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APPLICATION NUMBER:

203667Orig1s000

MEDICAL REVIEW(S)

Clinical Review
Gerald Willett, M.D.
NDA 203667
Norethindrone acetate 1.0 mg/ Ethinyl Estradiol 0.02 mg (Ferrous Fumarate placebo)

CLINICAL REVIEW

Application Type	NDA
Application Number	203667
Priority or Standard	Standard
Submit Date	July 9, 2012
PDUFA Goal Date	May 9, 2103
Division / Office	Division of Reproductive and Urologic Products (DRUP) / Office of Drug Evaluation III (ODE III)
Reviewer Name	Gerald Willett M.D.
Review Completion Date	April 10, 2013
Established Name	Norethindrone acetate (NA) and ethinyl estradiol (EE) chewable tablets and ferrous fumarate (FF) tablets
Trade Name	Pending
Therapeutic Class	Combination oral contraceptive (COC)
Applicant	Warner Chilcott, LLC
Formulation	Oral tablets, chewable
Dosing Regimen - Cycle Days (dose)	Days 1-24 (NA 1.0 mg/EE 0.02 mg) Days 25-28 (75 mg ferrous fumarate placebo)
Indication	For use by women to prevent pregnancy
Intended Population	Women of childbearing age

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List of Abbreviations and Definitions

AE	Adverse event
BMI	Body mass index
CI	Confidence interval
COC	Combination oral contraceptive
DRUP	Division of Reproductive and Urologic Products
EE	Ethinyl estradiol
FDA	Food and Drug Administration
FF	Ferrous fumarate
GCP	Good clinical practice
NA	Norethindrone acetate
NDA	New Drug Application
NE	Norethindrone
ODE III	Office of Drug Evaluation III
PI	Pearl Index
SAE	Serious adverse event
SD	Standard deviation
VTE	Venous thromboembolism

1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

Providing that agreement on labeling is obtained, approval is recommended for norethindrone acetate (NA) 1.0 mg and ethinyl estradiol (EE) 0.020 mg chewable tablets and 75 mg ferrous fumarate (FF) tablets for the Applicant's proposed indication of "for use by women to prevent pregnancy."

1.2 Risk Benefit Assessment

The proposed chewable regimen (24 days NA 1.0 mg/EE 0.02 mg followed by 4 days FF) is the same dosage and regimen as the approved Loestrin 24 Fe (tablets to be swallowed) which received approval on 17 Feb 06 under NDA 21-871. Clinical Pharmacology found that the Applicant had demonstrated bioequivalence for both active moieties (NA and EE) in a randomized, two-way, two treatment crossover study in 40 healthy female subjects (Study PR-08507)

This application for a chewable form of an approved product does not require a new contraceptive trial. In the contraceptive clinical study for Loestrin 24 Fe (under NDA 21-871), 743 women (18-45 years) were treated for up to six 28-day cycles providing 3,823 treatment-cycles of exposure. There were 5 on-treatment pregnancies that occurred during cycles in which no back-up contraception was used resulting in an acceptable Pearl Index (PI) of 1.82 (95% CI 0.59 - 4.25).

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Dr. Daniel Davis, the primary reviewer who reviewed data contained in NDA 21-871, did not find any drug-related serious safety findings or new safety signals. In the Loestrin 24 Fe clinical trial, there were no deaths. The 3 serious adverse events (SAEs) were partial thyroidectomy, thyroid cancer and back injury, which were not considered causally related to the study product. There were no cases of deep vein thrombosis (DVT) or pulmonary embolism (PE). There were no specific safety findings for this product that were different from the general combination oral contraceptives (COCs) class of drugs.

The only specific safety evaluation for the chewable product in this application is that of an oral irritation study (Study PR-10007). There were no clinically significant safety findings in this study. Some individuals had mild irritative/inflammatory gingival changes, but these were present in the greatest number at Screening and actually decreased over the course of the study.

1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies

There are no recommendations for postmarketing risk evaluation or mitigation strategies.

1.4 Recommendations for Postmarket Requirements and Commitments

There are no recommendations for postmarketing requirements or commitments.

2 Introduction and Regulatory Background

2.1 Product Information

The Applicant is seeking approval of a chewable COC with the same dosage and regimen as found in one of its approved products, Loestrin 24 Fe. The approved product contains the active hormones norethindrone acetate (1.0 mg) and ethinyl estradiol (0.02 mg). Following 24 days of active hormone use the patient then takes 4 days of placebo (without active hormone) that contains ferrous fumarate (75 mg).

Norethindrone and norethindrone acetate have been used in COCs for many years. Norethindrone (also known as norethisterone) was a component of one of the first three COCs in the 1960s. Ethinyl estradiol is the most commonly used

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estrogenic components of COCs and also dates from the earliest development of COCs.

The 24/4 regimen of COC use has been studied primarily over the past 10 years. Another regimen, of 21 days active hormone/7 days placebo, was predominantly used before the 24/4 regimen and remains in common use today. One researcher published a study that suggested higher contraceptive efficacy with a 24 day regimen (Dinger et al.). This study evaluated a 24/4 COC with drospirenone and compared the contraceptive failure with this regimen to 21 day regimens with other progestins.

Dinger J, Minh TD, Buttman N, Bardenheuer K. Effectiveness of oral contraceptive pills in a large U.S. cohort comparing progestogens and regimen. *Obstet Gynecol* (2011) 117(1):33-40.

The main benefit for chewable COCs is ease of use for patients who have a difficulty swallowing tablets.

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2.2 Currently Available Treatments for Proposed Indication

Contraceptive methods for females include:

- Barrier methods (condom, diaphragm, cervical cap)
- COCs
- Progestin-only oral contraceptives
- Intrauterine devices (levonorgestrel-containing and copper-containing)
- Injectable contraceptives
- Contraceptive implants
- Contraceptive vaginal rings
- Surgical sterilization (tubal ligation, intratubal obstructive devices)

Amongst COCs presently approved in the US, there are 3 different estrogens and a larger number of different progestins as listed below:

Estrogens

- Ethinyl estradiol
- Mestranol
- Estradiol valerate

Progestins

- Norethindrone
- Norethindrone acetate
- Norgestrel
- Levonorgestrel
- Desogestrel
- Norgestimate
- Drospirenone
- Dienogest

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For the combination of ethinyl estradiol and norethindrone acetate, the Applicant has the following approved products:

- Estrostep 21/Fe (EE = 0.02 mg / NA = 1.0 mg x 5 days, EE = 0.03 mg / NA = 1.0 mg x 7 days, EE = 0.035 mg / NA = 1.0 mg x 9 days, and 7 days placebo ferrous fumarate) (NDA 20-130 and NDA 21-276)
- Loestrin 21 1.5/30 (EE = 0.03 mg / NA = 1.5 mg x 21 days and 7 days placebo) (NDA 17-875)
- Loestrin 21 1/20 (EE = 0.02 mg / NA = 1.0 mg x 21 days and 7 days placebo) (NDA 17-876)
- Loestrin FE 1.5/30 (EE = 0.03 mg / NA = 1.5 mg x 21 days and 7 days placebo ferrous fumarate) (NDA 17-355)
- Loestrin FE 1/20 (EE = 0.02 mg / NA = 1.0 mg x 21 days and 7 days placebo ferrous fumarate) (NDA 17-354)
- Lo Loestrin FE (EE = 0.01 mg / NA = 1.0 mg x 24 days, then 2 days of EE 0.01 mg, then 2 days of placebo ferrous fumarate) (NDA 22-501)
- Loestrin 24 FE (EE = 0.02 mg / NA = 1.0 mg x 24 days and 4 days placebo ferrous fumarate) (NDA 21-871)

2.3 Availability of Proposed Active Ingredients in the United States

Ethinyl estradiol is the most commonly used estrogen in combination oral contraceptives, with nearly 50 years of marketing experience.

Norethindrone acetate has a similar long history of marketing experience.

COCs including the aforementioned products are produced by a number of different manufacturers. Most of these products are currently available as generics.

2.4 Important Safety Issues with Consideration to Related Drugs

COCs as a general class have a number of safety issues that have been well-recognized since their introduction in the 1960s. The following adverse events represent the major concerns described in contraceptive labeling:

- Vascular events, which may be fatal, including:
 - Deep venous thrombosis, pulmonary embolism, other venous thromboses
 - Myocardial infarction (especially in women >35 years who smoke)
 - Stroke (both ischemic and hemorrhagic types have been reported)
- Hepatic adenomas, hepatic nodular hyperplasia, cholestasis

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- Blood pressure increase
- Gallbladder disease
- Headaches
- Irregular uterine bleeding, amenorrhea, oligomenorrhea
- Nausea
- Breast tenderness
- Mood changes
- Hypertriglyceridemia

2.5 Summary of Presubmission Regulatory Activity Related to Submission



There was no specific presubmission regulatory activity related to the chewable product in this application.

2.6 Other Relevant Background Information

All of the relevant background information was conveyed in the preceding sections.

3 Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity

The submission quality of the clinical study 10007 (oral irritability) appears acceptable. There was clinical reason from initial review of this study to suggest an OSI inspection. See Section 4.4 for information regarding an inspection of a clinical pharmacology study (PR-08507).

3.2 Compliance with Good Clinical Practices

All three of the studies submitted in this application were performed in accordance with Good Clinical Practices.

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3.3 Financial Disclosures

All investigators who participated in Protocols PR-08507, PR-10007 and PR-07411 certified to not having a financial interest related to the outcomes of these studies.

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Chemistry Manufacturing and Controls

Dr. Raymond Frankewich had the following recommendation in his primary review:

“The Office of Compliance has not issued an overall “Acceptable” recommendation for the facilities involved in this application. Also, issues on labels/labeling are not satisfactorily resolved yet. Therefore, from the ONDQA perspective, this NDA is not ready for approval per 21 CFR 314.125(b)(6) and (13) in its present form until the above issues are satisfactorily resolved.”

4.2 Clinical Microbiology

Clinical microbiology is not required for this application

4.3 Preclinical Pharmacology/Toxicology

Dr. Raheja stated that from a Pharmacology/Toxicology viewpoint, NDA 203667 is recommended for approval. The pharmacology and toxicology of the active ingredients are well documented in the NDA for similar Warner Chilcott products.

4.4 Clinical Pharmacology

Dr. LaiMing Lee had the following recommendation in her primary review:

“The Division of Clinical Pharmacology-3/Office of Clinical Pharmacology (DCP-3 /OCP) has reviewed NDA 203667 for NA (1 mg) and EE (0.02 mg) chewable tablets and Fe (75 mg) tablets submitted to the Agency on July 9, 2012. We have found this NDA acceptable from a Clinical Pharmacology perspective provided that an agreement is reached between the sponsor and the Division regarding the labeling language.”

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4.5 Biostatistics

No biostatistical analysis was required for this application.

5 Sources of Clinical Data

5.1 Tables of Studies/Clinical Trials

The overview for the 3 studies (PR-08507, PR-10007, PR-07411) submitted by the Applicant are found in Table 1, Table 2 and Table 3 respectively.

Table 1: Bioavailability Study PR-08507 Comparing Swallowed versus Chewed Tablets

Protocol No. (Report No.)	Study Design	Treatment groups	Number of subjects	Age (range)
Start date/ Completion date				Ethnic origin of subjects
Country (No. of study sites)				
PR-08507 (RR-00508)	Phase 1 randomized single-dose (2-way) crossover	Approved tablet NA 1.0 mg/ EE 0.020 mg – Loestrin 24 (swallowed)	40 subjects enrolled	Median age of 25 years with range of 19-35 years
15 Dec 2007/ 31 Dec 2007			38 subjects completed	H/L W = 17 (42.5%) NH/L W = 15 (37.5%) NH/L B = 7 (17.5%) H/L NA = 1 (2.5%)
US (1 site in Austin, Texas)	Duration of treatment = 2 single-doses	Study tablet NA 1.0 mg/ EE 0.020 mg – Loestrin 24 (chewed)		

EE = ethinyl estradiol; NA = norethindrone acetate; H/L W = Hispanic/Latino White; NH/L W = Non-Hispanic/Latino White; NH/L B = Non-Hispanic/Latino Black; H/L NA = Hispanic/Latino Native American
 Source: NDA 203667; Listing of all clinical studies

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Table 2: Study PR-07411 (Safety Information Only)

Report No. (Protocol No.)	Study phase Study design	Treatment group	Subjects	Age (range in years) Race
Start date/ Completion date	Study duration			
Country (No. of study sites)				
PR-07411 (RR-00112)	Phase 1 Randomized single-dose (3 way) crossover	Study tablet NA 1.0 mg/ EE 0.020 mg – Loestrin 24 (formulation WC2061) (chewed, fasted)	42 subjects enrolled 40 completed	Median age 31 (21-45) Caucasian 32 (76.2%) Black 9 (21.4%) Native American 1 (2.4%)
20 Aug 2011 05 Sep 2011		Study tablet NA 1.0 mg/ EE 0.020 mg – Loestrin 24 (formulation WC3040-2F) (chewed, fasted)		
U.S. (1)		Study tablet NA 1.0 mg/ EE 0.020 mg – Loestrin 24 (formulation WC3040-2F) (chewed, fed)		

EE = ethinyl estradiol; NA = norethindrone acetate

Note: Formulation WC2061 is used in the approved Loestrin 24 Fe

Source: NDA 203667; Listing of all clinical studies

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Table 3: Phase 1 Oral Irritability Study PR-10007

Report No. (Protocol No.)	Study phase Study design	Treatment group	Subjects	Age range in years (mean) Race
PR-10007 (RR-01708)	Single center, open-label, uncontrolled trial	Study tablet – one daily NA 1.0 mg/ EE 0.020 mg – Loestrin 24 (chewed)	56 subjects enrolled 52 completed	Mean age = 34.4 Range 19-45 Asian 3 (5.4%) African-American 7 (12.5%) Caucasian 46 (82.1%)
29 Feb 2008/ 28 Apr 2008	Duration = 24 days			
U.S. (1)				

EE = ethinyl estradiol; NA = norethindrone acetate
 Source: NDA 203667; Listing of all clinical studies

5.2 Review Strategy

The clinical review for this application centered on:

- Oral irritability study
- Safety findings from the clinical pharmacology studies
- 4-month safety update
- Postmarketing safety review of Loestrin 24 FE

5.3 Discussion of Individual Studies/Clinical Trials

5.3.1 Bioavailability Study PR-08507 (Report RR-00508)

Medical Officer's Comment:

See the Clinical Pharmacology review of this study for details regarding study design and pharmacokinetic results. This reviewer will focus on the clinical safety analysis and safety results in this section.

5.3.1.1 Analysis of Safety

Safety measurements in this study included the following:

- Medical history
- Physical examination

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- Cervical cytology (if not performed in the last 3 months or is test report was not available)
- Vitals signs
- Clinical laboratory testing (chemistry, hematology, urinalysis, serology for HIV, HbsAg and Anti-HCV, urine drug screen, serum pregnancy test)
- Electrocardiogram
- Adverse event recording

5.3.1.2 Safety – Extent of Exposure

Of the 40 subjects randomized to take part in the study, 38 subjects completed both treatment periods, receiving a single Loestrin 24 Tablet (swallowed) in one treatment period and a single Loestrin 24 Tablet (chewed) in the other treatment period. Treatments were separated by a 14-day washout period.

Subject 203 was withdrawn from the study for a positive serum pregnancy screen. Subject 208 withdrew from the study on December 28, 2007, 13 days after dosing in Period 1 due to personal reasons.

5.3.1.3 Safety – Deaths, Serious Adverse Events (SAEs), Discontinuations due to Adverse Events

In this study there were no deaths, no SAEs and no discontinuations due to adverse events.

5.3.1.4 Safety – Common Adverse Events (AEs)

The most commonly reported AEs were:

- Headache (4 events in 4 subjects; 3 events following the Loestrin 24 Tablet chewed and 1 event following the Loestrin 24 Tablet swallowed)
- Nausea (4 events in 4 subjects; all 4 events following the Loestrin 24 Tablet chewed)
- Early menstrual period (2 events in 2 subjects; 1 event following the Loestrin 24 Tablet chewed and 1 event following the Loestrin 24 Tablet swallowed)
- Menstrual spotting (2 events in 2 subject; 1 events following the Loestrin 24 Tablet chewed and 1 event following the Loestrin 24 Tablet swallowed).

Medical Officer's Comment:

Although the Applicant separated out the adverse events between the chewed versus swallowed groups, the number of adverse events is too small to detect any differences. This reviewer would anticipate that the only

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plausible AE difference between the 2 dosing methods would relate to the local effect of chewing. This was studied in the oral irritation study that will be subsequently discussed in this review.

5.3.1.5 Safety – Clinical Laboratory Results and Electrocardiograms

All clinical laboratory results were reviewed by the clinical investigators. There were no out-of-range laboratory values classified as AEs. There were no out-of-range laboratory values which were deemed clinically significant. Results from the screening 12-lead ECG measurements were within normal limits or determined to be not clinically significant.

5.3.1.6 Safety – Physical examinations and vital signs

Results from all physical and vital sign measurements were judged to be within normal limits or not clinically significant.

5.3.2 Food Effects Study PR-07411 (Report RR-00112)

Medical Officer's Comment:

This study was submitted by the Applicant primarily for safety information. This reviewer will focus on the clinical safety analysis and safety results in this section.

5.3.2.1 Safety Analysis

Safety measurements in this study included the following:

- Medical history
- Physical examination
- Cervical cytology (if not performed in the last 3 months or is test report was not available)
- Vitals signs
- Clinical laboratory testing (chemistry, hematology, urinalysis, serology for HIV, HbsAg and Anti-HCV, urine drug and cotinine screen, serum pregnancy test)
- Electrocardiogram
- Adverse event recording

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5.3.2.2 Safety – Extent of Exposure

Of the 42 subjects randomized to take part in the study, 40 subjects completed all 3 treatment periods. Subject 507003 withdrew consent prior to dosing in Period 2. Subject 507005 was withdrawn from the study prior to dosing in Period 3.

5.3.2.3 Safety – Deaths, Serious Adverse Events, Discontinuations due to Adverse Events

In this study there were no deaths, no SAEs and no discontinuations due to adverse events.

5.3.2.4 Safety – Common Adverse Events

The most commonly reported AEs were nausea (9 subjects), abdominal cramps (9 subjects) and headache (7 subjects).

5.3.2.5 Safety – Clinical Laboratory Results and Electrocardiograms

There were no out-of-range laboratory values identified as adverse events or clinically significant.

5.3.2.6 Safety – Vital Signs

There were no vital sign values of clinical significance.

5.3.3 Oral Irritation Study PR-10007 (Report RR-01708)

5.3.3.1 Title

“A Clinical Study to Evaluate the Safety of Loestrin Oral Contraceptive Following Daily Use by Human Female Subjects.”

5.3.3.2 Study Objective

The objective of the study was to determine the irritation potential of an oral contraceptive tablet following daily use of the active formulations for 24 days.

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5.3.3.3 Study Design

This was an open-label, uncontrolled, single-center study to determine the irritation potential of the active formulation of an oral contraceptive when chewed daily for 24 days.

Subjects were given an oral soft-tissue examination at each visit (Days 3, 8, 24 and 28). This examination consisted of examination pre-dose and 30 minutes after dosing.

Subjects were instructed to use a non-hormonal (e.g., barrier) method of contraception while enrolled in the study and for 1 month following the completion of the study.

5.3.3.4 Inclusion Criteria

- Were females 18 to 45 years of age;
- Were in good general health and had a negative urine pregnancy test at Baseline;
- Were willing to switch to the study product during the course of the study if they were currently using oral, intravaginal, or transdermal combination contraceptives;
- Were willing to use a nonhormonal (e.g., barrier) method of contraception during the period of the clinical study, to be continued for 1 month after stopping use of the experimental medication
- Could read, understand, and sign an informed consent agreement.

5.3.3.5 Exclusion Criteria

- Were currently using hormonal contraception via the following routes and during the specified timeframes: progestational implants; progestin, estrogen or estrogen/progestational injectable drug therapy within 9 months; intrauterine within 3 months. Women who were currently on oral, intravaginal or transdermal COC were switched directly to study medication
- Were postmenopausal or perimenopausal (experiencing hot flashes, new menstrual irregularities, etc);
- Had any visible disease of the oral mucosa (i.e., a score of greater than "1" on the oral soft-tissue examination), which, in the opinion of the investigative personnel, would have interfered with the evaluation;
- Had any finding on the Screening pelvic examination or other clinical evaluations which, in the opinion of the investigator, would have placed

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- the subject at undue risk or otherwise interfered with the interpretation of study results;
- Had a known sensitivity to oral contraceptives;
 - Were age 35 or older and smoked;
 - Had a contraindication for the use of oral contraceptives (e.g., history of thrombophlebitis or thromboembolic disorders, known or suspected clotting disorders, cerebral vascular or coronary artery disease, known or suspected carcinoma of the breast, known or suspected estrogen-dependent neoplasia, genital bleeding of unknown cause, or a history of benign or malignant liver tumor or liver disorders);
 - Had dentures, which, in the opinion of the investigative personnel, would have resulted in reduced oral contact with the investigative drug;
 - Had participated in another clinical trial within 1 month prior to Screening, or received an investigational drug within the last 3 months prior to Screening. Subjects who participated in an Oral Contraceptive clinical trial, using FDA approved active ingredients, were to be enrolled 2 cycles after completing the preceding study;
 - Were receiving systemic or topical drugs or medication which, in the opinion of the investigative personnel, would have interfered with the study results; and/or
 - Were females who were pregnant, planning to become pregnant during the study, or were breastfeeding.

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5.3.3.6 Visit Schedule

The visit schedule is shown in Table 4.

Table 4: Visit Schedule for Study 10007

	SCR	Treatment Period					FV
		Day 1		D3	D8	D24	D28
		BLPD	PD30				
Informed consent	X						
Medical history	X						
Entry criteria	X						
Urine pregnancy test		X					X
Pelvic examination	X						
Oral soft-tissue exam	X	X	X	X	X	X	X
Blood pressure/pulse	X	X		X	X	X	X
Product dispensed		X					
Prior or concomitant meds	X	X		X	X	X	X
Adverse events		X	X	X	X	X	X

SCR = screening; BLPD = baseline pre-dose; PD30 = 30 minutes post-dose; D = day; FV = final visit
 Source: Report for Study 10007; page 19 of 498

5.3.3.7 Oral Soft-Tissue Examination

Oral soft-tissue examinations were performed at Screening, Baseline/Day 1 (pre-dose and 30 minutes after dosing), Day 3, Day 8, Day 24, and Day 28. The oral health investigator evaluated the intra-oral soft tissues for inflammation/irritation, abrasions, and/or infection, and recorded the results on an Oral Soft-Tissue Clinical Examination Form. The condition of the lips, buccal mucosa, labial mucosa, sublingual mucosa, attached gingivae, tongue, hard/soft palate, uvula, and oropharynx were rated as normal or abnormal. Any abnormalities were described, and the examiner indicated whether the abnormality was attributable to the study product. Irritation/inflammation of each area was scored using the following scale:

- 0 = Normal
- 1 = Erythema plus slight edema
- 2 = Moderate erythema and/or edema (i.e., beginning of tissue breakdown or slough)
- 3 = Severe irritation/inflammation (i.e., definite blistering, ulceration, or epithelial slough)

Abrasions reported by the subject or observed by the oral health investigator were also noted as present or absent. Everyday traumatic abrasions as a result of chewing, i.e., traumatic abrasions on the labial and buccal mucosa and tongue were not identified as irritation and were not reported as adverse events. Traumatic abrasions that were deemed clinically significant as a result from

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chewing the product were reported as adverse events. The locations of the abrasion(s) (i.e., lips, buccal mucosa, labial mucosa, sublingual mucosa, attached gingivae, tongue, hard/soft palate, uvula, and/or oropharynx) were specified and the severity of each abrasion was scored using the following scale:

- 0 = None
- 1 = Mild
- 2 = Moderate
- 3 = Severe

5.3.3.8 Subject Disposition

Of 56 subjects enrolled, 4 discontinued (2 with voluntary withdrawal and 2 lost to follow-up). The number of subjects who completed was 52 (92.9%)

5.3.3.9 Demographics

Table 5: Demographics in Study 10007

	Subject Data
Age (years)	
Mean (standard deviation)	34.4 (7.8)
Range	19-45
Race origin – N (%)	
Asian	3 (5.4%)
African-American	7 (12.5%)
Caucasian	46 (82.1%)
Ethnic origin – N (%)	
Hispanic or Latino	13 (23.2%)
Non Hispanic or Latino	43 (76.8%)

Source: Report for Study 10007; page 27 of 498

5.3.3.10 Efficacy

There were no efficacy determinations in this study.

5.3.3.11 Safety – Extent of Exposure

Of the 52 subjects who completed the study, 7 subjects did not dose as instructed. Four (4) subjects discontinued the study early and therefore received less than the 24-day course of treatment; 2 subjects discontinued after 15 days, 1 after 8 days, and 1 after 6 days from the Baseline (Day 1) Visit. For Subject 55, the tablet count at the end of the Day 24 Visit did not correspond to the diary recording. Subject stated she dosed 23 tablets although the pill-pack had 19 tablets missing. Subject should have dosed an additional 4 tablets.

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5.3.3.12 Irritation and Inflammation

For most of the oral regions there was no evidence of any irritation or inflammation throughout the study (lips, buccal mucosa, labial mucosa, sublingual mucosa, tongue, hard/soft palate). The area affected most by irritation and inflammation was the gingivae. However this was present in the greatest degree at Screening and diminished thereafter (Table 6). There was one subject with uvular irritation/inflammation at Day 8. There were two instances of irritation/inflammation of the oropharynx (one at Day 3 and the other at Day 8).

Table 6: Number (%) of Subjects with Gingival Irritation and Inflammation in Study 10007

Time Period (N)	n (%)
Screening (56)	8 (14.3%)
Baseline pre-dose (56)	6 (10.7%)
30 minutes post dose (56)	6 (10.7%)
Day 3 (53)	5 (9.4%)
Day 8 (53)	1 (1.9%)
Day 24 (52)	1 (1.9%)
Day 28 (53)	0

Source: Report for Study 10007; page 28 of 498

Medical Officer's Comment: The only oral site with notable irritation/inflammation was that of the gingivae and this area actually improved during the study. This reviewer concurs with the applicant that none of the irritation/inflammation findings were clinically significant in regard to the chewable tablets.

5.3.3.13 Abrasion

There were no subjects with abrasion at any of the oral regions identified in the previous section.

5.3.3.14 Serious Adverse Events (SAEs) and Adverse Events Leading to Discontinuation

There were no deaths, SAEs or adverse events leading to discontinuation.

5.3.3.15 Common Adverse Events

There were 13 adverse events reported for 12 subjects. Common adverse events are shown in Table 7.

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Table 7: Common Adverse Events in Study 10007 (N = 56)

Adverse Event	n (%)
Nasopharyngitis	2 (3.6%)
Pharyngolaryngeal pain	2 (3.6%)
Influenza	2 (3.6%)
Tooth fracture	2 (3.6%)
Cough	1 (1.8%)
Pharyngitis streptococcal	1 (1.8%)
Tachycardia	1 (1.8%)
Abdominal pain	1 (1.8%)
Heart rate increased	1 (1.8%)

Source: Report for Study 10007; page 69 of 498

Medical Officer's Comment:

The tooth fractures were not related to the study drug product. Subject 22 broke her tooth while eating a piece of candy. Subject 48 chipped her porcelain crown while eating an orange. The only adverse event in the table that may be potentially related to COCs is that of abdominal pain.

5.3.3.16 Vital Signs

There were no changes of clinical significance during the study

6 Review of Efficacy

There were no new clinical efficacy studies needed for the application.

6.1 Contraceptive Indication

The Applicant is relying on the efficacy data from Loestrin 24 Fe and the bioequivalence data from Study PR-08507.

7 Review of Safety

7.1 Methods

7.1.1 Components of NDA 203667 Used to Evaluate Safety

The key sections from the NDA 203667 application regarding safety were found in:

- Clinical Overview

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- Summary of Clinical Safety
- Study Reports for PR-10007, PR-08507 and PR-07411
- 4-month safety update
- Postmarketing safety for Loestrin 24 Fe

7.1.2 Categorization of Adverse Events

The coding system for adverse events was not listed in the report.

7.2 Adequacy of Safety Assessments

The only safety assessment needed for this application was the oral irritation study. This study was acceptable.

7.2.1 Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations

The overall exposure in the oral irritation study was acceptable.

7.2.2 Explorations for Dose Response

Not applicable for this submission.

7.2.3 Special Animal and/or In Vitro Testing

Not applicable for this submission.

7.2.4 Routine Clinical Testing

There were no clinically significant safety findings with any of the routine clinical testing in the 3 submitted studies.

7.2.5 Metabolic, Clearance, and Interaction Workup

See Section 4.4 and the clinical pharmacology review.

7.2.6 Evaluation for Potential Adverse Events for Similar Drugs in Drug Class

The most important adverse events when considering the safety of COCs is that of venous and arterial thromboembolic events (VTEs and ATEs. There were no VTEs or ATEs in the submitted studies for this application. Common adverse

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events identified in some of the submitted studies to this application that might be related to the COC class of drugs include nausea, headache, abdominal cramps and alterations of menses/uterine bleeding.

7.3 Major Safety Results

7.3.1 Deaths

There were no deaths in the studies submitted for this product.

7.3.2 Nonfatal Serious Adverse Events

There were no SAEs identified in any of the 3 submitted studies.

7.3.3 Discontinuations Due to Adverse Events

There were no discontinuations due to adverse events identified in any of the 3 submitted studies.

7.4.1 Common Adverse Events

The submitted studies for this application were small. The results were not pooled. Some of the most common events such as nausea, headache, abdominal cramps and menstrual irregularities are commonly seen with COCs. There were no new safety signals. As mentioned earlier for the oral irritation study, the 2 cases of tooth fracture were not related to the chewable study drug.

7.4.2 Laboratory Findings

There were no significant laboratory findings in the submitted studies.

7.4.3 Vital Signs

There were no new safety findings related to vital sign monitoring.

7.4.4 Electrocardiograms (ECGs)

Not applicable to this application

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7.4.5 Special Safety Studies/Clinical Trials

The only special safety studied requested was that of an irritation study for this chewable product. There was no evidence of any safety concerns for the oral cavity based on this study (PR-10107).

7.4.6 Immunogenicity

Not applicable for this submission.

7.5 Other Safety Explorations

None

7.5.1 Dose Dependency for Adverse Events

There were no dose-dependent safety findings, as only a single dose was studied.

7.5.2 Time Dependency for Adverse Events

There were no significant time-dependent safety findings.

7.5.3 Drug-Demographic Interactions

Not applicable for this submission.

7.5.4 Drug-Disease Interactions

Not applicable for this submission.

7.5.5 Drug-Drug Interactions

Not applicable for this submission.

7.6 Additional Safety Evaluations

None.

7.6.1 Human Carcinogenicity

Not applicable for this submission.

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7.6.2 Human Reproduction and Pregnancy Data

Not applicable for this submission.

7.6.3 Pediatrics and Assessment of Effects on Growth

Not applicable for this submission.

7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound

See Section 8 for overdose information on the approved Loestrin 24 Fe product. The drug abuse potential for COCs in general is very low. Overdose could lead to severe nausea and vomiting. The primary withdrawal effect is physiologic withdrawal bleeding.

7.7 4-Month Safety Update

There were no nonclinical or clinical studies conducted at the time of submission with the chewable product being proposed in this application. No clinical or nonclinical studies have been subsequently started.

No new safety findings from the medical literature were reported by the Applicant or identified by this reviewer for COCs containing norethindrone acetate/ ethinyl estradiol.

See Section 8 for the postmarketing experience.

7.7.1 Ongoing Studies

There are no ongoing studies of this product.

8 Postmarket Experience

In the 4-month safety update the Applicant submitted postmarketing information on Loestrin 24 Fe. This information covers the period from 17 Feb 2006 through 31 Oct 2012. In this time period which exceeds 6 years the following pertinent adverse events were reported (Table 8).

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Table 8: Postmarketing Adverse Event Reporting for Loestrin 24 Fe (17 Feb 2006 through 31 Oct 2012)

Preferred term	Total
Metrorrhagia	2930
Amenorrhea	1755
Dysmenorrhea	708
Hypomenorrhea	615
Drug dose omission	610
Nausea	526
Drug administration error	503
Abdominal discomfort, distention tenderness or pain	475
Menorrhagia	463
Vomiting	194
Mood swings or altered	188
Depression or depressed mood	87
Drug ineffective	84
Fetal exposure during pregnancy	73
Migraine	68
Blood pressure increased	38
Oligomenorrhea	36
Irritability	32
Vulvovaginal mycotic infection/candidiasis	28
Vision blurred	24
Skin discoloration or hyperpigmentation	23
Pulmonary embolism	21
Accidental drug intake by child	20
Fluid retention	20
Hypersensitivity	17
Contact lens intolerance	16
Ovarian cyst	12
Thrombosis	9
Deep vein thrombosis	8
Accidental exposure	7
Chloasma	6
Accidental overdose	4
Pulmonary thrombosis	2
Coronary artery thrombosis	1
Myocardial infarction	1
Anaphylactic reaction	1
Homicidal ideation	1
Jugular vein thrombosis	1
Venous thrombosis	1

Source: 4-month safety update to NDA 203667; Submission 6 Nov 2012.

Medical Officer's Comment:

Adverse events typically related to COCs and/or of special interest were included in the preceding table. Although sales figures and estimated incident rates were not provided by the Applicant the types of drug-related

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adverse events and relative proportions are similar to other COC postmarketing reports. There have not been any recent new postmarketing safety concerns related to norethindrone acetate or ethinyl estradiol. The appearance of 1 case of anaphylactic reaction in the prior table can justify its inclusion in the labeling. The Applicant has included homicidal ideation (1 case listed above) in its proposed label. This reviewer is not aware of any relationship to COCs or the need for this adverse event to be listed in the label.

9 Appendices

9.1 Labeling Recommendations

Labeling review is ongoing. A clinical addendum will be submitted to DARRTS when labeling is complete.

9.2 Advisory Committee Meeting

An advisory committee meeting is not warranted for this application.

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

/s/

GERALD D WILLETT
04/10/2013

CHRISTINA Y CHANG
04/10/2013

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

NDA/BLA Number: 203667 Applicant: Warner Chilcott Submission Date: 7-9-2012

Drug Name: Norethindrone acetate and ethinyl estradiol chewable tablets and ferrous fumarate tablets
NDA/BLA Type: 505 (b)(2)

On initial overview of the NDA/BLA application for filing:

	Content Parameter	Yes	No	NA	Comment
FORMAT/ORGANIZATION/LEGIBILITY					
1.	Identify the general format that has been used for this application, e.g. electronic CTD.	X			Electronic
2.	On its face, is the clinical section organized in a manner to allow substantive review to begin?	X			
3.	Is the clinical section indexed (using a table of contents) and paginated in a manner to allow substantive review to begin?	X			
4.	For an electronic submission, is it possible to navigate the application in order to allow a substantive review to begin (e.g., are the bookmarks adequate)?	X			
5.	Are all documents submitted in English or are English translations provided when necessary?	X			
6.	Is the clinical section legible so that substantive review can begin?	X			
LABELING					
7.	Has the applicant submitted the design of the development package and draft labeling in electronic format consistent with current regulation, divisional, and Center policies?	X			
SUMMARIES					
8.	Has the applicant submitted all the required discipline summaries (i.e., Module 2 summaries)?	X			
9.	Has the applicant submitted the integrated summary of safety (ISS)?			X	Not needed for this NDA
10.	Has the applicant submitted the integrated summary of efficacy (ISE)?			X	Not needed for this NDA; efficacy cross-referenced from NDA 21-871
11.	Has the applicant submitted a benefit-risk analysis for the product?	X			Benefit and risk conclusions are presented in the Clinical Overview of NDA 203667
12.	Indicate if the Application is a 505(b)(1) or a 505(b)(2). If Application is a 505(b)(2) and if appropriate, what is the reference drug?				505 (b)(2) Reference is NDA 21-871 (Loestrin 24 Fe)
DOSE					
13.	If needed, has the applicant made an appropriate attempt to determine the correct dosage and schedule for this product (i.e., appropriately designed dose-ranging studies)?			X	The dosage and schedule is the same as approved reference drug Loestrin 24 Fe
EFFICACY					
14.	Do there appear to be the requisite number of adequate and well-controlled studies in the application?	X			The bioequivalence and irritation studies

File name: 5_Clinical Filing Checklist for NDA_BLA or Supplement 010908

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
					are all that were required
15.	Do all pivotal efficacy studies appear to be adequate and well-controlled within current divisional policies (or to the extent agreed to previously with the applicant by the Division) for approvability of this product based on proposed draft labeling?	X			
16.	Do the endpoints in the pivotal studies conform to previous Agency commitments/agreements? Indicate if there were not previous Agency agreements regarding primary/secondary endpoints.	X			The studies followed the agreements for the reference drug (NDA 21-871)
17.	Has the application submitted a rationale for assuming the applicability of foreign data to U.S. population/practice of medicine in the submission?			X	
SAFETY					
18.	Has the applicant presented the safety data in a manner consistent with Center guidelines and/or in a manner previously requested by the Division?	X			
19.	Has the applicant submitted adequate information to assess the arrhythmogenic potential of the product (e.g., QT interval studies, if needed)?			X	
20.	Has the applicant presented a safety assessment based on all current worldwide knowledge regarding this product?		X		Adequate information is available in Annual Reports and periodic safety reports for NDA 21-871
21.	For chronically administered drugs, have an adequate number of patients (based on ICH guidelines for exposure ¹) been exposed at the dose (or dose range) believed to be efficacious?			X	
22.	For drugs not chronically administered (intermittent or short course), have the requisite number of patients been exposed as requested by the Division?			X	
23.	Has the applicant submitted the coding dictionary ² used for mapping investigator verbatim terms to preferred terms?			X	
24.	Has the applicant adequately evaluated the safety issues that are known to occur with the drugs in the class to which the new drug belongs?	X			
25.	Have narrative summaries been submitted for all deaths and adverse dropouts (and serious adverse events if requested by the Division)?			X	
OTHER STUDIES					
26.	Has the applicant submitted all special studies/data requested by the Division during pre-submission	X			Bioequivalence, food and irritation studies

¹ For chronically administered drugs, the ICH guidelines recommend 1500 patients overall, 300-600 patients for six months, and 100 patients for one year. These exposures MUST occur at the dose or dose range believed to be efficacious.

² The “coding dictionary” consists of a list of all investigator verbatim terms and the preferred terms to which they were mapped. It is most helpful if this comes in as a SAS transport file so that it can be sorted as needed; however, if it is submitted as a PDF document, it should be submitted in both directions (verbatim -> preferred and preferred -> verbatim).

File name: 5_Clinical Filing Checklist for NDA_BLA or Supplement 010908

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
	discussions?				have been submitted
27.	For Rx-to-OTC switch and direct-to-OTC applications, are the necessary consumer behavioral studies included (e.g., label comprehension, self selection and/or actual use)?			X	
PEDIATRIC USE					
28.	Has the applicant submitted the pediatric assessment, or provided documentation for a waiver and/or deferral?	X			Request for waiver has been submitted
ABUSE LIABILITY					
29.	If relevant, has the applicant submitted information to assess the abuse liability of the product?			X	
FOREIGN STUDIES					
30.	Has the applicant submitted a rationale for assuming the applicability of foreign data in the submission to the U.S. population?			X	
DATASETS					
31.	Has the applicant submitted datasets in a format to allow reasonable review of the patient data?	X			
32.	Has the applicant submitted datasets in the format agreed to previously by the Division?	X			
33.	Are all datasets for pivotal efficacy studies available and complete for all indications requested?			X	No contraceptive efficacy data are needed for this NDA submission
34.	Are all datasets to support the critical safety analyses available and complete?	X			
35.	For the major derived or composite endpoints, are all of the raw data needed to derive these endpoints included?			X	
CASE REPORT FORMS					
36.	Has the applicant submitted all required Case Report Forms in a legible format (deaths, serious adverse events, and adverse dropouts)?			X	Initial review has not indicated any deaths, SAEs or adverse dropouts in any of the 3 submitted studies
37.	Has the applicant submitted all additional Case Report Forms (beyond deaths, serious adverse events, and adverse drop-outs) as previously requested by the Division?			X	
FINANCIAL DISCLOSURE					
38.	Has the applicant submitted the required Financial Disclosure information?	X			
GOOD CLINICAL PRACTICE					
39.	Is there a statement of Good Clinical Practice; that all clinical studies were conducted under the supervision of an IRB and with adequate informed consent procedures?	X			

IS THE CLINICAL SECTION OF THE APPLICATION FILEABLE? ___ Yes ___

If the Application is not fileable from the clinical perspective, state the reasons and provide comments to be sent to the Applicant.

No potential clinical review issues for the 74 day letter have been identified at this point in time.

File name: 5_Clinical Filing Checklist for NDA_BLA or Supplement 010908

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

Gerald Willett MD	8-29-2012
Reviewing Medical Officer	Date
Lisa Soule MD	8/29/12
Clinical Team Leader	Date

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

/s/

GERALD D WILLETT
08/30/2012

LISA M SOULE
08/30/2012