mg NA / 20 µg EE; Formulation: WC2061)
LSM: Least-square means
[a] N=32 as a terminal phase rate constant could not be determined for 4 subjects who received the Test treatment and 2 subjects who received the Reference treatment

Absorption:
Following a single dose oral administration of MINASTRIN 24 Fe under a fasting condition, plasma NE and EE concentrations increased until T_{max} were reached at 0.7-4 hours and decreased over the remainder of the sampling period. Mean (SD) pharmacokinetics (PK) parameters of NE and EE are summarized in Tables 3 and 4.

Table 3: Mean (SD) Plasma PK Parameters of NE Following a Single Dose of a MINASTRIN 24 Fe Capsule (Study PR-00810; N=38)

Parameter	NE
$AUC_{0\text{-}tldc}$ (pg·hr/mL)	42474.0 (19476.2)
AUC_{inf} (pg·hr/mL)	43175.2 (19729.4)
C_{max} (pg/mL)	9255.0 (3339.6)
T_{max} (hr)[a]	1.1 (0.7-4.0)
$t_{½}$ (hr)	9.2 (2.6)

[a] Median (minimum-maximum)

Table 4: Mean (SD) Plasma PK Parameters of EE Following a Single Dose of a MINASTRIN 24 Fe Capsule (Study PR-00810; N=38)

Parameter	EE
$AUC_{0\text{-}tldc}$ (pg·hr/mL)	523.6 (146.0)
AUC_{inf} (pg·hr/mL)	597.0 (171.7)[b]
C_{max} (pg/mL)	61.9 (20.2)
T_{max} (hr)[a]	2.0 (1.0-4.0)
$t_{½}$ (hr)	13.5 (7.5)[b]

[a] Median (minimum-maximum)
[b] N=34 as a terminal phase rate constant could not be determined for 4 subjects

Food Effect
In a 2-way crossover study (Study PR-06011) in 24 healthy, non-smoking, premenopausal females, C_{max} values were decreased by 35% and 34% for NE and EE, respectively, and median T_{max} values were delayed by 2 hours and 1.5 hours for NE and EE, respectively, when MINASTRIN 24 Fe capsules were administered with a high fat and high calorie meal. However, the 90% CIs for NE and EE AUC were within the BE limits of 80.00-125.00% indicating that the extent of NE and EE absorption was not affected by administration with food (Tables 5 and 6).

Table 5: Summary of the Assessment of Food Effect on NE PK Parameters Following a Single Dose of a MINASTRIN 24 Fe Capsule with Food (Test) or without Food (Reference) (Study PR-06011; N=24)

Parameter	Geometric Mean		LSM Ratio x 100 (Test/Reference)	90% CI
	Test	Reference		
$AUC_{0\text{-}tldc}$ (pg·hr/mL)	49242	42961	114.6	108.8-120.8
AUC_{inf} (pg·hr/mL)	50488	43886	115.0	109.3-121.11
C_{max} (pg/mL)	5548	8491	65.3	53.9-79.3

LSM: Least-square means

Table 6: Summary of the Assessment of Food Effect on EE PK Parameters Following a Single Dose of a MINASTRIN 24 Fe Capsule with Food (Test) or without Food (Reference) (Study PR-06011; N=24)

Parameter	Geometric Mean		LSM Ratio x 100 (Test/Reference)	90% CI
	Test	Reference		
$AUC_{0\text{-}tldc}$ (pg·hr/mL)	568.4	600.1	94.7	89.1-100.8
AUC_{inf} (pg·hr/mL)[a]	703.5	705.7	99.7	91.7-108.3
C_{max} (pg/mL)	38.3	57.6	66.5	57.5-76.8

LSM: Least-square means

[a] N=20 as a terminal phase rate constant could not be determined for 1 subject who received the Test treatment and 3 subjects who received the Reference treatment

Distribution, Metabolism, and Excretion

No new distribution, metabolism, and excretion studies were conducted with MINASTRIN 24 Fe. Distribution, metabolism, and excretion of NE and EE are expected to be the same as those from Loestrin® 24 Fe. The Sponsor is proposing to use the information regarding NE and EE distribution, metabolism, and excretion from Loestrin® 24 Fe for labeling.

Drug-Drug Interactions (DDI):

No new DDI studies were conducted with MINASTRIN 24 Fe. The Sponsor is proposing to use the information used regarding DDI from Loestrin® 24 Fe for labeling.

Use in Specific Populations:

- Pediatric use: No pediatric studies were conducted with MINASTRIN 24 Fe. The Sponsor's pediatric waiver request is pending from the Pediatric Review Committee's (PeRC) approval. This is scheduled to be discussed on February 13, 2013.
- Renal or hepatic impairment: No studies were conducted in patients with renal or hepatic impairment. MINASTRIN 24 Fe is contraindicated for liver tumors or liver disease.

Bioanalytical Methods:

Acceptance criteria and method performance for NE and EE concentration measurements are in compliance with the Agency's *Bioanalytical Method Validation Guidance* and the bioanalytical methods are acceptable.

Human plasma samples were analyzed using a validated gas chromatography-mass spectrometry (GC-MS) method for the determination of NE and EE concentrations in the pivotal BE study (Study PR-00810) and the food effect study (Study PR-06011). Incurred sample reanalysis (ISR) was conducted on approximately 5.3% and 5.0% of the study samples in the pivotal BE study and food effect study, respectively. Approximately 90% and 80% of the NE ISR results from the pivotal BE study and food effect study, respectively, and 84% and 84% of the EE ISR results from the pivotal BE study and food effect study, respectively, met the acceptance criteria of being within ±20% of the original reported concentration value for at least 67% of the ISR samples.

An OSI consult requesting inspections of the clinical and bioanalytical sites of the pivotal BE study was made on August 17, 2012. There were no significant objectionable issues identified

and the Form FDA 483 was not issued. Details of the OSI inspection findings can be found in Dr. Michael Skelly's OSI consult review dated December 11, 2012 in DARRTS. See Appendix Section 4.2 of this review.

2 Question Based Review

2.1 General Attributes

2.1.1 What is MINASTRIN 24 Fe and what is its active pharmacological ingredient?

MINASTRIN 24 Fe provides a 28 day COC regimen consisting of one yellow capsule that contains the active ingredients (i.e., NE and EE) taken daily for 24 days, followed by one maroon placebo capsule taken daily for 4 days.

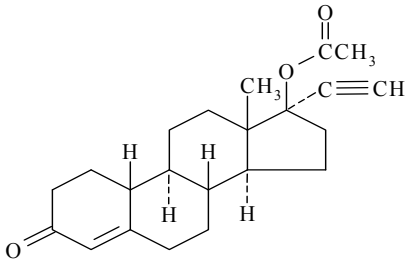
- 24 oval, transparent, pale yellow capsules each containing 1 mg NA and 20 μg EE
- 4 oval, opaque, maroon capsules each containing 75 mg Fe

Each yellow capsule also contains the following inactive ingredients: sesame oil, linoleoyl polyoxylglycerides, DL-α-tocopherol, dehydrated alcohol, gelatin, sorbitol, and glycerin.

Each maroon capsule contains Fe, soybean oil, lecithin, yellow beeswax, gelatin, sorbitol, glycerin, FD&C Blue No. 1, FD&C Red No. 40, and titanium dioxide. The Fe capsules do not serve any therapeutic purpose.

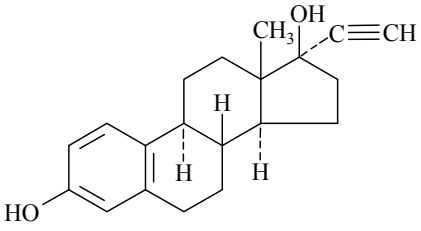
The chemical name of NA is [19-Norpregn-4-en-20-yn-3-one, 17-(acetyloxy)-, (17α)-] and the empirical formula is $C_{22}H_{28}O_3$. The structural formula is shown in Figure 1.

Figure 1: Structural Formula of NA



The chemical name of EE is [19-Norpregna-1,3,5(10)-trien-20-yne-3,17-diol, (17α)-] and the empirical formula is $C_{20}H_{24}O_2$. The structural formula is shown in Figure 2.

Figure 2: Structural Formula of EE



2.2 General Clinical Pharmacology

2.2.1 What is the relevant Clinical Pharmacology information submitted in this NDA?

This NDA contains the following:

- Draft product label in physician labeling rule (PLR) format

- Information on the composition of drug products used in the clinical studies
- Full clinical study reports of 3 Clinical Pharmacology studies
- Bioanalytical study reports and method validation reports
- Request of waiver for pediatric studies

The Clinical Pharmacology studies submitted to this NDA are summarized in the Table 7 below.

Table 7: Summary of Clinical Pharmacology Studies

Study	Objective	Population	Dosing Regimen	Design
PR-00810 TBM formulation	Pivotal BE	40 healthy, nonsmoking, premenopausal females (18-35 yrs)	Treatment A: MINASTRIN 24 Fe capsule Treatment B: Loestrin® 24 Fe tablet Both treatments were single dose under fasting	Open label, single dose, two treatment, two-way crossover study
PR-06011 TBM formulation	Food Effect	26 healthy, nonsmoking, premenopausal females (18-45 yrs)	Treatment A: MINASTRIN 24 Fe capsules with food Treatment B: MINASTRIN 24 Fe capsules without food Both treatments were single dose	Open label, single dose, two treatment, two-way crossover study
PR-00910 Non-TBM formulation	Relative BA	40 healthy, nonsmoking, premenopausal females (18-45 yrs)	Treatment A: WC3042 (b)(4) capsule Treatment B: Loestrin® Fe tablet Both treatments were single dose	Open label, single dose, two treatment, two-way crossover study

MINASTRIN 24 Fe refers to the TBM product (formulation: WC3042-05) and WC3042 (b)(4) refers to an earlier development formulation (non-TBM formulation).

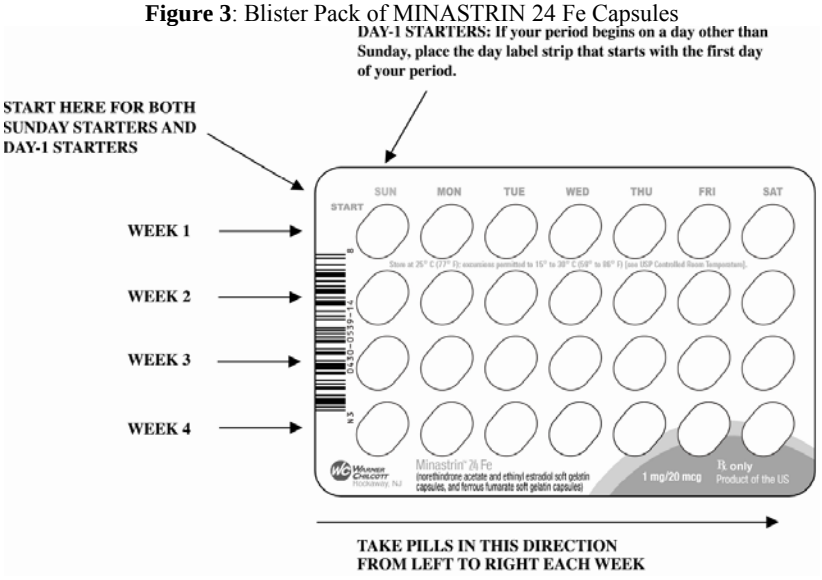
2.2.2 What is the proposed mechanism of action?

COCs lower the risk of becoming pregnant primarily by suppressing ovulation. Other possible mechanisms may include cervical mucus changes that inhibit sperm penetration and endometrial changes that reduce the likelihood of implantation.

2.2.3 What are the administration instructions and dosing regimen?

MINASTRIN 24 Fe capsules are to be taken orally at the same time every day. MINASTRIN 24 Fe capsules must be taken in the order directed on the blister pack (Figure 3). The MINASTRIN 24 Fe pill pack has 24 "active" yellow pills to be taken for 24 days, followed by 4 "inactive" maroon pills to be taken for the next 4 days (28 day regimen).

Figure 3: Blister Pack of MINASTRIN 24 Fe Capsules



MINASTRIN 24 Fe capsules should not be skipped or taken at intervals exceeding 24 hours. MINASTRIN 24 Fe capsules may be administered without regard to meals.

2.2.4 Is BE between MINASTRIN 24 Fe capsules and Loestrin® 24 Fe tablets established adequately?

Yes. BE between MINASTRIN 24 Fe capsules and Loestrin® 24 Fe tablets regarding both NE and EE was established in a 2-way crossover study (Study PR-00810) in 38 healthy, non-smoking premenopausal females (age: 18-35 years; body mass index [BMI]: 19.0-29.9 kg/m^2).

In each of the 2 treatment periods, subjects received a single dose of one of the following Test or Reference treatments according to the randomization schedule following an overnight fasting of at least 8 hours:

- Test: One MINASTRIN 24 Fe capsule (1 mg NA / 20 µg EE; Formulation: WC3042-05)
- Reference: One Loestrin® 24 Fe tablet (1 mg NA / 20 µg EE; Formulation: WC2061)

All capsules/tablets were administered orally with 240 mL ambient-temperature water. Fasting continued for at least 4 hours following drug administration, after which a standardized lunch was served. Water was allowed *ad libitum* until 1 hour pre-dose and beginning 1 hour after drug administration. Treatment periods were separated by at least 14 days. Blood samples were collected at pre-dose and for 60 hours post-dose in each treatment period for PK characterization.

BE Analysis for NE:
The 90% CIs for the difference between the Test (MINASTRIN 24 Fe capsule) and Reference (WC2061 tablet) least-square means (LSM) with respect to NE for the parameters C_{max}, AUC_{0-tldc}, and AUC_{inf} using natural log transformed data were within the BE limits of 80.00-125.00%. The BE analysis results for NE are summarized in Table 8 below.

Table 8: Summary of BE Analysis Results of NE PK Parameters Following a Single dose of a MINASTRIN 24 Fe Capsule (Test) or a WC2061 Tablet (Reference) (Study PR-00810; N=38)

Parameter	Geometric Mean		LSM Ratio x 100 (Test/Reference)	90% CI
	Test	Reference		
AUC_{0-tldc} (pg·hr/mL)	38711	42500	91.1	87.4-94.9
AUC_{inf} (pg·hr/mL)	39399	43128	91.4	87.6-95.3
C_{max} (pg/mL)	8588	8014	107.2	100.0-114.9

Test: One MINASTRIN 24 Fe capsule (1 mg NA / 20 µg EE; Formulation: WC3042-05)
Reference: One Loestrin® 24 Fe tablet (1 mg NA / 20 µg EE; Formulation: WC2061)

BE Analysis for EE:
The 90% CIs for the difference between the Test (MINASTRIN 24 Fe capsule) and Reference (WC2061 tablet) LSM with respect to EE for the parameters C_{max}, AUC_{0-tldc}, and AUC_{inf} using natural log transformed data were within the BE limits of 80.00-125.00%. The BE analysis results for EE are summarized in Table 9 below.

Table 9: Summary of BE Analysis Results of EE PK Parameters Following a Single dose of a MINASTRIN 24 Fe Capsule (Test) or a WC2061 Tablet (Reference) (Study PR-00810; N=38)

Parameter	Geometric Mean		LSM Ratio x 100 (Test/Reference)	90% CI
	Test	Reference		
AUC_{0-tldc} (pg·hr/mL)	503.2	520.5	96.7	92.1-101.6
AUC_{inf} (pg·hr/mL)[a]	576.7	580.4	99.4	94.2-104.8
C_{max} (pg/mL)	59.1	64.5	91.7	86.8-97.0

Test: One MINASTRIN 24 Fe capsule (1 mg NA / 20 µg EE; Formulation: WC3042-05)
Reference: One Loestrin® 24 Fe tablet (1 mg NA / 20 µg EE; Formulation: WC2061)
[a] N=32 as a terminal phase rate constant could not be determined for 4 subjects who received the Test treatment and 2 subjects who received the Reference treatment

It should be noted that the analysis for EE AUC_{inf} was performed using N=32 subjects as a terminal phase rate constant could not be determined for 4 subjects who received the Test treatment and 2 subject who received the Reference treatment. These 6 subjects were excluded from the BE analysis based on AUC_{inf}. Excluded subjects were Subjects 505011, 505016, 505019, and 505039 from the Test treatment and Subjects 505005 and 505020 from the Reference treatment.

Details of the pivotal BE study can be found in Appendix Section 4.1.1 of this review.

2.2.5 What are the PK parameters of NE and EE following a single dose oral administration of a MINASTRIN 24 Fe capsule?

Following a single dose oral administration of a MINASTRIN 24 Fe capsule under fasting condition, plasma NE and EE concentrations increased until T_{max} were reached at 0.7-4 hours and decreased over the remainder of the sampling period. Mean (SD) PK parameters of NE and EE are summarized in Tables 10 and 11.

Table 10: Mean (SD) Plasma PK Parameters of NE Following a Single Dose of a MINASTRIN 24 Fe Capsule (Study PR-00810; N=38)

Parameter	NE
$AUC_{0\text{-tldc}}$ (pg·hr/mL)	42474.0 (19476.2)
AUC_{inf} (pg·hr/mL)	43175.2 (19729.4)
C_{max} (pg/mL)	9255.0 (3339.6)
T_{max} (hr)[a]	1.1 (0.7-4.0)
$t_{½}$ (hr)	9.2 (2.6)

[a] Median (minimum-maximum)

Table 11: Mean (SD) Plasma PK Parameters of EE Following a Single Dose of a MINASTRIN 24 Fe Capsule (Study PR-00810; N=38)

Parameter	EE
$AUC_{0\text{-tldc}}$ (pg·hr/mL)	523.6 (146.0)
AUC_{inf} (pg·hr/mL)	597.0 (171.7)[b]
C_{max} (pg/mL)	61.9 (20.2)
T_{max} (hr)[a]	2.0 (1.0-4.0)
$t_{½}$ (hr)	13.5 (7.5)[b]

[a] Median (minimum-maximum)
[b] N=34 as a terminal phase rate constant could not be determined for 4 subjects; Excluded subjects: 505011, 505016, 505019, and 505039.

The obtained mean concentration-time profiles for NE and EE are presented in Figures 4 and 5, respectively.

Figure 4: Mean NE Plasma Concentration-Time Profiles Following a Single Dose of a MINASTRIN 24 Fe Capsule (Test) or WC2061 Tablet (Reference) (Study PR-00810; N=38)

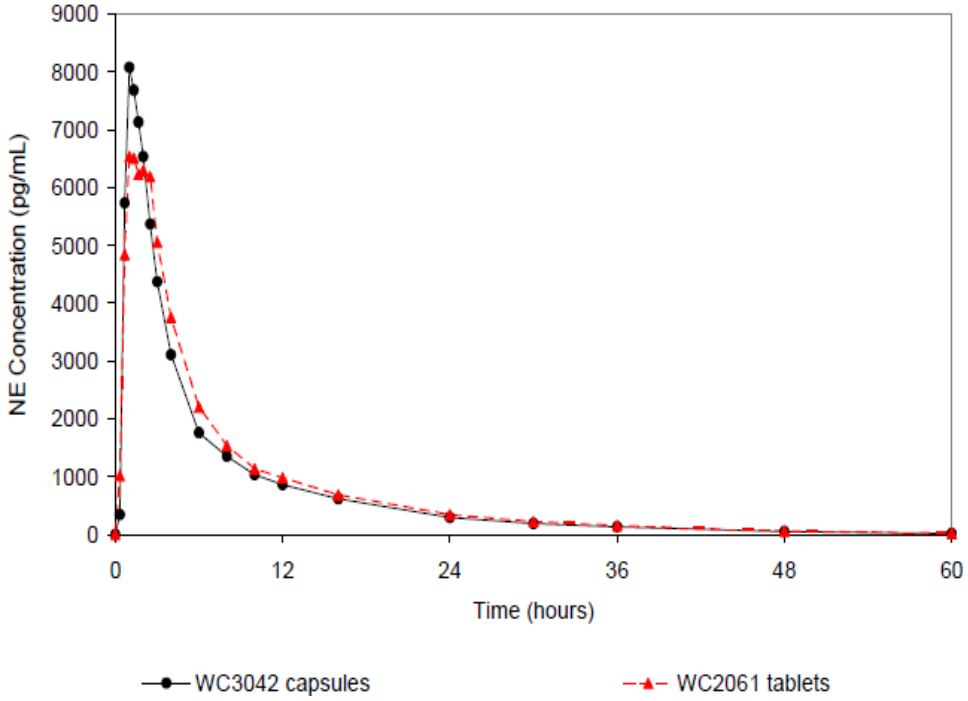
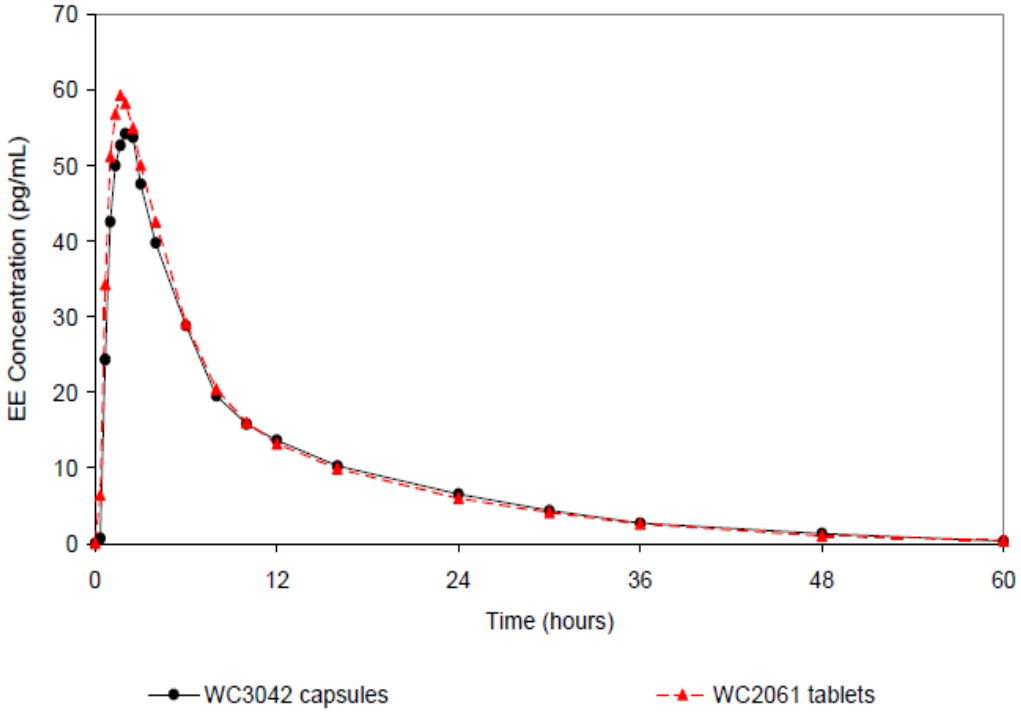


Figure 5: Mean EE Plasma Concentration-Time Profiles Following a Single Dose of a MINASTRIN 24 Fe Capsule (Test) or WC2061 Tablet (Reference) (Study PR-00810; N=38)



2.2.6 Did food intake affect the PK of NE and EE?

Yes. When MINASTRIN 24 Fe capsules were administered with a high fat and high calorie meal, the median T_{max} values were delayed by 2 hours and 1.5 hours for NE and EE, respectively, and C_{max} values were decreased 35% and 34% for NE and EE, respectively. However, food intake did not affect the AUCs of NE and EE as the 90% CIs were within the BE limits of 80.00-125.00% indicating that the extent of NE and EE absorption was not affected by administration with food.

Sponsor conducted a food effect study to assess the effect of food on the BA of NE and EE following oral administration of MINASTRIN 24 Fe capsules. This was a single-center, open-label, randomized, balanced, 2-treatment, 2-period, 2-sequence crossover study that was conducted in 26 healthy, non-smoking, premenopausal females (age: 18-45 years; BMI: 19.0-29.9 kg/m^2). All subjects received Test (fed) and Reference (fasting) treatments orally with 240 mL ambient-temperature water following an overnight fasting of at least 10 hours.

The results for the assessment of food effect on NE and EE PK are summarized in Tables 12 and 13 below.

Table 12: Summary of NE PK Parameters following a Single dose of a MINASTRIN 24 Fe Capsule with Food (Test) or without Food (Reference) (Study PR-06011; N=24)

Parameter	Geometric Mean		LSM Ratio x 100 (Test/Reference)	90% CI
	Test	Reference		
$AUC_{0\text{-}tldc}$ (pg·hr/mL)	49242	42961	114.6	108.8-120.8
AUC_{inf} (pg·hr/mL)	50488	43886	115.0	109.3-121.11
C_{max} (pg/mL)	5548	8491	65.3	53.9-79.3

Table 13: Summary of EE PK Parameters following a Single dose of a MINASTRIN 24 Fe Capsule with Food (Test) or without Food (Reference) (Study PR-06011; N=24)

Parameter	Geometric Mean		LSM Ratio x 100 (Test/Reference)	90% CI
	Test	Reference		
$AUC_{0\text{-}tldc}$ (pg·hr/mL)	568.4	600.1	94.7	89.1-100.8
AUC_{inf} (pg·hr/mL)[a]	703.5	705.7	99.7	91.7-108.3
C_{max} (pg/mL)	38.3	57.6	66.5	57.5-76.8

[a] N=20 as a terminal phase rate constant could not be determined for 1 subject who received the Test treatment and 3 subjects who received the Reference treatment

The analysis for EE AUC_{inf} was performed using N=20 subjects as a terminal phase rate constant could not be determined for 1 subject who received the Test treatment and 3 subjects who received the Reference treatment. These 4 subjects were excluded from the food effect analysis.

It should be noted that a single dose administration of Loestrin® 24 Fe tablet (RLD) with food decreased the C_{max} of NE by 11% and increased the NE AUC by 27%. For EE, food decreased the C_{max} by 30% but did not affect the AUC (i.e., the 90% CI for EE AUC was within the BE limits of 80.00-125.00%). Reference is made to Dr. Myong-Jin Kim's Clinical Pharmacology review under NDA 021871 dated February 17, 2006 in DARRTS.

In addition, the Phase 3 safety and efficacy Study PR-03903 submitted to the original NDA 021871 for Loestrin® 24 Fe was conducted without regard to food intake and it is stated that "Loestrin® 24 Fe tablets may be administered without regard to meals" under the Dosage and Administration section of the current Loestrin® 24 Fe product label. Reference is made to Dr. Daniel Davis' Clinical review under NDA 021871 dated February 17, 2006 in DARRTS.

Arithmetic mean (SD) PK parameters of NE and EE following a single dose of a MINASTRIN 24 Fe capsule with food (Test) or without food (Reference) are summarized in Tables 14 and 15.

Table 14: Mean (SD) Plasma PK Parameters of NE Following a Single Dose of a MINASTRIN 24 Fe Capsule with Food (Test) or without Food (Reference) (Study PR-06011; N=24)

Parameter	Test	Reference
$AUC_{0\text{-}tldc}$ (pg·hr/mL)	52550.8 (19569.4)	46578.8 (18139.4)
AUC_{inf} (pg·hr/mL)	53830.4 (19837.6)	47444.8 (18197.0)
C_{max} (pg/mL)	6592.1 (3804.2)	9007.1 (3095.1)
T_{max} (hr)[a]	3.3 (0.7-10.0)	1.3 (1.0-3.0)
$t_{½}$ (hr)	11.0 (2.8)	11.0 (3.2)

[a] Median (minimum-maximum)

Table 15: Mean (SD) Plasma PK Parameters of EE Following a Single Dose of a MINASTRIN 24 Fe Capsule with Food (Test) or without Food (Reference) (Study PR-06011; N=24)

Parameter	Test	Reference
$AUC_{0\text{-}tldc}$ (pg·hr/mL)	614.6 (261.7)	652.7 (287.9)
AUC_{inf} (pg·hr/mL)	781.3 (370.3)[b]	763.5 (366.7)[c]
C_{max} (pg/mL)	42.3 (19.3)	59.3 (15.4)
T_{max} (hr)[a]	3.5 (1.0-12.0)[b]	2.0 (1.3-4.0)[c]
$t_{½}$ (hr)	19.1 (11.2)	16.9 (8.2)

[a] Median (minimum-maximum)
[b] N=23 as a terminal phase rate constant could not be determined for 1 subject who received the Test treatment; Excluded subject: 505201.
[c] N=21 as a terminal phase rate constant could not be determined for 3 subjects who received the Reference treatment; Excluded subjects: 505203, 505215, and 505223.

The obtained mean concentration-time profiles for NE and EE are presented in Figures 6 and 7, respectively.

Figure 6: Mean NE Plasma Concentration-Time Profiles Following a Single Dose of a MINASTRIN 24 Fe Capsule with Food (Test) or without Food (Reference) (Study PR-06011; N=24)

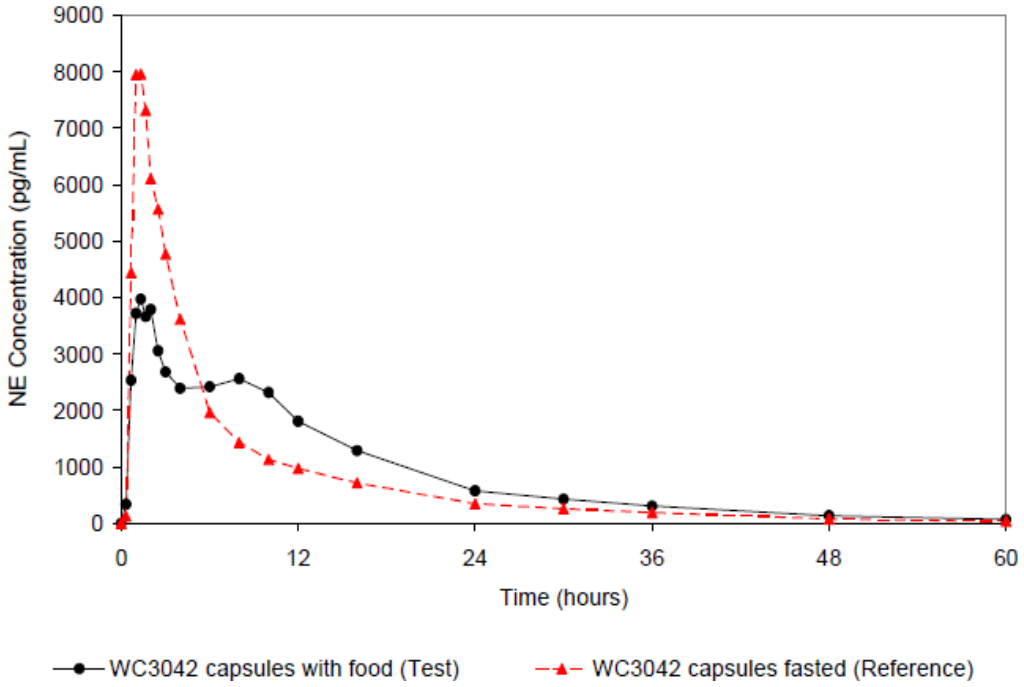
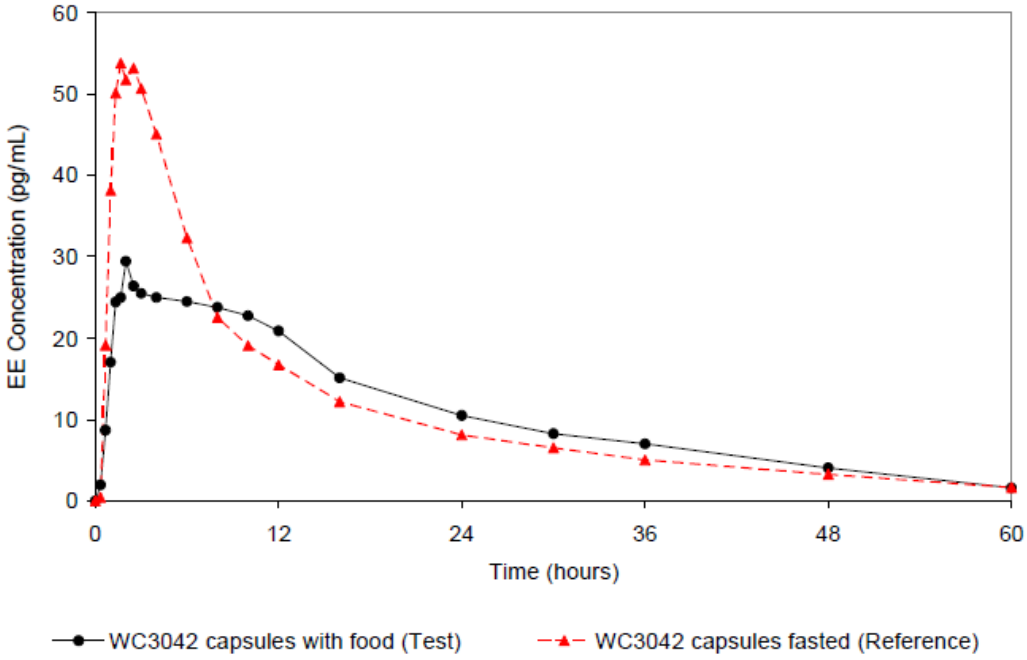


Figure 7: Mean EE Plasma Concentration-Time Profiles Following a Single Dose of a MINASTRIN 24 Fe Capsule with Food (Test) or without Food (Reference) (Study PR-06011; N=24)



2.3 Intrinsic Factors

2.3.1 What is the Sponsor's justification of the pediatric waiver request and is it acceptable?

The Sponsor's pediatric waiver request is pending for the Agency's PeRC's approval and it is scheduled to be discussed on February 13, 2013.

No studies were performed in post-pubertal adolescents under the age of 18 under this NDA as well as NDA 021871 for Loestrin® 24 Fe. However, the Sponsor believes that the efficacy and safety of MINASTRIN 24 Fe in post-pubertal adolescents under the age of 18 are expected to be the same as that established in women aged 18 to 35.

The Sponsor requested a full waiver of the requirement for pediatric studies associated with the submission of this NDA. Considering the target population, the Sponsor's request is acceptable from the Clinical Pharmacology standpoint.

2.3.2 Did the Sponsor conduct PK studies in population with renal or hepatic impairment?

No. The Sponsor did not conduct studies with MINASTRIN 24 Fe capsules nor Loestrin® 24 Fe (NDA 021871) in patients with renal or hepatic impairment. MINASTRIN 24 Fe capsules are contraindicated for liver tumors and liver disease. Given that the target population is premenopausal women, usage of MINASTRIN 24 Fe in patients with renal or hepatic impairment would be relatively small and therefore, is less of a concern. However, the product label should clearly state that studies in patients with renal or hepatic impairments were not conducted.

2.4 Extrinsic Factors

2.4.1 Did the Sponsor conduct any DDI studies?

No new DDI studies were conducted with MINASTRIN 24 Fe capsules. The Sponsor is proposing to use the information used regarding DDI from Loestrin® 24 Fe for labeling that includes the following information: *Drugs or herbal products that induce certain enzymes (for example, cytochrome P450 [CYP] 3A4) may decrease the effectiveness of COCs or increase breakthrough bleeding. Counsel patients to use a back-up or alternative method of contraception when enzyme inducers are used with COCs.*

2.5 General Biopharmaceutics

2.5.1 What is the quantitative composition of the drug products used in the clinical trials of this application?

The composition of the drug product is summarized in the Table 16 below:

Table 16: Comparison of the TBM Formulation of MINASTRIN 24 Fe Capsules and Marketed Loestrin® 24 Fe Tablets

Component	MINASTRIN 24 Fe Capsules (WC3042-05)		Loestrin® 24 Fe Tablets	
	mg/capsule	% w/w	mg/tablet	% w/w
NA, USP[1]	(b) (4)			
EE, USP[1]				
Sesame oil, NF				
Linoleoyl polyoxylglycerides, NF				
(b) (4)				
Dehydrated alcohol, USP				
(b) (4)				
Total				
(b) (4)				

1
2
3

Studies PR-00810 and PR-06011 were conducted with the TBM formulation of MINASTRIN 24 Fe capsules.

2.6 Bioanalytical Methods

2.6.1 Did the Sponsor use validated bioanalytical methods to generate data in the clinical studies?

Yes. Bioanalytical method validation and study reports were submitted for all studies that were reviewed. Acceptance criteria and method performance for NE and EE concentration

measurements are in compliance with the Agency's *Bioanalytical Method Validation Guidance* and the bioanalytical methods are acceptable.

Plasma samples from the BE study (Study PR-00810) and food effect study (Study PR-06011) were analyzed for NE and EE using a validated GC-MS method. ISR was conducted on approximately 5.3% and 5.0% of the study samples from the pivotal BE study and food effect study, respectively. Approximately 90% and 80% of the NE ISR results from the pivotal BE study and food effect study, respectively, and 84% and 84% of the EE ISR results from the pivotal BE study and food effect study, respectively, met the acceptance criteria of being within ±20% of the original reported concentration value for at least 67% of the ISR samples.

An OSI consult requesting inspections of the clinical and bioanalytical sites of the pivotal BE study was made on August 17, 2012. There were no significant objectionable issues identified and the Form FDA 483 was not issued. Details of the OSI inspection findings can be found in Dr. Michael Skelly's OSI consult review dated December 11, 2012 in DARRTS. See Appendix Section 4.2 of this review.

The bioanalytical methods are summarized in Table 17.

Table 17: Summary of Bioanalytical Methods

Study Number	Study Title	Biological Matrix	Analyte	Method	Dynamic Range
PR-00810	Single Dose BE Study	Plasma	NE	GC-MS	25-25000 pg/mL
		Plasma	EE	GC-MS	2.5-250 pg/mL
PR-06011	Food Effect Study	Plasma	NE	GC-MS	25-25000 pg/mL
		Plasma	EE	GC-MS	2.5-250 pg/mL

3 Detailed Labeling Recommendations

The following Clinical Pharmacology related parts of the Sponsor's proposed label were submitted in this NDA. ~~Strikes~~ are used for deletion and double underline is used for addition for the OCP's preliminary response to the Sponsor's proposal. Please note that Sections illustrated below does not necessarily reflect the entire corresponding Section of the product label.

Reviewer's Comment: *COC drug class labeling language was adopted from the most recently approved product labels of Beyaz® (NDA 022532; current label approved on April 10, 2012) and Natazia® (NDA 022252; current label approved on March 14, 2012) as applicable.*

Full Prescribing Information

2 DOSAGE AND ADMINISTRATION

2.1 How to Take Minastrin 24 Fe

To achieve maximum contraceptive effectiveness, ~~Minastrin 24 Fe~~ TRADENAME must be taken exactly as directed. Take one (b) (4) (b) (4) capsule by mouth at the same time every day (b) (4) apsules must be taken in the order directed on the blister pack.

Reviewer's Comment: *Per the CMC review team, MINASTRIN 24 Fe will be referred to as "capsules" not* (b) (4) *and corrections should be made throughout the product label accordingly (other applicable parts of the product label are not shown).*

7 DRUG INTERACTIONS

No drug~~-drug~~ interaction studies were conducted with ~~Minastrin 24 Fe~~ TRADENAME. Consult the labeling of all concurrently-used drugs to obtain further information about interactions with hormonal contraceptives or the potential for enzyme alterations.

7.1 (b) (4) **Effects of Other Drugs on Combined Oral Contraceptives**

(b) (4)

Substances diminishing the efficacy of COCs: Drugs or herbal products that induce certain enzymes including cytochrome P450 3A4 (CYP3A4), may decrease the effectiveness of COCs or increase breakthrough bleeding. Some drugs or herbal products that may decrease the effectiveness of hormonal contraceptives include phenytoin, barbiturates, carbamazepine, bosentan, felbamate,

griseofulvin, oxcarbazepine, rifampicin, topiramate and products containing St. John's wort. Interactions between oral contraceptives and other drugs may lead to breakthrough bleeding and/or contraceptive failure. Counsel women to use an alternative method of contraception or a back-up method when enzyme inducers are used with COCs, and to continue back-up contraception for 28 days after discontinuing the enzyme inducer to ensure contraceptive reliability.

Substances increasing the plasma concentrations of COCs: Co-administration of atorvastatin and certain COCs containing EE increase AUC values for EE by approximately 20%. Ascorbic acid and acetaminophen may increase plasma EE concentrations, possibly by inhibition of conjugation. CYP3A4 inhibitors such as itraconazole or ketoconazole may increase plasma hormone concentrations.

Human immunodeficiency virus (HIV)/ Hepatitis C virus (HCV) protease inhibitors and non-nucleoside reverse transcriptase inhibitors: Significant changes (increase or decrease) in the plasma concentrations of estrogen and progestin have been noted in some cases of co-administration with HIV/HCV 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.

(b) (4)

7.2 Effects of Combined Oral Contraceptives on Other Drugs

COCs containing EE 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.

Women on thyroid hormone replacement therapy may need increased doses of thyroid hormone because serum concentration of thyroid-binding globulin increases with use of COCs.

7.3 Interference with Laboratory Tests

The use of contraceptive steroids may influence the results of certain laboratory tests, such as coagulation factors, lipids, glucose tolerance, and binding proteins.

Reviewer's Comment: *Edits were made to make this Section consistent with the COC drug class language on the recently approved product label of Beyaz® (i.e., NDA 022532; current label approved on April 10, 2012).*

8 USE IN SPECIFIC POPULATIONS

8.7 Hepatic Impairment

(b) (4) The pharmacokinetics of TRADENAME has not been studied in subjects with hepatic impairment. ~~However, s~~Steroid hormones may be poorly metabolized in patients with (b) (4). Acute or chronic disturbances of liver function may necessitate the discontinuation of COC use until markers of liver function return to normal ~~and COC causation has been excluded~~ *[see Contraindications (4) and Warnings and Precautions (5.3)]*.

Reviewer's Comment: *Edits were made to make this Section consistent with the recently approved product label of Natazia® (i.e., NDA 022252; current label approved on March 14, 2012).*

12 CLINICAL PHARMACOLOGY

12.3 Pharmacokinetics

Absorption

In a single-dose, two-way-crossover clinical study conducted in 38 healthy, non-smoking premenopausal women under fasting condition, MINASTRIN 24 Fe was bioequivalent to LOESTRIN 24 Fe based on the exposure (AUC) and peak concentration (Cmax) of norethindrone and ethinyl estradiol.

Reviewer's Comment: *Description of the BE study was added to the beginning of the Absorption subsection.*

4 Appendices

4.1 Individual Study Reviews

4.1.1 BE Study: Study PR-00810

Title: A Study to Assess the BE of NE and EE Following Oral Administration of MINASTRIN 24 Fe Capsules Compared to Loestrin® 24 Fe Tablets in Healthy Female Volunteers,

Objectives: To assess the BE of NE and EE following oral administration of a MINASTRIN 24 Fe capsule (Test) compared to a Loestrin® 24 Fe tablet (Reference) in healthy female volunteers.

Clinical Study Center: Algorithme Pharma Inc., Mount-Royal, Quebec, Canada
Clinical Study Period: November 12, 2010-December 19, 2010

Bioanalytical Study Center: (b) (4)
Bioanalysis Period: December 6, 2010-January 23, 2011

Study Design, Treatments, and Drug Administration:
This was a single-center, open-label, randomized, 2-treatment, 2-period, 2-sequence, crossover study conducted in 40 healthy non-smoking females (18-35 years of age) with a BMI within the range of 19.0-29.9 kg/m^2.

In each treatment period, subjects checked into the clinic on the evening before the day of dosing and remained in-house until 36 hours after dosing. Outpatient visits were at 48 and 60 hours post-dose in each treatment period. Blood samples were collected pre-dose and through 60 hours post-dose for PK characterization.

All subjects received a single dose of one of the following Test or Reference treatments in each of the 2 treatment periods according to the randomization schedule following an overnight fasting of at least 8 hours:

- Test: One MINASTRIN 24 Fe capsule (1 mg NA / 20 µg EE; Formulation: WC3042-05)
- Reference: One Loestrin® 24 Fe tablet (1 mg NA / 20 µg EE; Formulation: WC2061)

All capsules/tablets were administered orally with 240 mL ambient-temperature water. Fasting continued for at least 4 hours following drug administration, after which a standardized lunch was served. Water was allowed *ad libitum* until 1 hour pre-dose and beginning 1 hour post-dose. Treatment periods were separated by at least 14 days.

Inclusion Criteria:

- Healthy, non-smoking females of any race between ages of 18-35 years at screening.
- Females with BMI in the range of 19.0-29.9 kg/m².
- Subjects who had history of regular menstrual periods.
- Subjects that were sexually inactive, or sexually active and 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 intra-uterine device (IUD) in place for at least 3 months

Exclusion Criteria:
Subjects who had any of the following criteria were excluded from the study:

- Pregnant or lactating females
- Tobacco or nicotine use in any form during the previous 6 months
- History or presence of alcoholism or drug abuse within the past 2 years
- Hypersensitivity or idiosyncratic reaction to estrogens or other hormonal agents
- Use of any substances known to be strong inhibitors of 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
- Use of any other oral contraceptive containing estrogens or any form of hormone therapy by any route during the 28 days prior to study start or use of medroxyprogesterone acetate contraceptive injection (e.g., Depo-Provera®) during the year prior to study start
- Use of alcohol-, xanthine-, or caffeine-containing foods or beverages within 72 hours prior to dosing or use of grapefruit-containing foods or beverages within 7 days prior to dosing
- Use of any over the counter (OTC) products, non-prescription preparations (including vitamins, minerals, and phytotherapeutic / herbal / plant-derived preparations) within 14 days prior to study start, unless deemed acceptable by the Investigator
- History or presence of significant: cardiovascular, pulmonary, hepatic, renal, hematologic, gastrointestinal, endocrine, gynecological, immunologic, dermatologic, neurologic, psychiatric, neoplastic or other disease which in the opinion of the investigator will interfere with the course of the study or pose a significant safety risk to the subject

Demographics of Subjects:
The mean age of the 40 subjects enrolled in the study was 28 (range: 18-35 years) with a mean BMI of 23.9 kg/m^2 (range: 20.1-29.7 kg/m^2). There were 36 Caucasians (90%), 3 Black or African Americans (7.5%), and 1 from other race groups (2.5%).

Concomitant Medication and Diet Restrictions:
No medication (including OTC products) was allowed during the 14 days preceding the study or throughout the study. This prohibition included vitamin supplements and herbal remedies.

Subjects were prohibited from smoking for the duration of the study. The consumption of alcohol-, caffeine- or xanthine-containing food or beverages was prohibited for 72 hours before each dose and throughout the blood sampling periods. The consumption of grapefruit-containing food or beverages was prohibited for 7 days before each dose and throughout the blood sampling periods.

Subjects who tested positive for cotinine, alcohol, or drugs in tests performed prior to dosing in either treatment period were withdrawn from the study.

PK Characterization:
Blood samples for plasma NE and EE concentration measurements were collected at pre-dose and 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 in each treatment period.

The following non-compartment PK parameters were calculated for plasma NE and EE:

- C_{max}: the maximum serum concentration observed

- $AUC_{0\text{-}tldc}$: the area under the serum concentration-time profile; calculated from time 0 to the last determinable concentration by the linear trapezoidal rule
- AUC_{inf}: the area under the serum concentration-time profile extrapolated to infinity
- T_{max}: the time of the maximum observed concentration
- k_{el}: terminal phase elimination rate constant (the negative slope of the log plasma concentration vs. time)
- $t_{1/2}$: terminal phase elimination half-life ($\ln 2/k_{el}$)

No value of k_{el}, AUC_{inf}, or $t_{1/2}$ was reported for cases that did not exhibit a terminal log-linear phase in the concentration versus time profile.

Sample Size Determination:
No detail information on sample size determination was provided in the application. In the study report, Sponsor states that "forty (40) healthy subjects were enrolled into the study; this number was considered adequate to evaluate the objectives of the study."

Reviewer's Comment: *The sample size of 40 appears to be adequate for BE assessment.*

Statistical Analysis for BE Assessment:
Analysis of variance (ANOVA) was performed on the natural log-transformed PK parameters C_{max}, AUC_{0-tldc}, and AUC_{inf}. The ANOVA model included sequence, treatment, and period as fixed effects and subject nested within sequence as a random effect. Each ANOVA included calculation of LSM, differences between adjusted treatment means, and the standard error associated with these differences. Statistical analyses were conducted using SAS®. The 90% CIs for the difference between treatments LSM were calculated for the parameters C_{max}, AUC_{0-tldc}, and AUC_{inf} using natural log-transformed data. The 90% CIs were expressed as a percentage relative to the LSM of the Reference treatment.

Safety Assessments:
- A vital signs assessment, urine drug, cotinine and alcohol screen, and serum pregnancy screen were repeated prior to dosing in each treatment period.
- Physical examination, vital signs assessment, electrocardiograms (ECG), clinical laboratory tests (hematology, serum biochemistry, and urinalysis), and serum pregnancy test were conducted at the final visit, 60 hours post-dose.
- Concomitant medication use was recorded at all visits; all adverse events (AE) were recorded.

Bioanalytical Method:
Bioanalysis was conducted at (b) (4) Human plasma samples were analyzed using a GC-MS method for the determination of NE and EE concentrations. Plasma samples were stored in the freezer at -20°C until sample analysis. The analytes were extracted from plasma into toluene. Extraction was followed by several clean-up steps, resulting in a final dichloromethane extract. After a two-step derivatization, 1-2 µL of the derivatized samples were injected for analysis. The GC-MS analysis was performed in the chemical ionization mode (negative ions) using ammonia as reagent gas. The GC-MS method was developed and validated with the dynamic range of 25-25000 pg/mL for NE and 2.5-250 pg/mL for EE.

The stability of NE and EE in human plasma samples was demonstrated during method validation; NE was stable in human plasma at room temperature for 144 hours and stable for

approximately 3 years at -20ºC ± 5ºC. EE was stable in human plasma at room temperature for 94 hours and stable for at least 97 days at -20ºC ± 5ºC. The established long term stability for both NE and EE was sufficient to cover the period of 73 days from the beginning of the BE study towards the end of bioanalysis. NE and EE were shown to be stable during 3 freeze-thaw cycles. Sample extracts were stable at room temperature for more than 6 days and sample derivatives were shown to be stable in the auto-sampler more than 10 days.

All calibration standards were prepared freshly each day by spiking 25 µL of corresponding NE or EE working solution into 1000 µL plasma. The quality control (QC) samples were prepared from the NE or EE stock solutions at the beginning of the study by spiking 25 µL of corresponding NE or EE working solution into 1000 µL plasma. The nominal QC sample concentrations for NE and EE were 75, 2500, and 20000 pg/mL and 7.5, 30, and 200 pg/mL, respectively. After preparation of the QC samples, they were stored at the same conditions as the study samples in the freezer at -20ºC ± 5ºC.

Accuracy during sample analysis was expressed as percent difference from theoretical concentration (i.e., %RE). For plasma NE the %RE ranged from -2.9% to 3.3% for calibration standards and -3.7% to 0.5% for QCs. For plasma EE the %RE ranged from -4.0% to 2.9% for calibration standards and -2.9% to 2.9% for QCs.

Precision of the calibration standards and QC samples during sample analysis was expressed as the percent coefficient of variation (%CV). For plasma NE the %CV ranged from 3.5% to 7.9% for calibration standards and 7.4% to 9.5% for QCs. For plasma EE the %CV ranged from 3.2% to 7.1% for calibration standards and 6.5% to 11.3% for QCs.

Linearity during sample analysis was described as the mean r^2 of the standard curves. The mean r^2 value was 0.995 for plasma NE and 0.996 for plasma EE.

ISR was conducted on 80 out of 1516 study samples (approximately 5.3%). The incurred samples were selected as follows: one sample in the range of C_{max} and one sample from the elimination phase. Out of the 80 samples, plasma NE concentration and plasma EE concentration values of 72 (90%) and 67 (83.6%) samples, respectively, were within ±20% of the original result and confirmed the reproducibility of the bioanalytical method.

An OSI consult requesting inspections of the clinical and bioanalytical sites of this pivotal BE study was made on August 17, 2012. There were no significant objectionable issues identified and the Form FDA 483 was not issued. Details of the OSI inspection findings can be found in Dr. Michael Skelly's OSI consult review dated December 11, 2012 in DARRTS. See Appendix Section 4.2 of this review.

Reviewer's Comment: *Acceptance criteria and assay performance for NE and EE bioanalysis are in compliance with the Agency's Bioanalytical Method Validation Guidance and the bioanalytical method are acceptable.*

Disposition of Subjects:
Forty (40) healthy, non-smoking, premenopausal females were enrolled into the study. Thirty-eight (38) subjects completed both treatment periods having received a single oral dose of the Test and Reference treatments. The following 2 subjects did not complete the study and were excluded from the BE analysis:

- Subject 505022: withdrew consent before dosing in Period 2 and only received one MINASTRIN 24 Fe capsule.

- Subject 505036: withdrew consent before dosing in Period 2 and only received one Loestrin® 24 Fe (WC2061) tablet

Protocol Deviations:
All enrolled subjects satisfied the entry criteria and received the correct treatment and dose. No use of concomitant medications was reported. There were no deviations that affected subject safety or any of the outcomes of the study. The following 4 subjects had a blood sample that was not collected due to the reasons listed below:

- Subject 505013: Difficulty with vein/catheter at 8 hour post-dose (Period 1)
- Subject 505011: Difficulty with vein/catheter at 40 min post-dose (Period 2)
- Subject 505030: Subject did not show up for the blood sample return visit at 48 hours post-dose (Period 2)
- Subject 505040: Subject did not show up for the blood sample return visit at 48 hours post-dose (Period 2)

None of these were considered to be significant enough to be excluded from the study enrollment or data analysis by the Investigator.

Reviewer's Comment: *The T_{max} of Period 2 for Subject 505011 was 2.5 hours post-dose and the missing sample was not the C_{max} sample. The 48 hour post-dose samples in Period 2 were missing from both Subjects 505030 and 505040 but their 60 hour post-dose samples in Period 2 were obtained adequately. This reviewer agrees that none of these were significant enough to excluded these subjects from the BE analysis as only one non-C_{max} sample from each individual was missing.*

PK and BE Assessment Results:
Following administration of a MINASTRIN 24 Fe capsule (Test) or WC2061 tablet (Reference), plasma NE and EE concentrations increased until T_{max} were reached at 0.7-4 hours and decreased over the remainder of the sampling period. Mean (SD) PK parameters of NE and EE are summarized in Tables A-1-1 and A-1-2.

Table A-1-1: Mean (SD) Plasma PK Parameters of NE Following a Single Dose of a MINASTRIN 24 Fe Capsule (Test) or WC2061 Tablet (Reference) (N=38)

Parameter	Test	Reference
$AUC_{0\text{-tldc}}$ (pg·hr/mL)	42474.0 (19476.2)	46141.2 (20102.6)
AUC_{inf} (pg·hr/mL)	43175.2 (19729.4)	46823.0 (20604.4)
C_{max} (pg/mL)	9255.0 (3339.6)	8485.8 (2720.4)
T_{max} (hr)[a]	1.1 (0.7-4.0)	1.7 (0.7-6.0)
$t_{½}$ (hr)	9.2 (2.6)	8.7 (2.4)

Test: One MINASTRIN 24 Fe capsule (1 mg NA / 20 µg EE; Formulation: WC3042-05)
Reference: One Loestrin® 24 Fe tablet (1 mg NA / 20 µg EE; Formulation: WC2061)
[a] Median (minimum-maximum)

Table A-1-2: Mean (SD) Plasma PK Parameters of EE Following a Single Dose of a MINASTRIN 24 Fe Capsule (Test) or WC2061 Tablet (Reference) (N=38)

Parameter	Test	Reference
$AUC_{0\text{-tldc}}$ (pg·hr/mL)	523.6 (146.0)	539.2 (145.9)
AUC_{inf} (pg·hr/mL)	597.0 (171.7)[b]	609.3 (154.7)[c]
C_{max} (pg/mL)	61.9 (20.2)	65.9 (14.6)
T_{max} (hr)[a]	2.0 (1.0-4.0)	1.7 (0.7-4.0)
$t_{½}$ (hr)	13.5 (7.5)[b]	12.8 (6.1)[c]

Test: One MINASTRIN 24 Fe capsule (1 mg NA / 20 µg EE; Formulation: WC3042-05)
Reference: One Loestrin® 24 Fe tablet (1 mg NA / 20 µg EE; Formulation: WC2061)
[a] Median (minimum-maximum)
[b] N=34 as a terminal phase rate constant could not be determined for 4 subjects who received the Test treatment; Excluded subjects: 505011, 505016, 505019, and 505039.
[c] N=36 as a terminal phase rate constant could not be determined for 2 subjects who received the Reference treatment; Excluded subjects: 505005 and 505020.

The obtained mean concentration-time profiles for NE and EE are presented in Figures A-1-1 and A-1-2, respectively.

Figure A-1-1: Mean NE Plasma Concentration-Time Profiles Following a Single Dose of a MINASTRIN 24 Fe Capsule (Test) or WC2061 Tablet (Reference) (N=38)

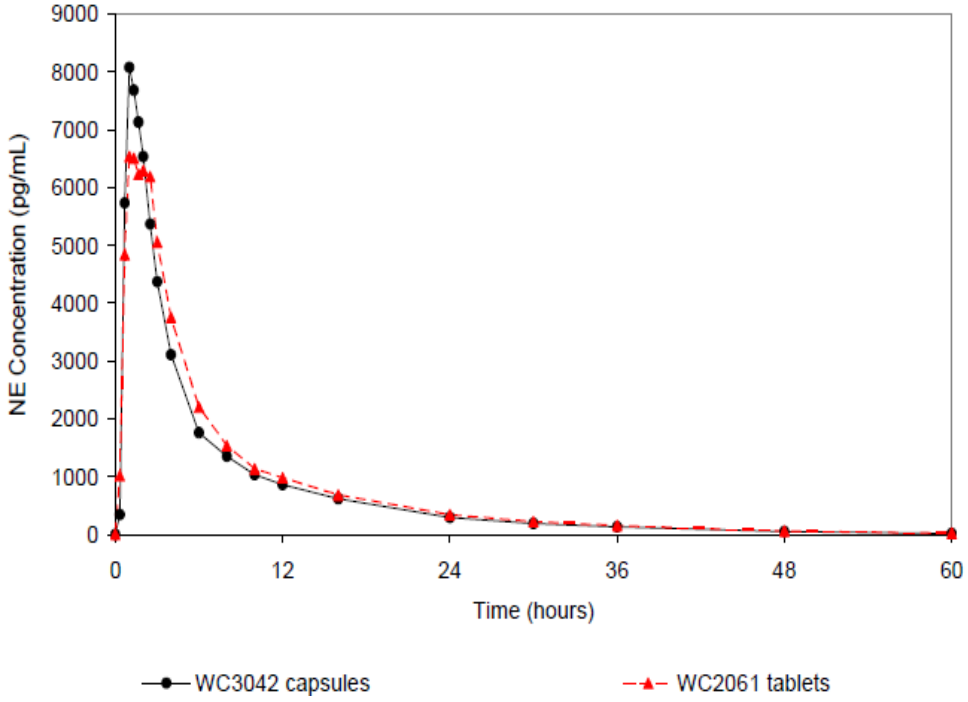
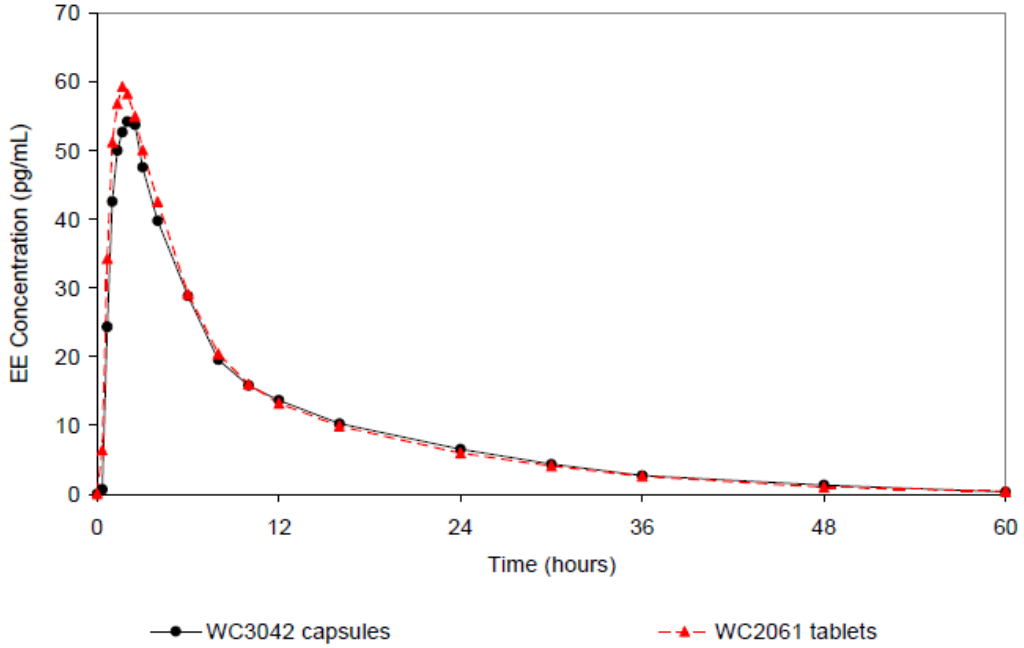


Figure A-1-2: Mean EE Plasma Concentration-Time Profiles Following a Single Dose of a MINASTRIN 24 Fe Capsule (Test) or WC2061 Tablet (Reference) (N=38)



The 90% CIs for the difference between the Test (MINASTRIN 24 Fe capsule) and Reference (WC2061 tablet) LSM with respect to both NE and EE for the parameters C_{max}, AUC_{0-tldc}, and AUC_{inf} using natural log transformed data were within the BE limits of 80.00-125.00%.

Reviewer's Comment: *While details of power calculation were not provided, Sponsor states the following in their study report: "The study had greater than 90% power to conclude BE between the 2 formulations."*

Table A-1-3: Summary of BE Analysis Results of NE PK Parameters
Following a Single dose of a MINASTRIN 24 Fe Capsule (Test) or a WC2061 Tablet (Reference) (N=38)

Parameter	Geometric Mean		LSM Ratio x 100 (Test/Reference)	90% CI
	Test	Reference		
AUC_{0-tldc} (pg·hr/mL)	38711	42500	91.1	87.4-94.9
AUC_{inf} (pg·hr/mL)	39399	43128	91.4	87.6-95.3
C_{max} (pg/mL)	8588	8014	107.2	100.0-114.9

Test: One MINASTRIN 24 Fe capsule (1 mg NA / 20 µg EE; Formulation: WC3042-05)
Reference: One Loestrin® 24 Fe tablet (1 mg NA / 20 µg EE; Formulation: WC2061)

Table A-1-4: Summary of BE Analysis Results of EE PK Parameters
Following a Single dose of a MINASTRIN 24 Fe Capsule (Test) or a WC2061 Tablet (Reference) (N=38)

Parameter	Geometric Mean		LSM Ratio x 100 (Test/Reference)	90% CI
	Test	Reference		
AUC_{0-tldc} (pg·hr/mL)	503.2	520.5	96.7	92.1-101.6
AUC_{inf} (pg·hr/mL)[a]	576.7	580.4	99.4	94.2-104.8
C_{max} (pg/mL)	59.1	64.5	91.7	86.8-97.0

Test: One MINASTRIN 24 Fe capsule (1 mg NA / 20 µg EE; Formulation: WC3042-05)
Reference: One Loestrin® 24 Fe tablet (1 mg NA / 20 µg EE; Formulation: WC2061)
[a] N=32 as a terminal phase rate constant could not be determined for 4 subjects who received the Test treatment and 2 subjects who received the Reference treatment

Reviewer's Comment: *The Sponsor's BE analysis results appear to be adequate. It should be noted that the analysis for EE AUC_{inf} was performed using N=32 subjects as a terminal phase rate constant could not be determined for 4 subjects who received the Test treatment and 2*

subject who received the Reference treatment. These 6 subjects were excluded from the BE analysis based on AUC_{inf}. Excluded subjects were Subjects 505011, 505016, 505019, and 505039 from the Test treatment and Subjects 505005 and 505020 from the Reference treatment.

This reviewer concludes that BE between MINASTRIN 24 Fe capsules and Loestrin® 24 Fe (WC2061) tablets regarding both NE and EE has been established following a single dose administration under fasting condition.

Safety Results:
Per Sponsor, 14 (36%) of the 39 subjects who received MINASTRIN 24 Fe capsules reported 20 mostly mild treatment emergent adverse events (TEAE), the most common of which were nausea (3 events in 3 subjects) and acne (3 events in 3 subjects).

Fourteen (36%) of the 39 subjects who received WC2061 tablets reported 20 mostly mild TEAEs, the most common of which were nausea (2 events in 2 subjects), vessel puncture site reaction (2 events in 2 subjects), and paraesthesia (2 events in 2 subjects).

No serious AEs (SAE) were reported. Changes noted in laboratory test values were small and were not thought to be drug related. No significant changes in vital signs, physical examinations, or ECGs were observed during the study. Single oral doses of MINASTRIN 24 Fe capsules and WC2061 tablets were well tolerated.

Reviewer's Comment: *It appears that the Test (MINASTRIN 24 Fe capsules) and Reference (Loestrin® 24 Fe [WC2061] tablets) treatments had similar safety profiles.*

Conclusion:
BE between MINASTRIN 24 Fe capsules and Loestrin® 24 Fe tablets regarding both NE and EE has been established following a single dose administration under fasting condition.

4.1.2 Food Effect Study: Study PR-06011

Title: A Study to Assess the Effect of Food on the PK of EE and NE Following Oral Administration of MINASTRIN 24 Fe Capsules in Healthy Female Volunteers.

Objectives: To assess the PK of EE and NE following oral administration of a MINASTRIN 24 Fe capsule under fasting condition (Reference) as compared to a MINASTRIN 24 Fe capsule under fed condition (Test) in healthy female volunteers.

Clinical Study Center: Algorithme Pharma Inc., Mount-Royal, Quebec, Canada
Clinical Study Period: October 30, 2011-November 15, 2011

Bioanalytical Study Center: (b) (4)
Bioanalysis Period: November 29, 2011-January 27, 2012

Study Design, Treatments, and Drug Administration:
This single-center, open-label, randomized, balanced, 2-treatment, 2-period, 2-sequence crossover food-effect study was conducted under medical supervision in 26 healthy, non-smoking, premenopausal females (age: 18-45 years; BMI: 19.0-29.9 kg/m^2). All subjects received the following Test and Reference treatments orally with 240 mL ambient-temperature water following an overnight fasting of at least 10 hours:

- Test: One MINASTRIN 24 Fe capsule (1 mg NA/20 µg EE) under fed condition
- Reference: One MINASTRIN 24 Fe capsule (1 mg NA/20 µg EE) under fasting condition

The formulation number of the capsules is WC3042-05, batch number is 1122973, and the capsules were manufactured by (b) (4)

Subjects reported to the clinic at least 10 hours prior to study drug administration and remained in house until 36 hours post-dose. Outpatient visits were at 48 and 60 hours post-dose in each treatment period.

Subjects assigned to the Test treatment received a standardized high-fat (approximately 50% of total caloric content of the meal), high-calorie (800-1000 calories) breakfast, and it was consumed over a 25-30 minute period. Within 5 minutes of having completed the breakfast, a single MINASTRIN 24 Fe capsule was orally administered with 240 mL of ambient-temperature water. No additional food was permitted until 4 hours post-dose. A single MINASTRIN 24 Fe capsule was given orally to subjects assigned to the Reference treatment with 240 mL of ambient-temperature water under fasting condition. No food was permitted until 4 hours post-dose. Treatment periods were separated by at least 7 days. Blood samples were collected pre-dose and through 60 hours post-dose for PK characterization.

Inclusion Criteria:

- Healthy, non-smoking females of any race between ages of 18-45 years at screening.
- Females with BMI in the range of 19.0-29.9 kg/m².
- Subjects who had history of regular menstrual periods.
- Subjects that were sexually inactive, or sexually active and 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

Exclusion Criteria:
Subjects who had any of the following criteria were excluded from the study:

- Pregnant or lactating females
- Tobacco or nicotine use in any form during the previous 6 months
- History or presence of alcoholism or drug abuse within the past 2 years
- Hypersensitivity or idiosyncratic reaction to estrogens or other hormonal agents
- Use of any prescription medications / products within the 14 days prior to Day -1, Period 1 unless deemed acceptable by the Investigator in consultation with the Sponsor
- Use of any substances known to be strong inhibitors of 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
- Use of any other oral contraceptive containing estrogens or any form of hormone therapy by any route during the 28 days prior to study start or use of medroxyprogesterone acetate contraceptive injection (e.g., Depo-Provera®) during the year prior to study start
- Use of any OTC products, non-prescription preparations (including vitamins, minerals, and phytotherapeutic / herbal / plant-derived preparations) within 14 days prior to study start, unless deemed acceptable by the Investigator
- History or presence of significant: cardiovascular, pulmonary, hepatic, renal, hematologic, gastrointestinal, endocrine, gynecological, immunologic, dermatologic, neurologic, psychiatric, neoplastic or other disease which in the opinion of the investigator will interfere with the course of the study or pose a significant safety risk to the subject

Demographics of Subjects:
The mean age of the 26 subjects enrolled in the study was 36 (range: 24-45 years) with a mean BMI of 24.4 kg/m^2 (range: 19.9-29.7 kg/m^2). There were 23 Caucasians (88.5%), 3 Black or African Americans (11.5%).

Concomitant Medication and Diet Restrictions:
No medication (including OTC products) was allowed during the 14 days preceding the study and throughout the entire study. This prohibition included vitamin supplements and herbal remedies.

The consumption of alcohol-, caffeine- or xanthine-containing food or beverages was prohibited for 24 hours before each dose and throughout the blood sampling periods. The consumption of grapefruit-containing foods or beverages was prohibited for 7 days before each dose and throughout the blood sampling periods.

Subjects who tested positive for cotinine, alcohol, or drugs in tests performed prior to dosing in either treatment period were withdrawn from the study.

PK Characterization:
Blood samples for PK characterization were collected at pre-dose (within 2 hours prior to study drug administration) and 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.

The following non-compartment PK parameters were calculated for plasma NE and EE:

- C_{max}: the maximum serum concentration observed

- $AUC_{0\text{-}tldc}$: the area under the serum concentration-time profile; calculated from time 0 to the last determinable concentration by the linear trapezoidal rule
- AUC_{inf}: the area under the serum concentration-time profile extrapolated to infinity
- T_{max}: the time of the maximum observed concentration
- k_{el}: terminal phase elimination rate constant (the negative slope of the log plasma concentration vs. time)
- $t_{1/2}$: terminal phase elimination half-life (ln $2/k_{el}$)

No value of k_{el}, AUC_{inf}, or $t_{1/2}$ was reported for cases that did not exhibit a terminal log-linear phase in the concentration versus time profile.

Sample Size Determination:
No detail information on sample size determination was provided in the application.

Reviewer's Comment: *The sample size of 24 appears to be adequate for food effect assessment.*

Statistical Analysis for Food Effect Assessment:
ANOVA were performed on the natural log-transformed PK parameters C_{max}, AUC_{0-tldc}, and AUC_{inf}. The ANOVA model included sequence, treatment, and period as fixed effects and subject nested within sequence as a random effect. Each ANOVA included calculation of LSM, differences between adjusted treatment means and the standard error associated with these differences. Statistical analyses were conducted using SAS®. The 90% CIs for the difference between treatments LSM were calculated for the parameters C_{max}, AUC_{0-tldc}, and AUC_{inf} using natural log-transformed data. The 90% CIs were expressed as a percentage relative to the LSM of the Reference treatment.

Safety Assessments:
- A vital signs assessment, urine drug, cotinine and alcohol screen, and serum pregnancy screen were repeated prior to dosing in each treatment period.
- Physical examination, vital signs assessment, ECGs, clinical laboratory tests (hematology, serum biochemistry, and urinalysis), and serum pregnancy test were conducted at the final visit, 60 hours post dose.
- Concomitant medication use was recorded at all visits; all adverse events were recorded.

Bioanalytical Method:
Bioanalysis was conducted at (b) (4) Human plasma samples were analyzed using a GC-MS method for the simultaneous determination of NE and EE concentrations. Plasma samples were stored in the freezer at -20°C until sample analysis. The analytes were extracted from plasma into toluene. Extraction was followed by several clean-up steps, resulting in a final dichloromethane extract. After a two-step derivatization, 1-2 µL of the derivatized samples were injected for analysis. The GC-MS analysis was performed in the chemical ionization mode (negative ions) using ammonia as reagent gas. The GC-MS method was developed and validated with the dynamic range of 25-25000 pg/mL for NE and 2.5-250 pg/mL for EE.

The stability of NE and EE in human plasma samples was demonstrated during method validation; NE was stable in human plasma at room temperature for 144 hours and stable for approximately 3 years at -20ºC ± 5ºC. EE was stable in human plasma at room temperature for 94 hours and stable for at least 97 days at -20ºC ± 5ºC. The established long term stability for both NE and EE was sufficient to cover the period of 89 days from the beginning of the food

effect study towards the end of bioanalysis. NE and EE were shown to be stable during 3 freeze-thaw cycles. Sample extracts were stable at room temperature for more than 6 days and sample derivatives were shown to be stable in the auto-sampler for more than 10 days.

All calibration standards were prepared freshly each day by spiking 25 µL of corresponding NE or EE working solution into 1000 µL plasma. The QC samples were prepared from the NE or EE stock solutions at the beginning of the study by spiking 25 µL of corresponding NE or EE working solution into 1000 µL plasma. The nominal QC sample concentrations for NE and EE were 75, 2500, and 20000 pg/mL and 7.5, 30, and 200 pg/mL, respectively. After preparation of the QC samples, they were stored at the same conditions as the study samples in the freezer at -20ºC ± 5ºC.

Accuracy during sample analysis was expressed as %RE. For plasma NE the %RE ranged from -6.5% to 5.6% for calibration standards and -5.2% to 4.2% for QCs. For plasma EE the %RE ranged from -2.8% to 5.1% for calibration standards and -4.9% to -0.9% for QCs.

Precision of the calibration standards and QC samples during sample analysis was expressed as %CV. For plasma NE the %CV ranged from 2.4% to 6.9% for calibration standards and 6.3% to 12.5% for QCs. For plasma EE the %CV ranged from 2.6% to 7.4% for calibration standards and 4.4% to 11.7% for QCs.

Linearity during sample analysis was described as the mean r^2 of the standard curves. The mean r^2 value was 0.994 for plasma NE and 0.996 for plasma EE.

ISR was conducted on 50 out of 999 study samples (approximately 5.0%). The incurred samples were selected as follows: one sample in the range of C_{max} and one sample from the elimination phase. Out of the 50 samples, plasma NE concentration and plasma EE concentration values of 40 (80%) and 47 (84%) samples, respectively, were within ±20% of the original result and confirmed the reproducibility of the bioanalytical method.

Reviewer's Comment: *Acceptance criteria and assay performance for NE and EE bioanalysis are in compliance with the Agency's Bioanalytical Method Validation Guidance and the bioanalytical method is acceptable.*

Disposition of Subjects:
Twenty six (26) healthy, non-smoking premenopausal females were enrolled into the study. Twenty five (25) subjects completed both treatment periods. The following subject did not complete the study and was excluded from the food effect analysis:

- Subject 505209: withdrew consent after completing Period 1

In addition, Subject 505207 was excluded from the food effect analysis per protocol due to the presence of a measurable concentration of EE in a pre-dose sample. As a result, 24 subjects were included in the food effect analysis.

Protocol Deviations:
All enrolled subjects satisfied the entry criteria and received the correct treatment and dose. No use of concomitant medications was reported. There were no deviations that affected subject safety or any of the outcomes of the study. The following subject had a blood sample that was not collected due to the reasons listed below:

- Subject 505224: Subject did not show up for the blood sample return visit (60 hour post-dose of Period 1)

This was not considered to be significant enough to be excluded from the study enrollment or data analysis by the Investigator.

Reviewer's Comment: *This reviewer agrees that this was not significant enough to be excluded from the data analysis.*

PK and Food Effect Assessment Results:
Following administration of a MINASTRIN 24 Fe capsule with food (Test) or without food (Reference), plasma NE and EE concentrations increased until T_{max} were reached at 0.7-12 hours and decreased over the remainder of the sampling period. Mean (SD) PK parameters of NE and EE are summarized in Tables A-2-1 and A-2-2.

Table A-2-1: Mean (SD) Plasma PK Parameters of NE
Following a Single Dose of a MINASTRIN 24 Fe Capsule with Food (Test) or without Food (Reference) (N=24)

Parameter	Test	Reference
$AUC_{0\text{-}tldc}$ (pg·hr/mL)	52550.8 (19569.4)	46578.8 (18139.4)
AUC_{inf} (pg·hr/mL)	53830.4 (19837.6)	47444.8 (18197.0)
C_{max} (pg/mL)	6592.1 (3804.2)	9007.1 (3095.1)
T_{max} (hr)[a]	3.3 (0.7-10.0)	1.3 (1.0-3.0)
$t_{½}$ (hr)	11.0 (2.8)	11.0 (3.2)

[a] Median (minimum-maximum)

Table A-2-2: Mean (SD) Plasma PK Parameters of EE
Following a Single Dose of a MINASTRIN 24 Fe Capsule with Food (Test) or without Food (Reference) (N=24)

Parameter	Test	Reference
$AUC_{0\text{-}tldc}$ (pg·hr/mL)	614.6 (261.7)	652.7 (287.9)
AUC_{inf} (pg·hr/mL)	781.3 (370.3)[b]	763.5 (366.7)[c]
C_{max} (pg/mL)	42.3 (19.3)	59.3 (15.4)
T_{max} (hr)[a]	3.5 (1.0-12.0)[b]	2.0 (1.3-4.0)[c]
$t_{½}$ (hr)	19.1 (11.2)	16.9 (8.2)

[a] Median (minimum-maximum)
[b] N=23 as a terminal phase rate constant could not be determined for 1 subject who received the Test treatment; Excluded subject: 505201.
[c] N=21 as a terminal phase rate constant could not be determined for 3 subjects who received the Reference treatment; Excluded subjects: 505203, 505215, and 505223.

The obtained mean concentration-time profiles for NE and EE are presented in Figures A-2-1 and A-2-2, respectively.

Figure A-2-1: Mean NE Plasma Concentration-Time Profiles Following a Single Dose of a MINASTRIN 24 Fe Capsule with Food (Test) or without Food (Reference) (N=24)

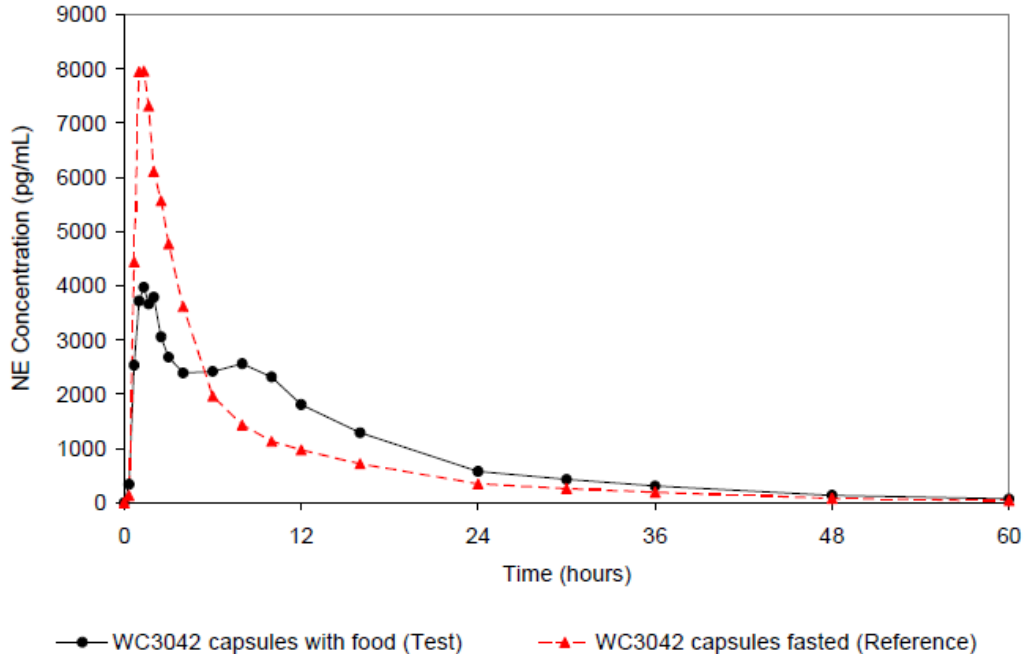
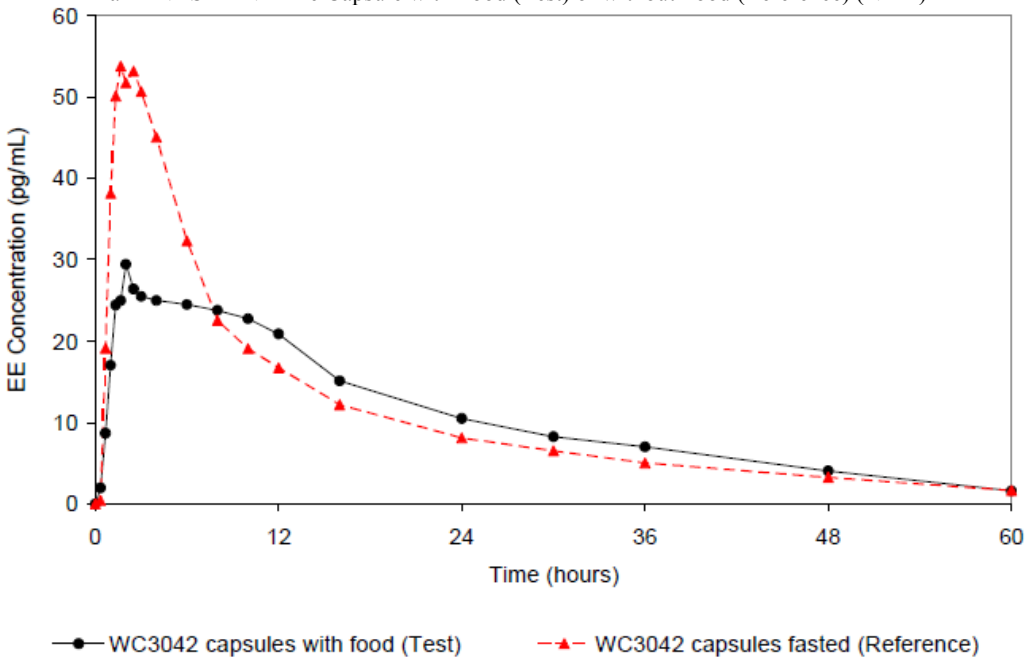


Figure A-2-2: Mean EE Plasma Concentration-Time Profiles Following a Single Dose of a MINASTRIN 24 Fe Capsule with Food (Test) or without Food (Reference) (N=24)



C_{max} values were decreased by 35% and 34% for NE and EE, respectively, and median T_{max} values were delayed by 2 hours and 1.5 hours for NE and EE, respectively, when MINASTRIN 24 Fe capsules were administered with a high fat and high calorie meal. However, the 90% CIs for the difference between the Test (MINASTRIN 24 Fe capsule with food) and Reference (MINASTRIN 24 Fe capsule without food) LSM with respect to both NE and EE for the parameters AUC_{0-tldc}, and AUC_{inf} using natural log transformed data were within the BE limits of 80.00-125.00%.

Reviewer's Comment: *While details of power calculation were not provided, Sponsor states the following in their study report: "The study had greater than 90% power to conclude BE (i.e., no effect) between the 2 treatments."*

Table A-2-3: Summary of NE PK Parameters following a Single dose of a MINASTRIN 24 Fe Capsule with Food (Test) or without Food (Reference) (N=24)

Parameter	Geometric Mean		LSM Ratio x 100 (Test/Reference)	90% CI
	Test	Reference		
$AUC_{0\text{-}tldc}$ (pg·hr/mL)	49242	42961	114.6	108.8-120.8
AUC_{inf} (pg·hr/mL)	50488	43886	115.0	109.3-121.11
C_{max} (pg/mL)	5548	8491	65.3	53.9-79.3

Table A-2-4: Summary of EE PK Parameters following a Single dose of a MINASTRIN 24 Fe Capsule with Food (Test) or without Food (Reference) (N=24)

Parameter	Geometric Mean		LSM Ratio x 100 (Test/Reference)	90% CI
	Test	Reference		
$AUC_{0\text{-}tldc}$ (pg·hr/mL)	568.4	600.1	94.7	89.1-100.8
AUC_{inf} (pg·hr/mL)[a]	703.5	705.7	99.7	91.7-108.3
C_{max} (pg/mL)	38.3	57.6	66.5	57.5-76.8

[a] N=20 as a terminal phase rate constant could not be determined for 1 subject who received the Test treatment and 3 subjects who received the Reference treatment

Reviewer's Comment: *The Sponsor's results of BE analysis for the assessment of food effect on NE and EE PK appear to be adequate. It should be noted that the analysis for EE AUC_{inf} was performed using N=20 subjects as a terminal phase rate constant could not be determined for 1 subject who received the Test treatment and 3 subjects who received the Reference treatment. These 4 subjects were excluded from the BE analysis based on AUC_{inf}. Excluded subjects were Subjects 505201 from the Test treatment and Subjects 505203, 505215, and 505223 from the Reference treatment.*

For NE, median T_{max} was delayed from 1.3 to 3.3 hours and C_{max} decreased 35% when MINASTRIN 24 Fe capsules were administered with food. However, the 90% CI for NE AUC was within the BE limits of 80.00-125.00% indicating that the extent of NE absorption was not affected by administration with food.

For EE, median T_{max} was delayed from 2.0 to 3.5 hours and C_{max} decreased 34% when MINASTRIN 24 Fe capsules were administered with food. However, the 90% CI for EE AUC was within the BE limits of 80.00-125.00% indicating that the extent of EE absorption was not affected by administration with food.

It should be noted that a single dose administration of Loestrin® 24 Fe tablet with food decreased the C_{max} of NE by 11% and increased the NE AUC by 27%. For EE, food decreased the C_{max} by 30% but did not affect the AUC (i.e., the 90% CI for EE AUC was within the BE limits of 80.00-125.00%). Reference is made to Dr. Myong-Jin Kim's Clinical Pharmacology review under NDA 021871 dated February 17, 2006 in DARRTS.

In addition, the Phase 3 safety and efficacy Study PR-03903 submitted to the original NDA 021871 for Loestrin® 24 Fe was conducted without regard to food intake and it is stated that "Loestrin 24 Fe tablets may be administered without regard to meals" under the Dosage and Administration section of the current Loestrin® 24 Fe product label. Reference is made to Dr. Daniel Davis' Clinical review under NDA 021871 dated February 17, 2006 in DARRTS.

This reviewer concludes that administration of MINASTRIN 24 Fe capsules with food decreased the rate but not the extent of NE and EE absorption and MINASTRIN 24 Fe capsules may be administered without regard to meals.

Safety Results:
Per Sponsor, 13 (52%) of the 25 subjects who received the MINASTRIN 24 Fe capsule with food reported 27 mostly mild TEAEs, the most common of which were headache (5 events in 5 subjects) and diarrhea (2 events in 2 subjects). Eleven (42%) of the 26 subjects who received the MINASTRIN 24 Fe capsule fasted reported 32 mostly mild TEAEs, the most common of which were headache (6 events in 5 subjects), abdominal pain (4 events in 3 subjects) and diarrhea (2 events in 2 subjects).

No significant changes in vital signs or physical examination results were observed during the study. No SAEs were reported. The overall nature and frequency of AEs seen in this study were consistent with what would be expected in subjects receiving single doses of orally administered NE and EE.

Reviewer's Comment: *It appears that both treatments had similar safety profiles.*

Conclusion:
When MINASTRIN 24 Fe capsules were administered with food the median T_{max} values were delayed by 2 hours and 1.5 hours for NE and EE, respectively, and C_{max} values decreased 35% and 34% for NE and EE, respectively. However, the 90% CIs for NE and EE exposure (i.e., AUC) were within the BE limits of 80.00-125.00% indicating that the extent of NE and EE absorption was not affected by administration with food. This supports the proposed dosage and administration instruction of MINASTRIN 24 Fe capsules being administered without regard to meals.

4.2 Office of Scientific Investigations Consult Report

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: December 7, 2012

TO: Hylton V. Joffe, M.D., M.M.Sc.
Director, Division of Reproductive and Urologic Products
Office of New Drugs

FROM: Michael F. Skelly, Ph.D.
Pharmacologist, Bioequivalence Branch
Division of Bioequivalence and GLP Compliance
Office of Scientific Investigations

THROUGH: Sam H. Haidar, R.Ph., Ph.D.
Chief, Bioequivalence Branch
Division of Bioequivalence and GLP Compliance
Office of Scientific Investigations
and
William H. Taylor, Ph.D.
Director,
Division of Bioequivalence and GLP Compliance
Office of Scientific Investigations

SUBJECT: Review of EIR Covering NDA 204-426, Norethindrone Acetate and Ethinyl Estradiol, Sponsored by Warnert Chilcott (U.S.), LLC

At the request of DRUP, the Division of Bioequivalence and GLP Compliance (DBGC) conducted inspections for the following bioequivalence study:

Study Number: PR-00810
Study Title: "A Study to Assess the Bioavailability of Ethinyl Estradiol and Norethindrone Following Oral Administration of WC3042-05 Capsules Compared to Loestrin Tablets in Healthy Human Volunteers"

The audits included thorough examination of study records, facilities, and equipment, and interviews and discussions with the firms' management and staff.

Clinical Site: Algorithme Pharma, Inc.
Mount-Royal, Canada

Clinical portions of the study were audited at Algorithme by ORA Investigator Hugh McClure, November 5 to November 9, 2012. Form FDA 483 was not issued.

Analytical Site: (b) (4)

Analytical portions of the study were audited at (b) (4) by ORA Investigator Terrance Thomas and OSI/DBGLPC Scientist Michael F. Skelly, (b) (4) Form FDA 483 was not issued for this study.

Conclusions:

Following the above inspections, the DBGLPC reviewer recommends the following:

- Pharmacokinetic data from study PR-00810, Project UA253 are acceptable for review.

Final Classifications:

NAI: **Algorithme**
Mount Royal, Canada
FEI 3006174665

NAI: (b) (4)

CC:
CDER OSI PM TRACK
OSI/DBGLPC/Taylor/Haidar/Dejernett/Skelly/CF
OND/DRUP/Joffe/Lucarelli
OCP/DCPIII/Bashaw/Lee/Kim/Yu
OCP/DCPIII/Li (re: NDA 204-654)
CIN-DO/HFR-CE4530/McClure
DAL-DO/HFR-SW1515/Thomas
Draft: MFS 12/6/12
Edits: SHH 12/7/2012
DSI: 6369; O:\BE\EIRCOVER\204426.war.noreth.doc
FACTS: 1435606

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

/s/

MICHAEL F SKELLY
12/07/2012

SAM H HAIDAR
12/07/2012

WILLIAM H TAYLOR
12/11/2012

4.3 Clinical Pharmacology Filing Memo

Office of Clinical Pharmacology New Drug Application Filing and Review Form			
General Information About the Submission			
	Information		Information
NDA Number	204426	Brand Name	WC3026
OCP Division	DCP3	Generic Name	NA / EE
Medical Division	DRUP	Drug Class	Combination oral contraceptive (COC)
OCP Reviewer	Chongwoo Yu, Ph.D.	Indication(s)	Prevention of pregnancy
OCP Team Leader	Myong-Jin Kim, Pharm.D.	Dosage Form	Soft gelatin capsules
Secondary Reviewer	Myong-Jin Kim, Pharm.D.	Dosing Regimen	1 mg NA and 0.02 mg EE taken daily for 24 days followed by one ferrous fumarate soft gelatin capsule taken daily for 4 days
Date of Submission	June 21, 2012	Route of Administration	Oral
Estimated Due Date of OCP Review	February 21, 2013	Sponsor	Warner Chilcott Company, LLC
PDUFA Due Date	April 21, 2013	Priority Classification	Standard
Division Due Date	March 31, 2013		

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:	X	1		PRO-00910
multiple dose:				
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 1:				
Phase 2:				
Phase 3:				
PK/PD:				
Phase 1 and/or 2, proof of concept:				
Phase 3 clinical trial:				
Population Analyses -				
PK:				
PD:				
II. Biopharmaceutics				
Absolute bioavailability:				
Relative bioavailability -				
solution as reference:				
alternate formulation as reference:				
Bioequivalence studies -				
traditional design; single / multi dose:	X	1		PR-00810
replicate design; single / multi dose:				
Food-drug interaction studies:	X	1		PR-06011
Dissolution:				
(IVIVC):				
Bio-wavier request based on BCS				
BCS class				
III. Other CPB Studies				
Irritation and sensitization				
Genotype/phenotype studies:				
Chronopharmacokinetics				
Pediatric development plan				
Immunogenicity profile				
Thorough QT study				
Literature References				
Total Number of Studies		3		

Other comments	
	Comments
QBR questions (key issues to be considered)	1. Establishment of BE between WC3026 and Loestrin® 24 Fe 2. Evaluation of food effect involving WC3026 3. OSI inspection on clinical and bioanalytical sites for the pivotal BE study 4. Acceptability of bioanalytical method validation and performance
Other comments or information not included above	• A formal OSI consult on clinical and bioanalytical study sites will be requested.

Clinical Pharmacology Filing Memo

NDA: 204426
Compound: WC3042 (1 mg norethindrone acetate [NA] and 0.02 mg ethinyl estradiol [EE])
Sponsor: Warner Chilcott Company, LLC

Date: 8/16/2012
Reviewer: Chongwoo Yu, Ph.D.

Introduction:
Warner Chilcott submitted New Drug Application (NDA) 204426 for WC3042 in accord with Section 505 (b)(1) on June 21, 2012 to seek an approval for prevention of pregnancy. WC3042 is a new dosage form for oral contraception consisting of one soft gelatin capsule (WC3042-05 formulation) containing 1 mg NA and 0.02 mg EE taken daily for 24 days followed by one ferrous fumarate soft gelatin capsule (WC3042-(b) (4) formulation) taken daily for 4 days to facilitate a 28-day regimen. The proposed regimen is the same as the approved regimen for Warner Chilcott's Loestrin® 24 Fe (NA and EE tablets, USP and ferrous fumarate tablets) which received approval as an oral contraceptive on February 17, 2006 under NDA 021871. (b) (4)

Clinical Pharmacology Studies in this NDA
This application contains full reports of the following 3 studies including 2 studies that used the final to-be-marketed (TBM) formulation:

Table 1: Summary of Clinical Pharmacology Studies submitted to NDA 204426

Type of Study	Protocol Number / Report Number (eCTD section)	Study Objective(s)	Study Design and Type of Control	Test Product(s); Dosage Regimen; Administration Route	Number of Subjects Enrolled/ Completed	Healthy Subjects or Diagnosis of Patients	Duration of Treatment	Study Status; Type of Report
BA	PR-00810 / RR-06511 (5.3.1.2)	Comparative BA WC3042 capsule (Formulation WC3042-05) vs WC2061 tablet	Randomized single-dose (2-way) crossover	WC3042 capsule (Formulation WC3042-05); single capsule; oral WC2061 tablet; single tablet; Oral	40 / 38 (38 evaluable for PK analysis)	Healthy female volunteers	2 single doses	Completed; Full
BA	PR-06011 / RR-04012 (5.3.1.1)	Food effect WC3042 capsule (Formulation WC3042-05) with food vs fasted	Randomized single-dose (2-way) crossover	WC3042 capsule; single capsule with food or single capsule fasted; Oral	26 / 25 (24 evaluable for PK analysis)	Healthy female volunteers	2 single doses	Completed; Full
Bioavailability Study – Alternate Formulation								
BA	PR-00910 / RR-06611 (5.3.1.2)	Comparative BA WC3042 capsule (Formulation WC3042-(b) (4) vs WC2061 tablet	Randomized single-dose (2-way) crossover	WC3042 capsule (Formulation WC3042-(b) (4) single capsule; oral WC2061 tablet; single tablet; Oral	40 / 39 (39 evaluable for PK analysis)	Healthy female volunteers	2 single doses	Completed; Full

BA: bioavailability; WC3042 capsules and WC2061 tablets (Loestrin 24 Fe active tablet) contain 1.0 mg norethindrone acetate/ 0.020 mg ethinyl estradiol

Note that approval of Formulation WC3042-(b) (4) (Study PR-00910) is not being sought.

Drug Product Formulation:
(b) (4)

(b) (4) The unit dose composition for WC3042 capsules is provided in Table 2:

Table 2: The TBM Formulation WC3042

	Formulation WC3042-05	
Component	mg/capsule	% w/w
Norethindrone acetate USP[1]	(b) (4)	
Ethinyl estradiol USP[1]		
Sesame oil NF		
Linoleoyl polyoxylglycerides NF (b) (4)		
(b) (4)		
Dehydrated alcohol USP		
Soft gelatin capsule shell (b) (4)		
Total		
(b) (4)		

Absorption, Distribution, Metabolism, and Excretion (ADME)
Only single dose studies assessing BE and food effect were conducted using WC3042. The Sponsor is proposing to use the available information of Loestrin® 24 Fe for WC3042.

Drug-Drug Interactions:
No DDI studies were conducted with WC3042.

Specific Populations:
- Pediatric use: No pediatric studies were conducted. Pediatric waiver request is submitted in this NDA.
- Renal or hepatic impairment: No studies were conducted in patients with renal or hepatic impairments.

Bioanalytical Method Validation:
Bioanalysis was conducted at (b) (4) Human plasma samples were analyzed using a gas chromatography-mass spectrometry (GC-MS) method for the simultaneous determination of norethindrone (NE) and EE. In this method, the analytes were extracted from plasma into toluene. Extraction was followed by several clean-up steps, resulting in a final dichloromethane extract. After a two-step derivatization, 1–2 µL of the derivatized samples were injected for analysis. The GC-MS analysis was performed in the chemical ionization mode (negative ions) using ammonia as reagent gas. Incurred sample reanalysis (ISR) was conducted on approximately 5.3% and 5.0% of the study samples in the BE study (Study PR-00810) and food effect study (Study PR-06011), respectively. An Office of Scientific Investigation (OSI) consult requesting inspections of the clinical and bioanalytical sites of the pivotal BE study (Study PR-00810) will be requested.

Recommendation:
The Office of Clinical Pharmacology/Division of Clinical Pharmacology 3 finds that the Clinical Pharmacology section for NDA 204426 is fileable.

Comments for the Sponsor:
None

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/s/

CHONGWOO YU
08/16/2012

MYONG JIN KIM
08/16/2012

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/s/

CHONGWOO YU
01/09/2013

MYONG JIN KIM
01/10/2013
I concur.

BIOPHARMACEUTICS REVIEW Office of New Drug Quality Assessment			
Application No.:	NDA 204426	**Biopharmaceutics Reviewer:** Elsbeth Chikhale, PhD	
Submission Date:	June 21, 2012		
Division:	Division of Reproductive and Urologic Products	**Biopharmaceutics Team Leader:** Angelica Dorantes, PhD	
Applicant:	Warner Chilcott Company, LLC	**Acting Supervisor:** Richard Lostritto, PhD	
Trade Name:	Menostrin 24 Fe (norethindrone acetate and ethinyl estradiol) capsules	**Date Assigned:**	July 12, 2012
Generic Name:	Norethindrone acetate (NA) and ethinyl estradiol (EE) capsules	**Date of Review:**	March 6, 2013
Indication:	Prevention of pregnancy	**Type of Submission:** 505(b)(2) Original New Drug Application	
Dosage form/ strengths	Soft gel capsules/ 1 mg NA and 20 µg EE per capsule		
Route of Administration	Oral		

SUMMARY

Submission: This 505(b)(2) New Drug Application is for a combined oral contraceptive (COC) drug product containing 1 mg norethindrone acetate (NA) and 20 µg ethinyl estradiol (EE) per soft gelatin capsule taken orally once a day for 24 days followed by one 75 mg ferrous fumarate (Fe) capsule taken orally once a day for 4 days to facilitate a 28 day regimen.

Review: The Biopharmaceutics review for this NDA is being focused on the evaluation and acceptability of: **1)** the proposed dissolution methodology, and **2)** the dissolution acceptance criteria.

RECOMMENDATION

The following dissolution method and acceptance criteria are acceptable.

Drugs Name	Dosage Form	USP Apparatus	Speed (rpm)	Medium	Acceptance Criteria
Norethindrone and Ethinyl Estradiol	IR Soft Gelatin Capsule	USP 2 (Paddle)	75	900 mL pH 4.5 buffer in water containing 0.03% CTAB at 37°C	Norethindrone: (b) (4)% in 30 minutes Q = (b) (4)% in180 minutes Ethinyl Estradiol: Q= (b) (4)% in 60 minutes

From the Biopharmaceutics perspective, NDA 204426 for Menostrin 24 Fe (norethindrone acetate and ethinyl estradiol) capsules containing 1 mg norethindrone acetate and 20 µg ethinyl estradiol per capsule is recommended for **APPROVAL**.

Elsbeth Chikhale, Ph.D.
Biopharmaceutics Reviewer
Office of New Drug Quality Assessment

Angelica Dorantes, Ph.D.
Biopharmaceutics Team Leader
Office of New Drug Quality Assessment

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/s/

ELSBETH G CHIKHALE
03/06/2013

ANGELICA DORANTES
03/06/2013

PRODUCT QUALITY - BIOPHARMACEUTICS
FILING REVIEW

NDA Number	204-426
Submission Date	6/21/12
Product name, generic name of the active	Norethindrone acetate (NA) and ethinyl estradiol (EE)
Dosage form and strength	Soft Gelatin Capsules: 1 mg NA and 0.020 mg EE/capsule
Route of Administration	Oral
Applicant	Warner Chilcott Company, LLC
Clinical Division	Division of Reproductive and Urologic Products
Type of Submission	Original NDA – 505(b)(2)
Biopharmaceutics Reviewer	Elsbeth Chikhale, Ph.D.
Biopharmaceutics Team Leader	Angelica Dorantes, Ph.D.

The following parameters for the ONDQA's Product Quality-Biopharmaceutics filing checklist are necessary in order to initiate a full biopharmaceutics review (i.e., complete enough to review but may have deficiencies).

ONDQA-BIOPHARMACEUTICS **A. INITIAL** OVERVIEW OF THE NDA APPLICATION FOR FILING				
	Parameter	**Yes**	**No**	**Comment**
1.	Does the application contain dissolution data?	x		
2.	Is the dissolution test part of the DP specifications?	x		Proposed dissolution method: • USP Apparatus 2 • 900 mL buffer pH 4.5 (with 0.03% CTAB) • 75 rpm Proposed acceptance criteria: Q= (b)(4) % at (b)(4) min for EE Q= (b)(4) % at (b)(4) min for NA
3.	Does the application contain the dissolution method development report?		x	The dissolution method development report needs to be requested.
4.	Is there a validation package for the analytical method and dissolution methodology?	x		Provided in 3.2.P.5.3
5.	Does the application include a biowaiver request?		x	
6.	Does the application include an IVIVC model?		x	
7.	Is information such as BCS classification mentioned, and supportive data provided?		x	
8.	Is information on mixing the product with foods or liquids included?		x	

9.	Is there any in *vivo* BA or BE information in the submission?	x		An in vivo bioequivalence study of the proposed drug product to the reference drug product (Loestrin® 24 Fe - tablets) is provided in the NDA.

PRODUCT QUALITY - BIOPHARMACEUTICS
FILING REVIEW

B. FILING CONCLUSION				
	Parameter	**Yes**	**No**	**Comment**
10.	**IS THE BIOPHARMACEUTICS SECTIONS OF THE APPLICATION FILEABLE?**	x		
11.	If the NDA is not fileable from the product quality-biopharmaceutics perspective, state the reasons and provide **filing** comments to be sent to the Applicant.			
12.	If the NDA is not fileable from the biopharmaceutics perspective, state the reasons and provide **filing** comments to be sent to the Applicant.			
13.	Are there any **potential review** issues to be forwarded to the Applicant for the 74-day letter?	x		The comment below should be send to the Applicant

Biopharmaceutics Comments for the 74-Day Letter:

The provided dissolution data indicate that the proposed dissolution method may not be appropriate for your drug product. Please provide the dissolution method development report with complete detailed information supporting the selection of this method for the evaluation of the dissolution rate of NA and EE.

The dissolution method development report should include the following information:

a. Solubility data for each drug substance covering the pH range;
b. Detailed description of the dissolution test being proposed for the evaluation of the proposed drug product and the developmental parameters used to select the proposed dissolution method as the optimal test for the proposed product (*i.e., selection of the equipment/ apparatus, in vitro dissolution media, agitation/rotation speed, pH, assay,* (b)(4) *etc.*). Include the data supporting the selection of the type and amount of surfactant. The testing conditions used for each test should be clearly specified. The dissolution profile should be complete (*i.e., 15, 20, 30, 45, & 60 minutes*) and cover at least (b)(4) % of drug release of the label amount or whenever a plateau (i.e., no increase over 3 consecutive time-points) is reached. We recommend that at least twelve samples be used per testing variable;
c. Provide the complete dissolution profile data (*individual, mean, SD, profiles*) for NA and EE. The dissolution data should be reported as the cumulative

percentage of drug dissolved with time (*the percentage is based on the product's label claim*); and

d. Include the complete dissolution data for the testing conducted to demonstrate the discriminating capability of the selected dissolution test as well as the supportive validation data for the dissolution method (i.e., method robustness, etc.) and analytical method (precision, accuracy, linearity, stability, etc.) for each drug component (NA and EE).

For the setting of the dissolution acceptance criteria of your product (NA and EE), the following points should be considered:

e. The dissolution profile data (*i.e., 15, 20, 30, 45, & 60 minutes*) from the clinical batches and primary (registration) stability batches should be used for the setting of the dissolution acceptance criteria of your proposed drug product [i.e., specification-sampling time point and specification value for NA and EE].

f. The in vitro dissolution profile should encompass the timeframe over which at least (b) (4) % of the drug is dissolved or where the plateau of drug dissolved is reached, if incomplete dissolution is occurring.

g. The selection of the specification time point should be where Q = (b) (4) % dissolution occurs. However, if you have a slowly dissolving product or includes a BCS-Class 2, poor-soluble drug, a two-point specifications option may be adequate for your product. The first time point should be during the initial dissolution phase (i.e., 15-20 minutes) and the second time point should be where Q = (b) (4) % dissolution occurs.

h. The dissolution acceptance criterion should be based on average dissolution data (n=12).

Note that the final determination on the acceptability of the proposed acceptance criterion for your proposed product will be made during NDA review process based on the provided data.

{See appended electronic signature page}
Elsbeth Chikhale, Ph.D. 8/16/12
Biopharmaceutics Reviewer Date
Office of New Drug Quality Assessment

{See appended electronic signature page}
Angelica Dorantes, Ph.D. 8/16/12
Biopharmaceutics Team Leader Date
Office of New Drug Quality Assessment

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/s/

ELSBETH G CHIKHALE
08/16/2012

ANGELICA DORANTES
08/16/2012

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING FORM/CHECKLIST FOR NDA/BLA or Supplement

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

	Content Parameter	Yes	No	N/A	Comment
Criteria for Refusal to File (RTF)					
1	Has the applicant submitted bioequivalence (BE) data comparing to-be-marketed product(s) and those used in the pivotal clinical trials?	x			A single dose BE study using WC3042 (test) and Loestrin® 24 Fe (reference)
2	Has the applicant provided metabolism and drug-drug interaction information?			x	Refers to available information of distribution, metabolism, and excretion (i.e., Loestrin® 24 Fe label)
3	Has the sponsor submitted bioavailability data satisfying the CFR requirements?	x			
4	Did the sponsor submit data to allow the evaluation of the validity of the analytical assay?	x			
5	Has a rationale for dose selection been submitted?	x			BE approach to a reference product (i.e., Loestrin® 24 Fe)
6	Is the clinical pharmacology and biopharmaceutics section of the NDA organized, indexed and paginated in a manner to allow substantive review to begin?	x			
7	Is the clinical pharmacology and biopharmaceutics section of the NDA legible so that a substantive review can begin?	x			
8	Is the electronic submission searchable, does it have appropriate hyperlinks and do the hyperlinks work?	x			
Criteria for Assessing Quality of an NDA (Preliminary Assessment of Quality)					
	Data				
9	Are the data sets, as requested during pre-submission discussions, submitted in the appropriate format (e.g., CDISC)?	x			
10	If applicable, are the pharmacogenomic data sets submitted in the appropriate format?			x	
	Studies and Analyses				
11	Is the appropriate pharmacokinetic information submitted?	x			
12	Has the applicant made an appropriate attempt to determine reasonable dose individualization strategies for this product (i.e., appropriately designed and analyzed dose-ranging or pivotal studies)?			x	BE approach to a reference product (i.e., Loestrin® 24 Fe)
13	Are the appropriate exposure-response (for desired and undesired effects) analyses conducted and submitted as described in the Exposure-Response guidance?			x	BE approach to a reference product (i.e., Loestrin® 24 Fe)
14	Is there an adequate attempt by the applicant to use exposure-response relationships in order to assess the need for dose adjustments for intrinsic/extrinsic factors that might affect the pharmacokinetic or pharmacodynamics?			x	BE approach to a reference product (i.e., Loestrin® 24 Fe)

15	Are the pediatric exclusivity studies adequately designed to demonstrate effectiveness, if the drug is indeed effective?			x	
16	Did the applicant submit all the pediatric exclusivity data, as described in the WR?			x	
17	Is there adequate information on the pharmacokinetics and exposure-response in the clinical pharmacology section of the label?	x			
	General				
18	Are the clinical pharmacology and biopharmaceutics studies of appropriate design and breadth of investigation to meet basic requirements for approvability of this product?	x			
19	Was the translation (of study reports or other study information) from another language needed and provided in this submission?			x	

IS THE CLINICAL PHARMACOLOGY SECTION OF THE APPLICATION FILEABLE? ___Yes___

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

None.

Chongwoo Yu — 8/16/2012

Reviewing Clinical Pharmacologist — Date

Myong-Jin Kim — 8/16/2012

Team Leader — Date

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING FORM/CHECKLIST FOR NDA/BLA or Supplement

Clinical Pharmacology Filing Memo

NDA: 204426
Compound: WC3042 (1 mg norethindrone acetate [NA] and 0.02 mg ethinyl estradiol [EE])
Sponsor: Warner Chilcott Company, LLC

Date: 8/16/2012
Reviewer: Chongwoo Yu, Ph.D.

Introduction:
Warner Chilcott submitted New Drug Application (NDA) 204426 for WC3042 in accord with Section 505 (b)(1) on June 21, 2012 to seek an approval for prevention of pregnancy. WC3042 is a new dosage form for oral contraception consisting of one soft gelatin capsule (WC3042-05 formulation) containing 1 mg NA and 0.02 mg EE taken daily for 24 days followed by one ferrous fumarate soft gelatin capsule (WC3042-(b) (4) formulation) taken daily for 4 days to facilitate a 28-day regimen. The proposed regimen is the same as the approved regimen for Warner Chilcott's Loestrin® 24 Fe (NA and EE tablets, USP and ferrous fumarate tablets) which received approval as an oral contraceptive on February 17, 2006 under NDA 021871. The Sponsor intends to discontinue marketing of Loestrin® 24 Fe upon approval of WC3042.

Clinical Pharmacology Studies in this NDA
This application contains full reports of the following 3 studies including 2 studies that used the final to-be-marketed (TBM) formulation:

Table 1: Summary of Clinical Pharmacology Studies submitted to NDA 204426

Type of Study	Protocol Number / Report Number (eCTD section)	Study Objective(s)	Study Design and Type of Control	Test Product(s); Dosage Regimen; Administration Route	Number of Subjects Enrolled/ Completed	Healthy Subjects or Diagnosis of Patients	Duration of Treatment	Study Status; Type of Report
BA	PR-00810 / RR-06511 (5.3.1.2)	Comparative BA WC3042 capsule (Formulation WC3042-05) vs WC2061 tablet	Randomized single-dose (2-way) crossover	WC3042 capsule (Formulation WC3042-05); single capsule; oral WC2061 tablet; single tablet; Oral	40 / 38 (38 evaluable for PK analysis)	Healthy female volunteers	2 single doses	Completed; Full
BA	PR-06011 / RR-04012 (5.3.1.1)	Food effect WC3042 capsule (Formulation WC3042-05) with food vs fasted	Randomized single-dose (2-way) crossover	WC3042 capsule; single capsule with food or single capsule fasted; Oral	26 / 25 (24 evaluable for PK analysis)	Healthy female volunteers	2 single doses	Completed; Full
Bioavailability Study – Alternate Formulation								
BA	PR-00910 / RR-06611 (5.3.1.2)	Comparative BA WC3042 capsule (Formulation WC3042 (b) (4) vs WC2061 tablet	Randomized single-dose (2-way) crossover	WC3042 capsule (Formulation WC3042 (b) (4) single capsule; oral WC2061 tablet; single tablet; Oral	40 / 39 (39 evaluable for PK analysis)	Healthy female volunteers	2 single doses	Completed; Full

BA: bioavailability; WC3042 capsules and WC2061 tablets (Loestrin 24 Fe active tablet) contain 1.0 mg norethindrone acetate/ 0.020 mg ethinyl estradiol (b) (4)

Drug Product Formulation:
The liquid fill is encapsulated in soft gelatin capsule shells (b) (4) (Aclar) blisters. The unit dose composition for WC3042 capsules is provided in Table 2:

Table 2: The TBM Formulation WC3042

	Formulation WC3042-05	
Component	mg/capsule	% w/w
Norethindrone acetate USP[1]		(b) (4)
Ethinyl estradiol USP[1]		
Sesame oil NF		
Linoleoyl polyoxylglycerides NF (b) (4)		
(b) (4)		
Dehydrated alcohol USP		
Soft gelatin capsule shell (b) (4)		
Total		
(b) (4)		

Absorption, Distribution, Metabolism, and Excretion (ADME)
Only single dose studies assessing BE and food effect were conducted using WC3042. The Sponsor is proposing to use the available information of Loestrin® 24 Fe for WC3042.

Drug-Drug Interactions:
No DDI studies were conducted with WC3042.

Specific Populations:
- Pediatric use: No pediatric studies were conducted. Pediatric waiver request is submitted in this NDA.
- Renal or hepatic impairment: No studies were conducted in patients with renal or hepatic impairments.

Bioanalytical Method Validation:
Bioanalysis was conducted at (b) (4) Human plasma samples were analyzed using a gas chromatography-mass spectrometry (GC-MS) method for the simultaneous determination of norethindrone (NE) and EE. In this method, the analytes were extracted from plasma into toluene. Extraction was followed by several clean-up steps, resulting in a final dichloromethane extract. After a two-step derivatization, 1–2 µL of the derivatized samples were injected for analysis. The GC-MS analysis was performed in the chemical ionization mode (negative ions) using ammonia as reagent gas. Incurred sample reanalysis (ISR) was conducted on approximately 5.3% and 5.0% of the study samples in the BE study (Study PR-00810) and food effect study (Study PR-06011), respectively. An Office of Scientific Investigation (OSI) consult requesting inspections of the clinical and bioanalytical sites of the pivotal BE study (Study PR-00810) will be requested.

Recommendation:

The Office of Clinical Pharmacology/Division of Clinical Pharmacology 3 finds that the Clinical Pharmacology section for NDA 204426 is fileable.

Comments for the Sponsor:

None

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING FORM/CHECKLIST FOR NDA/BLA or Supplement

Office of Clinical Pharmacology *New Drug Application Filing and Review Form*			
General Information About the Submission			
	Information		Information
NDA Number	**204426**	**Brand Name**	**WC30** (b) (4)
OCP Division	**DCP3**	**Generic Name**	**NA / EE**
Medical Division	**DRUP**	**Drug Class**	**Combination oral contraceptive (COC)**
OCP Reviewer	**Chongwoo Yu, Ph.D.**	**Indication(s)**	**Prevention of pregnancy**
OCP Team Leader	**Myong-Jin Kim, Pharm.D.**	**Dosage Form**	**Soft gelatin capsules**
Secondary Reviewer	**Myong-Jin Kim, Pharm.D.**	**Dosing Regimen**	**1 mg NA and 0.02 mg EE taken daily for 24 days followed by one ferrous fumarate soft gelatin capsule taken daily for 4 days**
Date of Submission	**June 21, 2012**	**Route of Administration**	**Oral**
Estimated Due Date of OCP Review	**February 21, 2013**	**Sponsor**	**Warner Chilcott Company, LLC**
PDUFA Due Date	**April 21, 2013**	**Priority Classification**	**Standard**
Division Due Date	**March 31, 2013**		

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:	X	1		PRO-00910
multiple dose:				
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 -				

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING FORM/CHECKLIST FOR NDA/BLA or Supplement

ethnicity:				
gender:				
pediatrics:				
geriatrics:				
renal impairment:				
hepatic impairment:				
PD:				
Phase 1:				
Phase 2:				
Phase 3:				
PK/PD:				
Phase 1 and/or 2, proof of concept:				
Phase 3 clinical trial:				
Population Analyses -				
PK:				
PD:				
II. Biopharmaceutics				
Absolute bioavailability:				
Relative bioavailability -				
solution as reference:				
alternate formulation as reference:				
Bioequivalence studies -				
traditional design; single / multi dose:	X	1		PR-00810
replicate design; single / multi dose:				
Food-drug interaction studies:	X	1		PR-06011
Dissolution:				
(IVIVC):				
Bio-wavier request based on BCS				
BCS class				
III. Other CPB Studies				
Irritation and sensitization				
Genotype/phenotype studies:				
Chronopharmacokinetics				
Pediatric development plan				
Immunogenicity profile				
Thorough QT study				
Literature References				
Total Number of Studies		3		

Other comments

	Comments
QBR questions (key issues to be considered)	1. Establishment of BE between WC30 (b) (4) and Loestrin® 24 Fe 2. Evaluation of food effect involving WC30 (b) (4) 3. OSI inspection on clinical and bioanalytical sites for the pivotal BE study 4. Acceptability of bioanalytical method validation and performance
Other comments or information not included above	• A formal OSI consult on clinical and bioanalytical study sites will be requested.

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/s/

CHONGWOO YU
08/16/2012

MYONG JIN KIM
08/16/2012