CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

022573Orig1s000

SUMMARY REVIEW

Summary Review for Regulatory Action

Date	December 22, 2010
From	Scott Monroe, MD
Subject	Division Director Summary Review
NDA	NDA 022573
Applicant Name	Warner Chilcott Company, LLC
Date of Submission	November 26, 2009
PDUFA Goal Date	December 26 (with 3 month extension)
Proprietary Name	Pending
Established (USAN) Name	Norethindrone (NE) and ethinyl estradiol (EE) chewable tablets and ferrous fumarate (FF) chewable tablets
Dosage Forms/Strengths	Chewable tablets: (0.8 mg NE/0.025 mg EE) tablets and 75 mg FF tablets (placebo)
Proposed Indication	For use by women to prevent pregnancy
Proposed Regimen	One (NE/EE) tablet daily x 24 days followed by one FF (placebo) tablet daily x 4 days
Action	***Approve (see Section 13.1)***

Material Reviewed/Consulted OND Action Package, including:	**Names of Discipline Reviewers**
Medical Officer Review	Gerald Willett MD (Clinical Reviewer)
Statistical Review	Kate Dwyer PhD/Mahboob Sobhan PhD
Pharmacology Toxicology Review	Krishan Raheja DVM, PhD/Alexander Jordan PhD
CMC Review	Jane Chang PhD/Moo-Jhong Rhee PhD
Microbiology Review	Not required
Clinical Pharmacology Review	Christian Grimstein PhD/Myong-Jin Kim PharmD
DDMAC	Janice Maniwang PharmD/Carrie Newcomer PharmD
DSI	Roy Blay PhD/Tejashri Purohit-Sheth MD
CDTL Review	Lisa Soule MD (also Clinical Team Leader)
OSE/DMEPA	Denise Baugh PharmD/Todd Bridges RPh/Denise Toyer PharmD/Carol Holquist RPh
OSE/DRISK	Not required (PPI is class labeling)

OND=Office of New Drugs
CMC=Chemistry, Manufacturing and Controls
DDMAC=Division of Drug Marketing, Advertising, and Communication
OSE= Office of Surveillance and Epidemiology
DMEPA=Division of Medication Errors Prevention and Analysis
DSI=Division of Scientific Investigations
DRISK=Division of Risk Management
CDTL=Cross Discipline Team Leader

DIVISION DIRECTOR SUMMARY REVIEW

1. INTRODUCTION

NDA 022573 was submitted to obtain marketing approval for norethindrone (NE) and ethinyl estradiol (EE) chewable tablets and ferrous fumarate (FF) chewable tablets, a new combination oral contraceptive (COC). This combination oral contraceptive product (hereafter also referred to as NE/EE chewable tablets) is a new dosage strength (0.8 mg NE and 0.025 mg EE) and a new dosing regimen for the combination of NE and EE. The dosing regimen is one 0.8 mg NE/0.025 mg EE tablet daily for 24 days followed by one FF (placebo) tablet for 4 days. The FF tablets serve no direct therapeutic purpose but are included in the regimen to facilitate adhering to a 28-day cyclic dosing regimen. The Applicant currently markets several COC products that contain either NE or norethindrone acetate (NA) and EE. The daily dose of NE (0.8 mg) and EE (0.025 mg) in NE/EE chewable tablets is within the range of daily doses in currently marketed COC products. The proposed product (NE/EE chewable tablets) is not currently marketed in any country.

This Application contained the necessary chemistry, manufacturing and controls (CMC), preclinical toxicology (via cross-reference to previously approved NDA 17-576), clinical pharmacology, and clinical information to support approval. The Applicant conducted one adequate Phase 3 clinical trial (PR-00207) that was the primary source of the clinical safety and efficacy data for NE/EE chewable tablets.

No significant issues were identified during review of NDA 022573 that would preclude approval of NE/EE chewable tablets for the indication of "use by women to prevent pregnancy." The Pearl Index (an assessment of efficacy) for NE/EE chewable tablets was 2.01 pregnancies per 100 women-years of use in the single Phase 3 trial conducted by the Applicant. This value is comparable to that for other currently approved COCs. No safety issues that would affect approvability were identified during review of the Application. All reviewers, including the Clinical Reviewer (Dr. Willett) and the Clinical Team Leader (Dr. Soule), have recommended that NE/EE chewable tablets be approved for use by women to prevent pregnancy. I concur with their recommendations.

2. BACKGROUND

2.1 Description of the Product

Norethindrone and ethinyl estradiol chewable tablets and ferrous fumarate chewable tablets will be available in blister packs. Each 28-tablet blister pack contains in the following order:

- 24 light green tablets (active) each containing 0.8 mg NE and 0.025 mg EE.
- 4 brown tablets (non-hormonal placebo) each containing 75 mg FF. The FF chewable tablets do not serve any direct therapeutic purpose but are included to facilitate adhering to a 28-day cyclic dosing regimen.

Each light green tablet also contains the following inactive ingredients: D&C Yellow No. 10 aluminum lake, FD&C Blue No. 1 aluminum lake, FD&C Yellow No. 6 aluminum lake, lactose monohydrate, magnesium stearate, mannitol, microcrystalline cellulose, povidone, sodium starch glycolate, spearmint flavor, sucralose, and vitamin E.

One tablet is to be chewed and swallowed without water at approximately the same time each day. Tablets must be taken in the order directed on the blister pack (i.e., one active tablet daily for 24 consecutive days followed by one placebo tablet daily for 4 consecutive days).

Division Director's Comment

- *Norethindrone and norethindrone acetate, along with levonorgestrel, are considered by most clinicians to be one of the progestins that are associated with the lowest risk of venous thromboembolic events. Ethinyl estradiol is the estrogen that is used in almost all COCs currently marketed in the US. A dose of 0.025 mg EE/day is within the range of doses (0.020 mg to 0.035 mg) in the most commonly used COCs.*

2.2 Regulatory History

The clinical development program for NE/EE chewable tablets was conducted under IND 76,629. The Division of Reproductive and Urologic Products (DRUP) requested that the NDA include:

- An oral irritation study because the proposed product would provide higher exposure to NE (0.8 mg) than that in approved Femcon (0.4 mg NE) chewable tablets.
- A single Phase 3 efficacy and safety trial that included at least 10,000 28-day treatment cycles. The trial also should include at least 200 women who completed thirteen 28-day cycles of product use.

Division Director's Comment

- *The Application included the requested clinical studies.*

2.3 Content of NDA

This Application contained the necessary chemistry, manufacturing and controls (CMC), preclinical toxicology (via cross-reference to previously approved NDA 17-576), clinical pharmacology, and clinical safety and efficacy information to support approval. The information includes the findings from (1) one adequate Phase 3 clinical trial (PR-00207) that was the primary source of the clinical safety and efficacy data for NE/EE chewable tablets, (2) one Phase 1 oral local tolerance study, and (3) four Phase 1 pharmacokinetic/bioavailability studies.

2.4 Recommendations of Primary Clinical Reviewer and Cross-Discipline Team Leader regarding Approvability

The primary Clinical Reviewer, Gerald Willett MD, stated the following in his Clinical Review signed on October 6, 2010:

> *"The risk benefit assessment is favorable for the primary indication of contraception. There is no evidence in the safety database submitted in this NDA to suggest that the use of 0.025 mg EE/0.8 mg NE by women will result in any new safety problem or will result in an increased incidence of any known combined oral contraceptive (COC)-related adverse event compared to similar COCs. There was one deep venous thrombosis (DVT) in the pivotal trial (Study PR-00207). The occurrence of 1-2 thromboembolic events in comparable size trials is not uncommon. The oral irritation study (PR-10107) did not show any significant irritative or abrasional findings in the oral cavity for this chewable tablet.*
>
> *The contraceptive benefit of this product is comparable to that of other approved COCs.*

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."

Dr. Willett did not recommend any postmarketing studies.

The Cross Discipline Team Leader (CDTL), Lisa Soule MD (who also was the Clinical Team Leader) stated the following in her Review signed on December 22, 2010:

"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."

Dr. Soule did not recommend any postmarketing studies

Division Director's Comment

- *I concur with the recommendations of both Drs. Willett and Soule that norethindrone and ethinyl estradiol chewable tablets and ferrous fumarate tablets be approved for "use by women to prevent pregnancy."*

3. CMC

In this Application, information regarding the active drug substances, NE and EE, was referenced to the respective manufacturers' Drug Master Files (DMFs) for which authorization letters from the DMF holders were provided. The respective DMFs were reviewed and found to be adequate.

The original NDA, supported by additional requested information submitted during the review, provided adequate information regarding the final drug product (NE/EE chewable tablets and FF chewable tablets) to support approval of the final drug product. The primary Chemistry Reviewer (Jane Chang PhD) made the following statements in her Summary of Chemistry Assessment:

"*… The specification for WC3026-5C [NE/EE] chewable tablets includes description, identification, uniformity of dosage unit, assay, degradation products, dissolution,* (b) (4) *, and hardness. Except for the dissolution method for WC3026-5C chewable tablets, the proposed specification is acceptable to ensure product identity, strength, purity, and quality. The acceptance criteria for the tests are acceptable based on their developmental studies, and the analytical methods for the tests are adequately validated. Per the review dated August 31, 2010 by the Biopharm reviewer, Dr. S. Suarez, the dissolution method for NE/EE tablets is acceptable as interim. The sponsor agreed to develop a more discriminating dissolution method and to submit the results within a year of expedition of the request. Stability data based on three registration batches and two additional batches support the proposed expiration dating period, 36-month when stored at 25°C (77°F); excursions permitted to 15 – 30°C (59 – 86°F).*

The request for a categorical exclusion from the preparation of an environmental assessment (EA) under 21 CFR 25.31(b) is acceptable."

Dr. Chang made the following statement in the Recommendation and Conclusion on Approvability section of her CMC Review signed on 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."*

Dr. Chang did not request any Phase 4 (Postmarketing) commitments.

In an Addendum, signed on December 20, 2010, to her primary CMC Review, Dr. Chang stated the following:

> *"After completion of CMC Review #1, revised labeling information was provided in the amendments dated 27-Sep-2010 and 16-Dec-2010. The information in the 16-Dec-2010 amendment confirms the previously agreed upon changes for Section 3 of Full Prescribing Information and Drug Listing Data Elements (see CMC Review #1, pages 116 and 121-122).*
>
> *The labeling changes do no affect the conclusion and recommendation of Review #1. From a chemistry, manufacturing, and controls review perspective, this NDA may be approved."*

Division Director's Comment

- *I concur with the assessments and recommendation by Dr. Chang that from a CMC perspective this NDA can be approved.*

4. NONCLINICAL PHARMACOLOGY/TOXICOLOGY

In concurrence with the Division's July 20, 2009 pre-NDA meeting communication, the nonclinical pharmacology and toxicology for NE and EE were addressed by cross-reference to the Applicant's previously approved NDA 17-576 for Ovcon® 50 (1.0 mg NE/0.05 mg EE tablets).

The primary Toxicology Reviewer, Krishan Raheja DVM, PhD, made the following recommendations in his Review signed on January 22, 2010:

> ***"Recommendations on approvability****: Pharmacology/toxicology recommends approval of NDA 022573 for contraception.*
>
> ***Recommendations for nonclinical studies****: The nonclinical pharmacology and toxicology of norethindrone and ethinyl estradiol are cross-referenced to Warner Chilcott's approved NDA 17-576 for Ovcon® 50 (norethindrone and ethinyl estradiol tablets, USP); the approved Ovcon 50 regimen includes the administration of 21 active tablets each containing the combination of 1 mg NE and 0.05 mg EE. The nonclinical pharmacology and toxicology of the inactive ingredients in* (b) (4) *[original proposed name for NE/EE tablets] are addressed by showing that the quantity of each inactive ingredients used in the manufacture of the tablets is below the maximum potency outlined in FDA's Inactive Ingredients Database or otherwise that the inactive ingredient is generally recognized as safe per 21 CFR regulations.*
>
> ***Recommendations on labeling****: Suggested draft labeling is presented in accordance with PLR and provided in SPL format and is acceptable (see pg. 6 of Dr. Raheja's review)."*

Division Director's Comment

- *I concur with the conclusions and recommendations of Dr. Raheja.*

5. CLINICAL PHARMACOLOGY/BIOPHARMACEUTICS

This NDA included the findings from three Phase 1 bioavailability and pharmacokinetics studies conducted to assess (1) the relative bioavailability of EE and NE following a single dose of NE/EE chewable tablets (Protocol PR-00807), (2) the effect of food following a single dose of NE/EE chewable tablets (Protocol PR-00907), and (3) the pharmacokinetic profiles of NE and EE following multiple dosing with NE/EE chewable tablets (Protocol PR-03808); an earlier multiple dose pharmacokinetic characterization study (Protocol PR-00707) was also included in the submission although not in support of the Application because the administration of drug in Protocol 00707 differed from that recommended in labeling for NE/EE chewable tablets.

5.1 Pharmacokinetics

5.1.1 Absorption

Both NE and EE are subject to first-pass metabolism after oral dosing, resulting in an absolute bioavailability of approximately 64% for NE and 43% for EE. Plasma NE and EE pharmacokinetics following single- and multiple-dose administrations of NE/EE chewable tablets in 17 healthy female volunteers are listed in Table 1. Maximum plasma concentrations occur within 2 hours after oral administration.

Following multiple-dose administration of NE/EE chewable tablets, mean maximum concentrations of NE and EE were increased by 126% and 14%, respectively, as compared to single-dose administration. Mean NE and EE exposures (AUC values) were increased by 239% and 55%, respectively, as compared to single-dose administration.

Table 1 Pharmacokinetic Parameter Values following Single and Multiple Dose Administration of NE/EE Chewable Tablets (Chewed and Swallowed without Water)

Dosing Regimen	Analyte	Arithmetic mean (%CV)			$t_{1/2}$ [A]
		Cmax (pg/mL)	Tmax (hrs)	AUC(0–24h) (pg•h/mL)	
Day 1 (Single Dose) N=17	NE	9,840 (36)	1.4 (49)	41,680 (47)	
	EE	147 (25)	1.2 (27)	903 (18)	
Day 24 (Multiple Dose) N=17	NE	22,200 (30)	1.6 (76)	141,200 (32)	10.8
	EE	168 (25)	1.2 (35)	1,400 (32)	17.1

NE = norethindrone; EE = ethinyl estradiol.
%CV = coefficient of variation; Cmax = maximum plasma concentration (pg/mL).
Tmax = time of the maximum measured plasma concentration (h).
AUC(0–24h) = area under the plasma concentration versus time curve from time 0 to 24h (pg•h/mL).
$t_{1/2}$ = apparent elimination half life (h).
[A] The harmonic mean for $t_{1/2}$ is presented.
Source: Table 1 of the to-be-approved Package Insert.

5.1.2 Food Effect

Single-dose administration of NE/EE chewable tablets with food (1) decreased the Cmax of NE by 47% but increased the extent of absorption (AUC) by 10-14% and (2) decreased the Cmax of EE by 39% but had no effect on the AUC.

Division Director's Comment

- *In spite of the effect of food on the absorption of NE/EE chewable tablets, the product may be taken without regard to food. Subjects in the Applicant's single Phase 3 clinical trial were not given specific instructions regarding taking NE/EE chewable tablets with or without food.*

5.1.3 Effects of Renal or Hepatic Impairment

The pharmacokinetics of NE/EE chewable tablets have not been studied in subjects with renal impairment. The pharmacokinetics of NE/EE chewable tablets have not been studied in subjects with hepatic impairment. Steroid hormones, however, may be poorly metabolized in patients with impaired liver function. Product labeling contraindicates the use of NE/EE chewable tablets in women with liver tumors, benign or malignant, or liver disease.

5.1.4 Effect of Water after Chewing NE/EE Chewable Tables

There was a small reduction of the Cmax for EE when NE/EE chewable tablets were chewed and swallowed with 45 mL water compared to the Cmax when tablets were chewed and swallowed without water. The mean Cmax and AUC values for NE and the mean AUC value for EE for tablets that were chewed and swallowed with 45 mL water, compared to the Cmax and AUC values (NE) and AUC value (EE) when tablets were chewed and swallowed without water, were within 80% - 125% of each other. These findings did not support bioequivalence for EE by the 2 dosing regimens (the lower bound for the difference for Cmax for EE was 76.5% instead of ≥ 80%). However, the findings supported bioequivalence for NE by the 2 dosing regimens. Based on these data, the Clinical Pharmacology Reviewer has recommended that labeling state that tablets are to be chew and swallowed without water.

Division Director's Comment

- *Based on my review of the PK findings, I do not believe that the restriction regarding chewing and swallowing without water is necessary. I based my assessment on the observation that (1) food had a much greater effect on reducing Cmax than chewing and swallowing with water and (2) Loestrin 24, which contains a lower dose of EE (0.02 mg instead of 0.025 mg, is not chewed, and is swallowed with water), is an effective COC. I do not object, however, to inclusion of the statement "Chew and swallow one tablet without water…" in labeling.*

5.2 Overall Assessment by Clinical Pharmacology Reviewer

The primary Clinical Pharmacology Reviewer, Christian Grimstein PhD, stated the following in his original Review signed on 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*."

Dr. Grimstein did not request any Phase IV commitment.

After review of the final agreed-to labeling, Dr. Grimstein made the following recommendation in an Addendum (signed on December 22, 2010) to his original review:

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

Division Director's Comment

- *I concur with Dr. Grimstein's overall assessment and final recommendation.*

6. CLINICAL MICROBIOLOGY

A microbiology consult was not needed or requested for this oral tablet product. The Applicant, at the request of the ONDQA reviewer, included acceptable testing for microbial limits per USP <1111> in the drug product specification.

7. CLINICAL/STATISTICAL-EFFICACY

7.1 Overview of Primary Phase 3 Clinical Trial and Subject Demographics

The Applicant conducted a single, multicenter, open-label, non-comparative, 12-month (thirteen 28-day treatment cycles), Phase 3 clinical trial (PR-00207) as the primary support for the safety and efficacy of NE/EE chewable tablets for use by women to prevent pregnancy. Sixty-nine (69) US sites participated, and a total of 1,677 women received at least one dose of NE/EE chewable tablets. Subjects who received at least one dose of NN/EE tablets and were evaluated for pregnancy at least once after beginning study medication (the Modified Intent to Treat [MITT] population) consisted of 1,570 women who were 18-46 years of age (mean [SD] age = 28.8 [7.1] years). In the MITT population, 1,251 subjects (79.7%) were ≤ 35 years of age and 319 (20.3%) were > 35 years of age at enrollment. The inclusion and exclusion criteria were, in general, consistent with those of other clinical trials for oral contraceptives. As in many contraceptive trials, women with a body mass index (BMI) > 35 kg/m^2 were to be excluded. The mean (±SD) weight of the subjects in the MITT population was 148.9 (±29.1) pounds (range: 74-243). The racial distribution of the subjects who received at least one dose of study drug was 72.0% Caucasian, 13.0% African-American, 11.2% Hispanic, 1.8% Asian, and 2.0% other.

Division Director's Comments

- *The racial distribution of the population appears fairly representative of the general US population.*
- *Although the Protocol for Study PR-00207 excluded women with a BMI of greater than 35 kg/m^2, the mean weight of subjects in the MITT population (148.9 pounds) was only 10 pounds less than that (i.e., 159 pounds) in the primary efficacy and safety study for another recently approved COC that did not have any weight limits or BMI restrictions. Nevertheless, women with a BMI of greater than 35 kg/m^2 were not studied in the current NDA, and this should be reflected in product labeling.*

7.2 Study Populations and Subject Disposition

A total of 1,700 subjects were enrolled in Study PR-00207. Of these, 1,677 women took at least one dose of study drug. A total of 686 women (40.9%) of the subjects discontinued prematurely for the reasons listed in Table 2.

Table 2 Study Populations, Subject Disposition, and Reasons for Premature Discontinuation (Study PR 00207)

Population/Disposition/Reason	Total
Total subjects enrolled	1,700
Total subjects treated [A]	1,677 (100%)
MITT population [B]	1,570 (93.6%)
PITT population [C]	1,251 (74.6%)
Prematurely discontinued from the study [D]	686 (40.9%)
• Lost to follow-up	271 (16.2%)
• Withdrawal of consent	149 (8.9%)
• Adverse event [E]	143 (8.5%)
• Other	75 (4.5%)
• Protocol violation	25 (1.5%)
• Lack of efficacy (pregnancy)	23 (1.4%)

[A] Defined as all subjects who received at least one dose of study drug. This is the safety population.
[B] Modified Intent to Treat population. 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.
[C] Pregnancy Intent to Treat population. Defined as the subgroup of the MITT population who were 18-35 years of age at enrollment.
[D] Percentages based on total subjects treated (n=1,677).
[E] Seven of the adverse events had an onset prior to the start of treatment. Thus there were 136 withdrawals due to treatment emergent adverse events.
Source: Modified from Table 6 from the primary Clinical Review signed on October 6, 2010.

Division Director's Comments

- *Among the 75 of 1,677 treated subjects with "other reasons" listed for premature termination, the 3 most common reasons included noncompliance (n=23), investigator site closure (illness of the investigator, n=20) and subject moving from the area (n=8).*
- *A premature discontinuation rate of 40.9% for a one year Phase 3 contraceptive clinical trial is within the range reported for other recently reviewed one year Phase 3 contraceptive clinical trials.*
- *A discontinuation rate of 8.5% due to adverse events also is similar to that for other recently reviewed one year Phase 3 contraceptive clinical trials. Seven of the adverse events had an onset prior to the start of treatment. Therefore, 136 (8.1%) withdrawals were due to treatment emergent adverse events.*

7.3 Efficacy Findings

7.3.1 Primary Assessment of Efficacy (On-Treatment Pregnancies)

The primary efficacy analysis in this and other contraceptive trials is the Pearl Index, which is computed as:

$$\text{Pearl Index} = \frac{\text{(number of "on-treatment" pregnancies) x 13 cycles/year}}{\text{(total number of completed 28-day treatment cycles)*}} \times 100$$

* Only cycles in which no back-up contraceptive methods were used are 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 at entry. Cycles during which an alternate birth control method was used were excluded from the analysis unless a pregnancy was conceived during that cycle. Pregnancies conceived after the onset of treatment with study drug and within 7 days after a subject's last tablet of study drug were included in the calculation of the Pearl Index as on-treatment pregnancies.

Division Director's Comment

- *The Division's recent thinking on the window in which conceptions are counted as treatment failures is that pregnancies conceived within 7 days after the last pill taken (whether active or placebo pill) are to be counted. This allows for inaccuracy in ultrasound dating of pregnancies, but acknowledges that contraceptive protection is not expected to be maintained beyond the last tablet in a 28-day treatment cycle.*

7.3.2 Primary Efficacy Findings

The PITT population consisted of 1,251 women aged 18-35 years at entry, who were assessed over a total of 12,297 treatment cycles during which no backup contraception was used. The Applicant identified 18 pregnancies for which the conception date was considered to be on-treatment. The FDA's primary Clinical Reviewer, however, identified one additional pregnancy for which an on-treatment date of conception could not be excluded resulting in a total of 19 on-treatment pregnancies. The MITT population (a secondary efficacy population) consisted of 1,570 women aged 18-46 years at entry, who were assessed over a total of 15,752 treatment cycles during which no backup contraception was used. A single on-treatment pregnancy was identified in the subjects who were > 35 years of age at entry.

7.3.3 Primary Efficacy Analysis

The Pearl Index values, based on on-treatment pregnancies in the PITT population (subjects ≤ 35 years of age at enrollment, the primary efficacy population) and the MITT population (subjects of all ages at entry) are listed in Table 3. Based on 19 on-treatment pregnancies and a total of 12,297 treatment cycles during which no backup contraception was used in the PITT population, the Pearl Index was calculated by the FDA statistician to be 2.01 (95% Confidence Interval [CI]: 1.21, 3.14).

Table 3 Pearl Index Values Based on On-treatment Pregnancies and Treatment Cycles during which No Back-Up Contraception Was Used (Study PR-00207)

Population	Subjects Treated (n)	On-Treatment Pregnancies (n) [A]	Cycles (n) [B]	Pearl Index (95% CI)
PITT [C]	**1,251**	**19**	**12,297**	**2.01 (1.21, 3.14)**
MITT [D]	1,570	20	15,752	1.65 (1.01, 2.55)

[A] Number of on-treatment pregnancies as assessed by FDA primary Clinical Reviewer.
[B] Includes only treatment cycles during which no backup contraception was used.
[C] Pregnancy intent to treat (PITT) population includes only women ≤ 35 years of age at entry. The PITT population is the primary efficacy population.
[D] Modified intent to treat (MITT) population includes women of all ages.
Source: Modified from Table 3 of the FDA Statistical Review, signed September 17, 2010.

Life table calculations also are commonly used as supportive assessments of contraceptive efficacy; these methods provide cumulative rates of pregnancy. Table 4 summarizes the results of the life table analysis of the cumulative pregnancy rate. For the PITT cohort, the cumulative

failure rate after 13 cycles of treatment was 2.00% (95% C.I.: 1.27%, 3.13%) based on 19 "on-treatment" pregnancies.

Table 4 Life Table Analysis of the Cumulative Failure Rates based on Thirteen 28-Day Treatment cycles (Study PR-00207)

Population	On-Treatment Pregnancies (n) [A]	Cumulative One Year Pregnancy Rate (95% CI)
PITT [B]	**19**	**2.00% (1.27%, 3.13%)**
MITT [C]	20	1.75% (1.27%, 2.40%)

[A] Number of on-treatment pregnancies as assessed by FDA primary Clinical Reviewer.
[B] Pregnancy intent to treat (PITT) population includes only women ≤ 35 years of age at entry. The PITT population is the primary efficacy population.
[C] Modified intent to treat (MITT) population includes women of all ages.
Source: Modified from Table 4 of the FDA Statistical Review, signed September 17, 2010.

Division Director's Comment

- *Both analyses (Pearl Index and life table) demonstrated that NE/EE chewable tablets was effective in reducing the risk of pregnancy. The effectiveness of NE/NE chewable tablets is comparable to that of other recently approved COCs.*

7.3.4 Effect of Weight on Effectiveness of NE/EE Chewable Tablets

The FDA Biostatistician performed a post hoc exploratory analysis to assess the effect of weight on efficacy. The mean and median BMI values at the start of the study for the PITT cohort were 24.0 kg/m^2 and 24.8 kg/m^2, respectively; approximately 16% of the subjects recruited in this study had a BMI greater than 30 kg/m^2. The Pearl Index for subjects in the PITT group with a BMI less than or equal to 30 kg/m^2 was 1.86 (95% C.I.: 1.04 to 3.06) compared to 2.89 (95% C.I.: 0.79 to 7.38) for subjects with a BMI between 30 - 35 kg/m^2.

Division Director's Comments

- *The effectiveness of NE/EE chewable tablets appears to be slightly reduced in women with a BMI > 30 kg/m^2. This observation, however, is based on a relatively small number of subjects (n=191) with a BMI > 30 kg/m^2 resulting in a wide 95% confidence interval that overlaps that of the Pearl Index for women with a BMI ≤ 30 kg/m^2 .*
- *Product labeling will include the statement that "the efficacy of NE/EE chewable tablets in women with a body mass index (BMI) of >35 kg/m^2 has not been evaluated."*

7.4 FDA Statistician's Assessment of Efficacy

The primary Biostatistical Reviewer, Kate Dwyer PhD, stated the following in her Statistical Review, signed on September 17, 2010:

> *"The study results support the efficacy of WC3026 [NE/EE chewable tablets], 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)."*

7.5 Overall Assessment of Efficacy

The Applicant has submitted an adequate clinical trial database supporting the efficacy of NE/EE chewable tablets. The Pearl Index, calculated by the FDA statistician, was 2.01 pregnancies per

100 women-years of use (95% CI: 1.21, 3.14), based on 19 on-treatment pregnancies in subjects ≤ 35 years of age and 12,297 28-day treatment cycles. Treatment cycles during which subjects used back-up contraception were excluded from the calculation. Women with a BMI of > 35 kg/m^2 were not enrolled in the Phase 3 clinical trial. Exclusion of subjects with a BMI of > 35 kg/m^2 in the Phase 3 clinical trial will be reflected in the Indications and Usage section of product labeling.

8. SAFETY

The primary Clinical Reviewer (Dr. Willett) has provided a thorough discussion and review of the safety findings for NE/EE chewable based on the data provided in NDA 022573. Dr. Willett did not identify any safety issues that would suggest that the overall safety profile for NE/EE chewable tablets would be less acceptable than that for other currently approved COCs. The following review of safety is focused on (1) the findings from Phase 3 Study PR-00207, which was the primary source of safety data, and (2) items of greatest potential concern to users of COCs.

8.1 Overview of Safety Database for NE/EE Chewable Tablets

Phase 3 Study PR-00207 was the primary source of data that supported the safety of NE/EE chewable tablets for the proposed indication of "use by women for prevention of pregnancy." The exposure to NE/EE chewable tablets in Study PR-00207 by cycles, partial cycles, and women-years, based on the primary Clinical Review, was as follows:

- Number of women who received one or more doses of NE/EE chewable tablets = 1,677
- Number of completed 28 day cycles (all 28 pills taken) = 15,548 cycles
- Number of partially completed 28 day cycles (at least 1, but < 28 pills) = 977 cycles
- Total women-years of exposure = 1,181 women-years
- Number of subjects completing one year of treatment: ≥ 746 women

Supportive safety data were provided by Phase 1 Study PR-10107 (24-day local oral tolerance study) and four Phase 1 clinical pharmacology studies.

Division Director's Comments

- *The size of the safety database is adequate for the proposed product. For a new contraceptive product that is based on a previously approved progestin (e.g., NE) and estrogen (e.g., EE), DRUP generally requires a minimum database that includes (1) the equivalent of 10,000 28-day cycles of treatment and (2) 200 subjects completing one year of treatment. Both of these criteria were exceeded in Study PR-00207.*
- *The findings from Phase 1 Study PR-10107 did not raise any concerns about the oral tolerance or safety of NE/EE chewable tablets. Only one of 54 enrolled subjects had a finding of an oral adverse event (minimal findings of mild irritation/inflammation at one study visit).*

8.2 Deaths and Non-fatal Serious Adverse Events

8.2.1 Deaths

No deaths were reported in the clinical development program.

8.2.2 Serious Adverse Events

A total of 23 subjects experienced 31 serious adverse events (SAEs) that had their onset after the onset of treatment and within 30 days of the end of treatment (see Table 5). Most were considered severe in intensity and considered to be either not related or unlikely related to study drug by the investigators. Four subjects (0.3%) had an SAE that was considered by the investigator to be possibly, probably, or definitely related to study treatment. These SAEs were depression (Subject 209/018), cholecystectomy (Subject 237/015), angina pectoris and hypertension (Subject 238/031), and blood pressure increased (Subject 265/044).

Table 5 Serious Adverse Events (All Treated Subjects [n=1677], Study PR-00207)

Site	Subject No.	Serious Adverse Event	Severity	Onset Day	Relation to Treatment [A]	Outcome
200	085	Viral meningitis	Severe	159	None	Recovered
		Headache	Severe	159	N/A [B]	Recovered
209	018	Depression	Mild	233	Possible	Ongoing
		Suicidal ideation	Severe	333	Unlikely	Recovered
221	025	Flank pain	Severe	33	Unlikely	Recovered
227	008	Asthma	Severe	193	None	Recovered
		Respiratory tract infection	Severe	193	None	Recovered
231	005	Anxiety	Severe	123	None	Recovered
		Major depression	Severe	123	None [C]	Recovered
231	018	Multiple fractures	Severe	267	None	Recovered
235	024	Chest pain (Depression)	Severe	18	None [C]	Recovered
237	015	Cholecystectomy	Severe	101	Possible	Recovered
238	002	Appendicitis	Severe	74	None	Recovered
238	031	Angina pectoris	Severe	230	Possible	Recovered
		Hypertension	Severe	230	Possible	Recovered
241	007	Suicidal ideation	Severe	10	Unlikely [C]	Recovered
241	058	Vomiting	Moderate	195	Unlikely	Recovered
		Abdominal pain	Moderate	195	Unlikely	Recovered
242	021	Chest pain	Mild	363	Unlikely	Recovered
243	065	Staph infection	Severe	220	None	Recovered
256	017	Intervertebral disc surgery	Mild	342	None	Recovered
259	046	Abdominal pain	Severe	126	Unlikely	Recovered
263	046	Cervical dysplasia	Severe	370	None	Ongoing
263	056	Hemorrhagic diarrhea	Severe	329	None	Recovered
		Dehydration	Severe	330	None	Recovered
		Ischemic colitis	Severe	330	None	Recovered
264	013	Lumbar vertebral fracture	Severe	25	None	Ongoing
265	044	Blood pressure increased	Moderate	217	Possible	Recovered
223	030	Deep vein thrombosis	Severe	12 days post study	N/A [C]	Recovered
255	015	Marked liver enzyme elevation (Hy's Law) Cholecystitis/Cholecystectomy	Severe	3-4 weeks post study	N/A [C]	Recovered
208	037	Mononucleosis Marked liver enzyme elevation (Hy's Law)	Severe	End of study	N/A	Ongoing

[A]: Investigator Assessment.
[B]: N/A = not provided.
[C]: FDA Clinical Reviewer also considered these as possibly related to treatment.
Source; Modified from Table 20 of the primary Clinical Review signed on October 6, 2010.

Division Director's Comments

- *In addition to the SAEs considered by the Investigators as possibly related to treatment, the primary Clinical Reviewer considered the adverse events of depression (Subject 231/005 and Subject 235/024), suicidal ideation (Subject 241/007), deep vein thrombosis (Subject 223/030), and cholecystitis/cholecystectomy/elevated liver enzymes (Subject 255/015) as possibly related to treatment.*
- *A single case of deep vein thrombosis (DVT) in a Phase 3 clinical trial that included >1,000 women-years of treatment is not of concern and is consistent with findings from other trials of COCs. This event had an onset 12 days after the subject's completing her participation in the clinical trial.*
- *Labeling for oral contraceptives includes class warnings regarding depression, hypertension, gallbladder disease, and thrombosis.*
- *Two subjects had markedly elevated liver enzyme and elevated bilirubin values that met the criteria for Hy's law, indicating significant liver injury. This is a very unusual finding in a trial for a hormonal contraceptive.*
  - *One subject (208/037) had an ALT value that was 9 x the upper limit of normal (ULN) at the final study visit, an AST value that was 7 x ULN, and a bilirubin value of more than 2 x ULN. She was diagnosed with mononucleosis.*
  - *The other subject (255/015) had an ALT 15 x ULN and a bilirubin value more than 2 x ULN. She was admitted for evaluation of upper GI pain and was diagnosed as having cholecystitis. She underwent a cholecystectomy, and liver function values returned to normal.*

  I do not believe that either of the cases of significant liver injury was directly related to treatment with NE/EE chewable tablets. Other studies have suggested, however, that the risk of developing gallbladder disease may be increased in COC users, and treatment with NN/EE tablets may have been responsible for the development of cholecystitis in subject 255/015. Neither of these cases, however, represents a signal of significant concern, particularly in light of the long history of safe use of oral contraceptives that contain NE/EE.
- *The number of subjects with SAEs, the total number of SAEs, and the types of SAEs that were observed in Study PR-00207 do not raise any concerns about the safety profile of NE/EE chewable tablets beyond those associated with other currently approved COCs.*

8.3 Discontinuations for Adverse Events

A total of 143 subjects (8.5%) discontinued from Study PR-00207 because of an adverse event (AE) (see Table 6). For 7 of the subjects, however, the onset of the adverse events preceded the initiation of treatment with study drug. Therefore, 136 (8.1%) withdrawals were due to treatment emergent adverse events. The most frequent AEs resulting in discontinuation from the trial were nausea (17 subjects), weight increased (14 subjects), acne (13 subjects), metrorrhagia (12 subjects), mood altered (6 subjects), and hypertension (6 subjects).

Table 6 Treatment Emergent Adverse Events Leading to Discontinuation in > 1 Subject (All Treated Subjects [n=1677], Study PR-00207)

Adverse Event - (Preferred Term)	N = 1677 No. (%) of Subjects
Nausea	17 (1.0)
Weight increased	14 (0.8)
Acne	13 (0.8)
Metrorrhagia	12 (0.7)
Mood altered	6 (0.4)
Hypertension	6 (0.4)
Irritability	5 (0.3)
Migraine	5 (0.3)
Libido decreased	5 (0.3)
Mood swings	5 (0.3)
Abdominal pain	4 (0.2)
Anxiety	4 (0.2)
Dysmenorrhea	4 (0.2)
Edema peripheral	3 (0.2)
Headache	3 (0.2)
Depression	3 (0.2)
Menstruation irregular	3 (0.2)
Vomiting	2 (0.1)
Dizziness	2 (0.1)
Crying	2 (0.1)

Source: Table 21 of the primary Clinical Review signed on October 6, 2010.

Division Director's Comments

- *If related adverse event terms are "bundled," 19 subjects withdrew for "psychiatric events" (mood altered [n=6], irritability [n=5], mood swings [n=5], depression [n=3]) and 15 subjects withdrew for menstrual bleeding related events.*
- *The types of AEs leading to discontinuation are those AEs observed in clinical trials for COCs. These adverse events and their frequency do not raise any new or unexpected safety concerns about NE/EE chewable tablets beyond those for COCs in general.*

8.4 Common Adverse Events

Treatment-emergent AEs were reported in 1,062 subjects (63.3%); AEs considered by the investigators to be treatment-related AEs were reported in 368 subjects (21.9%). Adverse events (both related and not related to treatment) that were reported in at least 2% of subjects are listed in Table 7. Upper respiratory tract infection (7.3%), nasopharyngitis (7.2%), nausea (6.1%), and sinusitis (5.4%) were the most frequently reported treatment-emergent AEs. The System Organ Classes (SOCs) in which AEs were most frequently reported were respiratory, thoracic and mediastinal disorders (23.9%), reproductive and breast disorders (18.4%), gastrointestinal disorders (16.0%), and infections and infestations (12.8%).

Table 7 Most Commonly Reported (≥ 2% of Subjects) Treatment-Emergent Adverse Events (All Treated Subjects [n=1677], Study PR-00207)

Adverse Event (Preferred Term)	Number (%) of subjects
Upper respiratory tract infection	122 (7.3)
Nasopharyngitis	121 (7.2)
Nausea	**102 (6.1) ***
Sinusitis	91 (5.4)
Headache	**80 (4.8)**
Urinary tract infection	80 (4.8)
Dysmenorrhea	**66 (3.9)**
Vaginitis bacterial	58 (3.5)
Acne	**54 (3.2)**
Vulvovaginal mycotic infection	**52 (3.1)**
Vomiting	**46 (2.7)**
Bronchitis	46 (2.7)
Weight increased	**38 (2.3)**
Smear cervix abnormal	36 (2.1)
Anxiety	**36 (2.1)**
Fungal infection	**35 (2.1)**
Diarrhea	**34 (2.0)**
Gastroenteritis viral	34 (2.0)

* A portion of the adverse events represented in bold font may be treatment-related based on known adverse events associated with combination oral contraceptives.

Source: Table 19 of the primary Clinical Review signed on October 6, 2010.

Division Director's Comments

- *The nature and frequency of the most common adverse events are similar to those reported in other clinical trials of COCs. The most commonly reported adverse events do not raise any safety concerns.*

8.5 Uterine Bleeding Patterns

All subjects were to keep daily diaries recording the occurrence and severity of bleeding. For this study, bleeding was defined as any day on which a subject had bleeding of any intensity, except light bleeding that did not require sanitary protection. Light bleeding that did not require the use of sanitary protection (aside from panty liners) was classified as spotting. Spotting/bleeding was characterized as "withdrawal bleeding/spotting" (hereafter called "scheduled bleeding/spotting") if it started (1) after the last day of active treatment and before starting the next treatment cycle or (2) within 4 days before the last day of active treatment and continuing through at least the first day after the end of active treatment. All other bleeding/spotting episodes were considered to be "intracyclic bleeding/spotting" by the Applicant (hereafter referred to as "unscheduled bleeding/spotting"). Unscheduled spotting/bleeding is likely to be more troublesome to subjects because it is unpredictable.

8.5.1 Unscheduled Bleeding/Spotting

Table 8 summarizes the incidence (percentage) of subjects with unscheduled bleeding and spotting and the mean number of days of bleeding or spotting in each 28-day treatment cycle. Over the interval from Cycle 2 through Cycle 13, the percentage of subjects with unscheduled bleeding or spotting in a treatment cycle decreased from 31.3% (Cycle 2) to 22.5 % (Cycle 13).

Over this interval the mean number of days with bleeding or spotting, across all subjects, ranged from 0.80 to 1.31 days. Among the subjects who had unscheduled bleeding or spotting, the mean number of days of bleeding/spotting from Cycle 2 through Cycle 13 ranged from 3.6 to 4.2 days per 28-day cycle.

Table 8 Summary of Bleeding Parameters for Subjects with Unscheduled Bleeding or Spotting (MITT Population, Study PR-00207)

Cycle Number	Incidence (%) of Subjects with Bleeding/Spotting n/N	(%)	Mean (SD) Number of Days of Bleeding or Spotting [A]		Mean (SD) Number of Days of Bleeding or Spotting [B]	
Cycles 2-13	1028/1424	(72.2)	1.19	(1.79)	3.7	(2.3)
Cycle 1	542/1462	(37.1)	1.91	(3.42)	5.2	(3.9)
Cycle 2	436/1393	(31.3)	1.31	(2.56)	4.2	(3.0)
Cycle 3	391/1322	(29.6)	1.24	(2.46)	4.2	(2.8)
Cycle 4	305/1243	(24.5)	0.98	(2.14)	4.0	(2.6)
Cycle 5	319/1206	(26.5)	1.05	(2.20)	4.0	(2.6)
Cycle 6	270/1162	(23.2)	0.88	(1.91)	3.8	(2.2)
Cycle 7	266/1134	(23.5)	0.92	(2.06)	3.9	(2.5)
Cycle 8	232/1097	(21.1)	0.82	(1.96)	3.9	(2.5)
Cycle 9	255/1062	(24.0)	0.98	(2.21)	4.1	(2.8)
Cycle 10	218/1031	(21.1)	0.79	(1.80)	3.7	(2.1)
Cycle 11	242/1021	(23.7)	0.97	(2.17)	4.1	(2.6)
Cycle 12	220/986	(22.3)	0.80	(1.84)	3.6	(2.3)
Cycle 13	217/964	(22.5)	0.89	(2.13)	4.0	(2.8)

[A] Includes all subjects for whom data were available. Subjects with no unscheduled bleeding or spotting in a 28-day treatment cycle were assigned a value of 0 in the calculation.
[B] Includes only those subjects who had unscheduled bleeding. Subjects with no unscheduled bleeding in a specific 28-day treatment cycle were not included in the calculation.
Source: Modified from Table 16, pg. 38 of Applicant's Summary of Clinical Safety and the Applicant's submission of September 21, 2010.

Division Director's Comment

- *The percentage of subjects with unscheduled bleeding or spotting in each 28-day treatment cycle decreased over the one year trial. The percentages of subjects with unscheduled bleeding or spotting and the number of days with unscheduled bleeding or spotting is consistent with that for other low dose COCs and is acceptable.*

8.5.2 Scheduled Bleeding/Spotting

Table 9 summarizes the incidence and percentage of subjects with scheduled (withdrawal) bleeding and the mean number of days of scheduled bleeding per each 28-day treatment cycle for those subjects who experienced withdrawal bleeding. The percentage of subjects with scheduled bleeding decreased from 78.6% in Cycle 1 to 56.6% in Cycle 13.

Division Director's Comments

- *A total of 15 subjects (0.9%) discontinued the study prematurely due to metrorrhagia or irregular menstruation.*
- *The overall bleeding/spotting pattern associated with the use of NE/EE chewable tablets is acceptable and does not raise any concerns.*

Table 9 Summary of Scheduled (Withdrawal) Bleeding Patterns (MITT Population, Study PR-00207)

Cycle No.	Incidence n/N	(%)	Mean (SD) Number of Days of Scheduled (Withdrawal) Bleeding [A]	
2-13	1294/1424	(90.9)	3.72	(1.25)
1	1149/1462	(78.6)	4.19	(1.78)
2	1038/1393	(74.5)	4.02	(1.59)
3	970/1322	(73.4)	3.95	(1.62)
4	863/1243	(69.4)	4.00	(1.50)
5	830/1206	(68.8)	3.86	(1.46)
6	789/1162	(67.9)	3.76	(1.49)
7	764/1134	(67.4)	3.75	(1.47)
8	728/1097	(66.4)	3.71	(1.35)
9	692/1062	(65.2)	3.75	(1.37)
10	633/1031	(61.4)	3.61	(1.31)
11	662/1021	(64.8)	3.65	(1.38)
12	631/986	(64.0)	3.67	(1.47)
13	546/964	(56.6)	3.10	(1.56)

[A] Values are based only on those subjects who had scheduled bleeding. Subjects who did not have scheduled bleeding in a specific 28-day cycle were not included in the calculation.
Source: Table 14 of the primary Clinical Review signed October 6, 2010 and Table 18, pg. 42 of the Applicant's Summary of Clinical Safety.

8.6 Overall Assessment of Safety

The primary source of data supporting the safety of NE/EE chewable tablets was obtained from Phase 3 Study PR-00207. The overall safety profile for NE/EE chewable tablets, based on the data provided in the Application, is comparable to that for other COCs currently approved for marketing in the US. A total of 136 of 1,677subjects (8.1%) terminated from Phase 3 Study PR-00207 because of a treatment emergent adverse event. The most frequently reported adverse events leading to discontinuation and the percentage of subjects reporting these adverse events were nausea (1.0%), weight increase (0.8%), acne (0.8%), metrorrhagia (0.7%), altered mood (0.4%), hypertension (0.4%), irritability (0.3%), migraine (0.3%), decreased libido (0.3%), and mood swings (0.3%). The most commonly reported adverse events (>2%) possibly related to treatment with study drug and the percentage of subjects reporting them included nausea (6.1%), headache (4.8%), dysmenorrhea (3.9%), acne (3.2%), vulvovaginal mycotic infection (3.1%), vomiting (2.7%), increased weight (2.3%), anxiety (2.1%), fungal infections (2.1%), and diarrhea (2.0%). The most commonly reported adverse events possibly related to treatment with study drug, as well as the frequency and types of adverse events leading to premature subject discontinuation from Study PR-00207, are similar to those reported for other COCs in Phase 3 clinical trials. These adverse events and their frequencies do not raise any safety concerns beyond those known to be associated with COCs.

Among the safety issues of greatest concern associated with the use of hormonal contraceptives are those related to thrombotic and thromboembolic events such as deep vein thrombosis (DVT), pulmonary emboli, and stroke. In the present Application, which contained safety data from more than 1,600 subjects and more than 15,500 28-day treatment cycles, there was one report of a DVT and no reports of pulmonary embolus or stroke. A single case of DVT in the clinical development program for NE/EE chewable tablets is not unexpected or worrisome.

In summary, there were no findings in the clinical development program for NE/EE chewable tablets that raised any new safety concerns beyond those generally associated with the use of COCs.

9. ADVISORY COMMITTEE MEETING

This Application was not presented to an Advisory Committee (AC) because DRUP did not believe that AC guidance was needed to make a regulatory decision concerning the approvability of this Application. In January 2006, the Advisory Committee for Reproductive Health Drugs (ACRHD) discussed oral contraceptive products. Among the areas of focus, was an extensive discussion of acceptable efficacy for oral contraceptive products and their labeling. The recommendations from the January 2006 meeting have been fully considered in (1) the review of this Application and (2) the Division's decision regarding the approvability and labeling of NE/EE chewable tablets.

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. Clinical experience with a wide variety of oral hormonal contraceptives supports DRUP's expectation that the efficacy and safety of NE/EE chewable tablets in postmenarcheal adolescents, like that of other previously approved oral contraceptives, will not differ from that in adult women.

11. OTHER RELEVANT REGULATORY ISSUES

Certification of Financial Interests

According to the primary Clinical Review, all investigators who participated in the Phase 1 and Phase 3 clinical trials certified to not having any financial conflicts.

Division of Scientific Investigation Inspections

The Clinical Reviewer did not identify any sites that raised concerns regarding data integrity problems or conflicting financial interests. DRUP, however, requested that the FDA's Division of Scientific Investigations (DSI) inspect 2 clinical sites. The sites were chosen based on the number of enrolled subjects and the lack of recent inspections. The data from both sites were assessed acceptable by DSI with no evidence of discrepancies or regulatory violations. Both sites received an assessment of "No Action Indicated" (NAI).

12. LABELING

The Applicant proposed 4 proprietary names ((b) (4)). All were found to be unacceptable by the Division of Medication Errors Prevention and Analysis (DMEPA) because of vulnerability to name confusion. Approved product labeling will include only the established name (norethindrone and ethinyl estradiol chewable tablets and ferrous fumarate chewable tablets) until the Applicant submits a proprietary name that is acceptable to DMEPA. The final carton and container labeling submitted by the Applicant on December 16, 2010 was acceptable to the DMEPA and CMC reviewers.

The package insert was submitted in the format prescribed by the Physician Labeling Rule (PLR) and followed "class labeling" for a combination oral contraceptive. 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 with the Applicant on the final Package Insert was reached on December 21, 2010.

13. DECISION/ACTION/RISK BENEFIT ASSESSMENT

13.1 Regulatory Action

The Applicant has provided sufficient information for me to conclude that norethindrone and ethinyl estradiol chewable tablets and ferrous fumarate chewable tablets will be a safe and effective combination oral contraceptive when used in accordance with to-be-approved product labeling. Based on the safety and efficacy data submitted in support of NDA 022573 and the agreed to product labeling, norethindrone and ethinyl estradiol chewable tablets and ferrous fumarate chewable tablets will be approved for the indication of "for use by women to prevent pregnancy."

13.2 Risk/Benefit Assessment

Safety considerations. The overall safety profile for norethindrone and ethinyl estradiol chewable tablets and ferrous fumarate chewable tablets (NE/EE chewable tablets), based on the data obtained in Study PR-00207, is comparable to that for other combination oral contraceptives approved for marketing in the U.S. These data do not raise any safety concerns regarding NE/EE chewable tablets beyond those that are known to be associated with the use of combination oral contraceptives in general. The chewable formulation is well tolerated, without evidence of causing oral irritation. The uterine bleeding pattern associated with the use of NE/EE chewable tablets also is acceptable.

Efficacy considerations. The Applicant has submitted acceptable and adequate clinical data supporting the efficacy of NE/EE chewable tablets. The Pearl Index, calculated by the FDA statistician, was 2.01 pregnancies per 100 women-years of use (95% CI: 1.21, 3.14), based on 19 on-treatment pregnancies in subjects ≤ 35 years of age and 12,297 28-day treatment cycles. Treatment cycles during which subjects used back-up contraception were excluded from the calculation. Women with a BMI of > 35 kg/m^2 were not enrolled in the primary Phase 3 clinical trial. This will be reflected in the Indications and Usage section of to-be-approved product labeling.

Overall Risk/Benefit Assessment. The overall risk/benefit profile for NE/EE chewable tablets is favorable and is acceptable for a combination oral contraceptive. NE/EE chewable tablets, which are to be chewed and swallowed without water, will provide for a lower daily dose of EE (0.025 mg) compared to that in the Applicant's currently marketed combination oral contraceptive (Femcon FE, 0.035 mg EE/0.4 mg NE) that also allows for tablets to be chewed prior to swallowing.

13.3 Recommendation for Postmarketing Risk Evaluation and Mitigation Strategies (REMS)

None.

13.4 Recommendations for other Postmarketing Requirements and Commitments

None.

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

/s/

SCOTT E MONROE
12/22/2010