CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-544

ADMINISTRATIVE DOCUMENTS

Time Sensitive Patent Information

Pursuant to 21 C.F.R. 314.53

The following is provided in accordance with the Drug Price Competition and Patent Term Restoration Act of 1984:

1. Trade Name: Seasonale®
2. Active Ingredient(s): Levonorgestrel and Ethinyl Estradiol
3. Strength(s): 0.15 mg/0.03 mg
4. Dosage Form: Tablets
5. Approval Date: N/A

This information should be provided for each individual patent submitted:

1. U.S. Patent Number: 5,898,032
2. Expiration Date: June 23, 2017
3. Type of Patent – Indicate all that apply:

☐ Drug Substance (Active Ingredient)	Y____	N__x_
☐ Drug Product (Composition/Formulation)	Y____	N__x_
✓ Method of Use	Y__x_	N____

If patent claims method(s) of use, please specify approved method(s) of use of method(s) of use for which approval is being sought that are covered by patent: For the Prevention on pregnancy

1. Name of Patent Owner: Medical College of Hampton Roads

U.S. Agent (if patent owner or applicant does not reside or have place of business in the US):
N/A

The following declaration statement is required by 21 CFR 314.53. If any of the submitted patents have Composition/Formulation or method of Use claims, it should be submitted for each patent that contains composition/formulation or method of use claims.

The undersigned declares that the above stated United States Patent Number 5,898,032 covers the composition, formulation, and/or method of use of Levonorgestrel and Ethinyl Estradiol Tablets, USP 0.15 mg/0.03 mg (name of drug product). This product is: Seasonale

- ☐ Currently approved under section 505 of the Federal Food, and Cosmetic Act.

  OR

- ✓ The subject of this application for which approval is being sought.

Signed: _____

Date: 7/12/2002

Title (optional): _____

Telephone Number (optional): _____

Abbreviated New Drug Application
Levia™ (levonorgestrel and ethinyl estradiol tablets, USP 0.1 mg/0.02 mg)
21 & 28 day Regimens

Section III. Patent Certification and Exclusivity Statement

1. Patent Certification Statement

Paragraph I Certification

In accordance with Section 505 (b)(2)(A) of the Federal Food, Drug and Cosmetic Act, Barr Laboratories, Inc., hereby certifies that in our opinion and to the best of our knowledge, there are no patents filed that claim **Levlite™** (levonorgestrel and ethinyl estradiol tablets, USP 0.1 mg/0.02 mg) 21 and 28 day regimens, **Nordette ™** (levonorgestrel and ethinyl estradiol tablets, USP 0.15 mg/0.03 mg) 21 and 28 day regimens or the drug substances that are components of the drug product on which investigations, relied upon for this application, were conducted or that claim an approved use of such drug.

2. Marketing Exclusivity Statement

According to the Approved Drug Products with Therapeutic Equivalence Evaluations, **Levlite™** (levonorgestrel and ethinyl estradiol tablets, USP 0.1 mg/0.02 mg) 21 and 28 day regimens and **Nordette ™** (levonorgestrel and ethinyl estradiol tablets, USP 0.15 mg/0.03 mg) 21 and 28 day regimens are not entitled to a period of marketing exclusivity under Section 505(j)(4)(D) of the Federal Food, Drug, and Cosmetic Act.

7/10/02
Date

Frederick J. Killion
Senior Vice President and General Counsel

16. Debarment Certification

Barr Laboratories, Inc. hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application.

This includes any person employed or contracted by Barr Laboratories, Inc. or any of its outside contractors, and clinical investigators for the following functions or services:

Christine Mundkur
Senior Vice President, Quality
and Regulatory Counsel

July 11, 2002
Date

EXCLUSIVITY SUMMARY for NDA # 21-544 SUPPL # _____

Trade Name Seasonale

Generic Name levonorgestrel & ethinyl estradiol

Applicant Name Barr Labs. HFD-580

Approval Date September 5, 2003

PART I: IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, but only for certain supplements. Complete Parts II and III of this Exclusivity Summary only if you answer "YES" to one or more of the following questions about the submission.

   a) Is it an original NDA? YES/_X__/ NO /___/

   b) Is it an effectiveness supplement? YES /___/ NO /__X_/

      If yes, what type(SE1, SE2, etc.)?

   c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "NO.")

      YES /_X__/ NO /___/

      If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

      If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

d) Did the applicant request exclusivity?

YES /_X_/NO /___/

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

3 years

e) Has pediatric exclusivity been granted for this Active Moiety? NA

YES /___/ NO /__X_/

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9.

2. Has a product with the same active ingredient(s), dosage form, strength, route of administration, and dosing schedule previously been approved by FDA for the same use? (Rx to OTC) Switches should be answered No - Please indicate as such).

YES /___/ NO /__X_/

If yes, NDA # _____ Drug Name

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9.

3. Is this drug product or indication a DESI upgrade?

YES /___/ NO /_X__/

IF THE ANSWER TO QUESTION 3 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9 (even if a study was required for the upgrade).

PART II: FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES
(Answer either #1 or #2, as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES /___/ NO /___/

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA #

NDA #

NDA #

2. Combination product.

If the product contains more than one active moiety (as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES /__X_/ NO /___/

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA # 18-668 and 18-782 Nordette 21 and Nordette 28

NDA # 20-860 Levlite

NDA # ANDA 75-866 Portia

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9. IF "YES," GO TO PART III.

PART III: THREE-YEAR EXCLUSIVITY FOR NDA'S AND SUPPLEMENTS

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2, was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

YES /_X__/ NO /___/

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as

bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

For the purposes of this section, studies comparing two products with the same ingredient(s) are considered to be bioavailability studies.

(a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES /_X__/ NO /___/

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval **AND GO DIRECTLY TO SIGNATURE BLOCK ON Page 9:**

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES /_X__/ NO /___/

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES /___/ NO /__X_/

If yes, explain:

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES /___/ NO /__X_/

If yes, explain:

(c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

Investigation #1, Study # SEA 301

Investigation #2, Study # SEA 301A (extension study)

Investigation #3, Study #

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

(a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1 YES /___/ NO /_X__/

Investigation #2 YES /___/ NO /__X_/

Investigation #3 YES /___/ NO /___/

If you have answered "yes" for one or more

investigations, identify each such investigation and the NDA in which each was relied upon:

NDA # _____ Study #
NDA # _____ Study #
NDA # _____ Study #

(b) For each investigation identified as "essential to the approval," does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1 YES /___/ NO /_X_/

Investigation #2 YES /___/ NO /__X_/

Investigation #3 YES /___/ NO /___/

If you have answered "yes" for one or more investigations, identify the NDA in which a similar investigation was relied on:

NDA # _____ Study #

NDA # _____ Study #

NDA # _____ Study #

(c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

Investigation #1, Study # SEA 301

Investigation #2, Study # SEA 301A (extension study)

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided

substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

(a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1	
IND # 60,399 YES /_X__/	NO /___/ Explain:
Investigation #2	
IND # 60,399 YES /_X_/	NO /___/ Explain:

(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

Investigation #1	
YES /___/ Explain _____	NO /___/ Explain _____
_____	_____
_____	_____
Investigation #2	
YES /___/ Explain _____	NO /___/ Explain _____
_____	_____

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES /___/ NO /_X_/

If yes, explain: _____

_____

_____

Preparer: Karen Anderson Date 9.05.03
Title: Project Manager

Signature of Office or Division Director Date

See electronic signature page

cc:
Archival NDA
HFD- /Division File
HFD- /RPM
HFD-610/Mary Ann Holovac
HFD-104/PEDS/T.Crescenzi

Form OGD-011347
Revised 8/7/95; edited 8/8/95; revised 8/25/98, edited 3/6/00

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

/s/

Donna Griebel
9/5/03 02:36:17 PM

PEDIATRIC PAGE

(Complete for all APPROVED original applications and efficacy supplements)

NDA/BLA # : 21-544 Supplement Type (e.g. SE5): Supplement Number:

Stamp Date: August 5, 2002 Action Date: September 5, 2003

HFD- 580 Trade and generic names/dosage form: Seasonale (levonorgestrel/ethinyl estradiol) Tablets

Applicant: Barr Laboratories Therapeutic Class: 3S

Indication(s) previously approved:

Each approved indication must have pediatric studies: Completed, Deferred, and/or Waived.

Number of indications for this application(s):1

Indication #1: Decrease risk of pregnancy - contraception

Is there a full waiver for this indication (check one)?

X - Yes: Please proceed to Section A.

☐ No: Please check all that apply: ____Partial Waiver ____Deferred ____Completed
NOTE: More than one may apply
Please proceed to Section B, Section C, and/or Section D and complete as necessary.

Section A: Fully Waived Studies

Reason(s) for full waiver:

☐ Products in this class for this indication have been studied/labeled for pediatric population
X Disease/condition does not exist in children
☐ Too few children with disease to study
☐ There are safety concerns
☐ Other:_____

If studies are fully waived, then pediatric information is complete for this indication. If there is another indication, please see Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section B: Partially Waived Studies

Age/weight range being partially waived:

Min____ kg____ mo.____ yr.____ Tanner Stage____
Max____ kg____ mo.____ yr.____ Tanner Stage____

Reason(s) for partial waiver:

☐ Products in this class for this indication have been studied/labeled for pediatric population
☐ Disease/condition does not exist in children
☐ Too few children with disease to study
☐ There are safety concerns
☐ Adult studies ready for approval
☐ Formulation needed
☐ Other:_____

If studies are deferred, proceed to Section C. If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section C: Deferred Studies

Age/weight range being deferred:

Min ____ kg____ mo.____ yr.____ Tanner Stage_____
Max____ kg____ mo.____ yr.____ Tanner Stage_____

Reason(s) for deferral:

- ☐ **Products in this class for this indication have been studied/labeled for pediatric population**
- ☐ **Disease/condition does not exist in children**
- ☐ **Too few children with disease to study**
- ☐ **There are safety concerns**
- ☐ **Adult studies ready for approval**
- ☐ **Formulation needed**

Other:_____

Date studies are due (mm/dd/yy): _____

If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section D: Completed Studies

Age/weight range of completed studies:

Min ____ kg____ mo.____ yr.____ Tanner Stage_____
Max____ kg____ mo.____ yr.____ Tanner Stage_____

Comments:

If there are additional indications, please proceed to Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.

This page was completed by:

{See appended electronic signature page}

_____
Regulatory Project Manager

cc: NDA
HFD-950/ Terrie Crescenzi
HFD-960/ Grace Carmouze
(revised 9-24-02)

FOR QUESTIONS ON COMPLETING THIS FORM CONTACT, PEDIATRIC TEAM, HFD-960
301-594-7337

Attachment A
(This attachment is to be completed for those applications with multiple indications only.)

Indication #2: _____

Is there a full waiver for this indication (check one)?

- ☐ **Yes: Please proceed to Section A.**

- ☐ **No: Please check all that apply: ____Partial Waiver ____Deferred ____Completed**
  NOTE: More than one may apply
  Please proceed to Section B, Section C, and/or Section D and complete as necessary.

Section A: Fully Waived Studies

Reason(s) for full waiver:

- ☐ **Products in this class for this indication have been studied/labeled for pediatric population**
- ☐ **Disease/condition does not exist in children**
- ☐ **Too few children with disease to study**
- ☐ **There are safety concerns**
- ☐ **Other:**_____

studies are fully waived, then pediatric information is complete for this indication. If there is another indication, please see Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section B: Partially Waived Studies

Age/weight range being partially waived:

Min ____	**kg**____	**mo.**____	**yr.**____	**Tanner Stage**____
Max____	**kg**____	**mo.**____	**yr.**____	**Tanner Stage**____

Reason(s) for partial waiver:

- ☐ **Products in this class for this indication have been studied/labeled for pediatric population**
- ☐ **Disease/condition does not exist in children**
- ☐ **Too few children with disease to study**
- ☐ **There are safety concerns**
- ☐ **Adult studies ready for approval**
- ☐ **Formulation needed**
- ☐ **Other:**_____

If studies are deferred, proceed to Section C. If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section C: Deferred Studies

Age/weight range being deferred:

Min____ kg____ mo.____ yr.____ Tanner Stage_____
Max____ kg____ mo.____ yr.____ Tanner Stage_____

Reason(s) for deferral:

- ☐ **Products in this class for this indication have been studied/labeled for pediatric population**
- ☐ **Disease/condition does not exist in children**
- ☐ **Too few children with disease to study**
- ☐ **There are safety concerns**
- ☐ **Adult studies ready for approval**
- ☐ **Formulation needed**
- ☐ **Other:_____**

Date studies are due (mm/dd/yy): _____

If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section D: Completed Studies

Age/weight range of completed studies:

Min____ kg____ mo.____ yr.____ Tanner Stage_____
Max____ kg____ mo.____ yr.____ Tanner Stage_____

Comments:

If there are additional indications, please copy the fields above and complete pediatric information as directed. If there are no other indications, this Pediatric Page is complete and should be entered into DFS.

This page was completed by:

{See appended electronic signature page}

Regulatory Project Manager

cc: NDA
HFD-960/ Terrie Crescenzi
(revised 1-18-02)

FOR QUESTIONS ON COMPLETING THIS FORM CONTACT, PEDIATRIC TEAM, HFD-960
301-594-7337

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

/s/

Karen Anderson
8/27/03 04:33:28 PM

DIVISION OF REPRODUCTIVE AND UROLOGIC DRUG PRODUCTS

CLINICAL TEAM LEADER MEMORANDUM

NDA	NDA 21-544
Type of Application	Original NDA
Applicant	Barr Research, Inc One Bala Plaza, Suite 324 Bala Cynwyd, PA 19004
Proprietary Drug Name	Seasonale®
Established Drug Name	(Levonorgestrel / ethinyl estradiol tablets) 0.15 mg / 0.03 mg
Indication	Prevention of pregnancy
Route of Administration	Oral
Dosage Form	Immediate release tablet
Dosage Strength	Each active tablet contains levonorgestrel (0.15 mg) and ethinyl estradiol (0.03 mg)
Dosing Regimen	One tablet daily taken in the following sequence: 84 active tablets followed by 7 inactive tablets
Date of Submission	August 5, 2002 (original submission); May 15, 2003 (Final Interim Safety Study Report for SEA 301A)
Date of Memorandum	September 5, 2003
Reviewer	Scott E. Monroe, MD Clinical Team Leader, DRUDP

EXECUTIVE SUMMARY

Recommendation regarding Approvability

Approval of Seasonale® for marketing as a combination oral contraceptive is recommended based on the data presented in the original NDA submitted on August 5, 2002, additional data and information submitted during the review process, and final revised labeling submitted on September 4, 2003.

Seasonale was shown to have acceptable efficacy (Pearl Index of 1.98) and an acceptable safety profile in the primary clinical trial (Study SEA 301). Additional supportive safety data were provided from the Applicant's safety extension trial (Study SEA 301A). There are no preclinical toxicology, chemistry, manufacturing, and controls (CMC), or biopharmaceutical deficiencies.

Recommendation on Phase 4 Studies and/or Risk Management Steps

The Applicant's ongoing safety extension trial (Study SEA-301A) should be completed per present protocol with submission of the final report [redacted] No specific risk management steps are warranted based on presently available safety data.

INTRODUCTION AND BACKGROUND

Seasonale: Dosing Regimen and Rationale

Seasonale is a combination oral contraceptive that contains 0.15 mg levonorgestrel and 0.03 mg ethinyl estradiol in each active tablet. The proposed dosing regimen is one active tablet daily for 84 days followed by 7 inactive (placebo) tablets (a 91-day or "extended" dosing cycle). The primary benefit of Seasonale, in addition to contraception, would be to reduce the number of planned menstrual periods to 4 per year in contrast to 13 menstrual periods per year as occurs with a conventional 28-day cycle oral contraceptive. The combination of 0.15 mg levonorgestrel and 0.03 mg ethinyl estradiol is the same dosage as that contained in each active tablet of Nordette, a combination oral contraceptive approved for marketing by the FDA in May, 1982, and Portia, the generic version of Nordette that is marketed by Barr Laboratories, the Applicant for the present NDA.

When oral contraceptives were first introduced in the 1960s, the dosage regimen was designed to induce withdrawal bleeding every 28 days. This 28-day regimen attempted to imitate as closely as possible the length of the normal menstrual cycle to make the pill more acceptable. For some women, the presence of a withdrawal bleed was reassuring to them, indicating that they were not pregnant. For other women, the prospect of eliminating monthly periods and the possible mitigation of perimenstrual symptoms is more important than the reassurance of withdrawal periods.

At the present time, there are no approved oral contraceptive drug products utilizing an extended dosing regimen (i.e., a dosing cycle of more than 28 days), either in the U.S. or elsewhere in the world. Off-label extended use of numerous types of oral contraceptives has been employed clinically for many years. Off-label extended use is presently utilized for patient convenience to avoid vaginal bleeding at unwanted times or for medical conditions such as endometriosis where long-term suppression of ovarian function is of benefit in alleviating the severe dysmenorrhea associated with this disorder.

Regulatory History

The initial pre-IND meeting was held November 2, 1999. The Applicant's initial plan for the pivotal study was to have all subjects start with 3 successive cycles of conventional 28-day cyclical oral contraceptive therapy. Subjects would then cross over to extended 91-day cycle oral contraceptive therapy for one year with either Seasonale (0.15 mg levonorgestrel and 0.03 mg ethinyl estradiol) or Seasonale Ultra Lo (0.10 mg levonorgestrel and 0.02 mg ethinyl estradiol). The Division of Reproductive and Urologic Drug Products (DRUDP), however, recommended a direct head-to-head comparative trial of Seasonale and Seasonale Ultra Lo to their approved 28-day counterparts (Nordette and Levlite, respectively).

A second pre-IND meeting was held on February 17, 2000. This meeting focused on clinical endpoints. The Applicant was proposing a number of primary objectives. DRUDP recommended that prevention of pregnancy should be the only primary endpoint. The Applicant also clarified at this meeting that they were not seeking a superiority claim for either Seasonale or Seasonale Ultra-Lo.

A pre-NDA teleconference was held April 23, 2002. During this teleconference, the Applicant stated that they intended to seek approval only for Seasonale [redacted] in their forthcoming submission.

Medical Officer's Comment

- *The Applicant initially proposed at their first pre-IND meeting a minimum of 4,800 months of exposure to the 2 study drugs (Seasonale and Seasonale Ultra–Lo. DRUDP recommended a minimum of 10,000 28-day cycle equivalents of study exposure to study drugs.*
- *The DRUDP meeting minutes do not specify whether 10,000 28-day cycle equivalents were required for each of Seasonale and Seasonale Ultra Lo or for the total number of study subjects (combined number of cycles in the Seasonale and Seasonale Ultra-Lo treatment groups). However, this Medical Officer, as well as the Primary Medical Reviewer, interpret the recommendation to mean 5,000 28-day treatment cycles equivalents for each of the Seasonale and Seasonale Ultra Lo treatment groups, with a combined total of 10,000 28-day cycle equivalents.*

OVERVIEW OF CLINICAL DATA SUBMITTED IN SUPPORT OF APPLICATION

NDA 21-544 was submitted under Section 505(b)(2) and included the following major components:

- **Study SEA 301.** A randomized, open-label, 1 year Phase 3 clinical trial in which the to-be-marketed product, Seasonale was compared to Nordette (a currently marketed combination oral contraceptive). Also included in this trial was a comparison of Seasonale Ultra-Lo to Levlite (a previously approved combination oral contraceptive).
- **Study SEA 301A**. An open label, on-going, 2-year safety extension study. Interim safety data and an Interim Final Safety Report based on this study were submitted as a safety update.
- Five bioavailability/bioequivalence studies.
- Safety and effectiveness data for Nordette (the previously approved 28-day cycle drug product). These data consisted primarily of the FDA Medical Officer's review of the original NDA for Nordette
- Other published clinical trials evaluating extended dose regimens for combination oral contraceptives.

PRINCIPAL CLINICAL TRIAL (STUDY SEA 301)

The principal Phase III clinical trial for assessment of contraceptive effectiveness and safety was Study SEA 301 ("A Phase III, Parallel, Randomized, Multicenter, Open-Label

Clinical Study To Evaluate the Efficacy and Safety of Seasonale Extended Oral Contraceptive Therapy – 84 Day Active Cycle").

Overall Study Design.

Study SEA 301 was a randomized, open label, 4-arm comparative, multicenter 1-year clinical trial. The 4 treatment groups were as follows:

1. **Seasonale 91-day extended dosing regimen**: One active tablet containing 0.15 mg levonorgestrel and 0.03 mg ethinyl estradiol daily x 84 days followed by a daily placebo tablets x 7 days.
2. **Nordette 28-day conventional dosing regimen**: One active tablet containing 0.15 mg levonorgestrel and 0.03 mg ethinyl estradiol daily x 21 days followed by a daily placebo tablets x 7 days.
3. **Seasonale Ultra-Lo 91-day extended dosing regimen**: One active tablet containing 0.10 mg levonorgestrel and 0.02 mg ethinyl estradiol daily x 84 days followed by a daily placebo tablets x 7 days.
4. **Levlite 28-day conventional dosing regimen**: One active tablet containing 0.10 mg levonorgestrel and 0.02 mg ethinyl estradiol daily x 21 days followed by a daily placebo tablets x 7 days.

Patients were randomized 2:2:1:1 to (Seasonale, Seasonale Ultra-Lo, Nordette or Levlite, respectively).

Medical Officer's Comment:

- [redacted] *the present NDA seeks marketing approval only for Seasonale. Therefore, this memorandum focuses on the clinical findings in the Seasonale and Nordette treatment groups.*

Study Population

The study population consisted of sexually active females (age 18-40) in a heterosexual relationship, at risk for pregnancy, fluent in English, capable of giving informed consent, and without contraindication to the use of oral contraceptive therapy.

At least 200 patients, age 18 to 35, were to complete one year of treatment in each of the two extended oral contraceptive treatment arms. One hundred (100) patients, age 18 to 35, were to complete 1 year of treatment in each of the two conventional 28-day oral contraceptive treatment arms. To accomplish the targeted completion, approximately 450 patients were to be enrolled in each of the extended oral contraceptive treatment arms and 225 patients were to be enrolled in each of the conventional oral contraceptive therapy arms.

Medical Officer's Comments:

- *The entry criteria, with one exception, were those normally employed in clinical trials to assess the efficacy and safety of oral contraceptive drug products and are acceptable.*

- *The exception was the exclusion of women with a history of abnormal bleeding (breakthrough or withdrawal bleeding that lasted 10 or more consecutive days, or spotting that lasted more than 10 consecutive days) while on a prior conventional oral contraceptive. Exclusion of such patients may have improved slightly the bleeding profiles observed in the clinical trial and should be mentioned in labeling.*
- *The plan to obtain 200 subjects who complete 1 year of treatment in the Seasonale group is appropriate and consistent with DRUDP's recommendations.*

Conduct of Study

The Schedule of Study Procedures was identical for subjects assigned to either the extended treatment or conventional treatment regimens with 2 exceptions. First, the times of the scheduled clinical visits differed slightly in the extended treatment and conventional treatment regimens to accommodate the differences in cycle lengths. Second, a subgroup of subjects in each of the extended treatment regimens had end-of-treatment endometrial biopsies. A Schedule of Major Study Procedures is provided in Table 1.

Table 1 Schedule of Major Study Procedures

Parameter	S	V-1	W-4	W-13, 26, 39 [A] or W-12, 24, 40 [B]	COT [C]
Informed Consent	X				
Medical and contraceptive history	X				X
Weight, vital signs	X	X		X	X
Pap smear	X				X
Randomization	X	X			
Lab tests (CBC, chemistry, lipid profile, UA performed centrally by [redacted])	X				X
Urine pregnancy test	X	X		X	X
Study drug distribution	X	X		X	
Study diaries distribution (MiniDoc and paper)		X	X	X	
Electronic diary download			X	X	X
Check for study drug compliance				X	X
Adverse event recording	X	X	X	X	X
Endometrial biopsy (subgroup only) [D]		X			X

S = screening, V = visit, W = week, COT = completion of therapy
A = Schedule for Seasonale group (91-day extended cycle subjects)
B = Schedule for Nordette group (28-day convention cycle subjects)
C = Normal completion was Week 52
D = Only for Seasonale group

Medical Officer's Comments

- *The monitoring procedures and Schedule of Major Study Procedures were appropriate and adequate. Of note is the inclusion of a urinary pregnancy test at each of the clinical visits (approximately every 3 months).*

- *An electronic diary was used to collect daily information on menstrual bleeding and compliance with taking of study drugs. This is the first Phase 3 study reviewed by DRUDP to use such a device. The Applicant was requested to provide the Primary Medical Reviewer with an electronic diary. The Primary Medical Reviewer's assessment of the diary was as follows: "The diary was sent to the agency and programmed in the same manner as it was given to the study subjects. This reviewer evaluated the electronic diary. The instructions and sample introductory session were acceptable and easy to understand. Upon completion of data entry, the reviewer found that the electronic diary locked to prevent data alteration. The diary was found to be an acceptable recording device for medication taking, bleeding/spotting, and peri-withdrawal symptom recording."*

Primary Efficacy Assessment ("On-Treatment Pregnancies") and Analysis

Definition of "On-Treatment Pregnancy"

Efficacy was evaluated from the overall pregnancy rate, calculated by the Pearl Index using all "on-treatment" pregnancies. On-treatment pregnancies were defined as those pregnancies for which the date of conception was on or after the first date of taking study drug and within 14 days following study drug discontinuation. Pregnancy was defined by a positive pregnancy test.

Medical Officer's Comments

- *The specific criteria used by the Applicant to identify and define an "on-treatment pregnancy" are those normally used in clinical trials of oral contraceptive effectiveness and are acceptable to DRUDP. Details are provided in the Primary Medical Review.*

Primary Efficacy Analysis

Pearl Index Calculations. For the primary calculation of effectiveness, all on-treatment pregnancies were included in the analyses, regardless of whether the treatment cycle was complete or the patient had used backup contraception during the conception cycle. However, for estimating time and number of subjects at risk for pregnancy (the denominator in the formula for calculating the Pearl Index), adjustments were made to exclude incomplete menstrual cycles or cycles in which backup contraception had been used.

Medical Officer's Comment

- *The criteria used to calculate the Pearl Index were acceptable and conservative (i.e., they might tend to decrease slightly the calculated or apparent efficacy of the study drugs relative to their true efficacy).*

Demographics

The baseline characteristics of the ITT population (all treated patients) and subjects 18-35 years of age for the Seasonale and the Nordette treatments groups are listed in Table 2.

Table 2 Baseline characteristics for the ITT and 18-35 years of age populations

	ITT Population		Subjects 18-35 Years of Age	
	Seasonale N=456	Nordette N=226	Seasonale N=397	Nordette N=195
Mean age	27.8 yrs	27.8 yrs	26.35 yrs	26.24 yrs
Mean wt.	156.4 lb	156.6 lb	156.6 lb	156.31 lb
Race				
Afr Amer	50 (10.9%)	29 (12.8%)	45 (11.34%)	22 (11.28%)
Asian	10 (2.2%)	2 (0.8%)	8 (2.02%)	2 (1.03%)
Caucasian	351 (77.0%)	169 (74.7%)	301 (75.82%)	150 (76.92%)
Hispanic	32 (7.0%)	18 (7.9%)	30 (7.56%)	13 (6.67%)
Other	13 (2.8%)	8 (3.5%)	13 (3.27%)	8 (4.10%)
Prior OC Usage				
Fresh start	35 (7.7%)	14 (6.2%)	32 (8.06%)	14 (7.18%)
Prior user	132 (29.0%)	70 (31.0%)	115 (28.97%)	60 (30.77%)
Continuous user	288 (63.2%)	142 (62.8%)	249 (62.72%)	121 (62.05%)
Smoker – yes	83 (18.2%)	35 (15.49%)	83 (20.91%)	35 (17.95%)

Medical Officer Comment

- *The Seasonale and Nordette treatment groups were well balanced and comparable to those generally enrolled in oral contraceptive safety and efficacy trials.*

Subject Disposition

The disposition of the subjects in the Seasonale and Nordette treatment groups (ITT population) is summarized in Table 3.

Table 3 Subject Disposition (ITT Population)

	Number (%) of Subjects	
	Seasonale	Nordette
Treated	456 (100%)	226 (100%)
Completed study	271 (59.4%)	161 (71.2%)
Discontinued prematurely	185 (40.6%)	65 (28.8%)
Reasons for Discontinuation		
Adverse event	68 (14.9%)	22 (9.7%)
Unacceptable bleeding *	35 (7.7%)	4 (1.8%)
Patient decision	47 (10.3%)	7 (3.1%)
Non-compliant	22 (4.8%)	9 (4.0%)
Lost-to-follow-up	39 (8.6%)	21 (9.3%)
Pregnant	4 (0.9%)	3 (1.3%)
Investigator discretion	2 (0.4%)	1 (0.4%)
Other	3 (0.7%)	2 (0.9%)

* Not an exclusive category. Subjects included in this category also reported as under "adverse event" or another category (e.g., patient decision).

Medical Officer's Comments

- *A higher percentage of subjects in the Seasonale group than in the Nordette group discontinued prematurely (40.6% vs. 28.8%). The principal reasons responsible for this difference in the percentage of subjects terminating prematurely in the Seasonale group were adverse events (Seasonale 14.9%; Nordette 9.7%), unacceptable bleeding (Seasonale 7.7%, Nordette 1.8%), and patient decision (Seasonale 10.3%, Nordette 3.1%).*
- *Information regarding the percentage of subjects discontinuing for "unacceptable bleeding" should be included in labeling as recommended by the Primary Medical Reviewer.*

Primary Efficacy Outcome

Total Number of Pregnancies

A total of 8 pregnancies were reported for subjects in the Seasonale treatment group. Of these 8 pregnancies, 4 were assessed as having occurred on-treatment. For the remaining 4 pregnancies, conception was assessed as having occurred either prior to treatment onset (n=1) or more than 14 days after the last dose of Seasonale (n=3).

A total of 4 pregnancies were reported for subjects in the Nordette treatment group. Of these 4 pregnancies, 3 were assessed as having occurred on-treatment. Conception for 1 of the 4 pregnancies was considered to have occurred more than 14 days after the last dose of Nordette.

Medical Officer's Comments

- *Both the Applicant and the FDA Primary Medical Reviewer were in agreement as to whether conception occurred on-treatment or off-treatment for all pregnancies in the Seasonale and Nordette treatment groups.*
- *The Primary Medical Reviewer's assessment of whether a pregnancy occurred on-treatment or off-treatment was based on his review of pregnancy source documents including uterine sonograms.*
- *This Medical Officer concurs with the Applicant's and the Primary Medical Reviewer's assignment of on-treatment and off-treatment pregnancies.*

Pearl Index Values

The Applicant submitted a revised Pearl Index calculation on May 5, 2003. This revision was necessary because the FDA biostatistician reviewing the Applicant's data identified a discrepancy in the correct number of "at risk" cycles to use in the denominator of the Pearl Index calculation. The Applicant acknowledged the error and sent in revised tables. The following two tables compare the Applicant's corrected calculation (Table 4) and the FDA statistician's results (Table 5), based on a conservative calculation of the Pearl Index. In this calculation, the on-treatment at risk period is based only on completed 91-day treatment cycles in the 18-35 year age range and excludes cycles where other birth control methods were utilized.

Table 4 Applicant's Revised Calculation of Pearl Index (Subjects 18-35 years old)

Treatment group	No. of Complete Cycles	No. of On-Treatment Pregnancies	Pearl Index
Seasonale	811 (a)	4	1.97
Nordette	1759 (b)	3	2.22

a. For Seasonale, a complete cycle is 91 days.
b. For Nordette, a complete cycle is 28 days.

Table 5 FDA Biostatistician's Calculation of Pearl Index (Subjects 18-35 years old)

Treatment group	No. of Complete Cycles	No. of On-Treatment Pregnancies	Pearl Index (95% CI)
Seasonale	809 (a)	4	1.98 (0.54, 5.03)
Nordette	1758 (b)	3	2.22 (0.46, 6.38)

a. For Seasonale, a complete cycle is 91 days.
b. For Nordette, a complete cycle is 28 days.

Life Table Estimates of Efficacy

The FDA biostatistician calculated the pregnancy rates for Seasonale and Nordette, based on a life table analysis, as 1.26% for Seasonale (95% C.I. from 0.02% to 2.50%) and 1.87% for Nordette (95% C.I. from 0% to 3.98%).

Medical Officer's Comments

- *The FDA biostatistician's Pearl Index calculation for Seasonale was only slightly different from that of the Applicant's (1.98 compared to 1.97).*
- *A Pearl Index of 1.98 for Seasonale is acceptable for the following reasons:*
  - *The Pearl Index for Nordette, a currently approved oral contraceptive and the active comparator in Study SEA 301, was 2.22.*
  - *Other currently approved oral contraceptives have had Pearl Indices of up to 2.39 in their pivotal clinical trials.*

Overall Assessment of Efficacy

Medical Officer's Comments

- *Utilizing conservative criteria for assessing the Pearl Index, Seasonale was found to have acceptable efficacy in terms of prevention of pregnancy. The Pearl Index for Seasonale in the principal efficacy trial (Study SEA 301) was 1.98. This estimate of efficacy was based on subjects 18- 35 years of age and excluded from the Pearl Index calculation (1) treatment cycles for which subjects reported using other birth control methods and (2) partial treatment cycles. No pregnancies in subjects > 35 years of age were reported in the Seasonale or Nordette treatment group. Using a Life Table Analysis, the effectiveness of Seasonale in study SEA 301 was 1.26% (95% C.I. from 0.02% to 2.50%). The Primary Medical Reviewer calculated the "perfect use" Pearl Index for Seasonale to be 0.99 in study SEA 301.*

- *The Pearl Index for Nordette, a currently approved 28-day cycle oral contraceptive, was 2.22 in Study SEA 301 utilizing the same conservative criteria. Using a Life Table Analysis, the effectiveness of Nordette was 1.87% (95% C.I. from 0% to 3.98%).*
- *Levonorgestrel 0.15 mg and ethinyl estradiol 0.03 mg in a 28-day cycle dosing regimen (Nordette) was approved more than 20 years ago as an effective and safe combination oral contraceptive. There is no theoretic concern or objective data from study SEA 301 to suggest that taking this contraceptive formulation in 91-day cycles (Seasonale: 84 consecutive days of active tablets followed by 7 days of placebo) instead of 28-day cycles (Nordette: 21 consecutive days of active tablets followed by 7 days of placebo) is likely to impede contraceptive efficacy for pregnancy prevention. On the contrary, there may be some contraceptive benefits to avoiding two of the three 7-day withdrawal periods (placebo treatment periods) that would occur over a 3-month period with a conventional 28-day contraceptive dosing regimen. During the placebo treatment period, there is a possibility that the ovary could escape from suppression, particularly if the patient delays her start of next dosing with active pills.*
- *This study utilized a daily electronic diary that had a daily signal alarm that prompted patients for data entry (and hence might have served as a prompt to take study medication. However, both the Primary Medical Reviewer and this Medical Officer do not feel that Seasonale needs to be marketed with a similar device to obtain efficacy similar to that observed in Study SEA 301.*
- *Product labeling should include the overall Pearl Index in the clinical section of the label.*

Exposure to Seasonale

Data to support the safety of Seasonale were provided by the Applicant in principal study SEA 301 and the safety extension study SEA 301A. Safety exposure to Seasonale and the active comparator Nordette are summarized in Table 6. Data are expressed as the number of treated patients and the number of 28-day treatment cycle equivalents. In Study SEA 301, 286 of 456 subjects (62.7%) in the Seasonale group completed at least 11 months of treatment. Subjects enrolled in Study 301A previously participated in Study SEA 301.

Table 6 Exposure to Seasonale (SEA 301 and SEA 301A 28-day Cycle Equivalents)

Study	Treatment	Total Patients Treated	28-day Cycle Equivalents
SEA-301 (Pivotal)	Seasonale	456	4,337
	Nordette	226	2,390
SEA-301 A (Safety Extension)	Seasonale	191	1,609
Total Exposure	***Seasonale***	***647***	***5,946***

Medical Officer's Comments

- *The total number of 28-day cycle equivalents (5,946) is acceptable and adequate.*

Safety Findings (Study SEA 301)

Most Commonly Reported Adverse Events

The most commonly reported adverse events in the Seasonale subjects are listed by decreasing frequency in Table 7.

Table 7 ***Most Frequently Reported Adverse Events in Seasonale Subjects (Study SEA 301)***

MedDRA term	Seasonale (N=456)		Nordette (N=226)	
	N	%	N	%
Nasopharyngitis	100	21.9	67	29.7
Headache Nos	94	20.6	64	28.3
Menorrhagia *	53	11.6	6	2.7
Sinusitis Nos	45	9.9	25	11.1
Sore throat	37	8.1	12	5.3
Nausea	34	7.5	20	8.9
Influenza	32	7.0	15	6.6
Back Pain	29	6.4	19	8.4
Fungal infection	27	5.9	11	4.9
Dysmenorrhea	26	5.7	9	4.0
URI	25	5.5	22	9.7

* Includes other bleeding-related adverse events such as intermenstrual bleeding, unexpected bleeding, and breakthrough bleeding

Medical Officer's Comments

- *The most striking difference between the 2 treatment groups was the category of "menorrhagia" that included a number of adverse events other than heavy bleeding (e.g., intermenstrual bleeding, unexpected bleeding, or breakthrough bleeding). Menorrhagia was reported 4 times more frequently in the Seasonale subjects (11.6%) compared to the Nordette subjects (2.6 %).*

Adverse Events Associated with Premature Termination

Sixty-eight (68) of 456 subjects (14.9%) in the Seasonale group and 22 of 226 subjects (9.7%) in the Nordette group terminated prematurely because of adverse events. Menorrhagia, the most common adverse associated with premature termination in the Seasonale group was reported as a reason for premature termination in 26 of 456 subjects (5.7%) and in 4 of 226 subjects (1.77%) in the Nordette group. When all instances of unacceptable vaginal bleeding were considered, 35 of 456 subjects (7.7%) in Seasonale group, compared to 1.8% in the Nordette group, withdrew prematurely from Study SEA 301 for this reason.

Medical Officer's Comments

- *Of the 35 subjects with unacceptable bleeding as a cause for premature termination, 26 had hematocrit and/or hemoglobin determinations at screening and at end of treatment. Although a small number of subjects in the Seasonale arm developed*

anemia (see laboratory adverse events section), none of these 26 subjects who terminated because of unacceptable bleeding were reported to have developed anemia (i.e., Hct < 35%, Hgb < 11.6 mg/dL). Ten of the 26 had a decrease in their hematology parameters, but not into the range classified as anemia. Thirteen of the 26 showed an increase, and three remained unchanged.

Serious Adverse Events

A total of 11 serious adverse events were reported in 11 Seasonale subjects (one event in each of 11 subjects). The reported serious adverse events were pulmonary embolus, intermittent syncope, appendectomy, disc surgery, worsening goiter, gunshot wound, mild concussion, cholecystectomy, food poisoning, meningoencephalitis, and motor vehicle accident. All were considered as not related to treatment with the exception of pulmonary embolus (likely related) and intermittent syncope (possibly related).

Medical Officer's Comments

- *The occurrence of thrombotic and thromboembolic adverse events are well known risks associated with the use of oral contraceptives. Review of the medical record by the Primary Medical Reviewer for Subject 38/34, who had a pulmonary embolus, did not disclose her to be at increased risk for a thromboembolic adverse event. There were no other reports of pulmonary embolus in any of the other treatment groups in study SEA 301 or in any subjects in the safety extension study SEA 301A.*
- *Oral contraceptives containing levonorgestrel are believed to be associated with a lower risk for the development of thrombotic or thromboembolic adverse events than oral contraceptives containing third generation progestins (e.g., desogestrel). Although subjects in the Seasonale treatment arm received more estrogen and progestin per year than those in the Nordette treatment arm, a single case of pulmonary embolus in this clinical study does not raise sufficient concern to recommend that Seasonale not be approved for prevention of pregnancy.*

Deaths

There were no reported deaths in any treatment group in Study SEA-301.

Laboratory Safety Findings

Specimens for laboratory safety measurements were obtained only at baseline and at the end of treatment.

Serum Lipid Changes

Mean changes in serum lipid values (end of treatment compared to baseline values) appeared to be similar in the Seasonale and Nordette treatment groups. As would be expected in women taking a combination oral contraceptive, there were small increases in serum concentrations of total cholesterol, triglycerides, and LDL-cholesterol in both treatment groups and a small decrease in HDL-cholesterol (Seasonale group).

Medical Officer's Comments

- *The percentages of patients who went from the normal range at baseline to above the normal range at final measurement was numerically slightly greater in the Seasonale*

group for triglycerides (5.3%) and LDL-cholesterol (17.2%) compared to those in the Nordette group (1.6% and 14.3%, respectively). These small differences are unlikely to be of clinical significance.

ALT, AST and Bilirubin Changes

Small and comparable percentages of subjects, who had serum concentrations of ALT, AST, or bilirubin within the normal range at baseline in the Seasonale and Nordette treatment groups, had values above the upper limit of normal (ULN) at the end of treatment.

Medical Officer's Comments

- *Small increases in serum ALT, AST, and bilirubin concentrations are known effects of treatment with combined oral contraceptives.*

Hemoglobin and Hematocrit Changes

The number and percentage of subjects in the Seasonale and Nordette groups who went from the normal range at baseline to below the lower limit of the normal range (< LLN) at their end of treatment assessment, as well as other shifts, are listed in Table 8.

Table 8 Change in Hemoglobin and Hematocrit Values (Baseline to End of Treatment)

		End of Treatment Value					
		Low		Normal		High	
Lab Parameter (nl range)	Baseline value	N	%	N	%	N	%
Seasonale Group							
Hemoglobin	L	2	25	6	75.0	0	0.0
(11.6-16.2 gm/dL)	N	3	0.8	357	98.9	1	0.3
	H	0	0.0	0	0.0	0	0.0
Hematocrit	L	1	10.0	9	90.0	0	0.0
(35-47%)	N	3	0.8	351	98.3	3	0.8
	H	0	0.0	2	100.0	0	0.0
Nordette Group							
Hemoglobin	L	1	50.0	1	50.0	0	0
(11.6-16.2 gm/dL)	N	0	0	186	100.0	0	0
	H	0	0	2	100.0	0	0
Hematocrit	L	1	25.0	3	75.0	0	0
(35-47%)	N	3	1.6	180	98.4	0	0
	H	0	0	3	100.0	0	0

Medical Officer's Comments

- *Although the percentage of subjects who shifted to below the normal range for hematocrit was numerically slightly lower in the Seasonale group (0.8%) compared to the Nordette group (1.6%), the magnitudes of the decreases were somewhat greater in the Seasonale subjects.*

- *In the Seasonale group, the number (and percentage) of subjects whose values shifted from < LLN at baseline to within the normal range at end of treatment for hemoglobin (6 of 8 subjects) and hematocrit (9 of 10 subjects) was greater than the number of subjects whose values shifted from within the normal range at baseline to < LLN at the end of treatment (hemoglobin: 3 of 361; hematocrit: 3 of 357).*
- *Although intermenstrual bleeding was very common in subjects in the Seasonale group in Study SEA 301, the effect of this bleeding on hemoglobin and hematocrit values does not appear to be of clinical concern.*

Endometrial Biopsy Findings

According to the Primary Medical Reviewer, baseline and final biopsy results were obtained in 50 Seasonale subjects and 61 Seasonale Ultra-Lo subjects. The expected increase in inactive glands and stromal decidualization was identified.

Medical Officer's Comments

- *The reported histologic changes are well-recognized findings for any woman on long-term combination estrogen/progestin oral contraceptive regimens.*
- *The endometrial histologic findings related to continuous combination therapy of different strengths have been well characterized over the last thirty years. Use of more combination oral contraceptive tablets per year (Seasonale subjects) should not represent an increased theoretical endometrial risk because the estrogen/progestin ratio for each tablet throughout the year remains the same as in a 28-day dosing regimen.*
- *There were no safety concerns from the endometrial biopsy evaluations.*

Vaginal Bleeding and Spotting (Scheduled Withdrawal Menses and Intermenstrual Bleeding and Spotting)

Subjects in the Seasonale group exhibited a greater number of days of intermenstrual bleeding and/or spotting than those in the Nordette comparator group (see Table 9). Any bleeding/spotting that was reported to have occurred on days when an active tablet was taken was classified as intermenstrual bleeding/spotting.

Table 9 Days of Intermenstrual Bleeding and/or Spotting by Treatment Cycle

Treatment Group	Cycle [A]	Number of Subjects	Days of Intermenstrual Bleeding/Spotting		
			Mean	Median	Mean / Median per "28-day cycle" [B]
Seasonale	1	446	15.1	12.0	3.8 / 3.0
	2	368	11.6	6.0	2.9 / 1.5
	3	309	10.6	6.0	2.7 / 1.5
	4	282	8.8	4.0	2.2 / 1.0
Nordette	1	218	2.1	1.0	
	2	213	1.9	1.0	
	3	209	1.6	1.0	
	4	198	1.3	1.0	
	10	172	1.7	1.0	
	11	165	2.0	1.0	
	12	163	1.6	1.0	
	13	162	1.6	1.0	

[A] For Seasonale, a cycle was 91 days in length; for Nordette a cycle was 28 days in length.
[B] Obtained by multiplying the 91-day cycle result by the factor (21/84) "to adjust" for the difference in cycle length compared to a 28-day conventional cycle.

Medical Officer's Comments

- *Although the mean and median number of intermenstrual bleeding/spotting days decreased over time in the Seasonale group, the mean and median values as well as the "adjusted mean value" of 2.2 days still exceeded those in the Nordette group, even in the final treatment cycle.*
- *This analysis, based on mean and median values, provided an incomplete picture of the observed bleeding/spotting patterns. Consequently, the Applicant was asked to provide an analysis based on the number of subjects with ≥ 7 days and ≥ 20 days of intermenstrual bleeding/spotting (see Table 10). In this Table, the data for the Nordette group have been partially combined (i.e., cycles 1-4 and 10-13 combined) to make the "at risk intermenstrual days" comparable in the 2 treatment groups (i.e., 84 days in each group).*
- *The percentages of subjects with 7 or more days of bleeding/spotting decreased over time in the Seasonale group, and in Cycle 4 was similar to that in the Nordette group. However, the percentages of subjects with ≥ 20 days of bleeding/spotting in the Seasonale group always exceeded that in the Nordette group.*
- *Information regarding intermenstrual bleeding, as recommended by the Primary Medical Reviewer, should be included in labeling.*
- *Although most women using Seasonale can expect to have more total days of intermenstrual bleeding/spotting, the total number of days of bleeding/spotting (menstrual plus intermenstrual bleeding/spotting days) over the course of a year is similar to that in the Nordette group. In addition, review of baseline and end of treatment hemoglobin and hematocrit values for Seasonale subjects in Study SEA 301 did not raise any safety concerns.*

- *In summary, the increase in intermenstrual bleeding/spotting, per se, does not appear to pose a safety concern for women who may choose to use Seasonale for prevention of pregnancy. Women will need to balance the convenience of fewer scheduled menstrual periods with Seasonale use (4 per year vs. 13 per year with a 28-day cycle oral contraceptive) against the inconvenience of more intermenstrual bleeding/spotting.*

Table 10 Number of Subjects with Intermenstrual Bleeding/Spotting

Days of intermenstrual bleeding/spotting	Percentage of subjects with ≥ 7 days or ≥ 20 days of intermenstrual bleeding/spotting			
Seasonale Group	Cycle 1 [A]	Cycle 2	Cycle 3	Cycle 4 [A]
≥ 7 days	65%	52%	50%	42%
≥ 20 days	35%	24%	20%	15%
Nordette Group	Cycles 1-4 [B]			Cycles 10-13 [B]
≥ 7 days	38%			39%
≥ 20 days	6%			4%

[A]. For Seasonale, intermenstrual bleeding/spotting refers to days 1-84 of each 91-day cycle.
[B]. For Nordette, intermenstrual bleeding/spotting refers to days 1-21 of a 28-day cycle x 4 cycles.

SAFETY EXTENSION STUDY (STUDY SEA 301A)

Study SEA 301A is an on-going safety extension study in which subjects who successfully completed Study 301 were eligible to enroll. Subjects who received either Seasonale or Nordette in study SEA 301 were assigned, for the most part, to Seasonale in study SEA 301A. Subjects who received either Seasonale Ultra-Lo or Levlite in study SEA 301 were assigned, for the most part, to Seasonale Ultra-Lo in study SEA 301A. The conduct and monitoring procedures for Study SEA 301A are similar to those in Study SEA 301. In May 2003, the Applicant submitted an interim Final Safety Report for Study SEA 301A based on a data cutoff date of January 24, 2003.

One hundred ninety one (191) and 160 subjects were initially assigned to receive Seasonale or Seasonale Ultra-Lo, respectively. Of the 191 subjects assigned to Seasonale, 86 had received treatment with a study drug other than Seasonale in SEA 301. At the time of data cutoff, a total of 1,609 28-day cycle equivalents of safety data had been obtained in Study SEA 301A. One death (a fatal motor cycle accident involving a subject receiving Seasonale Ultra-Lo, not related to treatment with study drug) was reported. Based on adverse events and laboratory values reported in the interim Final Safety Report for study SEA 301A, no new safety issues or safety concerns were identified regarding the use of Seasonale for the prevention of pregnancy. Consequently, no formal discussion of the safety findings from study SEA 301A is provided in this memorandum. The Primary Medical Reviewer, in his review of NDA 21-544, has provided a thorough written review and discussion of the safety findings obtained to date in Study SEA 301A.

ADEQUACY OF SAFETY DATA

For a new oral contraceptive product, DRUDP has generally required 10,000 28-day treatment cycles that include data from 200 subjects treated for 1 year. However, the composition of Seasonale active tablets (0.15 mg levonorgestrel and 0.03 mg ethinyl estradiol) is the same as Nordette (approved more than 20 years ago) and the recently approved generic version (Portia). In additional, Nordette and other levonorgestrel containing oral contraceptives containing < 0.05 mg ethinyl estradiol are considered to be among the safest of the presently available combination oral contraceptives. A recent review of the FDA's Adverse Event Reporting System (AERS) database for Nordette (see Primary Medical Review for specifics) supports this conclusion. In the present application, the Applicant has presented Seasonale safety data from a total of 5,946 28-day cycle equivalents (4,337 in study SEA 301 and 1,609 in study SEA 301A) that included more than 200 subjects treated for one year.

Medical Officer's Comment

- *Based on the considerations presented in the preceding paragraph, the Applicant has submitted sufficient safety data in NDA 21-544 to assess the safety of Seasonale for prevention of pregnancy.*

OVERALL ASSESSMENT OF SAFETY

There is a very large safety database for both of the active components of Seasonale (ethinyl estradiol and levonorgestrel). These components are found in a large number of approved combined oral contraceptives. Oral contraceptives containing levonorgestrel and < 0.05 mg ethinyl estradiol are generally considered to be among those with the lowest incidence of serious adverse events, particularly thrombotic and thromboembolic. Each active tablet of Seasonale contains 0.15 mg levonorgestrel and 0.03 mg ethinyl estradiol. This is the same formulation as that of Nordette, a safe oral contraceptive that was approved more than 20 years ago.

The dosing regimen for a 91-day cycle of Seasonale (84 days of active tablets followed by 7 days of placebo) exposes a woman to 9 additional weeks of exogenous estrogen and progestin compared to that for a woman using Nordette. Table 11 compares the annual exposure to levonorgestrel and ethinyl estradiol for a woman using Nordette, Seasonale, or Ovral.

Table 11 Exposure to Ethinyl Estradiol and Levonorgestrel (Seasonale vs. Other Approved Combination Oral Contraceptives)

	Nordette	Seasonale	Ovral
Ethinyl estradiol dose/tablet	0.03 mg	0.03 mg	0.05 mg
Levonorgestrel dose/tablet	0.15 mg	0.15 mg	0.25 mg *
# active tablets/cycle	21	84	21
# cycles/yr	13	4	13
# active tablets/yr	273	336	273
Total ethinyl estradiol/yr	8.19 mg	10.08 mg	13.65 mg
Total Levonorgestrel/yr	40.95 mg	50.4 mg	68.25 mg

* Contains 0.5 mg of dl norgestrel. Approximate content of levonorgestrel is 0.25 mg.

Although the annual exposure to ethinyl estradiol in a woman using Seasonale will be 23 % higher than in a woman using Nordette, it is 27% lower than the exposure resulting from the use of Ovral or other oral contraceptives containing 0.05 mg ethinyl estradiol. The report of a pulmonary embolus in 1 subject while taking Seasonale in study SEA 301 does not provide a sufficient signal to raise significant concern that the 91-day dosing regimen, compared to a 28-day dosing regimen, increases the risk for thromboembolic events. Standard postmarketing surveillance (through AERS) will be adequate to monitor for a possible increase in thrombotic and thromboembolic adverse events in women using Seasonale for the prevention of pregnancy.

The most significant adverse event related to the use of Seasonale (and the only clear difference in the safety profiles of Seasonale compared to that of Nordette) was increased intermenstrual bleeding and/or spotting. This adverse event led to more premature discontinuations in the Seasonale arm (7.7%) than in the Nordette arm (1.8%) in the principal safety and efficacy study (SEA-301). Although the percentage of women reporting this adverse event appeared to decrease with continued use over one year, 15% of the Seasonale subjects still had ≥ 20 days of intermenstrual bleeding/spotting in the fourth 91-day cycle of use compared to 4% of women using Nordette during a comparable period (cycles 10-13). The percentages of women with ≥ 7 days of intermenstrual during the fourth cycle of Seasonale and cycles 10-13 of Nordette were comparable in the Seasonale (42%) and Nordette (39%) groups.

Although most women using Seasonale can expect to have more total days of intermenstrual bleeding/spotting, the total number of days of bleeding/spotting (menstrual plus intermenstrual bleeding/spotting) over the course of a year was similar to that in women using Nordette. The increase in intermenstrual bleeding/spotting, per se, in Seasonale users does not appear to pose a safety concern (but rather a quality of life issue) for women who may chose to use Seasonale for prevention of pregnancy. There was no evidence in the hematology laboratory data from study SEA-301 that there were significant problems with anemia (hematocrit or hemoglobin values < 35.0% or < 11.6 gm/dL, respectively) in subjects using Seasonale. The percentage of Seasonale subjects with anemia at the end of treatment was comparable to that found in the Nordette arm. Women will need to balance the convenience of fewer scheduled menstrual periods with Seasonale use (4 per year vs. 13 per year) against the inconvenience of significantly more intermenstrual bleeding/spotting. Information describing the percentages of women with increased intermenstrual bleeding should be included in labeling for Seasonale.

In summary, there were no safety findings in either Study SEA 301 or Study SEA 301A that would preclude the approval of Seasonale for the prevention of pregnancy.

NON CLINICAL REVIEW ISSUES

Chemistry (CMC)

There are no outstanding CMC deficiencies. The Primary Chemistry Reviewer (Dr. Tran) recommended "Approval of Seasonale from a CMC perspective." The Office of Compliance issued an "Acceptable" recommendation on 2 June 2003 in their Establishment Evaluation Report.

Clinical Pharmacology and Biopharmaceutics

There are no outstanding clinical pharmacology and biopharmaceutics issues.

In her review of NDA 21-544, the Primary Clinical Pharmacology Reviewer, Dr. Kim stated the following: "The Office of Clinical Pharmacology and Biopharmaceutics/Division of Pharmaceutical Evaluation II (OCPB/DPE-II) has reviewed NDA 21-544 submitted on August 5, 2002. The overall Human Pharmacokinetic Section is *acceptable*. Labeling comments ..... should be conveyed to the sponsor as appropriate."

Suggested clinical pharmacology and biopharmaceutics labeling changes were submitted to, and accepted by, the Applicant.

Toxicology and Preclinical Pharmacology

There are no outstanding toxicology or preclinical pharmacology issues. No new toxicity studies were submitted in support of this NDA.

Division of Scientific Investigation

No study center inspections were conducted by the Division of Scientific Investigation (DSI). After his preliminary review of the NDA submission, the Primary Medical Reviewer concluded that such inspections were not warranted for this application. He based his recommendation on the following considerations: (1) the combination of levonorgestrel (0.15 mg) and ethinyl estradiol (0.03 mg) has been approved and marketed as Nordette for prevention of pregnancy for more than 20 years; (2) the primary clinical efficacy endpoint, prevention of pregnancy, was assessed by an objective method, a urinary pregnancy test, that in many instances was confirmed by another objective method, ultrasonography; (3) Study SEA 301 was conducted at 47 sites and no study center reported more than a single pregnancy in either the Seasonale or Nordette treatment groups; (4) source data (documentation) was provided that enabled the Primary Medical Reviewer to independently confirm the date of conception; and (5) daily menstrual cycle data (i.e., occurrence of bleeding and/or spotting) was collected by an electronic diary that minimized the possibly of site error or site bias. This Medical Officer concurred with the recommendation of the Primary Medical Reviewer that DSI site inspections were not warranted.

Division of Medication Errors and Technical Support (DMETS)

In their final consultation of August 15, 2003, DMETS concluded the following: "The Division of Medication Errors and Technical Support (DMETS) have not identified any additional proprietary or established names that have the potential for confusion with Seasonale since we conducted our proprietary name reviews dated December 14, 2001 (ODS consult 01-0240) and March 29, 2003 (ODS consult 01-0240-1).....Upon re-evaluation DMETS has concluded the potential for confusion is low, based upon the drug products differences in pharmacological class, indication for use, prescription legend classification, product strength and dosage formulation. Therefore, we have no objections to the use of the proprietary name, Seasonale from a safety perspective."

DMETS also stated that DDMAC had reiterated [redacted]

DMETS also expressed concern that the use of the term " [redacted] " on product packaging could be misleading and could be used for an "unsubstantiated claim." Lastly DMETS expressed concern that the term "extended-cycle oral contraceptive" in the first sentence of the proposed Package Insert "implies that these oral contraceptive tablets or dosing schedule provides an additional benefit over other oral contraceptive tablets or dosing schedules."

DRUDP does not consider the name "Seasonale" to be more misleading or more fanciful than other proprietary names for other oral contraceptive products. DRUDP finds the name Seasonale to be acceptable. DRUDP concurred that the term " [redacted] was misleading and inappropriate. Consequently, the Applicant replaced " [redacted] with the term "Extended Cycle Tablet Dispenser." This term is descriptive of the product and acceptable to DRUDP. DRUDP does not believe that the use of the term "extended-cycle oral contraceptive" in the first sentence of the Package Insert is inappropriate. It is only descriptive of 91-day Seasonale treatment cycle (84 active pills followed by 7 placebo pills) compared to a 28-day treatment cycle for presently available oral contraceptives.

Division of Drug Marketing, Advertising, and Communications (DDMAC)

[redacted]

Division of Surveillance, Research, and Communication Support (DSRCS)

The DSRCS made a number of general suggestions regarding the format of the Patient Labeling to improve patient comprehension. Based on their suggestions, the vocabulary was simplified to enhance patient comprehension. It was decided by DRUDP that it would not be possible to modify Patient Labeling to a [redacted] at this time because of oral contraceptive class labeling issues and requirements.

Labeling

Since Seasonale has a different dose administration schedule, different bleeding pattern, and a higher yearly hormonal exposure, specific labeling was written to address the differences from conventional 28-day combination oral contraceptives. The important new labeling sections include the following:

- A statement that indicates that, although studies to date have not shown an increased risk for thrombotic and thromboembolic disease, there may be an additional risk due to added exposure.
- A statement and table demonstrating that Seasonale has more intermenstrual bleeding and spotting than the 28-day comparator.
- Statements that advise women to strongly consider the possibility that they may be pregnant if they miss any of their expected withdrawal bleeds while taking Seasonale.
- Revised patient dosing directions.

Additionally, like other recent labels for combination oral contraceptives, the Pearl Index for Seasonale was included in the label.

There are no outstanding labeling issues. Final acceptable labeling (Package Insert and Brief and Detailed Patient Information Sheets) were received from the Applicant on September 4, 2003.

CONCLUSION

Overall Recommendation Regarding Approval

Approval of Seasonale® for marketing as a combination oral contraceptive is recommended based on the data presented in the original NDA submitted on August 5, 2002, additional data and information submitted during the review process, and final revised labeling submitted on September 4, 2003.

Seasonale was shown to have acceptable efficacy (Pearl Index of 1.98) and an acceptable safety profile in the primary clinical trial (Study SEA 301). Additional supportive safety data were provided from the Applicant's safety extension trial (Study SEA 301A). There are no preclinical toxicology, chemistry, manufacturing, and controls (CMC), or biopharmaceutical deficiencies.

Recommendation on Phase 4 Studies and/or Risk Management Steps

The Applicant's ongoing safety extension trial (Study SEA-301A) should be completed per present protocol with submission [redacted] No specific risk management steps are warranted based on presently available safety data.

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

/s/

Scott Monroe
9/5/03 04:07:50 PM
MEDICAL OFFICER

Donna Griebel
9/5/03 04:14:29 PM
MEDICAL OFFICER
I concur with this review and recommendation for approval..

T-Con Meeting Minutes

Date: August 27, 2003 **Time:** 2:30 – 3:00 PM **Location:** Office 17B45

NDA: 21-544 **Indication:** Contraception

Drug Name: Seasonale (levonorgestrel / ethinyl estradiol) Tablets

Sponsor: Barr Laboratories, Inc.

Meeting Type: Telephone Conference

Meeting Chair: Scott Monroe, M.D.- Medical Team Leader, Division of Reproductive and Urologic Drug Products (DRUDP; HFD-580)

Meeting Recorder: Karen Anderson, N.P. - Regulatory Project Manager, DRUDP (HFD-580)

FDA Attendees:
Scott Monroe, M.D. - Medical Team Leader, DRUDP (HFD-580)
Gerald Willett, M.D. - Medical Officer, DRUDP (HFD-580)
Karen Anderson, N.P. - Regulatory Project Manager, DRUDP (HFD-580)

External Attendee:
Carol Ben-Maimon – President and COO, Barr Research, Inc.
Howard Hait, Vice President, Data Management, Bio-Statistics and Commercial Marketing Support, Barr Research, Inc.
Joe Carrado - Senior Director, Clinical Regulatory Affairs
Christine Mundkur – Senior Vice President, Quality and Regulatory Counsel, Barr Research, Inc

Background: The sponsor proposes a 91-day oral contraceptive regimen (84 days of levonorgestrel and ethinyl estradiol tablets followed by 7 days of placebo).

Purpose of the Meeting: Discussion of Phase 4 commitments

Discussion Points:
- Sponsor agreed to complete the 2 year extension study SE 301A per protocol.
- Sponsor will
- Sponsor will
- Sponsor clarified data provided in their submission of August 25, 2003 concerning the percentage of Seasonale patients who did not have withdrawal bleeding in Study SEA 301A.

Action:
Sponsor has plans to submit to DDMAC and DRUDP

Minutes prepared: Karen Anderson, N.P. - Project Manager
Chair concurrence: Scott Monroe, M.D. - Medical Team Leader

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

/s/

Scott Monroe
8/29/03 02:12:15 PM

Meeting Minutes

Date: September 2, 2003 **Time:** 2:00 – 2:45 PM **Location:** Rm 17b45

NDA: 21-544 **Indication:** Contraception

Drug Name: Seasonale (levonorgestrel / ethinyl estradiol) Tablets

Sponsor: Barr Laboratories, Inc.

Meeting Type: Telephone Conference

Meeting Chair: Scott Monroe, M.D.- Medical Team Leader, Division of Reproductive and Urologic Drug Products (DRUDP; HFD-580)

Meeting Recorder: Karen Anderson, N.P. - Regulatory Project Manager, DRUDP (HFD-580)

FDA Attendees:
Scott Monroe, M.D. - Medical Team Leader, DRUDP (HFD-580)
Gerald Willett, M.D. - Medical Officer, DRUDP (HFD-580)
Karen Anderson, N.P. - Regulatory Project Manager, DRUDP (HFD-580)

External Attendee:
Carole Ben-Maimon – President and COO, Barr Research, Inc.
Howard Hait - Vice President, Data Management, Bio-Statistics and Commercial Marketing Support, Barr Research, Inc.
Christine Mundkur – Senior Vice President, Quality and Regulatory Counsel, Barr Research, Inc
Joe Carrado - Senior Director, Clinical Regulatory Affairs
Wayne Mulcahy - Senior Director, Clinical Regulatory Affairs
Amy Niemann – Vice President Proprietary Marketing
Sal Peritore – Associate Director Regulatory Affairs

Background: The sponsor proposes a 91-day oral contraceptive regimen (84 days of levonorgestrel and ethinyl estradiol tablets followed by 7 days of placebo). Action date September 5, 2003.

Purpose of the Meeting: Label discussion

Discussion Points:
- Clarification of label wording
- Location and order of the Detailed and Brief patient information
- Balanced description of expected bleeding patterns

Action:
- DRUDP to send revisions of draft September 3, 2003.

Minutes prepared: Karen Anderson, N.P. - Project Manager
Chair concurrence: Scott Monroe, M.D. - Medical Team Leader

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

/s/

Karen Anderson

9/4/03 06:14:51 PM

Meeting Minutes

Date: August 22, 2003 **Time:** 9:00 – 10:00 AM **Location:** Conference Rm 17b45

NDA: 21-544 **Indication:** Contraception

Drug Name: Seasonale (levonorgestrel / ethinyl estradiol) Tablets

Sponsor: Barr Laboratories, Inc.

Meeting Type: Telephone Conference

Meeting Chair: Scott Monroe, M.D.- Medical Team Leader, Division of Reproductive and Urologic Drug Products (DRUDP; HFD-580)

Meeting Recorder: Karen Anderson, N.P. - Regulatory Project Manager, DRUDP (HFD-580)

FDA Attendees:
Scott Monroe, M.D. - Medical Team Leader, DRUDP (HFD-580)
Gerald Willett, M.D. - Medical Officer, DRUDP (HFD-580)
Karen Anderson, N.P. - Regulatory Project Manager, DRUDP (HFD-580)
Charlene Williamson – Regulatory Project Manager, DRUDP (HFD-580)

External Attendee:
Carole Ben-Maimon – President and COO, Barr Research, Inc.
Howard Hait - Vice President, Data Management, Bio-Statistics and Commercial Marketing Support, Barr Research, Inc.
Christine Mundkur – Senior Vice President, Quality and Regulatory Counsel, Barr Research, Inc

Background: The sponsor proposes a 91-day oral contraceptive regimen (84 days of levonorgestrel and ethinyl estradiol tablets followed by 7 days of placebo).

Purpose of the Meeting: Discussion of dispenser description and a request for information

Discussion Points:
- Unacceptability of [redacted] as a dispenser descriptor
- Consideration of alternative of "Extended Cycle" dispenser
- Request for a table depicting scheduled bleeding in the studies

Action:
- Barr to send table by August 25, 2003.
- Barr to consider alternative to [redacted]
- PI will be sent email today and the PPI on Monday Aug. 25, 2003.

Minutes prepared: Karen Anderson, N.P. - Project Manager
Chair concurrence: Scott Monroe, M.D. - Medical Team Leader

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

/s/

Karen Anderson

9/4/03 06:13:10 PM

Meeting Minutes

Date: May 22, 2003 **Time:** 3:00 –3:45 PM **Location:** Conference Rm 17b45

NDA: 21-544 **Indication:** Contraception

Drug Name: Seasonale (levonorgestrel / ethinyl estradiol) Tablets

Sponsor: Barr Laboratories, Inc.

Meeting Type: Telephone Conference

Meeting Chair: Scott Monroe, M.D.- Medical Team Leader, Division of Reproductive and Urologic Drug Products (DRUDP; HFD-580)

Meeting Recorder: Karen Anderson, N.P. - Regulatory Project Manager, DRUDP (HFD-580)

FDA Attendees:
Donna Griebel, M.D. – Deputy Director, DRUDP (HFD-580)
Scott Monroe, M.D. - Medical Team Leader, DRUDP (HFD-580)
Gerald Willett, M.D. - Medical Officer, DRUDP (HFD-580)
Karen Anderson, N.P. - Regulatory Project Manager, DRUDP (HFD-580)

External Attendee:
Carole Ben-Maimon – President and COO, Barr Research, Inc.
Howard Hait - Vice President, Data Management, Bio-Statistics and Commercial Marketing Support, Barr Research, Inc.
Christine Mundkur – Senior Vice President, Quality and Regulatory Counsel, Barr Research, Inc
Joe Carrado - Senior Director, Clinical Regulatory Affairs
Wayne Mulcahy - Senior Director, Clinical Regulatory Affairs

Background: The sponsor proposes a 91-day oral contraceptive regimen (84 days of levonorgestrel and ethinyl estradiol tablets followed by 7 days of placebo).

Purpose of the Meeting: Advise sponsor of need to extend the review clock because of the quantity of new clinical data related to their submission of the final interim study report for the extension study (Study SEA-301A).

Discussion Points:
Extension of the review clock to August 15, 2003 based on the date of receipt of the complete submission.
Corrupt PDF file for final interim report– The PDF file for the final interim report that was submitted to the EDR contains several tables with incomplete data cells/fields.

Action:
- Barr to send the complete and corrected PDF and hard copy files to the NDA for Study 301A.
- Barr to provide combined line listings and SAS data files for lab data and adverse events for all patients who elected to extend from the 301 pivotal trail to the extension trial (combined listings and data files incorporating data by patient from both trials).

- Barr to send in a guide to the SAS transport files – headings and a master glossary.
- DRUDP to advise Barr that the extension for a major amendment is dated from the original action date and not the date of receipt of the complete submission – the revised action date is September 5, 2003.

Comment: DRUDP will make every effort to expedite the review.

Minutes prepared: Karen Anderson, N.P. - Project Manager
Chair concurrence: Scott Monroe, M.D. - Medical Team Leader

Reviewed: G. Willett 6/2/03
Reviewed S. Monroe 6/18/03
Reviewed: D. Griebel 6/20

APPEARS THIS WAY
ON ORIGINAL

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

/s/

Scott Monroe

6/23/03 05:35:42 PM

Meeting Minutes

Date: May 7, 2003 **Time:** 2:45 – 3:30 PM **Location:** Conference Rm 17b45

NDA: 21-544 **Indication:** Contraception

Drug Name: Seasonale (levonorgestrel / ethinyl estradiol) Tablets

Sponsor: Barr Laboratories, Inc.

Meeting Type: Telephone Conference

Meeting Chair: Scott Monroe, M.D.- Medical Team Leader, Division of Reproductive and Urologic Drug Products (DRUDP; HFD-580)

Meeting Recorder: Karen Anderson, N.P. - Regulatory Project Manager, DRUDP (HFD-580)

FDA Attendees:
Donna Griebel, M.D. – Deputy Director, DRUDP (HFD-580)
Scott Monroe, M.D. - Medical Team Leader, DRUDP (HFD-580)
Gerald Willett, M.D. - Medical Officer, DRUDP (HFD-580)
Karen Anderson, N.P. - Regulatory Project Manager, DRUDP (HFD-580)

External Attendee:
Carole Ben-Maimon – President and COO, Barr Research, Inc.
Howard Hait - Vice President, Data Management, Bio-Statistics and Commercial Marketing Support, Barr Research, Inc.
Christine Mundkur – Senior Vice President, Quality and Regulatory Counsel, Barr Research, Inc
Joe Carrado - Senior Director, Clinical Regulatory Affairs
Wayne Mulcahy - Senior Director, Clinical Regulatory Affairs

Background: The sponsor proposes a 91-day oral contraceptive regimen (84 days of levonorgestrel and ethinyl estradiol tablets followed by 7 days of placebo).

Purpose of the Meeting: Container labeling and other chemistry related issues. Clinical issues.

Discussion Points:
Revisions to the container labeling

- [redacted]
- [redacted]

Method Validation Package: All required copies should be submitted for all non-compendial test methods. Include the test methods, validation reports, list of samples to be submitted to the FDA labs and certificates of analysis of the samples.

Dissolution profiles: Based on the dissolution profiles of the clinical batches, dissolution acceptance criteria should be as follows:
Levonorgestrel: Q= [redacted] 30 minutes
Ethinyl estradiol: Q = [redacted] 30 minutes

Clinical issues:

- Total estrogen exposure in the cycle
- Request extension study: complete details to include narrative QA of data, demographics, and safety data.

Action:

- Barr to send revised container labeling and Method Validation package.
- The proposed dissolution acceptance criteria will be evaluated.
- Request for extension study details

Minutes prepared: Karen Anderson, N.P. - Project Manager
Chair concurrence: Scott Monroe, M.D. - Medical Team Leader

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

/s/

Karen Anderson
9/4/03 06:10:33 PM

Meeting Minutes

Date: April 17, 2003 **Time:** 10:45 – 11:15 AM **Location:** Office 17b30

NDA: 21-544 **Indication:** Contraception

Drug Name: Seasonale (levonorgestrel / ethinyl estradiol) Tablets

Sponsor: Barr Laboratories, Inc.

Meeting Type: Telephone Conference

Meeting Chair: Scott Monroe, M.D.- Medical Team Leader, Division of Reproductive and Urologic Drug Products (DRUDP; HFD-580)

Meeting Recorder: Karen Anderson, N.P. - Regulatory Project Manager, DRUDP (HFD-580)

FDA Attendees:
Scott Monroe, M.D. - Medical Team Leader, DRUDP (HFD-580)
Gerald Willett, M.D. - Medical Officer, DRUDP (HFD-580)
Karen Anderson, N.P. - Regulatory Project Manager, DRUDP (HFD-580)

External Attendee:
Carol Ben-Maimon – President and COO, Barr Research, Inc.
Howard Hait, Vice President, Data Management, Bio-Statistics and Commercial Marketing Support, Barr Research, Inc.
Christine Mundkur – Senior Vice President, Quality and Regulatory Counsel, Barr Research, Inc

Background: The sponsor proposes a 91-day oral contraceptive regimen (84 days of levonorgestrel and ethinyl estradiol tablets followed by 7 days of placebo).

Purpose of the Meeting: Follow-up on a fax sent by DRUDP to the sponsor asking for clarification of the data under clinical review for the NDA.

Discussion Points:
First bullet point- Complete your auditing of the extension study SEA-301A to date to allow for finalization of additional safety data for Seasonale.

The data will be completed and submitted at the end of the month. Changes will be highlighted.

Second bullet point – Provide case listings and totals of subjects on Seasonale and Nordette with no days of breakthrough bleeding or spotting (unanticipated bleeding/spotting) by cycle and for the entire study period.

Regarding those cases where there BTB or very little spotting – would like more demographic information such as age, weight (height?), pill taking status (new start or previous user). Also discussed inverse trend regarding decreased bleeding over increase of time used. Will need further evaluation to determine if the trend is related to adjustment to the product versus skewed by those who dropped out related to unacceptable bleeding.

Third bullet point – Provide the following table columns for Seasonale (sample provided in the fax). Submit as SAS transport (both to the document room and separately to the division).

Discussion of how the discontinuation of the product for bleeding effects the calculations. ITT table (total bleeding / cycle) – discussion of how medians were derived.

Fourth bullet point – Provide the cycle day definitions of anticipated and unanticipated bleeding/spotting episodes.

Clarification of what constitutes unscheduled vs. scheduled bleeding - continuation bleeding from placebo week in to the first week of active pills.

Action:

- Send in a complete database by the end of the moth with changes highlighted.
- We will send a grid outlining detailed case information requested to Barr.
- In return, Barr will send in a PDF/Word file and SAS transport file when completed.

Minutes prepared: Karen Anderson, N.P. - Project Manager
Chair concurrence: Scott Monroe, M.D. - Medical Team Leader

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

/s/

Karen Anderson
9/4/03 06:18:19 PM

Meeting Minutes

Date: February 5, 2003 **Time:** 1:00 – 1:30 PM **Location:** 17B30

NDA: 21-544 **Indication:** Contraception

Drug Name: Seasonale (levonorgestrel / ethinyl estradiol) Tablets

Sponsor: Barr Laboratories, Inc.

Meeting Type: Telephone Conference

Meeting Chair: Scott Monroe, M.D.- Medical Team Leader, Division of Reproductive and Urologic Drug Products (DRUDP; HFD-580)

Meeting Recorder: Karen Anderson, N.P. - Regulatory Project Manager, DRUDP (HFD-580)

FDA Attendees:
Scott Monroe, M.D. - Medical Team Leader, DRUDP (HFD-580)
Gerald Willett, M.D. - Medical Officer, DRUDP (HFD-580)
Sonia Castillo, Ph.D. –Statistician, Division of Biometrics II (DBII) @ DRUDP (HFD-715)
Karen Anderson, N.P. - Regulatory Project Manager, DRUDP (HFD-580)

External Attendee:
Carole Ben-Maimon – President and COO, Barr Research, Inc.
Howard Hait - Vice President, Data Management, Bio-Statistics and Commercial Marketing Support, Barr Research, Inc.
Christine Mundkur – Senior Vice President, Quality and Regulatory Counsel, Barr Research, Inc

Background: The sponsor proposes a 91-day oral contraceptive regimen (84 days of levonorgestrel and ethinyl estradiol tablets followed by 7 days of placebo).

Purpose of the Meeting: Statistical review and request for data.

Discussion Points:
- Request for the stats program used to calculate the data.

Action:
- Barr to send staticical program as a desk copy and as a submission to the NDA.
- Barr to fax pregnancy table.

Minutes prepared: Karen Anderson, N.P. - Project Manager
Chair concurrence: Scott Monroe, M.D. - Medical Team Leader

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

/s/

Karen Anderson

9/4/03 06:07:37 PM

9 Page(s) Withheld

Office of Drug Safety

MEMO

To: Daniel Shames, MD
Director, Division of Reproductive and Urologic Drug Products
HFD-580

From: Scott Dallas, R.Ph.
Safety Evaluator, Division of Medication Errors and Technical Support
HFD-420

Through: Denise Toyer, Pharm.D.
Team Leader, Division of Medication Errors and Technical Support
HFD-420

Carol Holquist, R.Ph.
Deputy Director, Division of Medication Errors and Technical Support
HFD-420

CC: Karen Anderson
Project Manager, Division of Reproductive and Urologic Drug Products
HFD-580

Date: August 15, 2003

Re: ODS Consult 01-0240-3;
Seasonale (Levonorgestrel and Ethinyl Estradiol Tablets);
NDA 21-544

This memorandum is in response to an August 5, 2003 request from your Division for a re-review of the proprietary name, Seasonale.

The Division of Medication Errors and Technical Support (DMETS) have not identified any additional proprietary or established names that have the potential for confusion with Seasonale since we conducted our proprietary name reviews dated December 14, 2001 (ODS consult 01-0240) and March 29, 2003 (ODS consult 01-0240-1). The Expert Panel expressed concern that the proprietary name, Seconal should be re-evaluated due to the potential for the names, Seasonale and Seconal to sound-alike. Upon re-evaluation DMETS has concluded the potential for confusion is low, based upon the drug products differences in pharmacological class, indication for use, prescription legend classification, product strength and dosage

formulation. Therefore, we have no objections to the use of the proprietary name, Seasonale from a safety perspective.

However, the Division of Drug Marketing, Advertising, and Communications (DDMAC) reiterated their concerns [redacted]

Additionally, DMETS reviewed the revised blister label and carton labeling submitted in the July 17, 2003 labeling amendment and the revised package insert labeling submitted in the August 1, 2003 labeling amendment. DMETS has identified the following areas of possible improvement in order to minimize the potential for medication errors.

General Comments:

1. The statement " [redacted] was changed on the revised labels and labeling to " [redacted] Previously DMETS was concerned that the statement " [redacted] would be used to promote the product, which could cause physicians to prescribe a [redacted] instead of the product "Seasonale". However, the new statement " [redacted] Tablet Dispenser" is even more prominent on the foil pouch and carton labeling. DMETS recommends the prominence of the statement " [redacted] Tablet Dispenser" which is only to indicate a packaging configuration should be decreased to minimize the potential for confusion.

   DDMAC also expressed their concern [redacted]

2. The first sentence of the Description section of the Package Insert reads in part, " Seasonale® (levonorgestrel and ethinyl estradiol tablets) is an extended-cycle oral contraceptive..." DMETS is concerned the terminology "extended-cycle" implies these oral contraceptive tablets or dosing schedule provides an additional benefit over other oral contraceptive tablets or dosing schedules. DMETS recommends the removal of the terminology "extended cycle".

The Division of Medication Errors and Technical Support (DMETS) considers this a final name review. However, if the approval of the NDA is delayed beyond 90 days from the date of this review, the name must be re-evaluated. A re-review of the name before NDA approval will rule out any objections based upon approvals of other proprietary/established names from this date forward.

If you have any questions or need clarification, please contact the project manager, Sammie Beam at 301-827-3242.