

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**21-490**

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

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**Clinical Pharmacology and Biopharmaceutics Review**  
**Division of Pharmaceutical Evaluation II**

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**NDA:** 21-490

**Brand Name:** Ovcon® 35 —

**Generic Name:** Norethindrone/Ethinyl Estradiol

**Sponsor:** Warner Chilcott, Inc.  
A subsidiary of Galen Holdings Plc.

**Relevant IND:** NA  
**Relevant NDA:** 17-716

**Date of Submission:** 02-APR-2002  
05-JUNE-2002 (Amendment No. 3)  
22-JAN-2003 (Amendment No. 14)

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

**Formulation:** Oral Chewable Tablet  
**Strength:** Norethindrone (0.4 mg)/Ethinyl Estradiol (0.035 mg)

**Indication:** Prevention of Pregnancy

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

**Acting Team Leader:** Venkat Jarugula, Ph.D.

**OCPB Division:** DPE-II

**ORM Division:** Reproductive & Urologic Drug Products

**1. EXECUTIVE SUMMARY**

This NDA is for a new dosage form, chewable tablet (Ovcon Chewable), of the currently marketed product Ovcon 35 28-day (0.4 mg Norethindrone, NE, and 35µg Ethinyl Estradiol, EE, tablets, USP; Ovcon Oral), for the prevention of pregnancy. Reference is made to the approved NDA 17-716 (Ovcon Oral) for information in support of clinical safety and efficacy. Ovcon Chewable, a mint-flavored oral contraceptive containing 0.4 mg NE and 35µg EE per tablet, has been developed by the sponsor

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Ovcon Chewable is also designed to provide a continuous 21-day regimen of active tablets followed by 7 placebo tablets.

In support of this NDA, the sponsor submitted two clinical pharmacology studies, a BE study to compare Ovcon Chewable chewed with Ovcon Oral swallowed (Report CR 01002), and an oral

irritation study (Report RR 00802). It should be noted that the approval of this NDA is based on the BE study. No clinical Phase III study was conducted with Ovcon Chewable.

The BE study supports that Ovcon Chewable chewed and Ovcon Oral swallowed whole are bioequivalent under fasting conditions. The proposed labeling of this NDA indicates that Ovcon Chewable may be chewed or swallowed whole. Although a BE study comparing Ovcon Chewable swallowed versus Ovcon Oral swallowed was not performed, the in-vitro dissolution data support the proposed labeling since the formulation changes are minor. Comparative in-vitro dissolution results of Ovcon Chewable and Ovcon Oral show that the dissolution profiles are similar for both EE and NE.

Since the BE study was conducted by administering Ovcon Chewable and Ovcon Oral with 240 mL of water, the dosage and administration section of the label should indicate that Ovcon Chewable is to be taken with water if it were to be chewed and swallowed.

### 1.1 Recommendation

The Office of Clinical Pharmacology and Biopharmaceutics/Division of Pharmaceutical Evaluation II (OCPB/DPE-II) has reviewed NDA 21-490 submitted on 02-April-2002. The overall Human Pharmacokinetic Section is *acceptable*. Labeling comments outlined in the Clinical Pharmacology section and the drug-drug interactions have been accepted by the sponsor on 28-Jan-2003.

Myong-Jin Kim, Pharm.D.

RD initialed by Venkat Jarugula, Ph.D., Acting Team Leader \_\_\_\_\_

FT signed by Venkat Jarugula, Ph.D., Acting Team Leader \_\_\_\_\_

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### Terms & Abbreviations

ANOVA.....	Analyses of Variance
BE.....	Bioequivalence
CI.....	Confidence Interval

EE.....	Ethinyl Estradiol
GC/MS.....	Gas Chromatography/Mass Spectrophotometry
LSM.....	Least-Squares Means
NE.....	Norethindrone
NLT.....	Not Less Than
Ovcon Chewable.....	Ovcon <sup>®</sup> 35 28-Day (Norethindrone 0.4 mg and Ethinyl Estradiol 35 µg Chewable Tablets)
Ovcon Oral.....	Ovcon <sup>®</sup> 35 28-Day (Norethindrone 0.4 mg and Ethinyl Estradiol 35 µg Tablets, USP)

### 3. SUMMARY OF CPB FINDINGS

The BE study supports that Ovcon Chewable chewed and Ovcon Oral swallowed whole are bioequivalent under fasting conditions. The 90% CI for the difference between formulation LSM for the parameters  $AUC_{0-4}$ ,  $AUC_{0-\infty}$ , and  $C_{max}$  using ln-transformed data for NE and EE were within 80.00 to 125.00 %.

The labeling of Ovcon Chewable proposes that Ovcon Chewable may be chewed or swallowed as whole. However, the BE study submitted in this NDA supports only Ovcon Chewable chewed. Since there are only minor formulation differences between Ovcon Chewable and Ovcon Oral, the comparative in-vitro dissolution results of Ovcon Chewable and Ovcon Oral were submitted to support that Ovcon Chewable swallowed and Ovcon Oral swallowed would be bioequivalent. In-vitro dissolution studies performed on 12 tablets each of Ovcon Chewable and Ovcon Oral showed that Ovcon Chewable and Ovcon Oral dissolution profiles were similar for both EE and NE. The calculated similarity factor ( $f_2$ ) values were 66.1 and 71.2 for EE and NE, respectively.

### 4. Question-Based Review

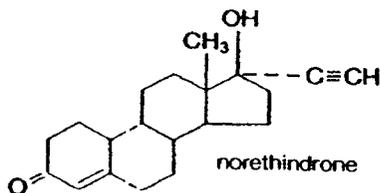
#### 4.1 General Attributes

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

#### Physico-chemical properties

##### NE:

- Structural formula

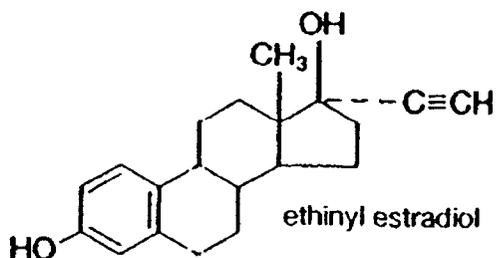


- Established Name: Norethindrone, USP
- Chemical Name: 17-hydroxy-19-nor-17 $\alpha$ -pregn-4-en-20-yn-3-one

- Molecular Weight: 298.42
- Molecular Formula:  $C_{20}H_{26}O_2$
- Appearance: White to creamy white crystalline powder

EE:

- Structural formula



- Established Name: Ethinyl estradiol, USP
- Chemical Name: 19-nor-17 $\alpha$ -pregna-1,3,5(10)-trien-20-yne-3,17-diol
- Molecular Weight: 296.40
- Molecular Formula:  $C_{20}H_{24}O_2$
- Appearance: —

**Drug Formulation**

**Table 1.** Comparison of Ovcon Chewable (Chewable tablet) and Ovcon Oral (Oral tablet) Formulations

Ingredient	Formulation Composition (%w/w)	
	Chewable tablet	Oral tablet
Norethindrone		
Ethinyl estradiol <sup>1</sup>		
Dibasic calcium phosphate — USP		
Lactose (Hydrous), NF		
Sodium starch glycolate, NF		
Povidone, USP		
Sucralose, NF		
Maltodextrin, NF		
Spearmint flavor		
Magnesium stearate		
FD&C yellow #6		
TOTAL	100	100

— for ethinyl estradiol

- The Ovcon Chewable formulation is based on the approved Ovcon Oral formulation (NDA 17-716; approved on March 27, 1975).
- The sponsor stated that the formulation, batch size, manufacturing process and equipment

used for Ovcon Chewable are the same as the currently approved Ovcon Oral from the active tablets only with the following exceptions:

- A new dosage form, chewable tablet
  - — colorant (FD&C Yellow #6)
  - Added flavor and sweetener components ( — spearmint flavor, sucralose and maltodextrin)
  - A — 2 excipients (dibasic calcium phosphate, USP and lactose, NF/EP)
  -
- Each Ovcon Chewable green placebo tablet contains only inactive pharmaceutical ingredients. It is the same as Ovcon Oral green placebo except the flavor and sweetener components (spearmint flavor, sucralose and maltodextrin) are added.
  -

The following lots were used in 2 studies (BE and Oral Irritation Studies):

Study No. (Report No.)	Study	Treatment	Bulk Tablet Lot No.	Packaged Tablet Lot No.	Batch Size	Manufacturing Site
PR 03801 (CR 01002)	BE	Ovcon Chewable	1E49898	1F42967	— tablets	Bristol-Meyers Squibb, Mayaguez, Puerto Rico
		Ovcon Oral	0K29866	1A30447	— tablets	
PR 07401 (RR 00802)	Oral Irritation	Ovcon Chewable	1E49898	1F42967	— tablets	

## 2. What is the proposed mechanism of action?

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

## 3. What are the proposed indication, dosage and route of administration?

Ovcon Chewable are indicated for the prevention of pregnancy. Ovcon Chewable may be chewed or swallowed whole.

### 4.2 General Clinical Pharmacology

NE 0.4 mg and EE 35 µg daily for 21 days are already used in the approved product, Ovcon Oral. Therefore, no clinical study was conducted with Ovcon Chewable except one oral irritation study (see MO review for detail, Study No PR 07401). In addition, a BE study was conducted to compare Ovcon Chewable chewed with Ovcon Oral swallowed.

To compare the BE of Ovcon Chewable relative to that for Ovcon Oral under fasting conditions, single-center, open-label, single-dose, randomized, two-period, two-treatment crossover BE study in 26 healthy, non-smoking female subjects was conducted. Subjects were randomized to receive a single oral dose of Ovcon Chewable (chewed and then swallowed with 240 mL of water) or a single oral dose of Ovcon Oral (swallowed whole with 240 mL of water).

Parameter	NE (Ovcon Chewable vs. Ovcon Oral) 90 % CI (ratio of LSM)	EE (Ovcon Chewable vs. Ovcon Oral) 90 % CI (ratio of LSM)
AUC <sub>0-t</sub> (pg•h/mL)	92.5 – 108.8 % (100.3%)	104.1 – 114.7 % (109.3%)*
AUC <sub>0-∞</sub> (pg•h/mL)	94.4 – 111.1 % (102.4%)**	103.0 – 112.7 % (107.7%)*
C <sub>max</sub> (pg/mL)	83.1 – 99.1 % (90.7 %)	111.2 – 121.0 % (116.0%)*

\*n=26 including Subject No. 13 in all PK analyses of EE

\*\*n=25 since AUC<sub>0-∞</sub> could not be calculated for Subject No. 10 in Periods 1 and 2.

- The 90% CI for the difference between formulation LSM for the parameters AUC<sub>0-t</sub>, AUC<sub>0-∞</sub>, and C<sub>max</sub> using ln-transformed data for NE and EE were within 80.00 to 125.00 %.
- This BE study supports that Ovcon Chewable chewed and Ovcon Oral swallowed whole are bioequivalent under fasting conditions.

Since there are only minor formulation differences between Ovcon Chewable and Ovcon Oral (see Drug Formulation section), the comparative in-vitro dissolution results of Ovcon Chewable and Ovcon Oral were submitted to support that Ovcon Chewable swallowed and Ovcon Oral swallowed would be bioequivalent (see In-Vitro Dissolution section).

The food-effect on the rate and the extent of NE and EE absorption with Ovcon Chewable has not been evaluated. However, it was reported that administration of a tablet formulation of NE acetate 1.0 mg/EE 10 µg with a high fat meal decreases rate, but not extent, of EE absorption. The extent of NE absorption is increased by 27% following administration with food (Boyd RA et al. J Clin Pharm 2003;43:52-8).

#### Are the active moieties in the plasma (or other biological fluid) appropriately identified?

Blood samples were collected for 60 hours post-dose (at pre-dose, 0.33, 0.67, 1, 1.33, 1.67, 2, 2.5, 3, 4, 6, 10, 15, 24, 36, 48, 60 hours) for determination of plasma NE and EE concentrations.

#### 4.3 General Biopharmaceutics

Both active pharmaceutical ingredients, NE and EE, are USP grade material and are manufactured by  Ovcon Chewable active and placebo tablets are manufactured, packaged and tested for release by Bristol-Myers Squibb Manufacturing Company.

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

The Ovcon Chewable formulation studied in the BE study (Study PR 03801) is the same as the to-be-marketed formulation.

#### 4.4 Analytical

	NE	EE

Study No.	PR-03801	PR-03801
Type of Biological Fluid	Plasma	Plasma
Assay Method	GC/MS	GC/MS
Sensitivity (LOQ)	—	—
Recovery	65.88% (low), 64.27% (medium), 64.50% (high)	64.92% (low), 84.13% (medium), 83.90 % (high)
Linearity	—	—
QC Sample	—	—
Inter-Assay Precision	— @ LOQ	— @ LOQ
Inter-Assay Accuracy	— @ LOQ	— @ LOQ
QC Sample	—	—
Intra-Assay Precision	— @ LOQ	— @ LOQ
Intra-Assay Accuracy	— @ LOQ	— @ LOQ

**COMMENT:**

- Analytical methods are acceptable. Both accuracy and precision are within acceptable values.

**In Vitro Dissolution**

**Table 2.** Summary of Dissolution Method and Sponsor's Proposed Specification for Ovcon Chewable.

Dosage Form	OVCON 35 (norethindrone and ethinyl estradiol chewable tablet)
Strength	0.4 mg norethindrone and 35 µg ethinyl estradiol
Apparatus	Apparatus 2, 75 rpm
Media	0.09% sodium lauryl sulfate in 0.1 N hydrochloric acid, 37°C
Volume	500 mL
Sampling Time	60 minutes
Analytical Method	HPLC, Method —
Number of tablets	6
Specification	Norethindrone / (Q) Ethinyl estradiol / (Q)

**COMMENTS:**

- The sponsor initially proposed a dissolution specification of NLT — (Q) at 60 minutes. Since the dissolution profile data of Ovcon Chewable show that approximately 90 % of NE and EE are dissolved by 30 minute sampling time (see Tables 3 & 4), the dissolution specifications of NLT — (Q) at 30 minutes were proposed to the sponsor (teleconference, 06-Jan-03).
- Subsequently, the sponsor proposed the NLT — (Q) at 30 minutes (Facsimile dated 07-Jan-03).
- Currently, the sponsor has no 30-minute dissolution data on stability samples of Ovcon Chewable. Therefore, it was agreed that the Agency's proposed dissolution specifications would be interim (NLT — (Q) at 30 minutes) until stability data are generated at 30 minute sampling time.

**Table 3.** In-Vitro Dissolution Profile Data of Ovcon Chewable and Ovcon Oral (n=12)

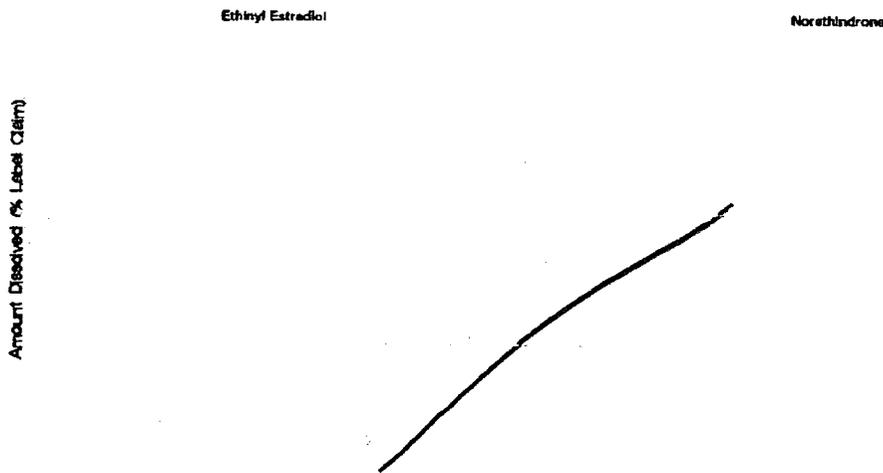
	Average Amount Dissolved (%LC) by Analyte and Sample Time (minutes)							
	Norethindrone (%LC)				Ethinyl Estradiol (%LC)			
	15	30	60	75	15	30	60	75
OVCON 35 Chewable tablet (Lot 1E49898)	86	96	99	98	91	93	100	99
OVCON 35 oral tablet (Lot 1A30447)	93	98	99	98	92	94	93	93
Specification			— (Q)				— (Q)	

- There are only minor formulation differences between Ovcon Chewable and Ovcon Oral (see Drug Formulation section).
- Dissolution profiles (n=12) were generated for both the Ovcon Chewable batch and the Ovcon Oral batch with the same dissolution method.
- Comparison of the dissolution data indicates that the dissolution profiles of Ovcon Chewable and Ovcon Oral batches are similar for both EE and NE. The calculated similarity factor (f2) values are 66.1 and 71.2 for EE and NE, respectively.
- The f2 factor values for both EE and NE remained >50 when one measurement of the dissolution time point was considered after – dissolution of both EE and NE at 15 minutes (i.e., 15 and 30 minutes were considered).

**COMMENT:**

- f2 values between 50 and 100 confirm that the dissolution profiles are similar for the Ovcon Chewable and the Ovcon Oral batches.

**Figure 1.** Comparison of In-Vitro Dissolution Profiles for Ovcon Chewable (Test) and Ovcon Oral (Reference) Batches.



**Table 4.** In-Vitro Dissolution Profile Data of 12 Tablets for the Ovcon Chewable Lot

Dissolution Profile Data for Exhibit Lot 1E49898 – Composite Sample								
Tablet	Amount Dissolved (%LC) by Analyte and Sample Time							
	Norethindrone (%LC)				Ethinyl Estradiol (%LC)			
	15 min	30 min	60 min	75 min	15 min	30 min	60 min	75 min
1								
2								
3								
4								
5								
6								
7								
8								
9								
10								
11								
12								
<b>Average</b>	86	96	99	98	91	93	100	99
<b>Minimum</b>								
<b>Maximum</b>								
Specification: (Q) at 60 minutes								

Table 5. In-Vitro Dissolution Profile Data of 12 Tablets for the Ovcon Oral Lot

Dissolution Profile Data for Reference Lot 1A30447								
Tablet	Amount Dissolved (%LC) by Analyte and Sample Time							
	Norethindrone (%LC)				Ethinyl Estradiol (%LC)			
	15 min	30 min	60 min	75 min	15 min	30 min	60 min	75 min
1								
2								
3								
4								
5								
6								
7								
8								
9								
10								
11								
12								
<b>Average</b>	93	98	99	98	92	94	93	93
<b>Minimum</b>								
<b>Maximum</b>								
Specification: (Q) at 60 minutes				Data source: Data packet 06-9002				

## 5. LABELING

The following edited labeling (Clinical Pharmacology and Drug Interactions section) has been accepted by the sponsor on 28-Jan-2003. The section of Clinical Pharmacology has been updated to include pharmacokinetics of EE and NE.

76 Draft Labeling Page(s) Withheld

## 6.2 Individual Study Reviews

### Bioequivalence Study (Study PR 03801, Research Report CR 01002)

*"A Study to Determine the BA of WC 2045 Tablets (Ovcon Chewable) Relative to that for NE 0.4 mg and EE 35 µg Tablets, USP (Ovcon Oral)"*

#### **OBJECTIVE:**

- To compare the BE of Ovcon Chewable relative to that for Ovcon Oral under fasting conditions

#### **SUBJECTS:**

- Of 26 healthy non-smoking female subjects and 2 alternates enrolled in the study, a total of 27 subjects completed the BE study. One subject, Subject No. 26, discontinued from the study prior to dosing in Period 2 due to a positive serum pregnancy result.
- The mean age of the subjects was 28 yrs (range, 20 – 34 yrs), the mean height was 163 cm (range, 150 – 173 cm), and the mean weight was 61.7 kg (range, 50.4 – 79.0 kg).

#### **DESIGN:**

- Phase I, single-center, open-label, single-dose, randomized, two-period, two-treatment crossover BE study
- Subjects were randomized to receive a single oral dose of Ovcon Chewable (chewed and then swallowed with 240 mL of water) **OR** a single oral dose of approved Ovcon Oral (swallowed whole with 240 mL of water) under fasting conditions (10 h overnight fast)
- Water was not permitted for 1 h before and 1 h after dosing
- A 28-day washout interval between the 2 dose administrations

#### **FORMULATIONS:**

- **Treatment A:** Ovcon Chewable (NE 0.4 mg and EE 35 µg); Manufactured by Bristol-Myers Squibb Co.; Lot No. 1F42967; Expiration date: Not available
- **Treatment B:** Ovcon Oral (NE 0.4 mg and EE 35 µg); Manufactured by Bristol-Myers Squibb Co.; Lot No. 1A30447; Expiration date: Nov 30 2002

**SAMPLE COLLECTION:**

- Blood samples were collected for 60 hours post-dose (at pre-dose, 0.33, 0.67, 1, 1.33, 1.67, 2, 2.5, 3, 4, 6, 10, 15, 24, 36, 48, 60 hours) for determination of plasma NE and EE concentrations

**PK ANALYSIS:**

- Statistical and PK analyses were performed on data from 26 subjects (Subject No. 1 – 25, 27)
- Noncompartmental PK parameters were calculated for plasma NE and EE.
- The  $AUC_{0-t}$ ,  $AUC_{0-\infty}$ ,  $AUC_{0-t}/AUC_{0-\infty}$ ,  $C_{max}$ ,  $t_{max}$ ,  $t_{1/2}$  and  $k_{el}$  PK parameters were calculated for plasma NE and EE.
- ANOVA were performed on the ln-transformed PK parameters  $AUC_{0-t}$ ,  $AUC_{0-\infty}$  and  $C_{max}$ .
- The ANOVA model included sequence, period and formulation as fixed effects and subject nested within sequence as a random effect.
- Consistent with the two one-sided test for BE, the 90% CI for the difference between drug formulation LSM of the ln-transformed parameters  $AUC_{0-t}$ ,  $AUC_{0-\infty}$  and  $C_{max}$  was calculated.
- No value of  $AUC_{0-\infty}$ ,  $t_{1/2}$  and  $k_{el}$  are reported for cases that did not exhibit a log-linear phase in the concentration vs. time profile.
- The CI are expressed as a percentage relative to the LSM of the reference formulation
- Ratios of means are expressed as a percentage of the LSM for the reference formulation
- The intrasubject variability for the  $AUC_{0-t}$ ,  $AUC_{0-\infty}$  and  $C_{max}$  PK parameters was derived from the analyses of the ln-transformed data

**ANALYTICAL METHODS:**

- Plasma NE and EE were analyzed using validated GC/MS methods.
- The analytical ranges for NE and EE were \_\_\_\_\_ pg/mL and \_\_\_\_\_ pg/mL, respectively.

**ADJUSTMENTS:**

- Subject No. 10 did not exhibit a terminal log-linear phase for NE concentration vs. time profiles in Periods 1 and 2. Therefore, no value of  $AUC_{0-\infty}$ ,  $t_{1/2}$  and  $k_{el}$  could be reported.

**Table 6. The Non-Zero Pre-Dose Concentrations**

Subject No.	Period	Formulation	Analyte	Pre-dose concentration (pg/mL)	$C_{max}$ (pg/mL)
8	1	B	EE		
10	1	A	NE		
12	2	B	EE		
13	2	A	EE		

- The non-zero pre-dose concentrations observed for Subject No. 8, 10, and 12 were less than 5% of the respective  $C_{max}$  values. Therefore, these subjects were not excluded from the PK and statistical analyses
- No non-zero pre-dose adjustments to the data sets of Subject No. 8, 10, and 12 were made since the non-zero pre-dose concentrations were reported in Period 1 (Subject No. 8 and 10), and the pre-dose EE concentration in Period 2 was not consistent with the end of the concentration vs. time profile in Period 1 (Subject No. 12)

- Subject No 13's pre-dose EE concentration was greater than 5 % of her respective  $C_{max}$  value in Period 2. Therefore, this subject was removed from all the main PK and statistical analyses for EE
- Additional PK and statistical analyses were performed which included data from Subject No. 13. No non-zero pre-dose adjustments were made for this subject since the pre-dose EE concentrations in Period 2 was not consistent with the end of the concentration vs. time profile in Period 1

**PK RESULTS:**

Parameter	NE (A vs. B) 90 % CI (ratio of LSM)	EE (A vs. B) 90 % CI (ratio of LSM)
AUC <sub>0-t</sub> (pg•h/mL)	92.5 – 108.8 % (100.3%)	104.3 – 115.4 % (109.7 %)*
AUC <sub>0-∞</sub> (pg•h/mL)	94.4 – 111.1 % (102.4 %)**	103.3 – 113.3 % (108.2 %)*
C <sub>max</sub> (pg/mL)	83.1 – 99.1 % (90.7 %)	111.0 – 121.1 % (115.9 %)*

\*n=25 since Subject No. 13 was excluded from all PK analyses of EE

\*\*n=25 since AUC<sub>0-∞</sub> could not be calculated for Subject No. 10 in Periods 1 and 2.

- The 90% CI for the difference between formulation LSM for the parameters AUC<sub>0-t</sub>, AUC<sub>0-∞</sub>, and C<sub>max</sub> using ln-transformed data for NE and EE were within 80.00 to 125.00 %.
- Ovcon Chewable and Ovcon Oral are BE under fasting conditions.
- The secondary analyses demonstrated a significant treatment effect for AUC<sub>0-t</sub>, AUC<sub>0-∞</sub>, and C<sub>max</sub> (p-values, 0.0044, 0.0081 and 0.0001, respectively).

Parameter	NE (A vs. B) 90 % CI (ratio of LSM)	EE (A vs. B) 90 % CI (ratio of LSM)
AUC <sub>0-t</sub> (pg•h/mL)	92.5 – 108.8 % (100.3%)	104.1 – 114.7 % (109.3 %)*
AUC <sub>0-∞</sub> (pg•h/mL)	94.4 – 111.1 % (102.4 %)**	103.0 – 112.7 % (107.7 %)*
C <sub>max</sub> (pg/mL)	83.1 – 99.1 % (90.7 %)	111.2 – 121.0 % (116.0 %)*

\*n=26 including Subject No. 13 in all PK analyses of EE

\*\*n=25 since AUC<sub>0-∞</sub> could not be calculated for Subject No. 10 in Periods 1 and 2.

- Additional PK and statistical analyses were performed which included data from Subject No. 13.
- The 90% CI for the difference between formulation LSM for the parameters AUC<sub>0-t</sub>, AUC<sub>0-∞</sub>, and C<sub>max</sub> using ln-transformed data for NE and EE were still within 80.00 to 125.00 %.

**Table 7. Mean ± SD (CV%) Pharmacokinetic Parameters of NE Following Single Dose Administration of Ovcon Chewable and Ovcon Oral in Healthy Female Subjects Under Fasting Condition.**

	NE						
	AUC <sub>0-t</sub> (pg•h/mL)	AUC <sub>0-∞</sub> (pg•h/mL)	AUC <sub>0-t</sub> /AUC <sub>0-∞</sub> (%)	C <sub>max</sub> (pg/mL)	t <sub>max</sub> (h)	t <sub>1/2</sub> (h)	k <sub>el</sub> (1/h)
Ovcon Chewable	16805.0 ± 7580.7 (45.1%)	18034.9 ± 7852.9 (43.5%)	92.7 ± 5.0 (5.4 %)	4210.6 ± 1628.8 (38.7 %)	1.24 ± 0.40 (32.1 %)	8.6 ± 3.7 (43.1 %)	0.093 ± 0.034 (36.6 %)
Ovcon	16660.4 ±	17605.5 ±	94.9 ± 2.3	4537.4 ± 1492.0	1.51 ± 0.42	7.2 ± 2.5	0.114 ± 0.059

<b>Oral</b>	7287.4 (43.7 %)	7717.5 (43.8 %)	(2.4 %)	(32.9 %)	(27.8 %)	(35.1 %)	(51.9 %)
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**Table 8.** Mean  $\pm$  SD (CV%) Pharmacokinetic Parameters of EE Following Single Dose Administration of Ovcon Chewable and Ovcon Oral in Healthy Female Subjects Under Fasting Condition.

EE							
	AUC <sub>0-4</sub> (pg•h/mL)	AUC <sub>0-24</sub> (pg•h/mL)	AUC <sub>0-4</sub> /AUC <sub>0-24</sub> (%)	C <sub>max</sub> (pg/mL)	t <sub>max</sub> (h)	t <sub>1/2</sub> (h)	k <sub>el</sub> (1/h)
<b>Ovcon Chewable</b>	976.4 $\pm$ 263.5 (27.0 %)	1065.8 $\pm$ 276.2 (25.9 %)	91.5 $\pm$ 3.7 (4.0 %)	131.4 $\pm$ 34.2 (26.1 %)	1.44 $\pm$ 0.33 (22.9 %)	17.1 $\pm$ 4.4 (25.5 %)	0.0427 $\pm$ 0.0096 (22.4 %)
<b>Ovcon Oral</b>	893.7 $\pm$ 241.2 (27.0 %)	986.9 $\pm$ 246.4 (25.0 %)	90.2 $\pm$ 4.3 (4.8 %)	113.5 $\pm$ 30.9 (27.2 %)	1.67 $\pm$ 0.36 (21.9 %)	16.5 $\pm$ 4.4 (26.5 %)	0.0449 $\pm$ 0.01258 (28.0 %)

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

**General Information About the Submission**

	Information		Information
NDA Number	21-490	Brand Name	Ovcon 35
OCPB Division (I, II, III)	DPE II	Generic Name	Norethindrone/Ethinyl Estradiol
Medical Division	DRUDP	Drug Class	Oral Contraceptive
OCPB Reviewer	Myong-Jin Kim	Indication(s)	Prevention of Pregnancy
OCPB Team Leader	Ameeta Parekh	Dosage Form	Chewable Tablet
		Dosing Regimen	0.4 mg/0.035 mg
Date of Submission	02/Apr/2002	Route of Administration	Oral
Estimated Due Date of OCPB Review	10/Jan/2003	Sponsor	Warner Chilcott, Inc.
PDUFA Due Date	31/Jan/2003	Priority Classification	3S
Division Due Date	24/Jan/2003		

**Clin. Pharm. and Biopharm. Information**

	"X" if included at filing	Number of studies submitted	Number of studies reviewed	Critical Comments If any
<b>STUDY TYPE</b>				
Table of Contents present and sufficient to locate reports, tables, data, etc.	X			
Tabular Listing of All Human Studies	X			
HPK Summary	X			
Labeling	X			
Reference Bioanalytical and Analytical Methods	X			
<b>I. Clinical Pharmacology</b>				
Mass balance:				
Isozyme characterization:				
Blood/plasma ratio:				
Plasma protein binding:				
Pharmacokinetics (e.g., Phase I) -				
Healthy Volunteers-				
single dose:				
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 2:				
Phase 3:				
<b>PK/PD:</b>				
Phase 1 and/or 2, proof of concept:				
Phase 3 clinical trial:				
<b>Population Analyses -</b>				
Data rich:				
Data sparse:				
<b>II. Biopharmaceutics</b>				
<b>Absolute bioavailability:</b>				
<b>Relative bioavailability -</b>				
solution as reference:				
alternate formulation as reference:				
<b>Bioequivalence studies -</b>				
traditional design; single / multi dose:	X	1	1	
replicate design; single / multi dose:				
<b>Food-drug interaction studies:</b>				
<b>Dissolution:</b>	X	1	1	
<b>(IVIVC):</b>				
<b>Bio-wavier request based on BCS</b>				
<b>BCS class</b>				
<b>III. Other CPB Studies</b>				
<b>Genotype/phenotype studies:</b>				
<b>Chronopharmacokinetics</b>				
<b>Pediatric development plan</b>				
<b>Literature References</b>	X	3	3	
<b>Total Number of Studies</b>		5	5	
<b>Filability and QBR comments</b>				
	"X" if yes	<b>Comments</b>		
<b>Application filable ?</b>	X	Reasons if the application is not filable (or an attachment if applicable) For example, is clinical formulation the same as the to-be-marketed one?		
<b>Comments sent to firm ?</b>		Comments have been sent to firm (or attachment included). FDA letter date if applicable.		
<b>QBR questions (key issues to be considered)</b>				
<b>Other comments or information not included above</b>				
<b>Primary reviewer Signature and Date</b>	Myong-Jin Kim			
<b>Secondary reviewer Signature and Date</b>	Venkat Jarugula			

CC: NDA 21-490, HFD-850 (L.Lesko, S.Huang), HFD-580 (D. Davis, S. Monroe), HFD-870 (A. Parekh, V. Jarugula, H. Malinowski, J. Hunt), CDR (B. Murphy)  
 CP&B Briefing attendees on January 15, 2003: Drs. S. Al-Habet, D. Davis, J. Hunt, V. Jarugula, A. Mitra, and A. Parekh,

**Background:**

This NDA is for a new dosage form, chewable tablet, of the currently marketed product Ovcon 35 28-day (norethindrone and ethinyl estradiol tablets, USP) for the prevention of pregnancy. Reference is made to the approved NDA 17-716 for Ovcon 35 28-day tablets.

The sponsor claims that the main differences in the new dosage form from the currently marketed product are as follows:

- Mode of administration
- Addition of a flavor and sweetener
-  two excipients, dibasic calcium phosphate, USP and lactose, NF/EP
-  the dye, FD&C yellow #6 aluminum lake

The sponsor submitted two clinical pharmacology studies to support NDA 21-490, a bioequivalence study (Report CR 01002) and an oral irritation study (Report RR 00802).

**Study PR 03801 (Research Report CR 01002)**

- Single-center, open-label, single-dose, randomized, two-period, two-treatment crossover bioequivalence study in 26 healthy, non-smoking female subjects
- Subjects are randomized to receive a single oral dose of Ovcon 35 chewable table (chewed and then swallowed with 240 mL of water) OR a single oral dose of approved Ovcon 35 tablet (swallowed whole with 240 mL of water)
- To compare the bioequivalence of Ovcon 35 chewable tablets (norethindrone 0.4 mg and ethinyl estradiol 0.035 mg) relative to that for norethindrone 0.4 mg and ethinyl estradiol 0.035 mg tablets, USP (Ovcon 35) under fasting conditions

**Study CS 900201 (Research Report RR 00802)**

- Single-center, open-label, single treatment oral irritation study
- To determine the irritation potential of a chewable, oral contraceptive following daily use, over a 21-day cycle, by women of childbearing potential

The sponsor provided the following:

1. Human Pharmacokinetics and Bioavailability section summary, full study report, and labeling
2. Drug formulation, in vitro release testing
3. Bioanalytical methods
4. Comparative dissolution profiles
5. Bioequivalence study assessing the currently approved Ovcon 35 oral tablets compared with Ovcon 35 chewable tablets
6. A clinical study assessing the potential for irritation of the oral mucosa by the chewable tablets
7. A list of references

The Ovcon 35 chewable tablet formulation studied in Study PR 03801 (Report CR 01002) is same as the to-be-marketed formulation.

**Recommendation:**

The Office of Clinical Pharmacology and Biopharmaceutics/Division of Pharmaceutical

Evaluation II find that the Human Pharmacokinetics and Bioavailability section for NDA 21-490 is fileable. However, Since the approval of NDA 21-490 is solely based on the BE study (Study PR 03801) and the clinical study assessing the potential for irritation of the oral mucosa by the chewable tablets (Study CS 900201), the route of administration used in the BE study (chewed and then swallowed) will be the only one considered for this NDA. If the sponsor plans to claim swallowing the tablet whole as a route of administration in the label, the data supporting this or rationale/justification must be provided by the sponsor.

The sponsor should submit any information on food effect if there are any studies performed.

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

\_\_\_\_\_  
Date

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

\_\_\_\_\_  
Date

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Myong-Jin Kim  
1/29/03 04:35:38 PM  
PHARMACOLOGIST

Venkateswar Jarugula  
1/29/03 05:11:06 PM  
BIOPHARMACEUTICS

## Filing Memo

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### Clinical Pharmacology and Biopharmaceutics Review

**NDA:** 21-490  
**Compound:** Ovcon 35 28-Day (Norethindrone/Ethinyl Estradiol)  
**Sponsor:** Warner Chilcott, Inc.

**Date:** 16/May/2002  
**Reviewer:** Myong-Jin Kim

#### Background:

This NDA is for a new dosage form, chewable tablet, of the currently marketed product Ovcon 35 28-day (norethindrone and ethinyl estradiol tablets, USP) for the prevention of pregnancy. Reference is made to the approved NDA 17-716 for Ovcon 35 28-day tablets.

The sponsor claims that the main differences in the new dosage form from the currently marketed product are as follows:

- Mode of administration
- Addition of a flavor and sweetener
- — two excipients, dibasic calcium phosphate, USP and lactose, NF/EP
- —, FD&C yellow #6 aluminum lake

The sponsor submitted two clinical pharmacology studies to support NDA 21-490, a bioequivalence study (Report CR 01002) and an oral irritation study (Report RR 00802).

#### Study PR 03801 (Research Report CR 01002)

- Single-center, open-label, single-dose, randomized, two-period, two-treatment crossover bioequivalence study in 26 healthy, non-smoking female subjects
- Subjects are randomized to receive a single oral dose of Ovcon 35 chewable table (chewed and then swallowed with 240 mL of water) OR a single oral dose of approved Ovcon 35 tablet (swallowed whole with 240 mL of water)
- To compare the bioequivalence of Ovcon 35 chewable tablets (norethindrone 0.4 mg and ethinyl estradiol 0.035 mg) relative to that for norethindrone 0.4 mg and ethinyl estradiol 0.035 mg tablets, USP (Ovcon 35) under fasting conditions

#### Study CS 900201 (Research Report RR 00802)

- Single-center, open-label, single treatment oral irritation study
- To determine the irritation potential of a chewable, oral contraceptive following daily use, over a 21-day cycle, by women of childbearing potential

The sponsor provided the following:

1. Human Pharmacokinetics and Bioavailability section summary, full study report, and labeling
2. Drug formulation, in vitro release testing
3. Bioanalytical methods
4. Comparative dissolution profiles
5. Bioequivalence study assessing the currently approved Ovcon 35 oral tablets compared with Ovcon 35 chewable tablets

6. A clinical study assessing the potential for irritation of the oral mucosa by the chewable tablets
7. A list of references

The Ovcon 35 chewable tablet formulation studied in Study PR 03801 (Report CR 01002) is same as the to-be-marketed formulation.

**Recommendation:**

The Office of Clinical Pharmacology and Biopharmaceutics/Division of Pharmaceutical Evaluation II find that the Human Pharmacokinetics and Bioavailability section for NDA 21-490 is fileable. However, Since the approval of NDA 21-490 is solely based on the BE study (Study PR 03801) and the clinical study assessing the potential for irritation of the oral mucosa by the chewable tablets (Study CS 900201), the route of administration used in the BE study (chewed and then swallowed) will be the only one considered for this NDA. If the sponsor plans to claim swallowing the tablet whole as a route of administration in the label, the data supporting this or rationale/justification must be provided by the sponsor.

The sponsor should submit any information on food effect if there are any studies performed.

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

\_\_\_\_\_  
Date

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

\_\_\_\_\_  
Date

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/s/  
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Myong-Jin Kim  
5/22/02 03:21:29 PM  
PHARMACOLOGIST

Ameeta Parekh  
7/15/02 12:15:54 PM  
BIOPHARMACEUTICS  
I concur

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

General Information About the Submission			
	Information		Information
NDA Number	21-490	Brand Name	Ovcon 35 28-day
OCPB Division (I, II, III)	DPE II	Generic Name	Norethindrone/Ethinyl Estradiol
Medical Division	DRUDP	Drug Class	Oral Contraceptive
OCPB Reviewer	Myong-Jin Kim	Indication(s)	Prevention of Pregnancy
OCPB Team Leader	Ameeta Parekh	Dosage Form	Chewable Tablet
		Dosing Regimen	0.4 mg/0.035 mg
Date of Submission	02/Apr/2002	Route of Administration	Oral
Estimated Due Date of OCPB Review		Sponsor	Warner Chilcott, Inc.
PDUFA Due Date		Priority Classification	S
Division Due Date	24/Jan/2003		

**Clin. Pharm. and Biopharm. Information**

	"X" if included at filing	Number of studies submitted	Number of studies reviewed	Critical Comments If any
<b>STUDY TYPE</b>				
Table of Contents present and sufficient to locate reports, tables, data, etc.	X			
Tabular Listing of All Human Studies	X			
HPK Summary	X			
Labeling	X			
Reference Bioanalytical and Analytical Methods	X			
<b>I. Clinical Pharmacology</b>				
Mass balance:				
Isozyme characterization:				
Blood/plasma ratio:				
Plasma protein binding:				
Pharmacokinetics (e.g., Phase I) -				
Healthy Volunteers-				
single dose:				
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 2:				
Phase 3:				
PK/PD:				
Phase 1 and/or 2, proof of concept:				
Phase 3 clinical trial:				

<b>Population Analyses -</b>				
	Data rich:			
	Data sparse:			
<b>II. Biopharmaceutics</b>				
<b>Absolute bioavailability:</b>				
<b>Relative bioavailability -</b>				
	solution as reference:			
	alternate formulation as reference:			
<b>Bioequivalence studies -</b>				
	traditional design; single / multi dose:	X	1	
	replicate design; single / multi dose:			
<b>Food-drug interaction studies:</b>				
	Dissolution:	X	1	
<b>(IVIVC):</b>				
<b>Bio-wavier request based on BCS</b>				
<b>BCS class</b>				
<b>III. Other CPB Studies</b>				
<b>Genotype/phenotype studies:</b>				
<b>Chronopharmacokinetics</b>				
<b>Pediatric development plan</b>				
	Literature References	X	3	
<b>Total Number of Studies</b>			5	
<b>Filability and QBR comments</b>				
		<b>"X" if yes</b>	<b>Comments</b>	
	<b>Application filable ?</b>	X	Reasons if the application <u>is not</u> filable (or an attachment if applicable) For example, is clinical formulation the same as the to-be-marketed one?	
	<b>Comments sent to firm ?</b>		Comments have been sent to firm (or attachment included). FDA letter date if applicable.	
<b>QBR questions (key issues to be considered)</b>				
<b>Other comments or information not included above</b>				
<b>Primary reviewer Signature and Date</b>		Myong-Jin Kim		
<b>Secondary reviewer Signature and Date</b>		Ameeta Parekh		