CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-840

CROSS DISCIPLINE TEAM LEADER REVIEW

Group Leader Memorandum
SEASONIQUE™

NDA:	**21-840**
Drug:	**SEASONIQUE™**
Dosage Form/Route:	**Tablet/Oral**
Strength:	**0.15 mg levonorgestrel/ 0.030 mg ethinyl estradiol - Days 1-84** **0.01 mg ethinyl estradiol -Days 85 - 91**
Applicant:	**Duramed Pharmaceuticals, Inc.**
Original Submission Date:	**October 21, 2004**
Medical Officer Completion Date:	**August 16, 2005**
Date of Memorandum:	**August 17, 2005**

Background and Regulatory History

In this application, the Sponsor is seeking approval for a 91-day extended cycle regimen of an oral contraceptive combination of levonorgestrel (LVG) and ethinyl estradiol (EE). This is the 2nd extended cycle regimen drug product that is sought by the Sponsor. The first formulation, SEASONALE®, received approval on September 5, 2003. The formulations for SEASONIQUE™ and SEASONALE® are identical for Days 1-84 (the active therapy days); both formulations employ 0.15 mg of LNG in combination with 0.03 mg of ethinyl estradiol. With SEASONIQUE™ the Sponsor has replaced the placebo tablets, in the SEASONALE® formulation, with 0.010 mg of ethinyl estradiol for days 85-91. The Sponsor [redacted]

Drug development for SEASONALE® was first discussed in a pre-IND meeting for this product held on November 2, 1999. At that meeting the Division of Reproductive and Urologic Drug Products (DRUDP) recommended a direct head-to-head comparative trial of SEASONALE® vs. an approved 28-day regimen with the same LNG and EE combination as in SEASONALE®. Following the initial pre-IND discussions, a teleconference was held with the Sponsor to relay the Division's expectation that SEASONALE® would show some clinical advantage over the conventional 28-day regimen in addition to comparable effectiveness. Study SEA-301 and SEA-301 A were submitted to IND 60, 399 on May 16, 2000 and August 9, 2001, respectively. Study

SEA-301, the primary study, was an open-labeled, four-arm, parallel, randomized, multicenter comparator trial of Seasonal, Nordette and Levlite. [redacted] NDA 21-544 for SEASONALE® was submitted on August 05, 2002. FDA review of Study SEA-301 found a Pearl Index (PI) of 1.98 (95%, CI 0.54, 5.03) compared to a PI of 2.22 and 3.75, for the approved products Nordette and Levlite, respectively. No new or unexpected serious safety concerns were demonstrated in the clinical studies. The review determined that 9-16% of SEASONALE® users in each 91-day cycle experienced amenorrhea for the 84 day active therapy period and for **this** small group "SEASONALE® had the intended effect of decreasing the frequency of bleeding." The review concluded that while users of SEASONALE® had more unanticipated bleeding and spotting than a 28-day cycle combination regimen utilizing the same dose of hormones, this bleeding and spotting did not present safety concerns. However, concern was expressed that "this bleeding and spotting could present quality of life issues for some patients leading to discontinuation of the drug product." Despite this concern of the primary reviewer, approval was recommended for NDA 21-554 and granted on September 05, 2003.

On October 12, 2001 Barr submitted to the SEASONALE® IND (IND 60, 399) questions regarding the DP3 regimens [DP3-84/10 (SEASONIQUE™) and DP3-84/30]. The two questions were related to total number of subjects in two proposed studies (Studies PSE 301 and PSE 302) to support an NDA and the design of the second study to collect endometrial biopsy data. The Division's (DRUDP) position was that it was premature for the Division to enter into any agreements and that the Sponsor should submit to a new IND, the rationale for proposing the number of patients to be studied and the need for designing a separate trial to provide endometrial biopsy data.

IND 63, 735 was submitted November 30, 2001 with protocols for Studies PSE 301 and PSE 302. The studies were allowed to proceed and 25 clinical comments were sent to the Sponsor. Among them were request to clarify if labeling or advertising claims other that the indication of prevention of pregnancy were anticipated for the DP3 dosing regimen based on Studies PSE 301 and PSE 302. Further the Sponsor was advised that Studies PSE 301 and PSE 302 would not support labeling or advertising claims regarding the clinical significance of the unique DP3 dosing regimen as compared to conventional dosing regimen.

A pre-NDA meeting was held with Barr/Duramed on August 30, 2004. Leading the discussion for DRUDP was Scott Monroe, MD. Discussion and decisions at the pre-NDA were as follows:

- The Division has no objection to your plan to file an NDA for the DP3dosing regimen containing 0.01 mg EE. The Division assumes that approval for pregnancy prevention will be sought only for this dose and that data from 0.03 mg EE arm of the Phase 3 protocols will be submitted only to support the safety of 0.01 mg EE dosage for this indication.
- We also assume that trials PSE-301 and PSE-302 will be used to support a single indication of prevention of pregnancy. Based on our understanding of the designs of the clinical trials, they would not support labeling or advertising claims regarding the clinical significance of the 7 days of additional ethinyl estradiol.
- The Division is particularly interested in the Sponsor including the additional analyses related to total days of bleeding and unexpected bleeding (with SEASONIQUE™) that were requested and provided to the Division during the review of SEASONALE®.

NDA 21-840 for SEASONIQUE™ was submitted by Duramed on October 21, 2005. It was administratively filed on December 14, 2005. In the 74 day letter to the Sponsor, which is sent to notify the Sponsor of any noted or potential deficiencies, the Division stated "Given the known risks associated with exogenous estrogen use in combined oral contraceptives for women of reproductive age, the Division will be looking very carefully to evaluate whether the addition of 10 micrograms per day of ethinyl estradiol for the seven days of the previous hormone free period of a 91-day regimen (SEASONALE®) provides sufficient clinical benefit to the patient using SEASONIQUE™ to justify risk."

Clinical

Clinical Efficacy

Two one-year, Phase 3, randomized, multicenter, open-labeled studies were submitted to support the efficacy and safety of SEASONIQUE™. Study PSE-301 was the primary study. For this study, 2, 049 subjects were randomized to received either DP3-84/10 (SEASONIQUE™; 1, 025 women randomized) or DP3-84/30 (1, 024 women randomized). No regulatory claims are being sought for DP3-84/30 based on this application. Of the 1,025 women randomized SEASONIQUE™, 1,013 took the study drug. Of the 1,013 women who took SEASONIQUE™, 534 or 52.7 % discontinued the study. Adverse events (19.7) and lost-to-follow-up (14.7%) were the primary reasons for discontinuation.

Contraceptive efficacy was the primary efficacy variable studied and was evaluated from the overall pregnancy rate for "On-treatment" pregnancies as assessed by the Pearl Index and life table cumulative (6-cycle) probability of pregnancy. "On-treatment" pregnancies

were those pregnancies for which the date of conception was determined to be on or after the first date of taking study medication but not more than 14 days after the date of the last dose of the active treatment pills (e.g. day 84 dose of the LNG/EE in the SEASONIQUE™ regimen). Any pregnancy that occurred during a partially completed cycle (i.e., before cycle day 84 for DP3-84/10 and DP3-84/30, before cycle day 25 for DP3-25/30, or before cycle day 21 for Nordette) was included in the Pearl Index calculation and the cycle in which the pregnancy occurred was considered a complete cycle. For the 91-day extended oral contraceptive (OC) regimen groups (DP3-84/30 and DP3-84/10), the formula for the Pearl Index is:

(100) x (number of pregnancies) x (4 cycles/year) ÷ (number of cycles completed).

The calculation of efficacy is based on completed cycles for women in the 18-35 year age range and excludes cycles where other birth control methods were utilized. One thousand five hundred seventy seven (1,577) 91-day cycles (equivalent to 5,125 28-day cycles) were analyzed. The applicant noted five "on-treatment pregnancies yielding a Pearl Index of 1.27. The Medical Officer's review noted two additional "on-treatment" pregnancies for a total of seven such pregnancies. The Pearl Index for SEASONIQUE™as calculated by the FDA statistician, based on seven "on-treatment" pregnancies, was determined to be 1.77 (95% CI 0.71,3.64).

Study PSE-302 was a randomized, multicenter, open-label, Phase 3 clinical trial conducted to provide supportive information on safety, including endometrial safety data, and efficacy. For this study, 380 subjects were randomized to received either DP3-84/10 (SEASONIQUE™; 95 subjects randomized), DP3-84/30 (96 subjects randomized), DP3 25/30 (94 subjects randomized) or Nordette® (95 subjects randomized). No regulatory claims are being sought for DP3-84/30 or DP3 25/30 based on this application. All of the 95 women randomized to SEASONIQUE™took the study drug. In this smaller study 51.6% (n=49) of the women who received SEASONIQUE™discontinued the study. Lost-to-follow-up (20.1%) was the primary reason for discontinuation.

One hundred Sixty Six (166) 91-day cycles (equivalent to 497 28-day cycles) were analyzed. One "on-treatment pregnancy" yielding a Pearl Index of 2.41 was obtained for SEASONIQUE™. The Medical Officer's review noted two additional "on-treatment" pregnancies for a total of seven such pregnancies. The corresponding values for DP3 84/30 were 153 cycles and Pearl Index of 2.61 and for DP3 25/30, 606 cycles and Pearl Index of 0. However, the clinical reviewing team notes that there were too few completed cycles to calculate accurate Pearl Indices for any of the drug products in this study.

The overall opinion of the clinical reviewing team is that SEASONIQUE™is efficacious for pregnancy prevention.

___1___ Page(s) Withheld

___X___ Trade Secret / Confidential

_____ Draft Labeling

_____ Deliberative Process

Clinical Safety

Two open-labeled controlled clinical trials and three bioavailability studies form the safety database that is included in the Sponsor's Integrated Summary of Safety. Sixty subjects (60) were treated with SEASONIQUE™ or its equivalent in the clinical pharmacology studies. The All-Subjects-Treated pooled safety data for Studies PSE 301 and PSE 302 include 1,101 subjects (with 14,526 cycles of exposure) treated with SEASONIQUE™ in these controlled clinical trials. For the two 12 month duration trials, 546 or 49.6% of the women completed the studies. There were no deaths in SEASONIQUE™-treated subjects. There were no myocardial infarctions, strokes or venous thromboembolic events. Twenty-five (25) subjects treated with SEASONIQUE™ reported one or more serious adverse events (SAE). The Medical Officer concluded that no new signals for unexpected serious adverse events were discovered in these trials for the use of SEASONIQUE™.

Across both studies, 6.3% of subjects discontinued the study due, at least in part, to bleeding and or spotting. This 6.3% may be a somewhat underestimation as PSE 302 was much smaller than PSE 301. Of the 6.3% who discontinued due to bleeding and or spotting, 3.27% withdrew for intermenstrual bleeding, 2.63 % for menorrhagia and 0.09% for irregular menstruation. The most common adverse event was intermenstrual bleeding occurring in 11.44% of subjects. Nasopharyngitis occurred in 7.27% of subjects.

5. Acceptable dissolution criteria for both drug substances (LVG and EE) should be finalized.

Items 1 through 3 and 5 were satisfactorily addressed. Labeling will not be addressed (see below).

From a Chemistry, Manufacturing and Controls standpoint, this NDA is approvable pending the resolution of final labeling.

Product Name

The proprietary name SEASONIQUE™ was found to be unacceptable by DMETS. The Division has no objection to the name.

Preclinical Pharmacology and Toxicology

The Pharmacology reviewer recommended approval of SEASONIQUE™ based on the previous approval of SEASONALE® as well as use of both active ingredients at doses equal or higher in other approved formulations for the same indication.

Biopharmaceutics

In support of the application for SEASONIQUE™ approval, the Sponsor submitted three bioavailability/bioequivalence studies. Study 10216207 was a multiple dose 91 day pharmacokinetic safety study in 30 subjects with DP-3 (0.15 mg LNG/0.030 mg EE for 84 days and 0.03 mg EE for 7 days. The study confirmed that increasing the duration of uninterrupted combination oral contraceptive treatment from the conventional 21 days to 84 days did not result in any further accumulation of drug.

Study 10416204 was a single dose crossover BE study in 30 subjects to test the blue combination LNG/EE SEASONIQUE™ tablet to-be-marketed formulation to the white combination LNG/EE SEASONIQUE™ clinical trial tablet formulation. The results of the study demonstrated that the color of the film coating did not affect the rate and the extent of LNG and EE absorption.

Study R00-570 was a single dose crossover relative BA study in 18 subjects under fasting conditions to test that the 0.03 mg EE yellow clinical trial formulation was BE to an equal does of an EE containing oral solution. The 90% confidence intervals about the ratio of the geometrics means for C_{max}, AUC_{0-t} and AUC_{inf} were within the 80% -125% limits concluding that EE 0.03 mg tablets is bioequivalent to the EE oral solution under fasting conditions.

The Sponsor has not performed formal exposure response relationships, drug-drug interaction, food-drug interaction or special population (hepatic and renal-impaired individuals) studies. The lack of data in hepatic and renal impaired individuals as well as the lack of drug-drug interaction studies could be addressed in the label.

Based on review of submitted data, the Office of Clinical Pharmacology and Biopharmaceutics found the Human Pharmacokinetic Section of NDA 21-840 to be acceptable.

Conclusions and Recommendations

SEASONALE®™ is the only approved extended cycle oral contraceptive. The Sponsor, Duramed/Barr received approval to market this drug product on September 5, 2003. Despite the intended purpose of the extended cycle SEASONALE® regimen to provide women with fewer days of bleeding compared to a conventional 28-day regimen when assessed over a year of use, only 9-16% of SEASONALE® users in each 91-day cycle experienced amenorrhea for the 84 day active therapy period. The Applicant for SEASONIQUE™ (Duramed) asserts, in the NDA and in correspondence made during the NDA reviewing period, that SEASONIQUE™ [redacted] relative to the previously approved product, SEASONALE®, which has no active drug product during the 85-91 day "hormone-free" interval.

The focus of the review for this reviewer was to evaluate whether there was sufficient data provided in the NDA to support a benefit for the 0.010 mg of ethinyl estradiol added in SEASONIQUE™ for days 85-91 of the contraceptive regimen that in the SEASONALE® regimen is represented by placebo pills. The submitted clinical trials (PSE-301 and PSE 302) for efficacy and safety did not include a SEASONALE® treatment arm; therefore, no direct comparative data was obtained in these studies to support the benefit of SEASONIQUE™ over the previously approved product.

The primary efficacy information for SEASONIQUE™ was from Study PSE-301. The active drug product combination in SEASONIQUE™ is identical to that of SEASONALE®, therefore, it was anticipated that SEASONIQUE™ would be efficacious and the Pearl Index of 1.77 for SEASONIQUE™ is acceptable. Because no SEASONALE® arm was included in Study SEA-301 one can not make a direct comparison [redacted] SEASONIQUE™ [redacted] than does SEASONALE®. The only inferences that can be made are those that are based on cross study comparisons which are descriptive, can not be supported by statistical testing, and are inherently biased due to different study conditions. That said, the Pearl Index for SEASONIQUE™ in Study PSE-301 of 1.77 appears numerically similar to the Pearl Index for SEASONALE® of 1.98 from Study SEA-301 in NDA 21-544. Of course, whether or not these numbers really represent a difference can not be determined as statistical testing can not be applied. However, the numbers suggest that there is no advantage for SEASONIQUE™ over SEASONALE® in terms of [redacted]. Whether or not one product offers an advantage over the other with respect to [redacted] is reasonably determined only in a direct comparison study that assesses what occurs (i.e. proportion of pregnancies) when subjects either miss or are late in taking day 1 of the active drug product combination for a new contraceptive cycle. [redacted]

The review of the safety database revealed no unanticipated serious adverse events during the maximum 1 year study duration. SEA-302 was a small study conducted primarily to obtain endometrial histology safety date on SEASONIQUE™. This study had additional treatment arms for DP3-84/30, DP3-25/30, and Nordette. Statistical comparisons between SEASONIQUE™ and these other treatment arms in this small study would not

be appropriate comparisons to support the benefit of the 0.010 mg of ethinyl estradiol for days 85-91 in the extended cycle SEASONIQUE™ contraceptive regimen. Nordette is an approved 28-day regimens. DP3-25/30 and DP3-84/30 are unapproved 28-day and 91 day (extended cycle) regimens, respectively.

The fixed combination drug product policy, §300.50, requires that each component make a contribution to the efficacy or safety of the combination drug product. Consistent with this, the clinical trial should demonstrate that the component adds to either efficacy or safety of the fixed combination drug product. Even though the component, ethinyl estradiol, is also one of the components in the active hormone phase of this product, I believe that the combination drug product policy requires that the addition of ethinyl estradiol to the phase of the regimen that was previously "hormone free" be supported by data demonstrating a contribution to either efficacy or safety of this extended cycle combination drug product. Even if there were no combination drug policy, scientific logic would argue that addition of an active hormone drug component to the portion of a regimen previously containing no hormone should be supported by data demonstrating a benefit.

This reviewer recommends that NDA 21-840 receive an Approvable action because the Sponsor has failed to demonstrate a need for the additional 10 micrograms of ethinyl estradiol for days 85-91 of the contraceptive regimen. Further, it is my determination that [redacted] demonstrated in the clinical trial for this product is unacceptable. I recommend that to support the additional estrogen, the Sponsor conduct a new randomized controlled comparative non-inferiority trial between SEASONIQUE™ and SEASONALE® to determine a whether or not a benefit exists for SEASONIQUE™with respect to [redacted]

Label

The recommendation is for an Approvable action. No labeling negotiations were held with the Sponsor

Shelley R. Slaughter, M.D, Ph.D.
Reproductive Medical Team Leader

cc: NDA 21-840,
HFD-580/D. Shames/S. Slaughter/R. Orleans/K. Kirchberg,

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

/s/

Shelley Slaughter
8/17/2005 01:25:03 PM
MEDICAL OFFICER

Appears This Way
On Original