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APPLICATION NUMBER:

204426Orig1s000

MEDICAL REVIEW(S)

CLINICAL REVIEW

Application Type	NDA
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Division / Office	DRUP/ODE III
Reviewer Name(s)	Daniel Davis, MD
Review Completion Date	March 25, 2013
Established Name	norethindrone acetate/ethinyl estradiol soft gelatin capsules and ferrous fumarate soft gelatin capsules
(Proposed) Trade Name	Minastrin 24 Fe
Therapeutic Class	Hormonal contraception
Applicant	Warner Chilcott Company, LLC
Formulation(s)	Capsule (soft gel)
Dosing Regimen	1 active capsule for 24 days; 1 inactive capsule for 4 days.
Indication(s)	Prevention of pregnancy
Intended Population(s)	Women of reproductive age

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1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

From a clinical perspective, this reviewer recommends approval of Minastrin 24 Fe soft gel capsules containing norethindrone acetate 1.0 mg and ethinyl estradiol 0.020 mg. It is the sponsor's intent to [REDACTED] (b) (4)

[REDACTED] with the new soft gel capsule upon its approval. The new product will be marketed only as a 28-day regimen.

1.2 Risk Benefit Assessment

The risk benefit profile for norethindrone and ethinyl estradiol has been well established and the current product contains the same amount of active hormones (norethindrone and ethinyl estradiol) as Loestrin 24 Fe, approved on 2-17-06 under NDA 21-871.

1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies

No special Phase 4 postmarketing studies or risk management steps are recommended. The long-term safety of norethindrone acetate and ethinyl estradiol combination products (including Loestrin 24 Fe and Loestrin 21 products) has been well established over the past 30 years. There is no reason to expect a different safety profile for this new capsule formulation that is shown to be bioequivalent to the marketed Loestrin 24 Fe oral tablets.

1.4 Recommendations for Postmarket Requirements and Commitments

None are recommended.

2 Introduction and Regulatory Background

2.1 Product Information

The proposed soft gelatin capsule (norethindrone acetate and ethinyl estradiol) is an oral contraceptive containing 1.0 mg norethindrone acetate and 0.020 mg ethinyl estradiol per capsule. The sponsor seeks approval for the capsule formulation and a 28-day regimen with 24 consecutive days of active capsules followed by 4 days of ferrous fumarate (placebo) capsules. The soft gelatin capsule is to be marketed only as a 28-day regimen; each capsule is swallowed whole.

Reviewer's comment:

In this review, the study drug will be called either WC3042-05 capsule (the name during development) or Minastrin 24 capsule (the proposed tradename) and the currently marketed product will be called Loestrin 24.

2.2 Tables of Currently Available Treatments for Proposed Indications

Over the past 30 years there have been several FDA-approved combination hormonal contraceptives (CHCs) containing norethindrone or norethindrone acetate (NA) and ethinyl estradiol (EE) on the US market. Many are generic versions of the original products. Ovcon-50, containing 1 mg NA and 0.050 mg EE, was approved under NDA 17-576 on August 28, 1975. Ovcon-35 (0.4 mg NA and 0.035 mg EE tablets) was approved under NDA 17-716 by the FDA on March 29, 1976. Loestrin 21 1.5/30 (1.5 mg NA and 0.030 mg EE tablets) was approved under NDA 17-875 on October 1, 1976. These three products have been marketed in the USA for over 37 years as a monophasic CHC available in both a 21-pill or 28-pill dispenser containing 21 active and 0 or 7 inert tablets. Other NA/EE products are Norinyl and Ortho Novum1/35, Loestrin 24 Fe, Lo Loestrin (NDA 22-501, 1.0 mg NA and 0.010 mg EE) and several triphasic CHCs containing the same two hormones.

2.3 Availability of Proposed Active Ingredient in the United States

Norethindrone and ethinyl estradiol are readily available and have been so since 1968.

2.4 Important Safety Issues with Consideration to Related Drugs

The most significant safety issue is with thromboembolic events (deep vein thrombosis [DVT] and pulmonary emboli [PE]) and cerebrovascular accidents (CVA), which can be fatal or debilitating. Such events are rare, however, occurring in 5-10 women per 10,000 CHC users.

2.5 Summary of Presubmission Regulatory Activity Related to Submission

There were no presubmission regulatory activities. Based on prior experience and similar submissions to the Division (NDA 21-490, Ovcon chewable tablet, approved on November 14, 2003; [REDACTED] (b) (4)

[REDACTED] the Applicant was aware of the studies needed for approval of a different formulation of an approved CHC.

2.6 Other Relevant Background Information

The proposed regimen, and consequently the exposure to norethindrone and EE, is the same as the approved regimen for Warner Chilcott's Loestrin® 24 Fe (norethindrone acetate and ethinyl estradiol tablets USP and ferrous fumarate tablets) which received approval as an oral contraceptive on February 17, 2006 under NDA 21-871. The Application contains results of Study PR-00810 (Report RR-06511) which show that

WC3042-05 capsules are bioequivalent to Loestrin 24 Fe tablets. Results of Study PR-06011 (Report RR-04012) indicate that WC3042-05 capsules can be taken without regard to meals. (b) (4)

3 Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity

There are no issues concerning the quality and integrity of the submission.

3.2 Compliance with Good Clinical Practices

The clinical pharmacology studies were in compliance with Good Clinical Practices and appropriate consent forms were signed.

3.3 Financial Disclosures

Form 3454 is signed by Tina de Vries, Vice president, Clinical Pharmacology and is included in the NDA submission. All investigators who participated in Studies PR-06011, PR-00810 and PR-00910 certified to having no financial interest in these studies. Therefore, a financial disclosure is not applicable.

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Chemistry Manufacturing and Controls

On 2-11-13 the Applicant amended the application to include information regarding product photostability. Report DP-31277 titled "Technical Report for WC3042 Photostability Studies" was added to NDA Module 3 Section 3.2.P.8.1. The report concludes that WC3042-05 capsules presented in primary packaging and tested under ICH photostability conditions showed a significant decrease in the assay of norethindrone acetate.

Available stability data generated under ICH long term stability conditions demonstrate that the product is stable. However, to ensure product protection from further exposure to light, the Applicant proposed to add an additional carton to the product packaging and additional storage instructions to the labeling. Section 1.14.1 was modified to include an additional cardboard carton and to include instructions to the patient to store the product in the wallet.

The FDA chemists Yichun Sun, PhD, and Donna Christner, PhD, reviewed the data and concluded on 3-7-13 from the ONDQA perspective that:

“The applicant of this NDA has provided sufficient CMC information to assure the identity, strength, purity, and quality of the drug product.”

4.2 Clinical Microbiology

There is no clinical microbiology report.

4.3 Preclinical Pharmacology/Toxicology

The preclinical review was done by Krishan Raheja, PhD, and completed on 11-23-12. He states: “No new nonclinical data was submitted and pharmacology and toxicology is referenced to sponsor’s approved NDA 21-871. Moreover, it is stated that both NA and EE are synthetic hormones which are widely used as components of both combined oral contraceptives (COCs) and hormone replacement therapy. Also daily doses of NA and EE proposed under present application are found in currently approved COCs. The inactive ingredients used in active capsules and in the ferrous fumarate capsules are compendial and are listed in the FDA’s Inactive Ingredients Database.” His recommendation is approval of NDA 204426 as a combination hormonal contraceptive for the prevention of pregnancy.

Reviewer’s comment:

I concur with his recommendation.

4.4 Clinical Pharmacology

The Application contains results of Study PR-00810 (Report RR-06511) which show that WC3042-05 capsules are bioequivalent to Loestrin 24 Fe tablets. Results of Study PR-06011 (Report RR-04012) indicate that WC3042-05 capsules can be taken without regard to meals. These 2 studies (i.e., Studies PR-00810 and PR-06011) were conducted with the to-be-marketed (TBM) formulation. One additional Clinical Pharmacology study, Study PR-00910 (relative bioavailability [BA] study), was conducted using a non-TBM formulation and it was not reviewed.

4.4.1 Mechanism of Action

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

4.4.2 Pharmacodynamics

No specific pharmacodynamic studies were conducted with the soft gel capsule.

4.4.3 Pharmacokinetics

In Study PR-00810 it was shown that the TBM capsules are bioequivalent to Loestrin 24 Fe tablets. The proposed regimen is the same as the approved regimen for the Sponsor's Loestrin 24 Fe (NA/EE tablets and Fe tablets) which received approval as a CHC for the prevention of pregnancy on February 17, 2006 under NDA 021871.

Reviewer's comment:

On 1-10-13, the clinical pharmacology review was completed by Chongwoo Yu, PhD. His recommendation follows:

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

I concur with his recommendation.

5 Sources of Clinical Data

5.1 Tables of Studies/Clinical Trials

There were 3 bioavailability studies performed, but only the first two in the table below are directly applicable to this NDA and the to-be-marketed drug.

Table 1: Summary of Bioavailability Studies

Study No (Report No)	Study Objective	Study Design	Enrolled / Completed Age	Analyte/ Parameter	90% Confidence Interval	Conclusions
PR-00810 (RR-06511)	Comparative BA of WC3042 capsule (Formulation WC3042-05) and WC2061 tablet	Single-center, randomized, single-dose crossover	40 / 38 18-35 years (38 evaluable for PK analysis)	NE		WC3042 capsules (Formulation WC3042-05) are bioequivalent to WC2061 tablets. Single oral doses of WC3042 capsules were well tolerated.
				Cmax	99.95 - 114.88	
				AUC0-t1dc	87.38 - 94.94	
				AUCinf	87.62 - 95.25	
				EE		
				Cmax	86.76 - 96.96	
PR-06011 (RR-04012)	Effect of food on BA of WC3042 capsule (Formulation WC3042-05)	Single-center, randomized, single-dose crossover	26 / 25 24-45 years (24 evaluable for PK analysis)	NE		WC3042 capsules with food decreased the rate but not the extent of NE and EE absorption. WC3042 capsules may be taken with or without food.
				Cmax	53.85 - 79.28	
				AUC0-t1dc	108.75 - 120.81	
				AUCinf	109.28 - 121.11	
				EE		
				Cmax	57.52 - 76.80	
AUC0-t1dc	89.05 - 100.75					
AUCinf	91.73 - 108.34					

5.2 Review Strategy

Because this NDA is a request to approve a different formulation of an approved CHC product, the primary requirement is to demonstrate bioequivalence to the reference drug. Most important for the approval are the clinical pharmacology and CMC reviews. The clinical review will assess the safety data from the clinical pharmacology trials, postmarketing annual reports, and the medical literature. All disciplines will review the label to make sure it is complete and accurate.

5.3 Discussion of Individual Studies/Clinical Trials

There were two clinical pharmacologic studies that are critical to the approval of this NDA application.

1) Study PR-00810 was conducted to assess the comparative NA/EE bioavailability of a WC3042 capsule to that of a Loestrin 24 tablet in 40 healthy female volunteers (median age 30; range 18–35 years). This single-center, open-label, randomized, balanced, single-dose, 2-treatment, 2-period, 2-sequence, crossover, comparative bioavailability study was conducted under medical supervision. All subjects received the following Test and Reference treatments:

- Test: One WC3042 capsule (1.0 mg NA/0.020 mg EE, Formulation WC3042-05)
- Reference: One Loestrin 24 tablet (1.0 mg NA/0.020 mg EE)

All capsules/tablets were administered orally with about 240 mL ambient-temperature water. Treatment periods were separated by at least 14 days. Forty subjects were dosed; 38 subjects completed both treatment periods and were evaluable for pharmacokinetic analysis. WC3042 capsules (Formulation WC3042-05) are bioequivalent to Loestrin 24 tablets. Single oral doses of WC3042 capsules and Loestrin 24 tablets were well tolerated.

2) Study PR-06011 was conducted to assess the effect of food on NA/EE bioavailability following oral administration of a WC3042 capsule in 26 healthy female subjects (median age 36; range 24–45 years). This single-center, open-label, randomized, balanced, 2-treatment, 2-period, 2-sequence crossover food-effect study was conducted under medical supervision. All subjects received the following Test and Reference treatments:

- Test: One WC3042 capsule (1.0 mg NA/0.020 mg EE) under fed conditions
- Reference: One WC3042 capsule (1.0 mg NA/0.020 mg EE) under fasted conditions

All capsules were administered orally with 240 mL ambient-temperature water. Treatment periods were separated by at least 7 days. Twenty-six subjects were dosed; 25 completed both treatment periods, and 24 were evaluable for pharmacokinetic analysis.

Reviewer's comment:

For a detailed analysis of these two studies, see the Clinical Pharmacology review by Chongwoo Yu, PhD. Based on the overall clinical pharmacology information submitted to support the NDA submission, he recommends approval provided that a satisfactory agreement is reached regarding the labeling language. I concur with his recommendation.

Michael F. Skelly, PhD, Pharmacologist, Bioequivalence Branch, Division of Bioequivalence and GLP Compliance (DBGC), FDA Office of Scientific Investigations conducted inspections for bioavailability Study PR-00810. The Clinical Site was in Mount Royal, Canada and the Analytical Site was in (b) (4). His brief report concluded that the PK data from Study PR-00810, Project UA253 are acceptable for review.

6 Review of Efficacy

Efficacy Summary

The efficacy of the approved reference drug product Loestrin 24 Fe is well established. Because the capsule has been shown to be bioequivalent to Loestrin 24 Fe, it is reasonable to assume that the efficacy of the new formulation with the soft gel capsule using the exact same dosing regimen will have acceptable efficacy. The Division did not recommend that a separate clinical trial for efficacy was needed and one was not done.

In the Loestrin 24 Fe clinical study submitted in the NDA 21-871, 743 women, 18 to 45 years of age, were treated with Loestrin 24 Fe for up to six 28-day cycles providing a total of 3,823 treatment-cycles of exposure. A total of 583 women completed 6 cycles of treatment. There were a total of 5 on-treatment pregnancies in 3,565 treatment cycles during which no backup contraception was used. The Pearl Index for Loestrin 24 Fe was 1.82 (0.59, 4.25) for all ages and 1.79 (0.49, 4.57) for 579 women age 18-35.

Whether the compliance will be better with this new formulation remains to be shown, but the contraceptive effectiveness should be at as good as the approved Loestrin 24 Fe oral tablet, assuming that the new formulation, Minastrin 24 Fe, is taken as directed.

6.1 Indication

Minastrin 24 Fe is indicated for the prevention of pregnancy in women of reproductive age.

6.1.1 Methods

A clinical trial for contraceptive efficacy was not required for this NDA application. Efficacy is based on the 2-17-06 approval for NDA 21-871, the original Loestrin 24 Fe 28-day oral tablets. Summary details are stated in the Efficacy Summary above.

7 Review of Safety

Safety Summary

As demonstrated by the 2 pharmacology studies in this NDA submission, the WC3042 capsules are bioequivalent to Loestrin 24. Therefore, the systemic safety profile of the WC3042 product is presumed to be equivalent to that of the approved reference drug product, Loestrin 24 Fe.

Safety information from an additional study using an alternate formulation of the WC3042 capsule (Formulation WC3042^{(b)(4)}), for which approval is not sought, is included in this NDA submission and showed no safety concerns.

The overall nature and frequency of adverse events seen were consistent with what would be expected in subjects receiving orally administered norethindrone acetate (NA) and ethinyl estradiol (EE). No serious adverse events were noted in these studies. The study drug WC3042 capsules were generally well tolerated.

Although the number of women exposed to the new capsule formulation for this product was small, CHCs containing norethindrone and ethinyl estradiol have been marketed since 1976. Extensive systemic safety data is available for the specific combination of NE 0.4 mg and EE 0.035 mg and for several products with higher amounts of NE (0.5 to 1.0 mg) and the same, lower or higher amounts of EE (0.010 to 0.050 mg). **The subject exposure to the new capsule formulation is adequate under these circumstances.**

7.1 Methods

7.1.1 Studies/Clinical Trials Used to Evaluate Safety

Two clinical pharmacology studies submitted with the NDA were used to assess safety for the proposed formulation. A total of 66 women were exposed to the new soft gel capsule formulation of Minastrin 24 Fe tablets in the two single-dose crossover studies.

7.1.2 Categorization of Adverse Events

Mild adverse events were reported: most common were nausea, headache, acne, venipuncture reactions, and abdominal pain. There were no serious adverse events or deaths. Vital signs were stable. ECG measurements were within normal limits.

7.1.3 Pooling of Data Across Studies/Clinical Trials to Estimate and Compare Incidence

This was not done and would not be meaningful because of the small number of subjects and the very limited exposure to the study drug in the short clinical pharmacology trials.

7.2 Adequacy of Safety Assessments

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

The overall exposure is adequate because of the extensive use of the same product marketed as an oral tablet and very similar oral combination hormonal contraceptive products over the past 45 years.

7.2.2 Explorations for Dose Response

None were performed or required.

7.2.3 Special Animal and/or In Vitro Testing

None were performed or required.

7.2.4 Routine Clinical Testing

All that was necessary for this NDA submission was the bioavailability (bioequivalence) study that was performed according to GCP (Good Clinical Practice) guidelines.

7.2.5 Metabolic, Clearance, and Interaction Workup

None were performed or required.

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

None were required or needed. As noted, there is extensive safety data for the combined use of norethindrone and ethinyl estradiol.

7.3 Major Safety Results

7.3.1 Deaths

There were no deaths in the studies submitted with this NDA.

7.3.2 Nonfatal Serious Adverse Events

The two studies (bioavailability and food effect) were not of sufficient size or duration to have any meaningful data for adverse events. Severity and causality of adverse events was analyzed by the Applicant.

Reviewer's comment:

I concur with the Applicant's conclusion that: "The overall nature and frequency of AEs seen in the studies were consistent with what would be expected in subjects receiving orally administered NA and EE. No serious AEs were noted. WC3042 capsules administered with food or fasted were generally well tolerated."

7.3.3 Dropouts and/or Discontinuations

With a combined total of 66 (40 + 26) subjects, 62 (38 + 24) were evaluable for the intended data. Dropouts and discontinuations were for minor reasons.

7.3.4 Significant Adverse Events

There were none in the two studies.

7.3.5 Submission Specific Primary Safety Concerns

There were none in the two studies.

7.4 Supportive Safety Results

The Applicant submitted the following documents as supportive safety results:

1. The 120-day safety update [Safety Information Amendment] was submitted to the NDA on October 1, 2012. No new significant information is reported that may reasonably affect the statement of Contraindications, Warnings and Precautions, and Adverse Reactions in the proposed labeling.
2. The NDA 21871 most recent annual report submitted on April 13, 2012 covering the reporting period through February 2012. NDA 204426 cross-references Warner Chilcott's NDA 21871 for Loestrin 24 Fe in support of the safety and efficacy of norethindrone acetate (NA) and ethinyl estradiol (EE).
3. A review of the literature on NA and EE through September 15, 2012; relevant abstracts of the clinical literature are provided in NDA Section 5.4 Literature References.
4. An updated 51-page summary of Loestrin 24 Fe's postmarketing safety data from February 17, 2006 (NDA 21-871 approval date) through September 26, 2012.

Reviewer's comment:

The above documents were reviewed and show no new significant safety signals or concerns. There is no marketing of the soft gelatin capsules outside of the US. There were no nonclinical or clinical studies conducted with WC3042 at the time of the submission and no nonclinical studies have been subsequently started.

A phase 1 clinical study, Study PR-03412.0, "A study to assess the comparative bioavailability of norethindrone acetate and ethinyl estradiol from WC3042 capsules in healthy female volunteers", was initiated in September 2012 under IND 109525 to assess the comparative bioavailability of EE and norethindrone (NE) when WC3042-05 capsules

are swallowed or chewed followed with liquid. The study is still being conducted and no results are available at this time.

7.4.1 Common Adverse Events

These are expected to be the same for the soft gelatin capsule as the reference drug. Therefore, the approved label will mirror the Loestrin 24 Fe label.

7.4.2 Laboratory Findings

Two subjects had 5 out-of-range clinical laboratory values that were deemed clinically abnormal by the investigator and were also reported as AEs. Subject 505214 had increased lactic dehydrogenase (LDH), aspartate aminotransferase (AST), alanine aminotransferase (ALT), and gamma-glutamyl transpetidase (GGT) at 60 hours post-dose (end of period 2, placebo treatment). Subject 505222 had decreased hemoglobin at 60 hours post-dose (end of period 2, placebo treatment). All 5 values were just slightly outside the normal range.

Reviewer's comment:

Both subjects were lost to follow-up. However, the abnormal lab values were just outside the normal ranges and I do not believe they were clinically significant.

7.4.3 Vital Signs

Physical examinations were performed at Screening and study final assessment visit; vital sign measurements were performed at Screening, at pre-dose of each treatment period, and at the study final assessment visit. Results from all physical and vital sign measurements were judged to be within normal limits or not clinically significant.

7.4.4 Electrocardiograms (ECGs)

Results from the screening 12-lead ECG measurements were within normal limits in Study PR-06011.

7.4.5 Special Safety Studies/Clinical Trials

There were none.

7.4.6 Immunogenicity

There are no issues or data on this topic.

7.5 Other Safety Explorations

Reviewer's comment:

There were no other safety explorations to note in this section of the NDA review.

7.5.1 Dose Dependency for Adverse Events

This section is not applicable.

7.5.2 Time Dependency for Adverse Events

This section is not applicable.

7.5.3 Drug-Demographic Interactions

There were none.

7.5.4 Drug-Disease Interactions

There were none.

7.5.5 Drug-Drug Interactions

There were no specific DDI studies or data presented with this NDA.

7.6 Additional Safety Evaluations

Reviewer's comment:

There were no other safety explorations to note in this section of the NDA review.

7.6.1 Human Carcinogenicity

No new or special data were submitted. Class labeling for CHCs has a short section on this topic.

7.6.2 Human Reproduction and Pregnancy Data

See the class label section of the final label for this product. No new data are presented.

7.6.3 Pediatrics and Assessment of Effects on Growth

None was required or performed.

7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound

See the approved label for overdose information.

7.7 Additional Submissions / Safety Issues

Reviewer's comment:

There were no other safety submissions or issues to note in this section of the NDA review.

8 Postmarket Experience

There has been extensive postmarketing experience with the same CHC product (Loestrin 24) since its approval in 2006 and with various combinations of NA/EE since 1975 (over 37 years ago).

9 Appendices

9.1 Literature Review/References

Review of the medical literature for NA/EE combination hormonal contraceptives shows a well established safety and efficacy profile. There are no major issues with this combination of norethindrone acetate and ethinyl estradiol when used by women of reproductive age for the prevention of pregnancy.

9.2 Labeling Recommendations

After labeling negotiations were completed, there are no further labeling recommendations. The new PLR format is used for the label.

The Applicant added to the blister pack labels and the carton labeling, as well as section 16.2 Storage Conditions of the insert labeling, the following statement: "Protect from light. Store blister card in wallet when not in use".

Manizheh Siahpoushan, PharmD, Safety Evaluator in the Division of Medication Error Prevention and Analysis (DMEPA, Office of Medication Error Prevention and Risk Management, Office of Surveillance and Epidemiology) stated the following in her review:

Pending CMC review of the submission and the acceptability of this change in the storage proposal, DMEPA finds the addition acceptable. However, the Applicant did not include this language in the Patient Labeling. If found to be acceptable by CMC, this statement or a similar one should also be included in the Patient Labeling, ideally under a section titled "How do I store my Minastrin 24 Fe?"

Reviewer's comment:

There were no major labeling issues. I agree with reviewer Siahpoushan concerning the addition of the language for storage of the product when not in use. Use of the PLR format will be helpful for both the healthcare provider who prescribes the product as well as the consumer who will use of product.

9.3 Advisory Committee Meeting

There was no need for an Advisory Committee meeting for this bioequivalent product that can be taken without regard to food.

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/s/

DANIEL DAVIS
03/25/2013
Primary clinical review

CHRISTINA Y CHANG
03/25/2013

CLINICAL FILING CHECKLIST FOR A NEW NDA/BLA

	Content Parameter	Yes	No	NA	Comment
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 needed 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 (<i>e.g.</i> , 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.
21.	For chronically administered drugs, have an adequate number of patients (based on ICH guidelines for exposure ²) been exposed at the dose (or dose range) believed to be efficacious?			X	Not needed because this is only a change in dosage from to an approved drug.
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 sponsor submitted the coding dictionary ³ used for mapping investigator verbatim terms to preferred terms?			X	
24.	Has the sponsor 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	The complete study reports contain sufficient safety data.
OTHER STUDIES					
26.	Has the applicant submitted all special studies/data requested by the Division during the pre-submission discussions with the sponsor?			X	Bioequivalence and food effect reports are submitted.
27.	For Rx-to-OTC switch and direct-to-OTC applications, are the necessary consumer behavioral studies included (<i>e.g.</i> , label comprehension, self selection and/or actual use)?			X	

² 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.

³ 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).

CLINICAL FILING CHECKLIST FOR A NEW NDA/BLA

	Content Parameter	Yes	No	NA	Comment
PEDIATRIC USE					
28.	Has the applicant submitted the pediatric assessment, or provided documentation for a waiver and/or deferral?	X			A full waiver is requested.
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 efficacy data are needed for this NDA.
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			
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			See the study reports.
CONCLUSION					
40.	From a clinical perspective, is this application fileable? If not, please state why.	X			

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter. **There are none.**

Daniel Davis, MD

8-16-12

Reviewing Medical Officer

Date

Lisa Soule, MD

8-16-12

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/

DANIEL DAVIS
08/16/2012
Clinical filing review.

LISA M SOULE
08/16/2012
I concur that NDA 204-426 is fileable.