CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-544

MEDICAL REVIEW

Division of Reproductive and Urologic Drug Products

Clinical Review

NDA 21-544

Seasonale

(ethinyl estradiol 30 μg/levonorgestrel 150 μg)

Barr Laboratories

September 4, 2003

CLINICAL REVIEW

NDA 21-544

Date submitted: August 5, 2002
Review completed: August 18, 2003

Reviewer:
Gerald D. Willett MD
Division of Reproductive and Urologic Drug Products

Applicant:
Barr Research
One Bala Plaza
Suite 324
Bala Cynwyd, PA 19004-1401
610-668-2989

Proposed Trade Name:
Seasonale

Chemical names for combination product:
Levonorgestrel
18,19-Dinorpregn-4-en-20-yn-3-one, 13-ethyl-17-hydroxy-, (17α)-, (-)-
Ethinyl estradiol
19-Norpregna-1,3,5(10)-trien-20-yne-3,17-diol, (17α)-

Dosage form:
Seasonale Tablets (Levonorgestrel and Ethinyl Estradiol, USP 0.15mg/0.03mg – 84 active tablets, 7 placebo)

Route of administration:
Oral

Proposed indication:
Seasonale Tablets are indicated for the prevention of pregnancy

Related INDs:
60,399 (Barr Laboratories, Prevention of Pregnancy)

Related NDAs:
NDA 18-668 Nordette

Related ANDA:
75-866 Generic levonorgestrel and ethinyl estradiol, 0.15mg/0.03mg, Portia (28 day regimen)
73-592 Generic levonorgestrel and ethinyl estradiol, 0.15mg/0.03mg, Levora (28 day regimen)

Table of Contents

Table of Contents **3**

Table of Tables **6**

Executive Summary **8**

I. Recommendations **8**

A. Recommendation on Approvability 8

B. Recommendation on Phase 4 Studies and/or Risk Management Steps 8

II. Summary of Clinical Findings **8**

A. Brief Overview of Clinical Program 8

B. Efficacy 9

C. Safety 11

D. Dosing 12

E. Special Populations 12

Clinical Review **13**

I. Introduction and Background **13**

A. Drug Established and Proposed Trade Name, Drug Class, Sponsor's Proposed Indication(s), Dose, Regimens, Age Groups 13

B. State of Armamentarium for Indication(s) 13

C. Important Milestones in Product Development 13

D. Other Relevant Information 15

E. Important Issues with Pharmacologically Related Agents 15

II. Clinically Relevant Findings from Chemistry, Animal Pharmacology and Toxicology, Microbiology, Biopharmaceutics, Statistics and/or Other Consultant Reviews 15

III. Human Pharmacokinetics and Pharmacodynamics 17

IV. Description of Clinical Data and Sources 17

A. Overall Data 17

B. Tables Listing the Clinical Trials 17

C. Postmarketing Experience 18

D. Literature Review 18

V. Clinical Review Methods 20

A. How the Review was Conducted 20

B. Overview of Materials Consulted in Review 21

C. Overview of Methods Used to Evaluate Data Quality and Integrity 21

D. Were Trials Conducted in Accordance with Accepted Ethical Standards. 21

E. Evaluation of Financial Disclosure 21

VI. Integrated Review of Efficacy 22

A. Brief Statement of Conclusions 22

B. General Approach to Review of the Efficacy of the Drug 22

C. Detailed Review of Trials by Indication 22

D. Reviewer's Efficacy Conclusions 39

VII. Integrated Review of Safety 40

A. Brief Statement of Conclusions 40

B. Description of Patient Exposure to Study Drugs 41

C. Methods and Specific Findings of Safety Review 43

D. Adequacy of Safety Testing 75

E. Summary of Critical Safety Findings and Limitations of Data 75

VIII. Dosing, Regimen, and Administration Issues 76

IX. Use in Special Populations 77

A. Evaluation of Sponsor's Gender Effects Analyses and Adequacy of Investigation 77

B. Evaluation of Evidence for Age, Race, or Ethnicity Effects on Safety or Efficacy 77

C. Evaluation of Pediatric Program 77

D. Comments on Data Available or Needed in Other Populations 77

X. Conclusions and Recommendations 78

XI. Appendix 79

Table of Tables

Table 1	Overview of Major Clinical Trials	18
Table 2	Published Oral Contraceptive Studies Utilizing an Extended Dosing Regimen	19
Table 3	Investigators with Potential Financial Conflicts	21
Table 4	Conventional (28-day) treatment cycle (Nordette and Levlite)	27
Table 5	Extended (91-day) treatment cycle (Seasonale and Seasonale Ultra-Lo)	27
Table 6	Demographic Characteristics: All Treated Patients (ITT Population)	31
Table 7	Demographic Characteristics: All Treated Patients 18-35 Years (PITT Population)	31
Table 8	Patient Disposition (ITT population)	32
Table 9	Sponsor's Revised Calculation of Pearl Index (Subjects 18-35 years old)	33
Table 10	FDA Biostatistician's Calculation of Pearl Index (Subjects 18-35 years old)	33
Table 11	Reported Pregnancies in the Seasonale Treatment Group	34
Table 12	Reported Pregnancies in the Nordette Treatment Group	36
Table 13	Reported Pregnancies in the Seasonale Ultra-Lo Treatment Group	37
Table 14	Reported Pregnancies in the Levlite Treatment Group	38
Table 15	Exposure to Study Drugs (SEA 301 and SEA 301A – 28-day Cycle Equivalents)	41
Table 16	Extent of Patient Exposure to Study Drugs (ITT Population) in Trial SEA 301	42
Table 17	Exposure to Study Drugs in Extension Trial SAE 301A	42
Table 18	Serious Adverse Events – Seasonale Treatment Group (Study SEA 301)	46
Table 19	Serious Adverse Events – Nordette Treatment Group (Study SEA 301)	47
Table 20	Serious Adverse Events - Seasonale Ultra-Lo Treatment Group (Study SEA 301)	48
Table 21	Serious Adverse Events – Levlite Treatment Group (Study SEA 301)	48
Table 22	Adverse Events Leading to Discontinuation from Study (Study SEA 301)	49
Table 23	Subject Discontinuation by Month Due to "Bleeding Problems" (ITT Population, SEA 301)	50
Table 24	Most Frequently Reported Adverse Events (SEA 301)	51
Table 25	Total Days of Bleeding and/or Spotting by Cycle (ITT Population, SEA 301)	52
Table 26	Total Days of Unscheduled Bleeding and/or Spotting by Cycle (ITT Population, SEA 301)	53
Table 27	Analysis of Unanticipated Bleeding/Spotting for Seasonale Subjects in SEA 301	54
Table 28	Analysis of Unanticipated Bleeding/Spotting for Nordette Subjects in SEA 301	54
Table 29	Percent Subjects Reporting Unexpected Bleeding/Spotting in Preceding Week (SEA 301)	55
Table 30	Mean and Median Subject Weights (Pounds) in Study SEA 301	56
Table 31	Screening and Endpoint Lipid and Hematology Mean Values (SEA 301)[A]	57
Table 32	Shift Analyses for Lipid and Hematology Values (Seasonale Group, SEA 301).	58
Table 33	Shift Analyses for Lipid and Hematology Values (Nordette Group, SEA-301)	59

Table 34 Seasonale Subjects with Anemia (SEA 301) 59
Table 35 Shift Analysis for Liver Function Tests (Seasonale Group, Study SEA 301) 60
Table 36 Shift Analysis for Liver function Tests (Nordette Group, Study SEA-301) 61
Table 37 Safety Findings from Pharmacology (BA/BE) Studies 62
Table 38 Percent of Subjects with Breakthrough Bleeding/Spotting on Nordette (NDA 18-668) 63
Table 39 Frequent Adverse Events in Nordette Subjects (Original NDA 18-668) 63
Table 40 Schedule of Events Study SEA-301A (extension study) 65
Table 41 SEA-301 Study Drug Assignments vs. Initial SEA-301A Study Drug Assignments 66
Table 42 Distribution of "Gap" Duration 67
Table 43 Disposition of Subjects in Study SEA 301A (Cutoff of January 24, 2003) 67
Table 44 Serious Adverse Events in Study SEA 301A 68
Table 45 Adverse Events Leading to Study Discontinuation in SEA-301A 69
Table 46 Reported Adverse Events (≥ 5%) in Study SEA 301A 70
Table 47 Laboratory Shift Table – Pre-Study SEA-301A Value (If Available) OR Last SEA-301 Value (If No Pre-Study SEA-301A Value Was Available) to Last SEA-301A Value 71
Table 48 Subjects on Seasonale with Bleeding Problems who Discontinued in SEA-301A 72
Table 49 Observed Total Number of Days of Bleeding and/or Spotting by Treatment Cycle (All Treated Patients - ITT) 73
Table 50 Observed Number of Days of Unscheduled Bleeding and/or Spotting by Cycle (ITT) 74
Table 51 Proportion of Patients With No Reported Bleeding and/or Spotting by Cycle 74
Table 52 Exposure to Ethinyl Estradiol (EE) and Levonorgestrel (LNG) (Seasonale vs. Other Approved Combination Oral Contraceptives 76

Clinical Review for NDA 21-544

Executive Summary

I. Recommendations

A. Recommendation on Approvability

Approval of Seasonale for prevention of pregnancy is recommended based on the sponsor's demonstration of an acceptable Pearl Index and an acceptable safety profile. Agreements with the sponsor concerning product labeling were reached on September 4, 2003.

B. Recommendation on Phase 4 Studies and/or Risk Management Steps

The ongoing extension study (SEA-301-A) should be completed per present protocol with submission of the final report

II. Summary of Clinical Findings

A. Brief Overview of Clinical Program

Barr Laboratories, Inc. has proposed an extended use of a combination oral contraceptive (COC) in this NDA. They are proposing that an approved contraceptive formulation utilizing 0.15 mg levonorgestrel and 0.03 mg ethinyl estradiol (prior approval as Nordette and generic Portia) be given as active pill for 84 consecutive days with a 7-day withdrawal period. Most oral contraceptives are given as 21 days active with a 7-day withdrawal. The primary benefit proposed by the sponsor for this regimen, in addition to contraception, is to reduce the number of withdrawal periods that women undergo while taking oral contraceptives.

To seek approval for this regimen, the sponsor has submitted a NDA (NDA 21-544) under Section 505(b)(2). Their application consists of the following major components:

- A single Phase 3 clinical trial (Study SEA 301) in which the to-be-marketed product, Seasonale (also referred to as Seasonale Lo in the submission) was compared to Nordette,

Seasonale Ultra-Lo (an unapproved combination oral contraceptive that also was under development by Barr Labs), and Levlite (a previously approved COC)

- Safety and effectiveness data from Nordette (the previously approved drug product)
- Interim safety data from an extension study that is evaluating Seasonale and Seasonale Ultra-Lo over a two year time period
- Other published clinical trials evaluating extended dose regimens for oral combination contraceptives
- Five bioavailability/bioequivalence studies

— the present NDA seeks marketing approval only for Seasonale. This review therefore focused on the clinical data for Seasonale and Nordette (the approved conventional oral contraceptive with the same doses of ethinyl estradiol and levonorgestrel as Seasonale).

B. Efficacy

Efficacy was based on Seasonale's ability to prevent pregnancy in the Phase 3 clinical trial. This was calculated by the Pearl Index (PI) using all "during treatment" pregnancies. During treatment pregnancies are defined as those for which conception occurs on or after the date of first taking study drug and extends through the 14 days following the last dose of study drug.

Although the total number of pregnancies recorded in the Seasonale arm was eight, this reviewer concurs with the sponsor that only four qualified as "during treatment" pregnancies. The sponsor supplied additional source sonographic documentation to verify this.

The most conservative approach to calculate the Pearl Index was employed. Only women age 18-35 were used in the calculation. All incomplete cycles (less than 91 days) and all cycles with additional birth control methods were excluded from the calculation. These criteria affect the denominator in the Pearl Index calculation.

During the course of this NDA review, the FDA biostatistics reviewer identified an error in the number of complete treatment cycles without backup contraception utilized by the sponsor as the denominator in their Pearl Index calculation. Utilizing the FDA biostatistician's corrected denominator (809 cycles instead of 951), the Pearl Index for Seasonale is 1.98 (95% CI: 0.54, 5.03). The sponsor subsequently concurred that the FDA calculation was correct and that their original calculation was incorrect. Compared to the Pearl Index for other approved combination oral contraceptives (which has been as high as 2.39 in Phase 3 clinical trials), the Pearl Index of 1.98 is acceptable.

The Pearl Index for Nordette in this trial (2.22) is higher than that seen in the trial leading to its approval in 1982 (PI = 0.48). Higher Pearl Index rates may be related to more frequent pregnancy testing, more accurate sonography, and possibly, poorer compliance. The original Nordette trial also had some women participating for as long as two years, which will improve the efficacy results expressed in terms of the Pearl Index.

In Study SEA 301, patients recorded pill taking and vaginal bleeding/spotting by means of an electronic diary that included a daily prompt. It can be argued that the daily diary prompt that allowed for a more accurate assessment of bleeding/spotting in the Seasonale pivotal trial could have also increased compliance. However, this prompt was present also for the Nordette group. The prompt did not appear to improve the Pearl Index for Nordette, which is more than four times greater than that seen with its original approval. Seasonale does not need to be marketed with a device that would provide a daily prompt.

Theoretically, the use of extended combination oral contraceptives, may increase pregnancy protection for some patients. There are two less time periods for withdrawal hormone effects during each Seasonale cycle. Some pregnancies may occur because of inadequate hormone levels at the beginning of a contraceptive pill cycle. There do not appear to be any theoretical reasons why extended oral contraceptive therapy should provide less pregnancy protection than conventional 28-day dosage regiments.

The daily diary, in addition to allowing for collection of more accurate information on vaginal bleeding, also potentially allowed for more accurate assessment of a "compliant" or "perfect" Pearl Index. The sponsor had compliance criteria based on the entire study time period. This reviewer assessed "compliant" Pearl Index by looking directly at pill taking during the time of conception. When subjects were assessed for compliance in their medication use during the period of their calculated conception date, this reviewer determined the compliant Pearl Index rates to be 0.99 and 1.47 for Seasonale and Nordette, respectively.

C. Safety

The safety database for Seasonale involves 456 subjects (ITT) in the pivotal SEA-301 study, 191 subjects in the SEA-301A extension study (105 of whom also received Seasonale ins SEA 301), and 155 subjects in 5 BA/BE studies. According to the discontinuation database, 271 subjects in the Seasonale arm of the pivotal SEA-301 study completed the one-year study. The sponsor stated that ITT Seasonale subjects from the pivotal study have contributed 4,337 "28-day" safety cycle month equivalents. Although a minimum of 10,000 28-day cycles is usually studied for new contraceptives, this is an approved contraceptive formulation dose (approved since 1982) that only differs in the dosing duration. This reviewer would consider a safety database that is equivalent to 5,000 cycle months to be sufficient for safety analysis.

The sponsor fulfilled the 5,000 cycle month equivalents by finalizing interim safety data from another 1,609 "28-day" safety cycle month equivalents from the 191 subjects taking Seasonale in the SEA-301A extension study. This brings the total cycle month equivalents to 5,946.

No new safety concerns have arisen to date from the Seasonale pivotal trial (SEA-301), the interim safety report from the extension trial (SEA-301A) and the BA/BE trials. One death was reported in the extension trial but this was related to a motorcycle accident and not related to Seasonale. Serious adverse events related to or possibly related to Seasonale (SEA-301 and SEA-301A) include one subject with a pulmonary embolus, three subjects with gallbladder disease, one subject with syncope, one subject with an ovarian cyst, and one subject with bleeding complications related to uterine fibroids.

The subject who developed the pulmonary embolus was 39 years old and weighed 202 pounds. She developed symptoms on day 320 of Seasonale Therapy (Cycle 3, day 47). She had no family history of thrombotic complications. She had engaged in recent air travel approximately three days before symptoms with a flight that lasted 1.5 hours. The sponsor subsequently tested this subject for medical conditions that would increase her risk for thromboembolic disease. All these laboratory tests were normal.

Seasonale does provide more yearly hormone exposure to a patient than a comparable 28-day regimen, but this is spread over more days rather than increasing the daily level. The yearly exposure with Seasonale falls approximately halfway between two approved combination oral contraceptives containing levonorgestrel and ethinyl estradiol (more exposure than LoOvral but less than Ovral). This one case of pulmonary embolism is not felt to constitute a signal that patients taking this regimen will be at greater risk for thromboembolic events than the presently approved oral contraceptives.

The primary adverse event related to Seasonale is unanticipated bleeding and/or spotting (i.e., bleeding and spotting between planned withdrawal bleeding). This event caused more discontinuations in the Seasonale arm compared to the Nordette arm in the pivotal study SEA-301 (7.7% versus 1.8%). During the first cycle of Seasonale, 35% of the subjects had 20 or more days of unexpected bleeding/spotting and 65% had 7 or more days. Although this side effect diminishes somewhat with use, approximately 15% of subjects still had 20 or more days of

unanticipated bleeding/spotting in the fourth cycle of use and approximately 40% had 7 or more days.

Despite the prolonged number of days of unanticipated bleeding/spotting in some subjects, it appears that the quantity of blood loss with this bleeding is usually of no clinical significance. There was no evidence in the hematology laboratory dataset from the pivotal SEA-301 trial that there are significant problems with anemia (hematocrits < 35.0%) in those subjects taking Seasonale. The number of Seasonale subjects with anemia during the study was comparable to that found in the Nordette arm. There was no problem with anemia in the subjects who prematurely discontinued in the Seasonale arm for reasons of unacceptable bleeding.

The label should accurately reflect the bleeding results from the clinical trials, especially in regard to the unanticipated bleeding/spotting.

D. Dosing

Dosing duration is the key difference in this combination oral contraceptive application. Active combination oral contraceptive tablets are being given for 84 days instead of 21 days before the seven-day hormonal withdrawal period (placebo tablets).

E. Special Populations

Combination oral contraceptives are intended for the population of women at risk for pregnancy. No formal pharmacokinetic studies of Seasonale were performed in different racial groups. No formal studies evaluated the effect of hepatic or renal disease on the disposition of Seasonale. The fact that steroid hormones may be poorly metabolized in patients with impaired liver function is already part of class labeling for oral contraceptives.

The sponsor has requested a full waiver of all pediatric studies since according to class labeling, the safety and efficacy of levonorgestrel and ethinyl estradiol tablets have been established in women of reproductive age and are expected to be the same for postpubertal adolescents under the age of 16 and for 16 years and older. A waiver is recommended.

Clinical Review

I. Introduction and Background

A. Drug Established and Proposed Trade Name, Drug Class, Sponsor's Proposed Indication(s), Dose, Regimens, Age Groups

The established drug name combination is levonorgestrel and ethinyl estradiol, 0.15mg/0.03mg. The proposed trade name is Seasonale. The active dose is proposed to be taken orally on a daily basis for 84 days. Following this, 7 placebo tablets will be taken daily during the contraceptive withdrawal period. This product is intended for women of reproductive age range at risk for pregnancy.

B. State of Armamentarium for Indication(s)

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 has been utilized for patient convenience or for medical conditions such as endometriosis.

The contraceptives that have been approved for extended use past 28 days have included medicated and inert IUDs, depot injectable medroxyprogesterone, and contraceptive subdermal implants (e.g., Norplant system).

C. Important Milestones in Product Development

The sponsor initially submitted their pre-IND meeting package to the Agency on October 6, 1999. The initial pre-IND meeting was held November 2, 1999. The sponsor'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 and then cross over to extended oral contraceptive therapy for one year. The Division of Reproductive and Urologic Drug Products (DRUDP) recommended a direct head-to-head comparative trial with the approved 28-day counterparts to the two Seasonale drug products to be studied [levonorgestrel and ethinyl estradiol: 0.15mg/0.03mg (Seasonale) and 0.10mg/0.02 mg (Seasonale Ultra-Lo), respectively] and to not perform the crossover from conventional to extended therapy.

The sponsor initially proposed a minimum of 4,800 months of study exposure for the two dose levels of Seasonale. The Division recommended a minimum of 10,000 cycles of study exposure. The Division meeting minutes do not specify whether 10,000 cycles were recommended per drug

product or whether the 10,000 cycles referred to the total number of study subjects (combined number of cycles in subjects taking Seasonale and Seasonale Ultra-Lo in the clinical trial). However, this reviewer interprets the recommendation to mean 5,000 28-day treatment cycles per dosage level with a total of 10,000 28-day cycle equivalents for both drug formulations. Both dosage levels of ethinyl estradiol/levonorgestrel have been approved products for over many years (Nordette > 20 years, Levlite > 4 years) and no new safety concerns have arisen with either of the approved drug products. Higher dosage levels of the same hormones also are available as Ovral, an oral contraceptive presently marketed in the US. The sponsor also was asked by the Division to enroll sufficient subjects to allow for 200 women completing a full year of treatment with each of the drug products.

The sponsor provided information with the pre-IND meeting package regarding their intended use of an electronic diary to gather information regarding pill taking and vaginal bleeding. The Division recommended that the diaries also collect information regarding the use of birth control methods other than study drug. The sponsor was also informed that any cycle in which additional or backup birth control was utilized would be eliminated as an "at risk" cycle in the primary efficacy analysis for pregnancy prevention.

There was a discussion of risk:benefit with the sponsor during a teleconference on November 12, 1999. There was an expectation that Seasonale should show some clinical advantage over conventional 28-day regimens in addition to comparable contraceptive effectiveness.

A second pre-IND meeting was held on February 17, 2000. This meeting focused on clinical endpoints. The sponsor was proposing a number of primary objectives. Prevention of pregnancy was recommended by the Division as the primary endpoint. The sponsor was provided with a number of recommendations regarding pregnancy assessment. The sponsor clarified at this meeting that they were not seeking a superiority claim, but that they would retain the Nordette and Levlite comparator arms to support approval. The Division informed the sponsor that any quality of life questionnaire would require validation and appropriate study design to consider as a labeling claim.

The sponsor submitted their IND on May 16, 2000. The sponsor was allowed to proceed with the study after Division review. Comment was made to the sponsor in regard to an exclusion of women with a history of breakthrough bleeding/spotting ≥ 10 consecutive days while on oral contraceptives. The sponsor was informed that this could lead to labeling restrictions.

On August 9, 2001 the sponsor submitted a protocol for an open-label 2-year extension study (SEA-301A) to gather further safety data with Seasonale. The study would allow extended contraceptive therapy with either Seasonale or Seasonale Ultra-Lo (84 days active/ 7 placebo) for all participants in SEA-301.

A pre-NDA teleconference was held April 23, 2002. At this time, the sponsor indicated their [redacted] The Division requested that the sponsor submit all information from all four arms of the pivotal Phase 3 study as well as information from the quality of life questionnaire.

Major interactions with the sponsor during the review process following NDA submission include the following:

- Source documentation to substantiate "on" or "off" treatment pregnancy occurrence
- Recalculation of the Pearl Index for Seasonale based on the correct number of treatment cycles (excluding cycles where other birth control methods had been used)
- Requesting the sponsor to submit quality assured safety data (cut off date of January 24, 2003) and a final interim safety report from the ongoing extension study (SEA-301A)
- Requesting the sponsor to clarify unscheduled bleeding/spotting patterns with new tables that provide line listed subject information per cycle.

D. Other Relevant Information

The pertinent clinical review information is covered in the other sections of the template. There is no additional information for this section.

E. Important Issues with Pharmacologically Related Agents

Important issues with oral contraceptives revolve around contraceptive efficacy and adverse events. Efficacy and safety have been well categorized for this pharmacologic class as a whole since its initiation in the 1960s. The most significant adverse events are thromboembolic and cardiovascular. Serious adverse events have decreased with reduction in daily doses of ethinyl estradiol and progestins. In the last ten years, epidemiological studies have also focused on newer progestins in relation to thromboembolic disorders.

II. Clinically Relevant Findings from Chemistry, Animal Pharmacology and Toxicology, Microbiology, Biopharmaceutics, Statistics and/or Other Consultant Reviews

Pharmacology/Toxicology and Microbiology

There are no significant review issues with Pharmacology/Toxicology or Microbiology.

Chemistry

Initial deficiencies identified by the FDA reviewing chemist were satisfactorily resolved by the sponsor.

Division of Drug Marketing, Advertising, and Communications

The Division of Drug Marketing, Advertising, and Communications (DDMAC) submitted their labeling review.

Division of Drug Risk Evaluation

The Division of Drug Risk Evaluation was consulted in regard to Seasonale's comparator product, Nordette. Review of the AERS database from 1983 through April 10, 2003 indicated a reporting rate average of about 27 reports per year. The only drug related death occurred in a Danish woman secondary to pulmonary embolism, which occurred three years after starting therapy. She was taking Microgynon (Nordette equivalent). Of 533 reports on Nordette in a twenty-year time span, there were 26 reports related to embolism and thrombosis (slightly more than one per year). Some of these patients were additionally found to have additional genetic predispositions for clotting abnormalities. Despite the difficulty in evaluating this form of reporting data, the number of adverse events for Nordette appears to be in a low range compared to other combination oral contraceptive products.

Division of Medication Errors and Technical Support

The Division of Medication Errors and Technical Support expressed no objections to the use of the name Seasonale in a memo dated March 29, 2003.

III. Human Pharmacokinetics and Pharmacodynamics

In support of this NDA, the sponsor submitted two pivotal and three supportive bioavailability/bioequivalence (BA/BE) studies.

Based on the results of the bioequivalence studies, Clinical Pharmacology and Biopharmaceutics found that the to-be-marketed Seasonale formulation is bioequivalent to both the reference listed drug Nordette and to the Seasonale CT formulation used in the clinical study, SEA-301.

Safety information from these BA/BE studies is presented in the safety section of this review.

IV. Description of Clinical Data and Sources

A. Overall Data

The original NDA submission consists of the following clinical data:

- Phase 3 Clinical Trial (SEA-301)
- Journal literature support for extended oral contraceptive use
- Medical officer's review of original NDA for Nordette (NDA 18-668)

Additional Clinical Material (Spontaneous Submissions and Division Requests)

- Four-month Safety Update which includes interim (not fully audited) report of open-label extension study
- Fully audited report of open-label extension study (dated May 7, 2003)
- Final interim report for extension study 301-A (Sponsor dated, May 13, 2003)
- Source sonographic data to assist in assessing conception dates in the Seasonale arm
- New tables to show unanticipated bleeding/spotting per cycle in the Seasonale arm
- New laboratory data shift tables to evaluate the full ITT population
- Additional laboratory information on the subject who developed a pulmonary embolus
- Two additional case summaries on subjects developing anemia
- Endometrial biopsy case report forms
- Additional submitted literature regarding oral contraceptives and thrombotic complications
- Revised Pearl Index calculations
- Procedural and quality control information for the Minidoc electronic diary and data assessment

B. Tables Listing the Clinical Trials

The clinical trials supporting NDA 21-544 are listed in Table 1.

Table 1 Overview of Major Clinical Trials

Study	Design	Treatment (levonorgestrel/ethinyl estradiol)
SEA-301	Four arm Parallel Randomized Multicenter Open-Label One year duration	Seasonale (150mcg/30mcg) 4 x 91 days (84 active/ 7 placebo) Nordette (150mcg/30mcg) 13 x 28 days (21 active/ 7 placebo) Seasonale Ultra-Lo (100mcg/20mcg) 4 x 91 days (84 active/ 7 placebo) Levlite (100mcg/20mcg) 13 x 28 days (21 active/ 7 placebo)
SEA-301A	Two arm Extension from SEA-301 Parallel Open label Multicenter Two year duration	Seasonale (150mcg/30mcg) 8 x 91 days (84 active/ 7 placebo) Seasonale Ultra-Lo (100mcg/20mcg) 8 x 91 days (84 active/ 7 placebo)

Source: Original and subsequent NDA submissions by sponsor

C. Postmarketing Experience

There is no specific postmarketing experience with this 91-day cyclic dosing regimen (84 days active tablets/ 7 days placebo tablets). There is, however, a large safety database extending over twenty years for this dosage combination of levonorgestrel and ethinyl estradiol administered in a 28-day cyclic manner (21 days active tablets/ 7 days placebo tablets). As mentioned earlier, the consultative review of AERS database does not indicate new safety concerns either related to new findings or an unexpectedly high number of known adverse events relating to this pharmacologic class of drugs.

D. Literature Review

The following table (Table 2) lists the pertinent journal articles related to extended combination oral contraceptive use.

Table 2 Published Oral Contraceptive Studies Utilizing an Extended Dosing Regimen

Citation	E/C	EE mcg	Progestin mcg	DEAP/W days	DS	MO Notes
Loudon NB - BMJ, 1977:2:187-190	202/ 107	50	Lynoestrenol 250	84/6	12 months	Open label 11% DC for spotting and BTB 6% DC for headaches Spotting and bleeding are low after 9 months No thromboembolic problems reported
Hammerlynck JV et al.- Contraception 1987;35(3):199-205	100/ not report ed	30-40	Varied LNG and Desogestrel	42/7 x1 and then 21/7 x 1	12 weeks	Open label, women already using these products with no problems 34 used LNG triphasic (50/30,75/40,125/30) 37 used LNG monophasic 150/30 29 used desogestrel 150 /30 Spotting and bleeding increases after day 21
De Voogd WS – Contraception 1991;4(2):107-112	116/ 105	30	Desogestrel 150	42/7	1 cycle	Not randomized, only one cycle studied
Cachrimanidou AC et al. – Contraception 1993; 48: 205-216	294/ 179	30	Desogestrel 150	63/7 or 21/7	5 Cycles (12 months)	Randomized, multicenter E/C for extended = 198/115 E/C for standard 3/1 = 96/64 Extended with more BTB/Spotting especially early, 13% DC for bleeding problems compared to 2% for standard Standard more DC for headaches (9% compared to 1.5% for extended) Less bleeding problems with continuous users compared to fresh start
Kovacs et al.– Br J Fam Plan 1994;19:274-275	203/ 59	30	LNG 150	84/7	12 months	One pregnancy was reported 73 women list BTB as one of the reasons for discontinuing
Cachrimanidou AC et al. – Contraception 1994; 50: 153-165	30/20	30	Desogestrel 150	63/7 or 21/7	12 months	Randomized 20 entered /13 completed the long interval regimen 10 entered/7 completed standard regimen Few effects on lipid metabolism Small increases in coagulation parameters but fibrinolytic system appears to remain in balance
Miller L, Notter KM – Obstet Gynecol 2001;98(5):771-778	90/53	30	Norgestrel 300	42/7 or 21/7	Approx 1 year	Extended use resulted in fewer bleeding days and no increase in mean spotting or bleeding episodes
Kwiecien M, et al. Contraception 2003; 67: 9-13	32/28	20	LNG 100	21/7 x 6 or 168 days contin-uous	6 months	Mean cumulative total bleeding and spotting days = 34.9 for conventional 25.9 for continuous women in the continuous needed sanitary protection for 18 days compared to 33 in the conventional

BTB = breakthrough bleeding
DC = discontinuation
DEAP/W = duration of extended active pills/withdrawal period
DS = duration of study
E/C = Entered/Completed
EE = Ethinyl estradiol
LNG = levonorgestrel
Source: Original submission, Vol 1.73; 4-month safety update

Medical officer's comments: The most pertinent of the above articles relating to extended use of oral contraceptives is the article by Kovacs et al. This study utilized the same contraceptive regimen utilized in the Seasonale study.

Noteworthy in Kovac's study was the fact that only 59 (29%) of the women completed the 12-month study. In a study population of 203, 73 women cited breakthrough bleeding as at least one of the reasons for discontinuing. Approximately 30 of those discontinuing listed breast tenderness and/or headaches as at least one of the reasons for discontinuation. All but three of the women were current oral contraceptive users, which allowed them to have prior experience against which to judge the new regimen.

Of the 59 women in Kovacs' study who completed 12 months of treatment, 42 experienced some breakthrough bleeding and 25 reported that they got headaches scattered throughout the cycle. Only one pregnancy was associated with the study, and this was in a woman who started her pill mid-cycle when she was already pregnant.

The Kovac article also mentions the theoretical disadvantage of the use of hormones for 48 weeks of the year compared to 39 weeks. The total hormonal dose is 23% greater than using Nordette in a conventional cyclic fashion and 73% of the total estrogen dose a woman would receive if she took a 50μg pill in the conventional cyclic fashion. The authors did not report any serious adverse events in this study such as thrombotic sequelae.

Although we do not have Kovac's original study data, it would appear that the benefits for extended oral contraceptive therapy may be limited to a subset of individuals taking combination oral contraceptives. Unpredictable bleeding appears to substitute for fewer menstrual periods. Perimenstrual symptoms such as breast tenderness and headache still appear to be common side effects. Although the authors support consideration of the extended regimen to the woman whose monthly menstruation is undesirable, they recommended that women who use the method be counseled about the likelihood of breakthrough bleeding.

V. Clinical Review Methods

A. How the Review was Conducted

The review was conducted utilizing the following:

- Review of the paper and electronic submission
- Independent data analysis utilizing JMP software
- Independent evaluation of the electronic diary
- Independent review of the literature
- Consultation for safety utilizing the AERS database
- Consultative meetings regarding the data findings and clinical issues
- Interactions with sponsor for clarification and additional data

B. Overview of Materials Consulted in Review

Materials consulted in review include:

- Paper and electronic submissions for NDA 21-544
- Consultation reports from the other disciplines
- Pubmed searches and journal review
- Library book and journal sources

C. Overview of Methods Used to Evaluate Data Quality and Integrity

Methods used to evaluate data quality and integrity include

- Review of possible bias based on financial ties
- Spot checking the electronic database with JMP analysis
- Seeking source documentation for efficacy analysis

D. Were Trials Conducted in Accordance with Accepted Ethical Standards

The study protocols and amendments were reviewed by the appropriate Institutional Review Boards (IRBs). Informed consent was obtained according to the ethical principles stated in the latest version of the Declaration of Helsinki (Republic of South Africa; 1996), and the applicable guidelines for Good Clinical Practice.

E. Evaluation of Financial Disclosure

None of the Investigators who participated in Trial SEA 301 identified any potential financial conflicts with the exception of the 3 Investigators listed in Table 3 below.

Table 3 Investigators with Potential Financial Conflicts

Participant	Activity	Compensation
[redacted]		

Source: Original NDA submission

Medical officer's comments: There was no indication of bias from the review of data from [redacted] sites (site [redacted] respectively). Because of the larger compensation amount accorded to [redacted] a more focused data review was performed

for his site —. There was no evidence that the data from this site was biased. The contraceptive efficacy (Pearl Index) for Seasonale and Nordette was calculated excluding site — and found to be 2.13 (95% CI: 0.59, 5.42) and 2.44 (95% CI: 0.51, 7.01), respectively. This revised Pearl Index excluding site — would also be acceptable for approval.

VI. Integrated Review of Efficacy

A. Brief Statement of Conclusions

Utilizing the most conservative criteria for assessing the Pearl Index, Seasonale has an acceptable pregnancy rate. The Pearl Index is 1.98 when evaluating women age 18- 35, excluding women who reported using other birth control methods at some point during the cycle, and excluding partial treatment cycles. The "perfect use" Pearl Index as computed by this reviewer is 0.99. Using a life Table Analysis, the effectiveness of Seasonale was 1.26% (95% C.I. from 0.02% to 2.50%).

The Nordette Pearl Index utilizing the same conservative criteria is 2.22. Using a life Table Analysis, the effectiveness of Nordette was 1.87% (95% C.I. from 0% to 3.98%).

This study utilized a daily electronic diary that had a daily signal alarm that prompted patients for data entry (and hence might also have served as a prompt to take study medication). However, this reviewer does not feel that Seasonale needs to be marketed with a similar device to obtain the reported efficacy.

B. General Approach to Review of the Efficacy of the Drug

The general approach to reviewing the efficacy of an oral contraceptive includes the following:

- Confirm the number of "during treatment" and "off treatment" pregnancies reported by the sponsor.
- Confirm that the cycle information provided by the sponsor is accurate and utilizes the appropriate age of the subjects.
- Verify the mathematical calculation of the Pearl Index

C. Detailed Review of Trials by Indication

Pivotal Clinical Trial

The pivotal phase III trial for contraceptive effectiveness and safety is 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"

Clinical Background

Medical officer's comments:

When oral contraceptives were introduced, 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.

Extended oral contraceptive therapy (a term used to designate a treatment cycle of greater than 28 days) has been used off-label for over 30 years for women with endometriosis to help alleviate the severe dysmenorrhea and attempt to stabilize the disease. This therapy has been termed pseudopregnancy based on the amenorrhea and stromal decidualization that occurs with long term combination oral contraceptive use. Women on this regimen did develop problems with breakthrough bleeding which some clinicians treated by adding additional conjugated estrogen or estradiol to their regimen. Although this approach does not always produce the full desired suppressive effect in all endometriosis patients, there have been no additional safety concerns over and above the known side effects and adverse events associated with conventional 28-day cyclic oral contraceptives.

Short-term extensions beyond 21 consecutive active pill days also have been used for patient convenience for many years, especially to avoid vaginal bleeding at unwanted times. Usage in this setting, however, generally tends to be less than the 84 day on/ 7 day off regimen proposed by the sponsor in this submission.

Primary Objectives

To demonstrate the efficacy and safety of two formulations of extended oral contraceptive therapy (Seasonale and Seasonale Ultra-Lo) taken for one year in women desiring pregnancy prevention.

Medical officer's comment: [redacted] the present NDA seeks marketing approval only for Seasonale.

Other Efficacy and Safety Objectives

A. To compare on an annual basis, in women receiving extended oral contraceptive therapy vs women receiving conventional oral contraceptive therapy, the following:

- Number of days of bleeding and severity-of bleeding
- Incidence and severity of common peri-menstrual complaints
- Self-reported Health-Related Quality of Life and patient satisfaction
- Composite incidence of all bleeding
- Incidence and severity of other adverse events

B. To evaluate the results of endometrial biopsies (incidence of hyperplasia and carcinoma) in a cohort of women who received extended oral contraceptive therapy

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 targeted to complete one year of treatment in each of the two extended OC therapy arms. One hundred (100) patients, age 18 to 35, were targeted to complete one year of treatment in each of the two conventional 28-day oral contraceptive therapy arms. Patients age 35 through 40 were also to be enrolled in the study. To accomplish the targeted completion, approximately 450 patients were planned for enrollment in each of the extended oral contraceptive therapy arms and 225 patients were planned for enrollment in each of the conventional oral contraceptives therapy arms. A total of approximately 1350 patients were planned for enrollment.

Medical officer's comments: The plan to obtain 200 subjects for completion of one year is appropriate and consistent with our Division's recommendations. Obtaining less than 200 "one year" completers in the comparator groups is not a problem since oral contraceptive trials can be performed without comparators. A review of the total number of "28-day equivalent cycles" is addressed in the safety section of this review.

Inclusion Criteria

Sexually active adult women (age 18 through 40), of childbearing potential, in a heterosexual relationship, at risk for pregnancy, who are in good health and who:

- Have a history of OC use for an interval of at least three successive cycles with regular withdrawal bleeding (bleeding during the pill-free interval or during the first three days of the successive cycle) prior to enrollment (Continuous Users) OR
  Had no prior history of OC use (Fresh Starts) OR

Had a history of OC use, but not within the six months prior to enrollment (Prior Users)
- Negative urine pregnancy test
- Signed informed consent
- Agree to use study oral contraceptive therapy as their primary birth control method.

Medical officer's comments: The sponsor amended the inclusions by removing the first bulleted item. This amendment is not felt to impact on the efficacy or safety analyses of the study. The inclusion criteria are acceptable.

Exclusion Criteria

- History of hypersensitivity to estrogen or progestin component of OCs
- History of alcohol or drug abuse which, in the opinion of the investigator, makes the patient unfit for participation in the study
- Active smoker older than 35 years of age
- Chronic use of any medication that might interfere with the efficacy of OCs (e.g. Rifadin, Rimactane, Rifamate, Rifater, barbiturates [Amytal], Fulvicin, Grifulvin V, Gris-Peg, Grisactin, Ultragris, ampicillin, Achromycin, Aureomycin, Cyclopar, Declomycin, Dynacin, Minocin, Vibramycin, Vibra-Tabs, or any generic equivalents)
- The use of antihyperlipidemic agents was not allowed
- History of being HIV or hepatitis C positive
- History of persistent noncompliance with any chronic medication
- History of having received injectable hormone therapy (e.g. Depo-Provera) within the 10 months prior to study enrollment or having a progestin-releasing intrauterine device (IUD) in place within three months prior to enrollment or having had a contraceptive implant removed within one month prior to enrollment
- Routine concomitant use of forms of contraception other than OCs (IUD, diaphragm, contraceptive sponge) with the exception of condoms.
- Patients who have had recent surgical or medical abortion, miscarriage, or vaginal or cesarean delivery must have had at least two normal menstrual cycles prior to enrollment
- History of abnormal bleeding (breakthrough or withdrawal bleeding that lasts 10 or more consecutive days, or spotting that lasts more than 10 consecutive days) while on conventional OCs (***Medical officer's comments: This may have labeling implications. Although women who have that much unscheduled bleeding on oral contraceptives may not enroll in a contraceptive study, this exclusion potentially enriches the population resulting in less irregular bleeding)***
- History of thromboembolic disorder, vascular disease, cerebral vascular or coronary artery disease
- Uncontrolled or untreated hypertension (systolic BP $\geq$ 140 mmHg and diastolic BP $\geq$ 90 mmHg on more than two occasions)
- Known or suspected carcinoma of the breast, endometrial carcinoma, or known or suspected estrogen-dependent neoplasia
- Undiagnosed abnormal genital bleeding
- History of hepatic adenomas or carcinomas

- History of cholestatic jaundice of pregnancy or jaundice with prior OC use
- History of diabetes mellitus, glucose intolerance or gestational diabetes
- History of clinically significant abnormal laboratory value at screening
- Any clinically significant abnormal finding or condition on history, screening, physical exam, pelvic exam, or any laboratory finding that contraindicates the use of OCs
- Had participated in any clinical investigation within 30 days prior to enrollment
- Had donated or sustained a loss of more than 500 mL of blood within 30 days prior to enrollment

Medical officer's comments:

Aside from the potential labeling implication for the bleeding exclusion, the rest of the exclusion criteria are acceptable.

Randomization (Treatment) Arms

Patients were randomized to one of the following:

- Low dose conventional oral contraceptive (Nordette-28; 150-mcg levonorgestrel/ 30-mcg ethinyl estradiol tablets x 21 days followed by placebo tablets x 7 days)
- Ultra-low dose conventional oral contraceptive (Levlite-28; 100-mcg levonorgestrel/ 20-mcg ethinyl estradiol tablets x 21 days followed by placebo tablets x 7 days)
- Low dose extended oral contraceptive (Seasonale 91-Day; 150-mcg levonorgestrel/ 30-mcg ethinyl estradiol tablets x 84 days followed by placebo tablets x 7 days)
- Ultra-low dose extended oral contraceptive (Seasonale Ultra-Lo 91-Day; 100-mcg levonorgestrel/ 20-mcg ethinyl estradiol tablets x 84 days followed by placebo tablets x 7 days)

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

Study Procedures

The Schedule of Events for patients assigned to either conventional or extended oral contraceptive therapy are summarized in Table 4 and Table 5.

Table 4 Conventional (28-day) treatment cycle (Nordette and Levlite)

Parameter	S	V-1	W-4	W-12, 24, 40	COT
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 centrally done by	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
QOL-baseline		X			
QOL – follow-up				X	X
Study drug compliance				X	X
Adverse event recording	X	X	X	X	X

S = screening, V = visit, W = week, COT = completion of therapy

Source: Original submission, vol 1.58

Table 5 Extended (91-day) treatment cycle (Seasonale and Seasonale Ultra-Lo)

Parameter	S	V-1	W-4	W-13, 26, 39	COT
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 centrally done by	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
QOL-baseline		X			
QOL – follow-up				X	X
Study drug compliance				X	X
Adverse event recording	X	X	X	X	X
Endometrial biopsy (cohort only)		X			X

S = screening, V = visit, W = week, COT = completion of trial

Source: Original submission, vol 1.58

Medical officer's comments: An electronic diary was requested from the sponsor. 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.

Discontinuation

Patients were to be discontinued from the study in the event of any of the following:

- Ten or more days of breakthrough bleeding when deemed necessary by the investigator
- Any condition that, in the opinion of the investigator, contraindicates the use of OCs
- Patient request
- Pregnancy
- Any adverse event that made continuation in the study impossible or inadvisable
- Patient lost to follow-up
- Patient discovered after enrollment not to have met study criteria
- Patient refused to cooperate with required study procedures
- Patient older than 35 years of age who began smoking while on study medication
- Patient who had clinic visit following the final week of a cycle that results in a lapse of study medication intake

Primary Efficacy Assessment

Efficacy was evaluated from the overall pregnancy rate, calculated by the Pearl Index using all "during treatment" pregnancies. During 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.

The following are the considerations/criteria that the sponsor indicated were to be used to estimate the date of conception.

> Conception date was calculated considering all available data such as sonogram data, quantitative hCG, qualitative hCG, pelvic examination, delivery date, and weight of infant at birth. If these approaches gave conflicting estimated dates of conception, the principal investigator made the final estimation of conception date. If it was unclear when conception occurred, the pregnancy was counted as a "during treatment" pregnancy and a conception date was imputed as the midpoint between the patient's last negative pregnancy test date and the date of the positive pregnancy test. In a few cases, the conception date was estimated from other information such as the estimated date of delivery.

Medical officer's comments: The criteria for "during treatment" pregnancy is acceptable. The most important objective evaluation for conception dating is an early ultrasound. Other data is supportive but carries less weight. This reviewer does not agree with the sponsor's imputed

assessment of conception date. If the conception date could not be accurately determined, the pregnancy was considered to be a "during treatment" pregnancy by the Medical Officer.

Pregnancy Testing/Assessment

Urine pregnancy testing was performed at screening. If the screening evaluation was completed more than two weeks prior to the initiation of study therapy, the urinary pregnancy test was repeated at Visit 1. The urinary pregnancy test utilized at the sites was [redacted]. Additional urinary pregnancy testing was performed at Weeks 12, 24, and 40 in the conventional oral contraceptives therapy arms and at Weeks 13, 26, and 39 in the extended oral contraceptive therapy arms.

During the course of the study and for two months following completion of the study, or early withdrawal from the study, all patients were instructed to contact the investigator immediately if they suspected that they might be pregnant. All pregnancies that occurred during the course of the study or in the two months following completion of the study were to be dated using ultrasound to establish the gestational age of the fetus.

Patients who became pregnant during the course of the study due to method failure were to be followed for eight weeks following delivery or termination of the pregnancy. Infants were to be followed for eight weeks following delivery.

Medical officer's comments: The pregnancy testing assessment and follow-up are acceptable.

Pearl Index Calculations

For the 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 at risk (the denominator in the formula for calculating the Pearl Index), adjustments were made to exclude incomplete cycles or cycles in which backup contraception had been used.

The sponsor calculated Pearl Indices for the following cohorts:

- **Primary efficacy cohort**. All treated patients between the ages of 18 and 35 years, excluding cycles (91 days for Seasonale/Seasonale Ultra-Lo and 28 days for Nordette/Levlite) where another birth control method (BCM) was used.
- **Compliant-users**. All treated patients excluding cycles (91 days for Seasonale/Seasonale Ultra-Lo and 28 days for Nordette/Levlite) where another form of BCM was used, the patient missed 2 or more pills, the patient took a disallowed medication, or overall treatment compliance across the study was <80%.
- **Protocol ITT population (PITT)**. All treated patients between the ages of 18 and 35 years
- **ITT population**. All treated patients
- **Less than 90 kg population**. The four cohorts listed above for patients with body weight of <90 kg.

Medical officer's comments: This reviewer disagrees with the definition for compliant-use Pearl Indices. Study medication use at the time of conception should be analyzed. Body weight analysis should concentrate on those of higher BMI (not lower), since there is data from other studies to indicate that oral contraceptives may be less efficacious in obese women.

In addition to the calculation of the Pearl Index, the pregnancy rates were calculated using a life table analysis.

Secondary Outcomes

The sponsor listed the following as "Other Outcomes Analyses":

- Number of days of bleeding (withdrawal menses and unscheduled bleeding/spotting) and severity of bleeding (withdrawal menses and unscheduled bleeding/spotting)
- Incidence and severity of common peri-menstrual complaints (headache, pain and cramping, bloating and/or swelling, weight gain, breast tenderness, irritability or mood changes, lower backache/back pain and acne)
- Self-reported Health-Related Quality of Life (HRQOL) and patient satisfaction
- Composite incidence of all bleeding
- Incidence and severity of other adverse events

Medical officer's comments: Aside from the HRQOL, which is discussed in the efficacy section, all the other secondary analyses are reviewed in the safety section of this review.

STUDY FINDINGS

Demographics

The demographics are presented in the following two tables. Table 6 represents the entire ITT population. Table 7 focuses on the 18-35 age group on which the primary efficacy analysis is based. .

Table 6 Demographic Characteristics: All Treated Patients (ITT Population)

	Seasonale N=456	Nordette N=226	Seasonale Ultra-Lo N=463	Levlite N=231
Mean age	27.8 yrs	27.8 yrs	27.8 yrs	27.3 yrs
Mean wt.	156.4 lb	156.5 lb	156.3 lb	153.9 lb
Race				
Afr Amer	50 (10.9%)	29 (12.8%)	53 (11.45%)	32 (13.85%)
Asian	10 (2.2%)	2 (0.8%)	5 (1.08%)	6 (2.6%)
Caucasian	351 (77.0%)	169 (74.7%)	361 (77.97%)	171 (74.03%)
Hispanic	32 (7.0%)	18 (7.9%)	36 (7.78%)	17 (7.36%)
Other	13 (2.8%)	8 (3.5%)	8 (1.73%)	5 (2.16%)
Prior OC Usage				
Fresh start	35 (7.7%)	14 (6.2%)	36 (7.78%)	21 (9.09%)
Prior user	132 (29.0%)	70 (31.0%)	150 (32.4%)	71 (30.74%)
Continuous user	288 (63.2%)	142 (62.8%)	277 (59.8%)	139 (60.17%)
Smoker – yes	83 (18.2%)	35 (15.49%)	97 (20.95%)	42 (18.18%)

Source: Original NDA submission

Table 7 Demographic Characteristics: All Treated Patients 18-35 Years (PITT Population)

	Seasonale N=397	Nordette N=195	Seasonale Ultra-Lo N=408	Levlite N=201
Mean age	26.3 yrs	26.24 yrs	26.38 yrs	26.21 yrs
Mean wt.	156.6 lb	156.31 lb	155.13 lb	153.3 lb
Race				
Afr Amer	45 (11.34%)	22 (11.28%)	45 (11.03%)	30 (14.49%)
Asian	8 (2.02%)	2 (1.03%)	5 (1.23%)	6 (2.9%)
Caucasian	301 (75.82%)	150 (76.92%)	321 (78.68%)	151 (72.95%)
Hispanic	30 (7.56%)	13 (6.67%)	29 (7.11%)	15 (7.25%)
Other	13 (3.27%)	8 (4.10%)	8 (1.96%)	5 (2.42%)
Prior OC Usage				
Fresh start	32 (8.06%)	14 (7.18%)	35 (8.58%)	20 (9.66%)
Prior user	115 (28.97%)	60 (30.77%)	133 (32.60%)	62 (29.95%)
Continuous user	249 (62.72%)	121 (62.05%)	240 (58.82%)	125 (60.39%)
Smoker – yes	83 (20.91%)	35 (17.95%)	97 (23.77%)	42 (20.29%)

Source: Original NDA submission

Medical officer's comments: The demographic data shows that the treatment arms appear similar. It is noted in both of the prior two tables that the number of fresh starts was quite low compared to prior and continuous users. This tends to bias the study population to those women who have had fewer problems with COCs or are more tolerant of side effects. A study population of entirely fresh starts may have had more discontinuations for unanticipated bleeding than was demonstrated in this study. This reviewer does not feel that fresh starts need to be specifically cautioned about possible adverse effects in the label more than prior users, but the clinical section of the label should specify the study population.

Patient Disposition

The disposition of all patients enrolled in the clinical trial is summarized in Table 8.

Table 8 Patient Disposition (ITT population)

	Seasonale	Nordette	Seasonale Ultra-Lo	Levlite
Treated	N=456	N=226	N=463	N=231
Completers	271 (59.4%)	161 (71.2%)	260 (56.2%)	157 (68.0%)
Discontinued	185 (40.6%)	65 (28.8%)	203 (43.8%)	74 (32.0%)
Reasons for Discontinuation (Categories not mutually exclusive, subjects could have more than one)				
Adverse event	68 (14.9%)	22 (9.7%)	88 (19.0%)	17 (7.4%)
Unacceptable bleeding	35 (7.7%)	4 (1.8%)	64 (13.8%)	2 (0.9%)
Patient decision	47 (10.3%)	7 (3.1%)	41 (8.9%)	22 (9.5%)
Non-compliant	22 (4.8%)	9 (4.0%)	16 (3.5%)	11 (4.8%)
Lost-to-follow-up	39 (8.6%)	21 (9.3%)	46 (9.9%)	16 (6.9%)
Pregnant	4 (0.9%)	3 (1.3%)	8 (1.7%)	7 (3.0%)
Investigator Discretion	2 (0.4%)	1 (0.4%)	0 (0.00%)	1 (0.4%)
Other	3 (0.7%)	2 (0.9%)	4 (0.9%)	0 (0.00%)

Source: Original NDA submission (Clinical data summary)

Medical officer's comments: Noteworthy in this table is the higher overall number of discontinuations in the Seasonale arm compared to the Nordette arm. The higher number of discontinuations in the Seasonale group is explained by more instances of adverse events and unacceptable bleeding, and more withdrawals due to patient decision. A large component of the Seasonale adverse event group consisted of subjects who had unacceptable bleeding. A total of 35 Seasonale subjects are listed with " unacceptable bleeding" as one of the reasons for their withdrawal from the study. The percentage difference in this category compared to Nordette (7.7% compared to 1.8%) is clinically significant. Inclusion of this difference is recommended for labeling. When reviewing the reasons for withdrawal due to patient decision, most appeared to be related to lifestyle changes (moving, marital, etc.). See the safety section for further discussion of discontinuation for adverse events.

Primary Efficacy Assessment and Endpoints

The sponsor submitted a revised Pearl Index calculation for the four treatment arms on May 5, 2003. This revision was necessary because the FDA biostatistician reviewing the sponsor's data identified a discrepancy in the correct number of "at risk" cycles to use in the denominator of the Pearl Index calculation. The sponsor acknowledged the error and sent in revised tables. The following two tables (Table 9 and Table 10) compare the sponsor's corrected results and the FDA statistician's results, based on the most conservative calculation of the Pearl Index. In this calculation, the on-treatment at risk period is based only on completed cycles in the 18-35 year age range and excludes cycles where other birth control methods were utilized.

Table 9 Sponsor'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
Seasonale Ultra-Lo	788	7	3.55
Levlite	1735	5	3.75

a. For Seasonale and Seasonale Ultra-Lo a complete cycle is 91 days.
b. For Nordette and Levlite, a complete cycle is 28 days.
Source: May 5, 2003 Sponsor submission

Table 10 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)
Seasonale Ultra-Lo	786	8	4.07 (1.78, 7.94)
Levlite	1733	5	3.75 (1.22, 8.60)

a. For Seasonale and Seasonale Ultra-Lo a complete cycles is 91 days.
b. For Nordette and Levlite, a complete cycle is 28 days.
Source: FDA Biostatistics Reviewer

Medical officer's comments:
The FDA biostatistician's Pearl Index calculation for Seasonale was only slightly different than that of the Sponsor's (1.98 compared to 1.97). A Pearl Index of 1.98 is acceptable for Seasonale in light of other oral contraceptive approvals that have allowed rates of up to 2.39. Seasonale's Pearl Index is also acceptable when compared to the Pearl Index of Nordette (2.22) in the pivotal SEA-301 trial.

The original NDA for Nordette (NDA-18-668) reported 3 pregnancies in 8,186 cycles (Pearl Index = 0.48) This rate is quite a bit lower than the rate for the Nordette arm in this present study (Pearl Index = 2.22). It is difficult to compare the pivotal Seasonale study with the original Nordette study, which was submitted in 1981. The principal differences between these studies, which were performed more than twenty years apart, include the following:

- *The original Nordette study had no scheduled pregnancy tests*
- *The original Nordette study included women up to age 38 in the Pearl Index*
- *The original Nordette study had 68 women who took Nordette for 18 cycles and 6 women who took Nordette for 23 cycles.*

[redacted] *it is concerning that the lower dose arms (levonorgestrel 100 mcg/ethinyl estradiol 20 mcg) both as extended and conventional use showed such high Pearl Indices. Other recent clinical trials have shown a*

higher Pearl Index for approved comparators relative to the original trials submitted in the original NDAs. It is possible that a combination of reduced subject compliance and low contraceptive strength is leading to these higher Pearl indices.

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

Pregnancy Case Listing for all arms of the SEA-301 study

Pregnancy Case Listings for Seasonale Treated Patients

Table 11 provides case listings for pregnancies in the Seasonale arm.

Table 11 Reported Pregnancies in the Seasonale Treatment Group

Site/ Pt #	Age/ Wt in pounds	User type	Drug Start date	Drug stop date	Preg test result	Conception Date*	Sponsor considers preg on/off drug	MO considers preg on/off drug	MO Evaluation of Compliance
7/4	26/133	Fresh start	10 Sept 00	7 Dec 00	Positive 8 Dec 00	Unknown Imputed to be 18 Oct 00	ON	ON	Not compliant
13/4	30/162	Contin.	3 Sept 00	3 Jun 01	Negative on 6 Jun 01 and 10 July 01	22 Jun 01 by sono	OFF	OFF	N/A
22/13	19/126	Fresh start	15 Oct 00	15 Jul 01	Positive 16 Jul 01	June 01 By sono	ON	ON	Compliant
26/33	25/148	Prior use	22 Oct 00	5 Nov 00	Positive 15 Jan 01	8 Oct 00 by sono	OFF	OFF	N/A
31/7	24/160	Contin.	17 Sept 00	17 Nov 00	Positive 26 Feb 01	3 Dec 00 by sono	OFF	OFF	N/A
37/19	26/187	Prior user	10 Sept 00	5 Nov 00	Positive 15 Jan 01	9 Oct 00 by sono	ON	ON	Compliant Weighed 85 kg
39/5	23/132	Contin.	17 Sept 00	6 Jun 01	Negative 12 Jun 01	25 Jul 01 by sono	OFF	OFF	N/A
48/25	23/190	Prior	29 Oct 00	31 Jan 01	5 mar 01	Imputed to be 2/14/01	ON **	ON	Not compliant

* If the actual conception date was unknown, it was imputed as the midpoint between the last negative pregnancy test and the date of the positive pregnancy test.

** The sponsor's information indicates that the conception occurred 2/7/01 (within 14 days of Seasonale discontinuation).

Source: Original NDA submission and Sponsor's April 10, 2003 source data

Medical officer's comments: The imputed values are not acceptable. The sponsor should just list the estimated conception date in these cases to be unknown.

After discussions with the sponsor and obtaining sonographic source documentation, the primary medical reviewer concurs with the sponsor's assessment that conception for the 4 subjects described below occurred off of study treatment.

Subject 13/4 had two negative pregnancy tests after stopping study drug and a sonographic estimation of conception 19 days after last study dose. Subject 26/33 was found by sonography confirmation to have conceived prior to study drug. Source documentation by sonography established that subject 31/7 conceived more than 14 days following last study drug dose and that subject 39/5 conceived more than a month following her last dose of study drug.

The sponsor judged compliance by diary compliance >80%, no use of alternative contraceptive methods, no use of disallowed medication, and no missing of two consecutive active pills. This reviewer judged compliance and method failure by assessing the weeks immediately prior to conception for compliant pill taking.

Subjects 22/13 and 37/19 are considered to be method failures by this reviewer. Subject 22/13 recorded taking Seasonale from 5/14/01 through 6/10/01. The conception date by sonography is 6/01/01. This meant that she took Seasonale for eighteen days prior to conception. Subject 37/19 took Seasonale for 29 days prior to conception without missing study medication. Calculation of the "perfect use" Pearl Index would be 2 x 400/ 809 or 0.99.

One subject in the Seasonale group who became pregnant was over 80 kg (subject 37/19).

Of the "during treatment" pregnancies, one ended in a suspected spontaneous abortion (7/4), one was a normal twin pregnancy (22/13), and one was a normal singleton term pregnancy (37/19). One subject was lost to follow-up (48/25).

Pregnancy Case Listings for Nordette treated subjects.

The case listings for pregnancies in the Nordette arm are presented in Table 12.

Table 12 Reported Pregnancies in the Nordette Treatment Group

Site/ Pt #	Age/ Wt in pounds	User type	Drug Start date	Drug stop date	Preg test result	Conception Date	Sponsor considers preg on/off drug	MO consider preg on/off drug	MO Evaluation of Compliance
26/34	26/156	Prior	26 Nov 00	11 July 01	Positive 30 Aug 01	3rd to 4th week of July by sonogram	Off	Off	N/A
32/10	21/183	Prior	13 Aug 00	31 Oct 00	Positive 30 Oct 00	9 Oct 00 by sonogram	On	On	Compliant
33/11	27/196	Cont	17 Sept 00	10 June 01	Positive 15 June 01	Imputed to be 23 Apr 01	On	On	Compliant
40/31	30/132	Prior	15 Oct 00	17 July 01	Positive 18 July 01	Imputed to be 23 May 01	On	On	Not compliant

Source: Original NDA submission

Medical officer's comments: This reviewer agrees with the sponsor's determination of three on-drug pregnancies and one off-drug pregnancy in the Nordette treated subjects. It appears from review of the electronic diary recordings that subjects 32/10 and 33/11 were compliant with study medication but subject 40/31 failed to record data on numerous occasions. The "perfect use" Pearl Index by this reviewer's assessment is 1.48 (complete cycles only, 18-35, excluding cycles utilizing other BCM).

Pregnancy Case Listings for Seasonale Ultra-Lo treated subjects.

Table 13 provides the case listings for pregnancies in the Seasonale Ultra-Lo arm.

Table 13 Reported Pregnancies in the Seasonale Ultra-Lo Treatment Group

Site/ Pt #	Age/ Wt in pounds	User type	Drug start date	Drug stop date	Preg test result	Conception Date	Sponsor considers preg on/off drug	MO consider preg on/off drug	MO Evaluation of Compliance
7/30	32/177	Prior	10/29/00	1/22/01	Positive 1/22/01	Imputed 12/22/00	On	On	Not compliant
9/9	21/145	Fresh Start	10/8/00	11/25/00	Negative 12/4/00	12/14/00? 12/21/00 by sono	Off	Off	
24/11	25/147	Cont	9/10/00	11/3/00	Negative 12/18/00	12/31/01 by sono	Off	Off	
26/19	24/146	Prior	10/15/00	4/6/01		1/03/01 by exam	On	On	Not compliant
29/47	23/137	Fresh Start	10/15/00	5/4/01	Positive 5/7/01	Imputed 4/17/01	On	On	Not compliant
30/39	31/214	Cont	10/1/00	10/28/00	Positive 11/9/00	9/14/00 by exam	**Off**	**On**	Not compliant
31/11	26/206	Cont	10/1/00	8/24/01	Negative 10/8/01 Positive 10/31/01	10/6/01 by sono	Off	Off	
34/41	19/226	Cont	10/22/00	3/25/01	Positive 3/26/01	3/6/01 by sono	On	On	Not compliant
34/42	20/288	Prior	10/22/00	3/16/01	Positive 5/01/01	4/12/01 by sono	Off	Off	
40/17	26/143	Cont	10/1/00	6/9/01	Positive 8/20/01	7/4/01 by sono	Off	Off	
41/14	23/233	Prior	9/24/00	3/22/01	Positive 3/22/01	Imputed 2/7/01	On	On	Not compliant
46/41	20/122	Prior	9/24/00	2/13/01	Positive 2/19/01	12/12/00 by sono and exam	On	On	Compliant
46/42	24/116	Prior	10/29/00	10/17/01	Positive 11/1/01	9/15/01 by sono	On	On	Compliant

Source: Original NDA submission

Medical officer's comments: This reviewer agrees with the sponsor's determination of on or off study drug at the time of conception for all the Seasonale Ultra-Lo pregnancies except for subject 30/39. Subject 30/39 did not have a sonogram to confirm that conception occurred prior to study drug. The "perfect use" Pearl Index by this reviewer's assessment is 1.02 (complete cycles only, 18-35, excluding cycles utilizing other BCM).

Pregnancy Case Listings for Levlite treated subjects.

Table 14 provides the case listings for pregnancies in the Levlite arm.

Table 14 Reported Pregnancies in the Levlite Treatment Group

Site/ Pt #	Age/ Wt in pounds	User type	Drug start date	Drug stop date	Preg test result	Conception Date	Sponsor considers preg on/off drug	MO considers preg on/off drug	MO Evaluation of Compliance
1/29	38/165	Cont	9/3/00	11/17/00	Positive 11/15/00 and 11/29/00	11/3/00 Not specified	On	On	Compliant (but excluded from (18-35) age group calculations
7/23	22/204	Prior	10/8/00	3/22/01	Positive 3/22/01	Imputed 2/8/01	On	On	Not compliant
17/23	31/307	Prior	11/12/00	1/23/01	Positive 2/2/01	12/21/01 Imputed	On	On	Not compliant
18/62	34/129	Cont	10/15/00	3/2/01	Positive 3/6/01	1/22/01 by sono and exam	On	On	Compliant
30/24	20/184	Fresh Start	9/17/00	5/27/01	Positive 6/25/01	4/13/01 to 4/23/01 by sono and exam	On	On	Compliant
32/48	30/167	Prior	9/10/00	5/26/01	Positive 5/29/01 & 6/7/01	5/24/01 Not specified	On	On	Compliant
48/9	28/139	Prior	10/22/00	1/8/01	Positive 1/8/01	9/27/00 by sono	Off	Off	

Source: Original NDA submission

Medical officer's comments: The reviewer agrees with the sponsor's determination of on or off drug determinations at the time of conception for all the Levlite pregnancies. Case 32/48 resulted in an ectopic pregnancy. The "perfect use" Pearl Index by this reviewer's assessment is 3.0 (complete cycles only, 18-35, exclude cycles utilizing other BCM)

Secondary Outcomes – Results

The sponsor primarily was evaluating bleeding and other adverse events in their secondary outcome analyses. These issues will be discussed further in the safety section. Outcomes related to the Health-Related Quality of Life (HRQoL) questionnaire will be discussed in this section.

The HRQoL questionnaire included a SF-36 to assess general quality of life and other items and scales to assess menstruation-specific quality of life and patient satisfaction. The questionnaire categories are presented in section 6 of the appendix in an abbreviated form.

Medical officer's comments: In regard to the quality of life findings, the sponsor found no statistically significant difference between treatment groups in most of the analyses. There were no noteworthy differences between Seasonale and Nordette in regard to most peri-withdrawal symptom complaints.

From a safety standpoint, the quality of life questionnaire data tend to support the daily diary assessment that Seasonale had more unexpected bleeding and spotting than Nordette subjects.

It is emphasized that stating conclusions from the quality of life data is problematic due to lack of validation of this questionnaire.

D. Reviewer's Efficacy Conclusions

Utilizing the most conservative criteria for assessing the Pearl Index, Seasonale has an acceptable pregnancy rate. The Pearl Index is 1.98 when evaluating women age 18- 35, excluding women who reported using other birth control methods at some point during the cycle, and excluding partial treatment cycles. The "perfect use" Pearl Index as computed by this reviewer is 0.99. Using a Life Table Analysis, the effectiveness of Seasonale was 1.26% (95% C.I. from 0.02% to 2.50%).

The Nordette Pearl Index utilizing the same conservative criteria is 2.22. This rate is higher than that seen when Nordette was initially approved in 1982 (PI = 0.48). Age (up to 38), study length (up to 2 years), and less pregnancy test evaluations may have contributed to the difference. Using a Life Table Analysis, the effectiveness of Nordette was 1.87% (95% C.I. from 0% to 3.98%).

This study utilized a daily electronic diary that had a daily signal alarm that prompted patients for data entry (and hence might also have served as a prompt to take study medication. However, this reviewer does not feel that Seasonale needs to be marketed with a similar device to obtain the reported efficacy.

Product labeling should include the overall Pearl Index in the clinical section of the label. This drug in a 28-day cycle dosing regimen was approved more than twenty years ago as an efficacious contraceptive. There is no theoretic concern or objective data from this trial to suggest that taking this contraceptive formulation in 91-day cycles (84 consecutive days of active tablets followed by 7 days of placebo) instead of 28 day cycles (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 time periods (placebo treatment periods) that would occur over a 3-month period with conventional contraceptive dosing regimens. During the withdrawal period, there is a possibility that the ovary could escape from suppression, particularly if the patient delays her start of dosing with active pills.

VII. Integrated Review of Safety

A. Brief Statement of Conclusions

The following points summarize the safety findings and limitations of data:

- The combination of the pivotal study SEA-301 and the SEA-301A extension study interim safety report provides enough 28-day cycle equivalents (5,946) to assess safety for Seasonale.

- The primary adverse event related to Seasonale is unanticipated bleeding and spotting. This event caused more discontinuations in the Seasonale arm compared to the Nordette arm in the pivotal study SEA-301. Although this side effect diminishes somewhat with use, 15% of the subjects still had over 20 days of unanticipated bleeding/spotting in the fourth cycle (91 days) of use and approximately 40% had greater than 7 days of unanticipated bleeding/spotting in the fourth cycle.

- Despite the prolonged number of days of unanticipated bleeding/spotting it appears that the quantity of blood loss with this bleeding is usually minimal. There was no evidence in the hematology laboratory dataset from the pivotal SEA-301 trial that there are significant problems with anemia (hematocrits < 35.0%) in those subjects taking Seasonale. The number of Seasonale subjects with anemia at the end of the study was comparable to that found in the Nordette arm. There was no problem with anemia in the subjects who prematurely discontinued in the Seasonale arm for reasons of unacceptable bleeding.

- The identification of one subject developing a pulmonary embolus while taking Seasonale does not provide a signal that the 91-day regimen duration compared to the 28-day regimen duration increases the risk for thromboembolic events. Due to the rarity of these events, standard postmarketing surveillance (AERS) is recommended to further monitor for these events.

- Seasonale showed the same amount of blood pressure changes and laboratory alterations when compared to Nordette and oral contraceptives in general.

B. Description of Patient Exposure to Study Drugs

Studies SEA 301 and SEA 301A

Table 15 presents the safety exposure to study drugs. This is expressed as the number of treated patients and the number of 28-day treatment cycle equivalents in the pivotal Phase 3 clinical trial (Study SEA 301) and the safety extension clinical trial (Study SEA 301A). Subjects enrolled in Study 301A previously participated in Study SEA 301. In Study SEA 301, 456 patients received one or more doses of Seasonale for a total of 4,337 28-day treatment cycle equivalents. In Study SEA 301A, 191 patients received one or more doses of Seasonale for a total of 1,609 28-day treatment cycle equivalents as of the data cutoff date of January 24, 2003.

Table 15 Exposure to Study Drugs (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
	Seasonale Ulltra-Lo	463	4,304
	Levlite	231	2,375
SEA-301 A (Safety Extension)	**Seasonale**	**191**	**1,609**
	Seasonale Ulltra-Lo	160	1,391
Total Exposure (Studies SEA 301 and SEA 301A combined)	***Seasonale***	***647***	***5,946***
	Seasonale Ulltra-Lo	623	5,695

Source: Sponsor submissions April 22, 2003 and final interim report for SEA-301A received May 29, 2003

Medical officer's comments: The total number of 28-day cycle equivalents (5,946) is acceptable.

Table 16 lists the extent of exposure to study drugs, expressed as months on study, for Study SEA 301. Two hundred eighty six (286) of 456 subjects (62.7%) in the Seasonale group completed at least 11 months of treatment.

Table 16 Extent of Patient Exposure to Study Drugs (ITT Population) in Trial SEA 301

	Seasonale (n=456)		Nordette (N=226)		Seasonale Ultra-Lo (N=463)		Levlite (N=231)	
Months on Study	N	%	N	%	N	%	N	%
≤1	21	4.6	9	4.0	19	4.1	12	5.2
>1-2	24	5.3	4	1.8	21	4.5	8	3.5
>2-3	24	5.3	12	5.3	28	6.0	8	3.5
>3-4	17	3.7	3	1.3	19	4.1	7	3.0
>4-5	19	4.2	0	0.0	14	3.0	6	2.6
>5-6	27	5.9	6	2.7	33	7.1	7	3.0
>6-7	2	0.4	2	0.9	10	2.2	5	2.2
>7-8	8	1.8	8	3.5	7	1.5	1	0.4
>8-9	12	2.6	4	1.8	12	2.6	6	2.6
>9-10	8	1.8	8	3.5	11	2.4	4	1.7
>10-11	8	1.8	0	0.0	10	2.2	3	1.3
≥11	286	62.7	170	75.2	279	60.3	164	71.0

Source: Original NDA submission – Clinical Data Summary

Medical officer's comments: The above table lists calendar months of exposure to study drugs. Of the 286 patients listed as having ≥ 11 months of exposure to Seasonale, 271 fully completed treatment in the Seasonale arm.

Table 17 lists the extent of exposure to Seasonale and Seasonale Ultra-Lo in the extension study expressed as number of 91-day extended cycles and approximate 28-day cycle equivalents.

Table 17 Exposure to Study Drugs in Extension Trial SAE 301A

	Seasonale		Seasonale Ultra-Lo	
91-day cycles	N [A]	Approximate 28-day cycle Equivalents [B]	N	Approximate 28-day cycle Equivalents [B]
entry	191		160	
≥ 1	169	549	142	461
≥ 2	143	465	115	374
≥ 3	122	397	107	348
≥ 4	61	198	64	208
Total	—	1,609	—	1,391

A. Completed cycles only for all times after entry
B. Obtained by multiplying each completed 91-day cycle by 3.25 (The conversion does not include any partial 91-cycles)
Source: May 13, 2003 summary report, page 44.

C. Methods and Specific Findings of Safety Review

1. Overview of combination oral contraceptives containing levonorgestrel and ethinyl estradiol

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. A table listing the NDA application numbers, approval dates and dosages for combination oral contraceptives that contain both ethinyl estradiol and levonorgestrel is found in the Appendix Section 4. These products include Ovral, Lo-Ovral, Nordette, Triphasil, Alesse, and Levlite. In addition, levonorgestrel is used alone as a contraceptive in Norplant, Norplant II, Mirena (an IUD), and Plan B (an emergency contraceptive).

Medical Officer's Comment:
Levonorgestrel containing contraceptives are generally considered to be among those with the lowest incidence of serious adverse events, particularly thrombotic and thromboembolic.

2. Safety Information From the Pivotal Trial (Study SEA 301)

a. Safety Assessments and Data Collection Methods

Safety was evaluated in the following manner for Study SEA-301:

- Subjects were informed to contact their investigator for any serious side effect
- Emergency contacts were established for expeditiously handling SAEs
- Subjects were provided with paper adverse events diaries to record the event and the start/stop dates
- The electronic diary additionally captured typical symptoms occurring around the time of a withdrawal period with weekly questions.
- Withdrawal type symptoms were also evaluated in the quality of life questionnaires
- Adverse event recording occurred at all study visits (Screen, Visit 1, Weeks 4, 13, 26, 39 and completion for Seasonale and Seasonale Ultra-Lo and Screen, Visit 1, Weeks 4, 12, 24, 40 and completion for Nordette and Levlite)
- Adverse events were classified according to the MedDRA system
- Clinical safety labs were performed at screening and completion of the study

Bleeding and spotting information during each cycle of treatment was collected from daily electronic patient diaries in regard to the following:

- The total number of bleeding and/or spotting days
- The number of "unscheduled" bleeding and/or spotting days (i.e., during the active pill period)

- The number of "scheduled" withdrawal bleeding and/or spotting days (i.e. during the placebo pill period)
- Each of the above expressed as percentages of the total number of days of possible bleeding and/or spotting (total, scheduled, and unscheduled)

For the bleeding/spotting data, the following approaches to calculating the number of bleeding/spotting days were used:

- **Cycle-adjusted**: the number of observed days of bleeding and/or spotting adjusted upward, if necessary in cases where the number of days for which data were reported was <91 days (Seasonale) or <28 days (comparator), to account for a 91-day extended regimen or 28-day conventional regimen cycle; both complete and partially completed cycles included in the calculation.

- **Observed**: the actual number of bleeding and/or spotting days reported used "as is" without any adjustment; both complete and partially completed cycles included in the calculation.

- **Cycle-adjusted – completed cycles**: the number of observed days of bleeding and/or spotting adjusted downward in cases where the electronic diary for a particular cycle was completed for more than the requisite number of days (i.e., >91 days or >28 days) to account for a 91 day extended regimen or 28-day conventional regimen cycle; only cycles with ≥ 90 days (Seasonale) or ≥ 28 days (comparator) included in the calculation.

- **Observed – completed cycles only**: the actual number of bleeding and/or spotting days reported used "as is" without any adjustment; only complete cycles included in the calculation.

Summary statistics presented are the number of patients, mean, standard deviation, minimum, 1st quartile, median, 3rd quartile, and maximum. In addition, for the total number of days of bleeding and/or spotting and unscheduled number of days of bleeding and/or spotting, the per cycle median for extended treatment is also express as a patient-month estimate. A number of different patient groupings were evaluated:

- All treated patients (ITT cohort)
- Patients who were compliant throughout the entire study
- All treated patients who completed the full one-year term of the study

Baseline and end of study endometrial biopsies were performed in a study subset. This subset study planned to enroll a total of 120 subjects across all treatment groups. The endometrial biopsy subset received both a baseline and final biopsy determination. A panel of three independent readers assessed the biopsies.

For the endometrial biopsy cohort, results of the gland evaluation were classified as follows:

- No endometrium

- Endometrium insufficient
- Inactive
- Atrophic
- Menstrual
- Proliferative
- Secretory
- Hyperplasia

The endometrial stroma was evaluated for the following parameters:

- General
- Edema
- Congestion
- Hemorrhage
- Necrosis
- Hyalinization
- Vascular proliferation
- Decidualization

b. Safety Findings

(1) **Deaths**

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

(2) **Serious Adverse Events**

Seasonale Treatment Group (Serious Adverse Events). Serious adverse events reported for the Seasonale treated subjects are listed in Table 18 by subject. Also listed is the likely relationship of the adverse events to study drug as assessed by the Investigator and whether the subject discontinued participation in the trial because of the adverse event. Serious adverse events were reported for 11 Seasonale subjects.