

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*  
**022573Orig1s000**

**CROSS DISCIPLINE TEAM LEADER REVIEW**

## Cross-Discipline Team Leader Review

<b>Date</b>	December 22, 2010
<b>From</b>	Lisa M. Soule, M.D.
<b>Subject</b>	Cross-Discipline Team Leader Review
<b>NDA/BLA #</b>	22-573
<b>Applicant</b>	Warner Chilcott, LLC
<b>Date of Submission</b>	November 25, 2009
<b>PDUFA Goal Date</b>	December 24, 2010 (extended)
<b>Proprietary Name / Established (USAN) names</b>	None approved to date Norethindrone (NE) and ethinyl estradiol (EE) chewable tablets and ferrous fumarate chewable tablets
<b>Dosage forms / Strength</b>	Tablets; 800 µg NE/25 µg EE for 24 days, followed by 75 mg ferrous fumarate for 4 days
<b>Proposed Indication(s)</b>	Prevention of pregnancy
<b>Recommendation:</b>	<b>Approval</b>

### 1. Introduction

This NDA seeks marketing approval for a combined oral contraceptive containing a novel dose combination of two established contraceptive hormones, the progestin norethindrone (NE) and the estrogen ethinyl estradiol (EE), in a chewable tablet. The combination of NE and EE is in a number of approved combined oral contraceptives (COCs). The proposed dose is novel, and the EE dose is lower than in other approved EE/NE products. The dose regimen is 24 continuous days of active, EE/NE chewable tablets, followed by four days of ferrous fumarate chewable tablets. The ferrous fumarate is not considered to have a therapeutic benefit, and is essentially a placebo.

The Applicant conducted five phase 1 studies (four clinical pharmacology and one safety) and one phase 3 study in support of this marketing application. The pivotal safety and efficacy trial was an open label, single arm, multicenter, 13-cycle trial. The trial enrolled over 1,600 women to meet the Division's exposure requirements for a new contraceptive regimen, allowing for a substantial discontinuation rate. The primary efficacy endpoint, the Pearl Index in women aged  $\leq 35$  years and based on cycles in which no other methods of birth control were used, was 2.01 per 100 women-years, which is comparable to other approved COCs. In addition, the Applicant conducted a 24-day phase 1 oral irritation study to evaluate the tolerability of this higher dose of NE in a chewable product. No safety issues specific to this chewable estrogen/progestin combination were observed.

The bleeding profile of EE/NE chewable is acceptable. The mean number of days of unscheduled bleeding/spotting may actually be greater than the mean number of days of withdrawal bleeding/spotting at each cycle, which may be considered a drawback by users. The overall profile of unscheduled bleeding/spotting appears similar to that seen in other, recently reviewed low EE COCs.

The Applicant initially submitted the proprietary name (b) (4), which was not found acceptable by the Division of Medication Errors Prevention and Analysis (DMEPA). The Applicant then submitted the names (b) (4), which were also found unacceptable. At the time of this review, a further proprietary name has not been submitted by the Applicant. This review will refer to the product as EE/NE chewable; however, other reviewers may cite the product as (b) (4) or WC3026, as it was referred to during product development.

## 2. Background

### 2.1 DESCRIPTION OF PRODUCT

EE/NE chewable is a combination oral contraceptive (COC) containing 25 µg of EE and 800 µg of NE, to be taken in the 24/4 regimen over a 28 day cycle for the prevention of pregnancy, as described in the preceding section. The combination tablets are taken for the first 24 days of the cycle, then tablets containing only ferrous fumarate are taken for four days. The ferrous fumarate is not considered to serve any therapeutic purpose; it is essentially placebo. The tablets are to be chewed and swallowed without water.

The combination of EE/NE has been approved since 1974, albeit in much higher doses. The Applicant has another chewable COC product, Femcon Fe, which contains 35 µg of EE and 400 µg of NE, taken in a 21/7 regimen. That product, which was approved in 2003, represents the only other approved chewable COC. No safety or efficacy concerns have been raised over the long history of use of EE/NE products, beyond the known and labeled adverse events observed with COCs generally, such as venous thromboembolism.

### 2.2 Regulatory History

The Applicant opened IND 76,629 in April 2007, following a preIND meeting in February 2007. At that meeting, the Division concurred that no further nonclinical data on NE or EE would be required. The Division also provided the following guidance:

- An oral irritation study should be conducted, as this product would provide higher exposure to NE than does Femcon Fe chewable.
- The contraceptive efficacy study should provide 10,000 28-day cycles of exposure, including 200 women completing 13 cycles of use.

(b) (4)

The protocol for Study PR-00207 was submitted for review, and the Division provided comments in June 2007. The Division recommended enrollment of women under age 18 if possible, and noted that restrictive entry criteria (such as  $BMI \leq 35 \text{ kg/m}^2$  or a “suspected genetic component” leading to higher risk of venous thromboembolic events [VTEs]) might be reflected in labeling. Cycles in which back-up or emergency contraception was used, or cycles in which no sexual activity occurred should be excluded from evaluable cycles used to calculate the Pearl Index or life table estimates of pregnancy rate.

The Applicant requested a pre-NDA meeting with the Division in 2009, but cancelled its request after receiving preliminary responses from the Division. The Division provided further guidance on the definition of “on treatment” pregnancies, to include those conceived from the initiation of study drug until seven days after the final tablet in the pill pack was taken (or after the final tablet was taken if treatment was stopped prior to the end of a cycle). The Division also made recommendations regarding the presentation of bleeding/spotting data.

### **2.3 Primary Clinical Reviewers’ Recommendation**

The primary medical reviewer, Dr. Jerry Willett, made the following recommendation in his review dated October 6, 2010:

*Approval is recommended for norethindrone 0.8 mg and ethinyl estradiol 0.025 mg chewable tablets and ferrous fumarate chewable tablets for the Applicant’s proposed indication of “for use by women to prevent pregnancy.”*

#### **Team Leader Comment:**

**I concur with Dr. Willett’s recommendation for approval.**

## **3. CMC/Device**

The primary Chemistry Reviewer, Jane Chang, Ph.D., made the following recommendations in her review dated September 9, 2010:

*This NDA has provided sufficient CMC information to assure the identity, strength, purity, and quality of the drug product. The Office of Compliance has made an “Acceptable” site recommendation. The labels have adequate information as required. Therefore, from the CMC perspective, this NDA is recommended for “Approval.”*

No postmarketing commitments or risk management steps were recommended.

### **3.1 General product quality considerations**

The drug substances NE and EE are both monographed in the USP. The relevant DMFs were referenced in this submission, and letters of authorization provided. The DMFs for NE were reviewed and found to be adequate in 2010. The DMFs for EE were reviewed and found to be adequate in 2009 and 2010. The drug product is an immediate release chewable tablet. Stability data on the drug product at 30-36 months at 25° C and 6 months at 40° C permitted granting a 36 month expiry for the drug product.

### **3.2 Facilities review/inspection**

Eight facilities involved in manufacture, testing, packaging and release of the drug product were evaluated by the Office of Compliance, which issued an overall satisfactory facilities recommendation on April 16, 2010. Five were found acceptable based on district recommendation, two on profile, and one on file review.

### **3.3 Other notable issues (resolved or outstanding)**

A biopharmaceutics review addressed the dissolution method development and specification. The reviewer, Sandra Suarez Sharp, Ph.D., concluded in her review dated July 29, 2010 that the proposed dissolution method was not acceptable because it is not sufficiently

discriminating, but that it would be accepted as interim for one year. In addition, the proposed dissolution specifications for both the EE/NE tablets and the ferrous fumarate tablets were considered too permissive. A specification of (b) (4) would be accepted as interim for the EE/NE tablets until a more discriminating dissolution method is accepted. A dissolution specification for ferrous fumarate tablets of (b) (4) (Q) of ferrous fumarate is dissolved in 30 minutes” was recommended.

This determination was conveyed to the Applicant, and the Applicant agreed to the proposed criterion for ferrous fumarate. The Applicant proposed an interim specification for EE/NE tablets of (b) (4) (Q) dissolved in 20 minutes, until the Applicant submits a more discriminating dissolution method (within a year). Dr. Sharp found this acceptable, and concluded in her memo dated August 31, 2010 that the two dissolution specifications had been agreed upon, and that she had no further comments.

#### **4. Nonclinical Pharmacology/Toxicology**

The Applicant did not conduct any new nonclinical studies, but cross-referenced the studies provided in NDA 17-576, approved in 1975 for Ovcon 50 tablets (50 µg EE/1 mg NE administered in a 21/7 regimen).

The primary Toxicology Reviewer, Krishan Raheja, D.V.M., Ph.D., made the following recommendations in his review dated January 22, 2010:

***Recommendations on approvability:*** *Pharmacology/toxicology recommends approval of NDA 022573 for contraception.*

Dr. Raheja did not recommend any additional nonclinical studies, and found the proposed labeling acceptable in his addendum dated September 20, 2010.

#### **5. Clinical Pharmacology/Biopharmaceutics**

The primary Clinical Pharmacology Reviewer, Christian Grimstein, Ph.D., stated the following in his review dated September 1, 2010:

*NDA 022573 is acceptable from a Clinical Pharmacology perspective, provided an agreement can be reached with the sponsor pertaining to labeling language.*

Following receipt of agreed-upon labeling from the Applicant, Dr. Grimstein concluded in an amendment to his review dated December 22, 2010:

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

Dr. Grimstein did not recommend any phase 4 commitments.

The clinical development program included four phase 1 clinical pharmacology studies in addition to the phase 3 trial and the oral irritation study. The phase 1 studies included a relative bioavailability study (PR-00807), two multiple dose pharmacokinetic (PK) studies (PR-03808 and PR-00707 [the latter is not directly relevant to this application as it used the tablet swallowed whole with 240 ml of water] and a food effect study (PR-00907). The relative bioavailability study showed that, compared to a solution of NE/EE, the tablet chewed

without water provided higher C<sub>max</sub> and AUC for EE, and slightly lower C<sub>max</sub> and slightly higher AUC for NE. The PK parameters for NE met the usual 80-125% criteria for bioequivalence of the two formulations, while the parameters for EE were outside the 80-125% criteria.

The mode of dosing was evaluated in this study by comparing C<sub>max</sub> and AUC for tablets chewed and swallowed without water and tablets chewed and followed with 45 ml of water. The C<sub>max</sub> for both EE and NE was slightly decreased when water was included; the AUC did not vary for either hormone whether taken with or without water.

The study evaluating food effect showed that dosing under fed conditions reduced the C<sub>max</sub> of both EE and NE. The AUC for EE was unchanged, while that for NE increased by about 14%. However, the clinical trial was conducted without regard to meals, so dosing instructions without respect to meals are acceptable to Dr. Grimstein.

The effects of renal and hepatic impairment have not been studied. Class labeling for COCs states that steroid hormones may be poorly metabolized in patients with impaired liver function. No specific drug-drug interaction studies were conducted; however, interactions of specific drugs with combined oral contraceptives generally are included in class labeling for combined hormonal contraceptives.

## 6. Clinical Microbiology

As the product is an oral tablet, no clinical microbiology review was warranted. The Applicant included accepting testing for microbial limits in the drug product specification.

## 7. Clinical/Statistical- Efficacy

### 7.1 OVERVIEW OF CLINICAL PROGRAM

Data from the following clinical studies were submitted in the NDA:

- One safety and efficacy contraception trial
- One oral irritation safety study

The phase 1 and phase 3 safety and efficacy studies are summarized in Table 1. Study PR-10107 is further discussed in Section 8.4.

**Table 1 Overview of Clinical Safety and Efficacy Studies**

Study	Objective	Design	Dose (mg)	# Subjects	Duration
<b>Phase 1 Study</b>					
PR-10107 US – 1 site	Oral Irritation	Single center, open label	To-be-marketed: 25 µg EE/0.8 mg NE x 24 days	54 (52 completers)	24 days
<b>Phase 3 Study – Primary Efficacy Trial</b>					
PR-00207 US – 69 sites	Pivotal Efficacy/Safety	Multicenter, open-label	To-be-marketed: 25 µg EE/0.8 mg NE x 24 days, ferrous fumarate x 4 days	1,677 (746 completed 360 days of treatment)	13 28-day cycles

Source: NDA Module 5.2- Applicant's Listing of Clinical Trials, p 2

In Study PR-00207, 1,700 subjects were enrolled at 69 US sites. Twenty-three subjects did not start study medication. The trial provided efficacy data based on 12,297 cycles (in women aged <36 years) and safety data based on 15,548 cycles. Almost 750 women completed 13 cycles of treatment.

**Team Leader Comment**

**The phase 3 trial met the Division's requirements regarding cycles of exposure and number of women completing 13 cycles of treatment.**

Entry criteria are detailed in Dr. Willett's review, but primary criteria for eligibility were those usually utilized in hormonal contraceptive trials. Briefly, entry criteria included age 18-45 years, regular menstrual cycles and body mass index (BMI)  $\leq 35$  kg/m<sup>2</sup>. Exclusion criteria included history of or "known or suspected genetic component" of thromboembolic disorders. Smokers of more than 15 cigarettes/day over the age of 35 years were excluded.

**Team Leader Comments**

- **When the protocol was reviewed, the Division discouraged the Applicant from employing the BMI exclusion. The Division is opposed to restricting enrollment in hormonal contraception trials on the basis of weight or BMI. There are both safety and efficacy concerns regarding the use of hormonal contraception by obese women. Obese women may achieve lower serum hormone concentrations, which could pose a particular concern with respect to efficacy for a lower dose product. Conversely, obesity is a risk factor for venous thromboembolism (VTE), a major safety issue with hormonal contraceptives. Safety and efficacy data obtained in obese women would be of great interest.**
- **On the other hand, a BMI of 35 kg/m<sup>2</sup> is not terribly restrictive; for a 5'4" woman, this would correspond to a weight of 204 lbs. The Applicant has voluntarily included a statement in the proposed labeling regarding lack of safety and efficacy data in women above a BMI of 35 kg/m<sup>2</sup>.**
- **I agree with inclusion of a statement in labeling (Indications and Usage sections) to disclose the fact that efficacy was not studied in heavier women.**

Trial instructions included dosing without regard to meals, but subjects were instructed to take the tablet without water at the same time each day. A Day 1 start was used (i.e., subjects switching from another COC began taking EE/NE chewable on the day they would have resumed use of their previous product, and new users began on the first day of their period). Subjects who did not adhere to the dosing regimen and missed a period were discontinued from further dosing until pregnancy had been ruled out. Adherent subjects who missed a period were instructed to take a home pregnancy test. Subjects who missed one active pill were instructed to take it as soon as remembered along with the current dose, i.e., taking 2 pills in one day. Subjects who missed two consecutive active pills in Week 1 or 2 were instructed to take the missed pills over two days and use backup contraception until they had taken seven consecutive active pills. Subjects who missed two or more consecutive active pills in Week 3 or 4 were instructed to take start a new pack immediately and use backup contraception until they had taken seven consecutive active pills. Women who experienced vomiting or diarrhea within 3-4 hours of pill-taking were instructed to follow the missed pills instructions.

Subjects underwent routine urine pregnancy testing at study visits (about every two months), as well as serum pregnancy testing at Screening and during the end of treatment visit. During the 28-day follow-up period after the End of Treatment visit, subjects were contacted to determine if they had had a period; if they had not, pregnancy testing was performed.

**Team Leader Comment**

**The pregnancy testing in this trial was quite rigorous.**

**7.2 Demographics**

The mean age was about 29 years, and the mean weight about 150 lbs. The mean BMI (not shown) was 25.0 kg/m<sup>2</sup>, with a range of 15-36 kg/m<sup>2</sup>. The Applicant considered all women who had not used COCs in the immediately preceding time period to be “new users.”

Table 2 shows the demographics of the modified Intent to Treat (MITT) population in Study PR-00207, which is defined as all subjects who received at least one dose of study drug and were evaluated for pregnancy at least once after beginning study medication.

**Team Leader Comments**

- **The racial distribution of the population appears fairly representative of the general US population.**
- **The mean weight is about 15 lbs. lower than seen in a recent comparable COC trial that did not restrict entry on the basis of BMI or weight.**
- **The Applicant uses a very broad definition of “new user,” including women who had not been using a COC immediately before enrollment. Thus, even a prior user with a long history of COC use, who had been off her prior product for as few as four weeks was considered a new user. While new users are usually expected to have higher pregnancy and AE rates, I would not necessarily hold this expectation for the “new users” in this trial.**

**Table 2 Study PR-00207 – Demographics and Baseline Characteristics – MITT Population**

<b>Parameter</b>	<b>(N=1570)</b>
Mean age (years ± SD)	28.8 ± 7.1
Age range (years)	18-46
Ethnic group (%)	
• Caucasian	1131 (72.0%)
• Black	204 (13.0%)
• Hispanic	176 (11.2%)
• Asian	28 (1.8%)
• Native American	7 (0.4%)
• Other	24 (1.5%)
Switchers	819 (52.2%)
New users (non-switchers)	751 (47.8%)
Current smokers	249 (15.9%)
Mean weight (lbs ± SD)	148.9 ± 29.1 lb
Weight range	74-243 lb

SD = standard deviation

Source: Study Report for PR-00207, Table 5, p 44

**7.3 Disposition of Subjects**

A total of 2,321 women were screened for the study, with 1,700 enrolled. Of these, 1,677 women took at least one dose of study drug. This constituted the safety population. A total of

686 women (41%) from the All Treated population (all women who took at least one dose of NE/EE chewable) discontinued prematurely for the reasons described in Table 3.

**Team Leader Comments**

- **The rate of premature discontinuation is typical of that seen for contraceptive trials, as is the distribution of reasons for premature discontinuation.**
- **Common reasons for discontinuation that were included in the “Other” category included noncompliance (N=23), site closure due to investigator illness (N=20) and subject moved (N=8).**

**Table 3 Study PR-00207 – Overall Subject Disposition**

<b>Disposition / Reason</b>	<b>0.025 mg EE / 0.8 mg NE</b>
Screened	2,321 (100%)
Subjects not qualified for enrollment	621 (26.8%)
<ul style="list-style-type: none"> <li>• Screen failure</li> <li>• Other</li> <li>• Changed mind</li> <li>• Could not comply</li> <li>• Spouse/partner refusal</li> </ul>	<ul style="list-style-type: none"> <li>• 416 (17.9%)</li> <li>• 102 (4.4%)</li> <li>• 86 (3.7%)</li> <li>• 15 (0.6%)</li> <li>• 2 (0.1%)</li> </ul>
Subjects enrolled in the study	1,700 (73.2%)
Subjects enrolled but did not receive medication	23 (0.9%)
<hr/>	
Subjects receiving study medication	1,677
MITT population	1,570 of 1677 (93.6%)
<ul style="list-style-type: none"> <li>• Age 18-35 years</li> <li>• Age &gt; 35 years</li> </ul>	<ul style="list-style-type: none"> <li>• 1251 of 1570 (79.7%)</li> <li>• 319 of 1570 (20.3%)</li> </ul>
Evaluable for IB assessment for cycles 2-13	1425 of 1677 (85.0%)
Subjects prematurely discontinuing study	686 of 1677 (40.9%)
<ul style="list-style-type: none"> <li>• Loss to follow-up</li> <li>• Withdrew consent</li> <li>• Adverse events</li> <li>• Other reasons</li> <li>• Protocol violation</li> <li>• Pregnancy</li> <li>• Death</li> </ul>	<ul style="list-style-type: none"> <li>• 271 (16.2%)</li> <li>• 149 (8.9%)</li> <li>• 143 (8.5%)</li> <li>• 75 (4.5%)</li> <li>• 25 (1.5%)</li> <li>• 23 (1.4%)</li> <li>• 0</li> </ul>
Completed subjects (MITT subjects finishing 360 days of treatment)	746 of 1677 (44.5%)

EE/NE = ethinyl estradiol / norethindrone; MITT = modified intent-to-treat (subjects who had at least one pregnancy test performed after starting treatment)

IB = Intracyclic bleeding (evaluable cycles had at least 14 evaluable diary days)

Source: Study Report for PR-00207; Table 4, p 39; Figure 1, p 41; Table 14.1.1, p 103

## 7.4 Efficacy Findings

### 7.4.1 Assessment of Efficacy

The primary endpoint in Study PR-00207 was the pregnancy rate, based on the Pearl Index for women aged 35 or younger, based on all evaluable cycles in which no other method of birth control was used. The Pearl Index is calculated as

$$\text{Pearl Index} = \frac{100 \times \text{number of pregnancies} \times 13 \text{ cycles/year}}{\text{Number of 28-day cycles of treatment}^*}$$

\* Only cycles in which no back-up contraceptive methods were used were included.

The primary analysis population was the pregnancy intent-to-treat (PITT) population, defined as all subjects who received at least one dose of study drug, were evaluated for pregnancy at least once after beginning study drug, and were between the ages of 18-35 years, with exclusion of any cycles in which an alternate method of birth control was used (also known as the PITT, non-BCM population).

#### Team Leader Comment

**The PITT population is the appropriate one for evaluation of the primary endpoint (Pearl Index), and cycles in which other contraception (including condoms) was used were appropriately excluded.**

Pregnancies conceived on drug or within 7 days after the last pill (either after the last placebo pill if the subject completed a cycle, or after the last EE/NE tablet if she stopped treatment before the end of a cycle) were included in calculation of the Pearl Index.

Life table methods are also commonly used to assess contraceptive efficacy; these provide cumulative rates of pregnancy at the end of the study, and at the end of each preceding cycle. Life tables do not typically exclude individual cycles for a given subject, such as a cycle in which an alternate method of birth control was used, so they are not directly comparable to the Pearl Index based on the PITT, non-BCM population.

### 7.4.2 Primary Efficacy Results

A total of 29 pregnancies were reported by the Applicant to have occurred in subjects in Study PR-00207, with 19 occurring on-treatment in women <36 years of age. There were no pregnancies conceived within seven days after discontinuing treatment. Dr. Willett identified one additional pregnancy to the 18 considered on-treatment by the Applicant, which was included in the FDA calculation of Pearl Index and life table pregnancy rate.

**Table 4 Timing of Conception**

Study PR-00207		
Timing of conception	N	Comment
Total # pregnancies	30	
Prior to starting treatment	1	
<b>On treatment</b>	<b>19</b>	1 subject did not provide information that confirmed the conception date, but the clinical reviewers consider it possible that she conceived on treatment.
<b>≤ 7 days after last E+P pill</b>	<b>0</b>	
<b>Unknown last E+P intake</b>	<b>0</b>	
Other excluded pregnancy	1	1 pregnancy occurred on treatment, in a 40 y/o subject; therefore not counted in the Pearl Index
> 7 to ≤ 14 days after last E+P pill	1	Occurred 12 days after last dose
> 14 days after last E+P pill	8	Occurred 15-26 days after last dose

**Bold = Pregnancies counted in computing the Pearl Index**

**Pearl Index**

The statistical reviewer, Kate Dwyer, Ph.D., reviewed the Applicant's data and recalculated the Pearl Index based on 19 pregnancies conceived on treatment or within 7 days after the last pill intake. The results of her analysis were provided a slightly higher Pearl Index than the Applicant's, because their calculation was based on only 18 pregnancies (see Table 5). The "gold standard analysis" relied upon by the Division is the PITT (non-BCM), which gives a Pearl Index of 2.01 (upper bound of the 95% confidence interval [CI] is 3.14). The MITT includes all subjects in the PITT, without any age restriction, so both analyses include an additional pregnancy for that cohort.

**Table 5 Pearl Index Calculation of Treatment Failure Rates using 7-Day after Last Pill Conception Rule**

	Population	Subject Exposed (n)	On-Treatment Pregnancies (n)	Cycles (n)	Pearl Index (95% CI)
<b>Applicant</b>	MITT	1,570	19	15,752	1.57 (0.94, 2.45)
	PITT	1,251	18	12,297	1.90 (1.13, 3.01)
<b>FDA</b>	MITT	1,570	20	15,752	1.65 (1.01, 2.55)
	PITT	<b>1,251</b>	<b>19</b>	<b>12,297</b>	<b>2.01 (1.21, 3.14)</b>

Source: Table 3, Statistical review by Kate Dwyer, Ph.D., dated September 17, 2010

**Team Leader Comment**

**The Pearl Index based on the US data provides evidence of acceptable contraceptive efficacy.**

**Life Table Analysis**

The Applicant provided a Year 1 life table estimate of the pregnancy rate based upon 18 pregnancies, while the Dr. Dwyer provided life table estimates based on the 19 pregnancies that occurred within 7 days after the last pill intake (see Table 6). Dr. Dwyer excluded only

those cycles in which back-up contraception was used, rather than censoring a subject as soon as she used back-up contraception.

**Table 6 Life Table Estimates of Treatment Failure Rates – Women 18-35 Years of Age with at Least One Complete Cycle of Treatment**

	Population	On-Treatment Pregnancies (n)	Cumulative Pregnancy Rate (95% CI)
<b>Applicant</b>	MITT	19	1.57%
	PITT	18	1.90%
<b>FDA</b>	MITT	20	1.75% (1.27%, 2.40%)
	PITT	19	2.00% (1.27%, 3.13%)

Source: Table 4, Statistical review by Kate Dwyer, Ph.D., dated September 17, 2010

**Team Leader Comment**

The life table estimates are very close to the Pearl Indices, and, like the Pearl Index, provide evidence of acceptable contraceptive efficacy.

**Statistician’s Conclusion**

The statistical reviewer, Kate Dwyer, Ph.D., confirmed the Applicant’s overall primary efficacy findings, although her calculations included one additional pregnancy identified by the clinical reviewer. Dr. Dwyer also conducted subgroup analyses by race and BMI. Although the Pearl Index was higher in African American subjects, it is not considered to be a reliable estimate due to the small numbers (four pregnancies among 161 subjects). Similarly, the results for women with BMI > 30 kg/m<sup>2</sup> showed a higher Pearl Index (see Table 7), but this rate is based on similarly small numbers.

**Table 7 Pearl Index Calculation of Treatment Failure Rates by BMI**

Population	BMI	Subject Exposed (n)	On-Treatment Pregnancies (n)	Cycles (n)	Pearl Index (95% CI)
<b>PITT</b>	BMI ≤ 30	1,060	15	10,497	1.86 (1.04, 3.06)
	BMI > 30	191	4	1,800	2.89 (0.79, 7.38)

Source: Table 6, Statistical review by Kate Dwyer, Ph.D., dated September 17, 2010

**Team Leader Comments**

- The four women with BMI > 30 kg/m<sup>2</sup> who became pregnant on treatment had BMIs of 30.3, 31.8, 32.3 and 34.3 kg/m<sup>2</sup>.
- The four pregnancies that occurred in these women represent 21% of all on-treatment pregnancies. The sample included 16% of subjects who had a BMI above 30. I do not consider that this indicates a disproportionate frequency of treatment failure in obese women.

Dr. Dwyer made the following conclusions and recommendations regarding contraceptive efficacy in the Executive Summary of her review dated September 17, 2010:

*The study results support the efficacy of WC3026, a 28-day low dose combination oral contraceptive (COC), in preventing pregnancy as demonstrated by the Pearl Index of 2.01 (95% Confidence Interval: 1.21 to 3.14).*

### 7.4.3 Key Secondary Efficacy Results

Characterization of the bleeding profile of EE/NE chewable was a secondary objective of the contraceptive study PR-00207. Subjects completed a daily diary that recorded occurrence and intensity of bleeding or spotting. The following bleeding intensity definitions were used:

- None: no vaginal bleeding
- Light: less than the subject's normal menses, but requiring use of sanitary protection
- Normal: like the subject's normal menses
- Heavy: more than the subject's normal menses

Light bleeding that required no use of sanitary protection (aside from panty liners) was classified as spotting.

A bleeding/spotting episode was defined as the number of days of bleeding/spotting that were preceded and followed by at least two bleeding-free days. Bleeding/spotting was characterized as withdrawal (herein referred to as "scheduled") if it started after the last day of active pill intake and before starting the next treatment cycle, or started within 4 days of the last active pill and continuing through at least the first day after the last active pill. All other bleeding/spotting episodes were considered "intracyclic" by the Applicant (herein referred to as "unscheduled"). Amenorrhea was defined as the absence of bleeding or spotting in a given cycle.

The Applicant initially reported bleeding data using 90-day reference periods, as recommended by the WHO, omitting the first cycle. However, at the Division's request, the Applicant also provided the following bleeding data based on 28-day cycles, which is consistent with the Division's current thinking on evaluating and reporting cycle control (see Table 8 and Table 9). Single missing days of bleeding data were imputed by using the maximum of the two bordering days' bleeding. If two or more consecutive days were missing, they were not imputed, and were considered non-evaluable. A cycle with fewer than 14 evaluable days was considered a non-evaluable cycle.

**Table 8 Study PR-00207 - Days with Unscheduled Bleeding, Unscheduled Spotting and Unscheduled Bleeding/Spotting per 28-Day Cycle\***

Cycle	Unscheduled Bleeding			Unscheduled Spotting			Unscheduled Bleeding and/or Spotting		
	N	Mean (SD)	Median	N	Mean (SD)	Median	N	Mean (SD)	Median
1	416	4.8 (3.5)	4	279	2.9 (2.6)	2	542	5.2 (3.9)	4
2	360	4.0 (2.8)	4	168	2.3 (2.0)	2	436	4.2 (3.0)	4
3	332	3.8 (2.5)	3	141	2.7 (2.6)	2	391	4.2 (2.8)	4
4	257	3.8 (2.4)	3	111	2.3 (1.7)	2	305	4.0 (2.6)	4
5	270	3.9 (2.5)	3	99	2.2 (1.6)	2	319	4.0 (2.6)	4
6	229	3.6 (2.2)	3	90	2.1 (1.6)	2	270	3.8 (2.2)	3
7	228	3.8 (2.4)	4	85	2.0 (1.6)	1	266	3.9 (2.5)	4
8	202	3.7 (2.3)	3	69	2.3 (2.5)	2	232	3.9 (2.5)	3
9	214	4.1 (2.7)	4	80	2.1 (1.6)	2	255	4.1 (2.8)	4
10	185	3.7 (1.9)	4	72	1.9 (1.3)	1	218	3.7 (2.1)	4
11	214	4.0 (2.4)	4	62	2.2 (2.6)	2	242	4.1 (2.6)	4
12	184	3.6 (2.2)	3	67	1.9 (1.4)	1	220	3.6 (2.3)	3
13	186	4.0 (2.9)	3	71	1.7 (1.1)	1	217	4.0 (2.8)	3

\* Excludes subjects who had no bleeding/spotting

Source: Based on Tables A, B and C, Applicant submission dated September 27, 2010

**Team Leader Comments**

- **Unscheduled bleeding remains fairly constant over 13 cycles, averaging four days per cycle. Unscheduled spotting is less frequent, and tends to decrease slightly over time. Unscheduled bleeding may be problematic to users; this is a common reason for discontinuation of lower dose COCs.**
- **However, unscheduled bleeding/spotting data are reported only for those subjects who experienced any unscheduled bleeding/spotting, and thus would represent over-estimates of the duration in the total population (i.e., women who experienced 0 days of unscheduled bleeding/spotting are not included in the descriptive data).**
- **As discussed in Dr. Willett's review, about 20-30% of subjects had unscheduled bleeding/spotting per cycle. Over the totality of Cycles 2-13, 72% had at least one episode of unscheduled bleeding/spotting.**

**Table 9 Study PR-00207 - Days with Scheduled Bleeding per 28-Day Cycle**

Cycle	N	Mean	Min	Median	Max
1	1462	3.0	0	5.0	17
2	1393	2.6	0	3.0	13
3	1322	2.3	0	3.0	15
4	1243	2.2	0	3.0	12
5	1206	2.1	0	3.0	13
6	1162	2.0	0	3.0	11
7	1134	1.8	0	3.0	12
8	1097	1.9	0	3.0	10
9	1062	1.8	0	3.0	10
10	1031	1.9	0	2.0	10
11	1021	1.6	0	2.0	11
12	986	1.7	0	2.0	11
13	964	1.8	0	2.0	12

Source: Based on Tables 4 and 8, Applicant submission dated August 3, 2010

**Team Leader Comments**

- Because Cycle 1 began on the first day of the subject's period, the number of bleeding days for this cycle is higher than subsequent cycles. Subsequent to Cycle 1, scheduled bleeding averages about two days per month; however, this figure does not include days with withdrawal spotting.
- In contrast to the data presented for unscheduled bleeding/spotting, these figures for scheduled bleeding include women who did not have withdrawal bleeds. Therefore, the actual duration in those women who continue to have withdrawal bleeds is likely to be higher than shown here.
- As discussed in Dr. Willett's review, the proportion of subjects with scheduled bleeding declined over successive cycles, from about 75% in Cycle 2 to 57% by Cycle 13.
- The profile of both scheduled and unscheduled bleeding/spotting should be described in labeling.

The Applicant reported that about 8% of subjects experienced amenorrhea in Cycle 2, as did about 18% in Cycles 12 and 13.

**7.5 Overall Assessment of Efficacy**

The contraceptive efficacy study conducted by the Applicant provided evidence of an acceptable level efficacy of EE/NE chewable in the prevention of pregnancy. The bleeding profile is acceptable, and appears comparable to that observed in women using other approved low dose COCs containing EE and various progestins.

**8. Safety**

The assessment of the clinical safety of EE/NE chewable is based on the phase 1 and phase 3 studies. These included a total of 1,731 subjects. In study PR-00207, subjects completed a total of 15,548 28-day cycles, with 746 women completing all 13 cycles. In Study PR-10107, 54 women were treated for 28 days, with 52 completers.

Safety evaluations included vital signs and laboratory monitoring, pregnancy testing and adverse event reporting, as well as a dedicated study to evaluate the potential for oral irritation for this chewable tablet.

**Team Leader Comment**

**The exposure evaluated by the Applicant is sufficient and meets the levels requested by the Division. The exposure exceeds ICH guidelines for drugs to be used on a chronic basis (1,500 subjects total, 300-600 for six months and 100 for 12 months).**

**8.1 Deaths and Serious Adverse Events**

**Deaths**

There were no deaths in any of the trials.

**Serious Adverse Events**

In Study PR-00207, 24 subjects (1.4%) experienced 32 serious adverse events (SAEs) (Table 10), including two subjects not reported by the Applicant as SAEs, but who met criteria for Hy's law regarding liver laboratory abnormalities. These were the SAEs of greatest potential concern; however, it does not appear that either case was drug-related. They are discussed further in Section 8.4. Other notable SAEs include four cases of depression/suicidal ideation, two of hypertension/blood pressure increase, and one deep vein thrombosis (DVT). Of the depression/suicidal ideation cases, two subjects had a preexisting history of major depression, and one of anxiety. The case of angina/hypertension occurred in a woman with a history of hypertension who was ruled out for myocardial infarction and cardiac disease. It is unclear whether the other report of increased blood pressure was in a subject who had been normotensive on entry. The DVT occurred in a woman 12 days after completing the study. No risk factors were described.

There were no SAEs in Study PR-10107.

**Table 10 Study PR-00207 – Serious Adverse Events**

Site-Subject #	SAE(s)
200-085	Viral meningitis Headache
209-018	Depression Suicidal ideation
221-025	Flank pain
227-008	Asthma Respiratory tract infection
231-005	Anxiety Major depression
231-018	Multiple fractures
235-024	Chest pain (Depression)
237-015	Cholecystectomy
238-002	Appendicitis
238-031	Angina pectoris Hypertension
241-007	Suicidal ideation
241-058	Vomiting Abdominal pain
242-021	Chest pain
243-065	Staph infection
256-017	Intervertebral disc surgery
259-046	Abdominal pain
262-024	Intervertebral disc protrusion
263-046	Cervical dysplasia
263-056	Hemorrhagic diarrhea Dehydration Ischemic colitis
264-013	Lumbar vertebral fracture
265-044	Blood pressure increased
223-030*	Deep vein thrombosis
255-015*	Marked liver enzyme elevation (Hy's Law) Cholecystitis Cholecystectomy
208-037*	Mononucleosis Marked liver enzyme elevation (Hy's Law)

\*Occurred at or after study completion

Source: Based on Table 20, Clinical Review by Gerald Willett, M.D., dated October 6, 2010

**Team Leader Comments**

- COCs carry a labeled warning regarding depression; although most of the subjects with this SAE had a preexisting condition, it is possible that it was exacerbated on study drug.
- Hypertension is also included as a warning in COC labeling.
- Although the DVT occurred after completion of study drug, I would still consider it a treatment-emergent SAE.

### **Withdrawals due to Adverse Events**

A total of 143 subjects in Study PR-00207 (8.5%) discontinued trial participation prematurely due to adverse events (AEs). See Table 11 for the most common AEs leading to early discontinuation. No subjects in Study PR-10107 discontinued due to AEs.

**Table 11 Study PR-00207 - Most Common AEs ( $\geq 0.5\%$ ) Leading to Early Discontinuation**

<b>Adverse Event (Preferred Terms)</b>	<b>N= 1,677 N (%)</b>
Mood altered/irritability/mood swings/depression/suicidal ideation	20 (1.2)
Nausea/vomiting	19 (1.1)
Weight increased	14 (0.8)
Acne	13 (0.8)
Metrorrhagia/vaginal hemorrhage	13 (0.8)
Migraine/headache	8 (0.5)

**Source: Study Report RR-03009; Table 14.3.5; pp 262-3**

### **Team Leader Comments**

- **The AEs leading to discontinuation are representative of those observed in COC trials.**

### **8.2 Common Adverse Events**

The Applicant provided a table of common adverse events, defined as those occurring in at least 2% of the safety population; Table 12 includes only those events that occurred in at least 2% of subjects in Study PR-00207; however, all events were considered, regardless of frequency, and similar terms have been bundled. System organ classes in which the AEs do not appear to be drug-related are not itemized as to specific preferred terms included.

In Study PR-10107, there were six AEs in five subjects: none of which appear to be drug-related.

**Table 12 Study PR-00207 - Common Adverse Events (≥ 2%)**

<b>System Organ Class, Preferred Term</b>	<b>N=1,677 n (%)</b>
<b>Respiratory, Thoracic and Mediastinal Disorders</b>	<b>400 (23.9)</b>
<b>Reproductive System and Breast Disorders</b>	<b>308 (18.4)</b>
Vaginitis bacterial + vulvovaginal mycotic infection + vaginal infection + vaginal candidiasis	134 (8.0)
Dysmenorrhea	66 (3.9)
Breast tenderness + breast pain	40 (2.4)
<b>Gastrointestinal disorders</b>	<b>268 (16.0)</b>
Nausea + vomiting	148 (8.8)
Abdominal pain + upper + lower + abdominal discomfort	37 (2.2)
<b>Infections and Infestations</b>	<b>214 (12.8)</b>
<b>Nervous System Disorders</b>	<b>139 (8.3)</b>
Headache + migraine + sinus headache + tension headache	126 (7.5)
<b>Investigations</b>	<b>136 (8.1)</b>
Laboratory test abnormal	48 (2.9)
Weight increased	38 (2.3)
Smear cervix abnormal	36 (2.1)
<b>Psychiatric Disorders</b>	<b>124 (7.4)</b>
Depression + mood swings + mood altered + affect lability + crying + suicidal ideation + tearfulness + major depression	69 (4.1)
Anxiety + nervousness + stress + acute stress disorder	40 (2.4)
<b>Skin and Subcutaneous Disorders</b>	<b>100 (6.0)</b>
Acne	54 (3.2)
<b>Renal and Urinary Disorders</b>	<b>88 (5.2)</b>
<b>Injury, Poisoning and Procedural Complications</b>	<b>73 (4.4)</b>
<b>Musculoskeletal and Connective Tissue Disorders</b>	<b>71 (4.2)</b>
<b>General Disorders and Administration Site Conditions</b>	<b>70 (4.2)</b>

Source: Study Report RR-03009; Table 14.3.2; pp 226-36

**Team Leader Comments**

- **Headaches, breast symptoms, nausea/vomiting, acne, increased weight, and mood disorders are likely to be drug-related.**
- **The AE profile is typical for a COC.**

**8.3 Laboratory Data and Vital Signs**

Laboratory and vital signs data are discussed in Dr. Willett's review, and, with one exception, did not raise concern. However, two subjects had liver function and bilirubin lab values that met the criteria for Hy's law, indicating a potential for severe hepatotoxicity. This is extremely unusual in a COC trial; although disturbance of liver function is included as a warning in COC labeling, this is more apparent in postmarketing experience, and is rarely observed in a clinical trial.

One subject had ALT at 9 x the upper limit of normal (ULN) at the final study visit, along with AST that was 7 x ULN and bilirubin of more than 2 x ULN. She was diagnosed with infectious hepatitis. The other subject had ALT 15 x ULN, AST not reported, and bilirubin more than 2 x ULN. She was admitted for evaluation of upper GI pain and cholecystitis was diagnosed. She underwent a cholecystectomy and liver function values returned to normal.

**Team Leader Comment**

**I do not believe that either of these Hy's law cases represents drug-related hepatic impairment. Both have a plausible underlying etiology. However, COCs are associated with gall bladder disease, so the second case may have been indirectly related to COC use. Nonetheless, I do not think these cases represent a signal of concern.**

**8.4 Special Safety Studies**

The only special study was an oral irritation study, which DRUP has commonly requested for chewable COC products. It enrolled 54 subjects for 24 days of daily dosing. The oral soft-tissue evaluation was done on five days over the course of dosing, and is described in Dr. Willett's review. Of 52 subjects who completed the study, only one was noted to have any evidence of irritation/inflammation, and she had only slight erythema, with no edema at the Day 28 visit.

**8.5 Safety Update**

A 120-day safety update was submitted by the Applicant in March 2010, which cross-referenced NDA 17-576 for Ovcon 50, another EE/NE product manufactured by the Applicant. In addition, nonclinical and clinical literature published through November 2009 was reviewed. There were no new or ongoing studies. No new safety findings were noted.

**8.6 Postmarketing Safety Findings**

EE/NE chewable is not currently marketed anywhere in the world, so there are no postmarketing safety data. However, there is extensive and reassuring postmarketing safety data available for higher dose EE/NE COCs.

**8.7 Overall Assessment of Safety**

The extent of exposure evaluated in the phase 1 and phase 3 studies exceeded that recommended by the ICH for chronically administered drugs. In the contraceptive trial, the extent of exposure was beyond that requested by the Division, with 15,548 28-day cycles completed.

There were no deaths in this development program. The rate of SAEs was about 1% and very few events are likely to be drug-related; exceptions to this include depressive symptomatology, hypertension and a DVT, all of which are known COC-related events. Discontinuations due to AEs occurred in 8.5% of subjects, a rate comparable to or even lower than other contraception trials, and were generally attributable to mood disorders, nausea, increased weight, bleeding complaints and headaches. This is a common profile for a COC. The common AEs (>2%) likely to be drug-related in the contraception study included headaches, mood disorders, breast symptoms, nausea/vomiting, acne and weight gain.

There were no signals of concern regarding laboratory values or vital signs. The two cases that met Hy's law criteria suggesting potential hepatotoxicity had plausible alternative etiologies. The special oral irritation safety study also did not suggest reason for concern.

Overall, the safety profile of EE/NE chewable for use in the prevention of pregnancy is acceptable.

## 9. Advisory Committee Meeting

No Advisory Committee meeting was deemed necessary for this non-NME product, which is bracketed by FDA approved doses of the same two contraceptive steroid hormones.

## 10. Pediatrics

The Applicant requested a full waiver of pediatric studies. The Pediatric Review Committee (PeRC) considered this application on August 18, 2010, and granted a partial waiver for ages 0 to 11 years (i.e., premenarcheal patients), because the risk of pregnancy does not exist in this population. The remainder of the PREA requirement has been fulfilled by extrapolation from studies on adult women. DRUP's long experience with a variety of hormonal contraceptives has supported the expectation that efficacy and safety results in postmenarcheal adolescents do not differ from those in adult women.

## 11. Other Relevant Regulatory Issues

### 11.1 Potential Financial Conflicts

The Applicant certified that it did not use any investigators debarred under Section 306 of the Federal Food, Drug and Cosmetic Act.

The Applicant submitted financial disclosure information for investigators in Study PR-00207 and PR-10107. All of these investigators were certified as having no financial arrangements as listed in 21 CFR 54.2.

### 11.2 DSI Inspections

Site inspections by DSI were requested for two sites that participated in Study PR-00207. These clinical sites were selected on the basis of having enrolled relatively large numbers of subjects and the significance of their contribution to overall efficacy. Both sites, one in Texas that enrolled 46 subjects, and one in North Carolina that enrolled 51 subjects, received favorable inspections and were classified as NAI (no action indicated). The conclusion reached by Roy Blay, Ph.D. in his July 27, 2010 review was

*The clinical investigator sites of Drs. Blumenau and Parker were inspected in support of this NDA. The study appears to have been conducted adequately, and the data generated by these clinical sites appear acceptable in support of the respective indication.*

## 12. Labeling

The Applicant initially proposed the trade name (b) (4) and then (b) (4), both of which were found unacceptable by the Division of Medication Error Prevention and Analysis (DMEPA). The Applicant subsequently requested the name (b) (4), followed by (b) (4), both of which were found unacceptable by DMEPA. The Applicant has not submitted an additional trade name for consideration to date.

Carton and container labeling was reviewed and was revised by the Applicant in accordance with recommendations made by DMEPA and by the CMC reviewer. The final carton and

container labeling submitted by the Applicant on December 17, 2010 was acceptable to the DMEPA and CMC reviewers.

The package insert was submitted in the format prescribed by the Physician Labeling Rule (PLR). Consults on the proposed label were obtained from the Study Endpoints and Label Development (SEALD) group and DDMAC, and recommendations conveyed to the Applicant as appropriate. Agreement on the label was reached on December 21, 2010.

## **13. Recommendations/Risk Benefit Assessment**

### **13.1 Recommended Regulatory Action**

I recommend that EE/NE chewable be approved for the indication of prevention of pregnancy.

### **13.2 Risk Benefit Assessment**

I recommend that EE/NE chewable be approved for the indication of prevention of pregnancy, based on acceptable evidence of efficacy and a favorable risk/benefit profile. The chewable formulation is well tolerated, without evidence of causing oral irritation. The safety profile as evaluated in over 15,000 cycles of exposure does not suggest that EE/NE chewable is at variance from the common safety profile expected of a low dose COC.

### **13.3 Recommendation for Postmarketing Risk Evaluation and Management Strategies**

No postmarketing risk management activities beyond labeling are recommended.

### **13.4 Recommendation for other Postmarketing Requirements and Commitments**

No postmarketing requirements or commitments are requested.

### **13.5 Recommended Comments to Applicant**

None

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
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/s/  
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LISA M SOULE  
12/22/2010

SCOTT E MONROE  
12/22/2010

I concur with Dr. Soule's overall assessment of efficacy and safety and her recommendation that this NDA be approved.