CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

22-262

SUMMARY REVIEW

Summary Review for Regulatory Action

Date	October 24, 2008
From	Scott Monroe, MD
Subject	Division Director Summary Review
NDA	NDA 22-262
Applicant Name	Duramed Research, Inc.
Date of Submission	December 26, 2007
PDUFA Goal Date	October 24, 2008
Proprietary Name / Established (USAN) Name	Proposed proprietary name: LoSeasonique™ Established name: (levonorgestrel/ethinyl estradiol tablets and ethinyl estradiol tablets)
Dosage Forms / Strength	Immediate release oral tablets containing: (1) levonorgestrel (LNG, 0.1 mg) plus ethinyl estradiol (EE, 0.02 mg) or (2) EE (0.01 mg)
Proposed Indication(s)	Use by women to prevent pregnancy
Proposed Regimen	One tablet daily. Packaged in a 91-day dispenser containing 84 LNG+EE tablets followed by 7 EE tablets
Action	*Approve (see Section 13.1)*

Material Reviewed/Consulted OND Action Package, including:	**Names of Discipline Reviewers**
Medical Officer Review	Ronald Orleans, MD
Statistical Review	Sonia Castillo, PhD; Mahboob Sobhan, PhD
Pharmacology Toxicology Review	Alexander Jordan, PhD; Lynnda Reid, PhD
CMC Review/OBP Review	Bogdan Kurtyka, PhD, Moo-Jong Rhee, PhD
Microbiology Review	Not required per CMC review
Clinical Pharmacology Review	Chongwoo Yu, PhD/Myong-Jin Kim, Pharm.D.
DDMAC	Lisa Hubbard, R.Ph
DSI	NA
CDTL Review	Lisa Soule, MD
OSE/DMEPA	Jinhee Lee, Pharm.D./Kellie Taylor, Pharm.D./Denise Toyer, Pharm.D./Carol Holquist, R.Ph
OSE/DRISK	Nancy Carothers /Jodi Duckhorn, MA

OND=Office of New Drugs
DDMAC=Division of Drug Marketing, Advertising, and Communication
OSE= Office of Surveillance and Epidemiology
DMEPA=Division of Medication Errors Prevention and Analysis
DSI=Division of Scientific Investigations
DRISK=Division of Risk Management
CDTL=Cross-Discipline Team Leader

DIVISION DIRECTOR SUMMARY REVIEW

1. INTRODUCTION

The objective of NDA 22-262 is to obtain marketing approval for LoSeasonique™, a lower dosage form of Seasonique™, a combination oral contraceptive (COC) that was approved for marketing in the U.S. in 2006. LoSeasonique tablets contain either (0.1 mg levonorgestrel [LNG, a progestin] plus 0.02 mg ethinyl estradiol [EE]) or 0.01 mg EE alone. LoSeasonique tablets are packaged in a 91-day pill dispenser that contains 84 LNG/EE tablets and 7 EE tablets. The dosing regimen is one LNG/EE tablet daily for 84 days followed by one EE tablet daily for 7 days. The dosage of LNG/EE in the LoSeasonique combination tablets is reduced by one third compared to that in the Seasonique combination tablets, which contain 0.15 mg LNG plus 0.03 mg EE. The dosing regimen and the composition of the EE alone tablets are the same for both the proposed and approved products. LoSeasonique is not approved for marketing in any foreign country.

The only significant review issues with NDA 22-262 concerned (1) the demonstrated efficacy of LoSeasonique and (2) the likely acceptability of the uterine bleeding pattern that was observed in women who used LoSeasonique tablets in the Applicant's single Phase 3 trial (Study DR-PSE-309). The overall efficacy of the proposed product, based on reported "on-treatment unplanned conceptions" (i.e., pregnancies), appears to be marginally lower than that of other low-dose COCs previously approved by the Division of Reproductive and Urologic Products (DRUP). Because of the extended dosing cycle of LoSeasonique (84 consecutive days of LNG/EE tablets followed by 7 days of EE tablets), women who use the product can expect to have only 4 scheduled (or planned) withdrawal periods per year, generally while taking the EE tablets. Most women who use the product, however, are likely to have, at least during the initial months of use, a greater number of days with unscheduled spotting/bleeding on days when they are taking LNG/EE tablets (treatment days 1-84), compared to women who use a COC with a 28-day dosing cycle. No safety issues, which would preclude approval of an oral contraceptive with acceptable efficacy, were identified during the review of NDA 22-262.

This Memorandum will focus on the following major review/approvability issues:

- The acceptability of the overall efficacy findings for an oral contraceptive product.
- The acceptability of the bleeding patterns (fewer days of scheduled bleeding/spotting but a greater number of days of unscheduled spotting/bleeding) that occur with the use of this product.
- The extent to which labeling can be used to describe clearly the efficacy of the product and the likely schedule/unscheduled bleeding pattern.

2. BACKGROUND

2.1 Description of the Product

The active components and dosing regimen for LoSeasonique have been described earlier in Section 1 of this Memorandum. Levonorgestrel is a gonane derivative of 19-nortestosterone, first approved in the U.S. in 1982, in the COC Nordette (NDA 18-668). Currently, there are

more than a dozen approved COCs containing LNG in the U.S. Combination OCs containing LNG are considered to be among the safest hormonal contraceptive products in terms of thromboembolic risk. The combination tablets in LoSeasonique (i.e., 0.1 mg LNG/0.02 mg EE) contain the same dosage of LNG and EE as that in the previously approved COCs Levlite and Alesse. The dosing cycle for these latter 2 products, however, is one combination tablet daily for 21 days followed by a daily placebo tablet for 7 days.

The first COC with an extended dosing cycle was Seasonale, approved in 2003 under NDA 21-544. Seasonale tablets contain 0.15 mg of LNG and 0.03 mg of EE, which are taken for 84 days, followed by 7 days of placebo tablets. Seasonique, another COC with an extended dosing cycle, was approved for marketing in 2006 (NDA 21-840). It provides the same daily dose of LNG plus EE for 84 days as in Seasonale, but replaces the 7 placebo tablets with 7 tablets containing 0.01 mg of EE. A lower dose version of Seasonale (Seasonale Lo, consisting of 84 daily tablets containing 0.1 mg LNG/0.02 mg EE followed by 7 daily placebo tablets was the subject of NDA 21-921. This NDA was withdrawn by the Applicant during the review cycle in light of (b) (4)
(b) (4)

2.2 Regulatory History

The protocol for Study DR-PSE-309 (the primary study supporting the efficacy and safety of LoSeasonique) was submitted to DRUP in June, 2005. Comments on the Statistical Analysis Plan were conveyed to the Sponsor in October, 2007, including requests to:

- Calculate the Pearl Index using 28-day cycle intervals as well as 91-day cycle intervals.
- Calculate the Pearl Index using all complete cycles in which no other birth control method, including condoms, was used.
- Calculate the Pearl Index using "on treatment" pregnancies defined as those occurring between the first day of treatment and through 14 days after the last dose of study drug. This was subsequently clarified by DRUP to mean within 14 days after the last dose of combination drug.

The Applicant responded to the statistical comments by agreeing to all requests. No pre-NDA meeting was requested.

2.3 Clinical Content of NDA

The Applicant conducted a single, multicenter, open-label, non-comparative clinical trial (Study DR-PSE-309) that treated 2,185 women in support of the safety and efficacy of LoSeasonique. Subjects were 18-41 years of age and were to be treated for up to 12 months. The NDA submission also included Study 99027, the bioequivalence study previously reviewed by the Office of Generic Drugs to support approval of Lessina. Lessina is a 28-day COC that includes 21 tablets each containing 0.1 mg LNG/0.02 mg EE and 7 placebo tablets.

2.4 Recommendations of Primary Medical Reviewer and Cross-Discipline Team Leader (Medical Team Leader) regarding Approvability

The primary Medical Reviewer, Ronald Orleans MD, stated the following in his review that was signed October 24, 2008:

> *"Approval of Lo Seasonique™ for prevention of pregnancy is recommended based on Duramed Research, Inc. (the Applicant) having demonstrated an acceptable Pearl Index and an acceptable safety profile for this product."*
>
> *"Based on the clinical trial data submitted to this NDA, this reviewer concludes that Lo Seasonique is safe and effective for the indication of prevention of pregnancy. The Pearl Index is 2.74 as determined by the Medical Reviewer and FDA Statistician and no serious safety concerns were demonstrated in the primary clinical study. Replacing the placebo tablets with the EE 10 mcg tablets in Lo Seasonique has not been shown in the primary study to adversely affect the safety profile of the medication. In addition, the total doses of both the LNG and EE contained in this drug are within the range of currently approved oral contraceptives."*

The Cross-Disciple Team Leader (CDTL, also the medical Team Leader), Lisa Soule MD, stated the following in her review signed October 24, 2008:

> *"I recommend that Lo Seasonique be approved for the indication "for use by women to prevent pregnancy."*
>
> *"The one-year clinical trial demonstrated a Pearl Index that is marginally higher than that of previously approved OCs, but which I believe to be acceptable. The product does not show any signal of decreased efficacy in heavier women, who were adequately represented in the trial. The safety profile does not differ from that expected for a low-dose OC. With clear labeling that describes accurately the efficacy demonstrated for this product, I believe it has demonstrated safety and efficacy acceptable to allow approval for marketing in the general population of women."*

Division Director's Comment

- *I concur with the overall recommendations of both Drs. Orleans and Soule that LoSeasonique be approved for the indication "for use by women to prevent pregnancy."*

3. CMC

The primary Chemistry Reviewer, Bogdan Kurtyka, PhD, made the following statement/recommendations in his review signed on September 15, 2008:

> *This NDA has provided sufficient information to assure the identity, strength, purity, and quality of Lo Seasonique over the proposed shelf life (18 months) when stored as labeled.*
>
> *Adequate controls for raw materials are in place, manufacturing processes are robust and adequately controlled, specifications ensure the identity, strength, quality, and purity of the drug product. The container/closure system is adequate to protect the drug product. Stability data assure that the product will be stable through the expiration date. Labeling is acceptable. Facilities are in compliance with cGMP.*

This NDA is recommended for "Approval" from a CMC perspective.

The formulation of the combination tablets of LoSeasonique (LNG/EE tablets, USP 0.1 mg/0.02 mg) is based on (b) (4) tablets, (b) (4) tablets were (b) (4) Barr's ANDA for Lessina tablets (b) (4) an FDA approved product also (b) (4) The only difference between these formulations is the color of the cosmetic film coat. The formulation of the 0.01 mg EE tablets used in LoSeasonique is identical to that of the 0.01 mg EE tablets used in the marketed product Seasonique.

The proposed container/closure system is identical to the one used in the approved drug products Seasonique (NDA 21-840) and Seasonale (21-544).

Division Director's Comment

- *I concur with the assessment/recommendation made by Dr. Kurtyka. There are no outstanding CMC issues.*

4. NONCLINICAL PHARMACOLOGY/TOXICOLOGY

The pharmacology and toxicology of LNG and EE are well established, and both ingredients have been used for more than 20 years in many approved COC products. No nonclinical studies were submitted in this NDA. The primary Pharmacology/Toxicology Reviewer, Alexander Jordan, PhD, made the following statements and recommendations in his review signed January 28, 2008:

Conclusions: *"Based on the approval of Seasonique under NDA 21-840, which has the same formulation and dosing schedule as Lo Seasonique, as well as use of both active ingredients at doses equal or higher in many other approved formulations for the same indication, Pharmacology considers Lo Seasonique safe for the proposed indication."*

Recommendations: *"Pharmacology recommends approval of NDA 22-262 for Lo Seasonique."*

Suggested labeling: *"Labeling will be similar to that for Seasonique."*

Unresolved toxicology issues (if any): *"None"*

Division Director's Comment

- *I concur with the conclusions and recommendations of Dr. Jordan.*

5. CLINICAL PHARMACOLOGY/BIOPHARMACEUTICS

The primary Clinical Pharmacology Reviewer, Chongwoo Yu, PhD, stated the following in his review, which he signed on May 13, 2008:

> *"The Office of Clinical Pharmacology/Division of Clinical Pharmacology III (OCP/DCP-III) has reviewed NDA 22-262 submitted on December 26, 2007 and April 3, 2008. The overall Clinical Pharmacology data submitted to support this NDA are acceptable provided that a mutually satisfactory agreement is reached regarding the labeling language."*

Dr. Yu noted that the LoSeasonique formulation for the combination tablets used in the clinical trial and in the to-be-marketed product is that of Lessina, the AB2-rated generic of Levlite. As stated previously, the sole difference between LoSeasonique and Lessina is a change in color of the nonfunctional film coating. The proposed EE tablet formulation is identical to that in the marketed Seasonique formulation. The NDA submission for LoSeasonique included the bioequivalence (BE) study submitted in support of the approval of the ANDA for Lessina, which was previously reviewed by the Office of Generic Drugs. This was BE Study 99027, which compared the 0.1 mg LNG/0.2 mg EE combination tablets of Levlite and Lessina. The Applicant is relying on the known distribution, metabolism and excretion profiles of Lessina and Seasonique, and provided only single dose pharmacokinetic (PK) data in the BE study.

Division Director's Comment

- *I concur with Dr. Yu's recommendation that the Clinical Pharmacology data are sufficient to support approval of LoSeasonique.*

6. CLINICAL MICROBIOLOGY

According to the primary Chemistry Reviewer, Dr. Kurtyka, the original Application did not contain a discussion of microbiological properties. The Applicant subsequently justified the absence of microbial testing of the drug product in an Amendment dated June 6, 2008. The Applicant stated in the Amendment that the microbiological safety of the drug product was assured because water level was controlled at multiple stages of the drug production to prevent microbial growth. Dr. Kurtyka further stated in his review:

> *"Two very similar formulations (Seasonale and Seasonique) were approved without microbial limit tests and marketed since.....The justification presented above is ADEQUATE and warrants the absence of microbial testing."*

Division Director's Comment

- *I concur with the assessment of Dr. Kurtyka.*

7. CLINICAL/STATISTICAL-EFFICACY

7.1 Overview of Clinical Program and Subject Demographics

The Applicant conducted a single, multicenter, open-label, non-comparative clinical trial (DR-PSE-309) that treated 2,185 women in support of the safety and efficacy of LoSeasonique. Subjects were 18-41 years of age and were to be treated for up to 12 months. The inclusion and exclusion criteria were consistent with those of other clinical trials for oral contraceptives. In contrast to many prior trials, however, there were no exclusion criteria based on subject weight or body mass index (BMI). The mean (±SD) weight of the subjects in the clinical trial was 158.7 (±41.3) pounds (range: 87 - 381). The racial distribution of the subjects who received at least one dose of study drug was 74.5% Caucasian, 11.7% African-American, 10.0% Hispanic, 1.6% Asian, and 2.2% other. Among all-treated subjects, 11% were "new" (first time) users of COCs, 59% were "continuous users" (had used COCs within

the prior 6 months, and 30% were "prior users" (had used COCs more than 6 months prior to study participation).

Division Director's Comments

- *The racial distribution of the population appears fairly representative of the general population.*
- *According to the medical Team Leader, the mean BMI (26.7 kg/m2) of subjects enrolled in Study DR-PSE-309 was similar to that in recent (1999-2002) NHANES data for women aged 20-29 (26.5) and aged 30-39 (27.5), suggesting that the clinical trial population was representative of the general population with respect to BMI.*

7.2 Efficacy Findings

7.2.1 Primary Assessment of Efficacy (On-Treatment Pregnancies)

The primary efficacy analysis in this and other contraceptive trials is the Pearl Index (PI), which is computed as:

$$\text{Pearl Index} = \frac{\text{(number of "on-treatment" pregnancies)}}{\text{(total number of completed 28-day cycle "equivalents"/13)}} \times 100$$

The primary analysis population, per the Applicant's analysis plan, was to be all subjects who completed at least one 91-day treatment cycle and were between the ages of 18-35 years. All pregnancies with an estimated date of conception (EDC) determined to be after the first dose of LoSeasonique and within 14 days after the subject's last combination tablet of LNG/EE were considered to be "on-treatment" pregnancies. All cycles during which an alternative method of birth control was used were excluded from the "total number of 28-day 'equivalent' cycles" in the calculation of the Pearl Index. Women were excluded from participation in the trial if they routinely used condoms for protection from sexually transmitted disease; however, condom use was required for the first 7 days after the initial start of treatment with LoSeasonique and if a subject missed 2 or more consecutive pills. All subjects started treatment with study drug on the first Sunday that included, or occurred after, the start of their menstrual period.

Division Director's Comments

- *All cycles during which an alternative method of birth control was used were excluded from the "total number of 28-day 'equivalent' cycles" in the calculation of the PI. However, all conceptions that were assessed as having occurred from the first day of use of study drug through 14 days after the subject's last LNG/EE tablet were classified as on-treatment pregnancies, without consideration of the subject's possible use of a backup method of contraception at or near the time of conception.*
- *For extended cycle COCs with a 91-day dosing regimen, some modification of the analysis for the Pearl Index is required. To allow for a better comparison to Pearl Index values obtained with COCs with 28-day dosing cycles, the total "at risk" exposure was expressed in terms of completed 28-day cycle equivalents, instead of complete 91-day treatment cycles, for the purpose of analysis.*

7.2.2 Primary Efficacy Findings

The Applicant identified 33 pregnancies for which the conception date was considered to be on-treatment (i.e., conception was assessed as having occurred after the first dose of LoSeasonique and within 14 days after the subject's last combination tablet of LNG/EE). The DRUP primary Medical Reviewer identified 3 additional pregnancies (Subject Nos. 8/801, 10/1096, and 37/37104) that he considered to have occurred while the subjects were on-treatment, for a total of 36 on-treatment pregnancies.

Division Director's Comments

- *The Applicant felt that Subject Nos. 8/801, 10/1096, and 37/37104 should not be considered as on treatment pregnancies because of what they believed was inadequate documentation that any of these subjects had conceived while using LoSeasonique. The medical Team Leader also reviewed in detail all available information supplied by the Applicant pertaining to these 3 subjects. She also concluded that, although the available information allowed for some doubt, the available data also did not exclude the possibility that these 3 subjects had conceived while using LoSeasonique. She therefore agreed with the primary Medical Reviewer that there were 36 on-treatment pregnancies in Clinical Trial DR-PSE-309.*
- *Although I concur with the Applicant that there is some uncertainty that Subject Nos. 8/801, 10/1096, and 37/37104 conceived while using LoSeasonique, I also concur with both the primary Medical Reviewer and the medical Team Leader that the possibility that these 3 subjects had conceived while using LoSeasonique cannot be excluded. Therefore, I concur that the primary efficacy analysis should be based on 36 on-treatment pregnancies.*

7.2.3 Primary Efficacy Analysis

The Pearl Index values (and associated 95% confidence intervals) based on the Applicant's determination of 33 on-treatment pregnancies and DRUP's determination of 36 on-treatment pregnancies are listed in Table 1. Based on 36 on-treatment pregnancies and a total of 17,068 completed 28-day cycle equivalents of treatment for subjects ≤ 35 years of age during which no backup contraception was used, the **Pearl Index** was calculated by the FDA statistician to be **2.74** (95% Confidence Interval: 1.92, 3.78).

Table 1 Pearl Index Values Based on Completed Treatment Cycles in which No Back-Up Contraception was used (Subjects 35 Years of Age or Less) (Study DR-PSE-309)

		Number of Completed 28-day Cycle Equivalents					
	Total Number of Subjects	Total Number	Cycles with Use of Back-up Birth Control	Cycles Without Use of Back-up Birth Control	Number of On-treatment Pregnancies	**Pearl Index**	95% Confidence Interval
Applicant*	1,728	17,974	909	17,065	33	**2.51**	(1.73, 3.53)
DRUP**	1,729	17,977	909	17,068	36	**2.74**	(1.92, 3.78)

* Analysis performed by Applicant and based on Applicant's determination of 33 on-treatment pregnancies.
** Analysis performed by FDA statistician and based on DRUP's determination of 36 on-treatment pregnancies.
Source: Primary Medical Review of NDA 22-262, Table 5.

Division Director's Comments

- *Based on 36 on-treatment pregnancies and a total of 17,068 completed 28-day cycle equivalents for subjects ≤ 35 years of age during which no backup contraception was used, the **Pearl Index** was calculated by the FDA statistician to be **2.74 (95% Confidence Interval: 1.92, 3.78)**.*
- *This is a conservative estimate of the Pearl Index in that on-treatment conceptions for 3 subjects included in the DRUP analysis were not fully verified pregnancies as described earlier in Section 7.2.2.*

Effect of Subject Weight on Efficacy

Many trials for hormonal contraceptive products have set exclusionary criteria to limit enrollment to women having BMIs of less than 30 - 35 kg/m2. Because of reports of reduced efficacy of low dose COCs in heavier women, DRUP has been encouraging Sponsors to enroll women into contraceptive clinical trials without consideration of weight or BMI. The effect of weight on the efficacy of LoSeasonique was therefore assessed. The number of on-treatment pregnancies for each weight decile is listed in Table 2.

Table 2 Baseline Weight Deciles and Number of Pregnancies per Decile

Weight Decile	Number of Subjects in Decile	Weight Range (lbs.)	Number of On-Treatment Pregnancies
1	220	87 - 116	2
2	206	117 - 125	3
3	222	126 - 133	5
4	231	134 - 140	2
5	219	141 - 148	6
6	211	149 - 157	2
7	223	158 - 170	3
8	215	171 - 187	5
9	220	188 - 217	3
10	218	218 - 391	5

Source: Medical Team Leader review for NDA 22-262, Table 8.

Division Director's Comment

- *Of the 36 on-treatment pregnancies, 18 occurred in the lower 5 deciles of weight, and 18 in the upper 5 deciles. Thirteen (13) of the 36 pregnancies (36%) occurred in the upper 3 deciles. Baseline weight, among the women included in Study DR PSE-309, did not have an obvious effect on the efficacy of LoSeasonique.*

7.2.4 Conclusion by FDA Statistician

The primary statistical reviewer, Sonia Castillo, PhD, calculated the Pearl Index value based on the data provided by the Applicant for Study DR-PSE-309. In her calculation, she included the 3 additional on-treatment pregnancies identified by the DRUP medical reviewers. The outcome of her analysis, based on completed 28-day cycle equivalents in

women ≤ 35 years of age at entry, is presented in Table 1. In the conclusion of her statistical review, Dr. Castillo made the following statement:

> *"From a statistical standpoint, the Sponsor has provided one adequate study that provides evidence of the effectiveness of LoSeasonique 91-day extended regimen oral contraceptive in the prevention of pregnancy."*

7.2.5 Overall Assessment of Efficacy

The Applicant has submitted an acceptable clinical trial database supporting efficacy for this low-dose extended cycle combination oral contraceptive. While the Pearl Index of 2.74 is marginally higher than that for other currently marketed low-dose COCs, this product does not appear to have diminished efficacy in heavier women, and therefore, with clear labeling, it provides acceptable contraceptive efficacy for the general population. Furthermore, it provides for a lower dose option for women who may be presently using a COC with an extended dosing cycle such as Seasonale or Seasonique or for women who might wish to use such a product for prevention of pregnancy.

8. SAFETY

The primary Medical Reviewer has provided a thorough discussion and review of the safety findings for LoSeasonique tablets based on the data provided in NDA 22-262. The medical Team Leader also has thoroughly reviewed the safety data. Neither Medical Officer identified any safety issues that would suggest that the overall safety profile for LoSeasonique tablets would be less acceptable than that for other currently approved COCs. The uterine bleeding profile associated with the use of LoSeasonique (described in Section 8.4), although not a safety issue, will not be acceptable to some women who decide to use the product. The expected bleeding profile consists of 4 scheduled withdrawal periods per year, but is also likely to include more unscheduled or breakthrough spotting and/or bleeding than that associated with a 28-day cycle COC. The following review of safety is focused mainly on items of greatest potential concern, and is not comprehensive, because of (1) the through and independent safety reviews by both the primary Medical Reviewer and the medical Team Leader and (2) their assessment that the overall safety profile of LoSeasonique does not raise any new safety concerns, beyond those normally associated with a COC. Of particular note is the absence of reports of any serious thromboembolic adverse event in the subjects who used LoSeasonique in the primary efficacy and safety clinical trial (Study DR-PSE-309)

8.1 Disposition of Subjects

A total of 2,185 women took at least one dose of LoSeasonique (identified as the safety population), and 1,950 subjects completed at least one 91-day cycle of drug use. The total exposure to study drug in the safety population was 6,442 x 91-day treatment cycles or approximately 20,937 x 28-day cycle equivalents. Based on the DRUP analysis, 1,233 subjects (56.4%) completed one full year of treatment. The overall disposition of study subjects and reasons for early discontinuation are summarized in Table 3.

Table 3 Subject Disposition and Reasons for Discontinuation (Safety Cohort, Study DR-PSE-309)

	Applicant's Analysis N (% of safety population)	DRUP Analysis N (% of safety population)
Safety Population	2,185 (100)	2,185 (100)
Completed study	1,249 (57.2)	1,233 (56.4)
Did not complete	936 (42.8)	952 (43.6)
Reason for Discontinuation		
Lost to follow-up	304 (13.9)	311 (14.2)
Adverse event	253 (11.6)	253 (11.6)
Patient request for withdrawal	225 (10.3)	226 (10.3)
Noncompliance with protocol	81 (3.7)	82 (3.8)
Pregnant	34 (1.6)	35 (1.6)
Other	22 (1.0)	28 (1.3)
Did not meet protocol requirements	14 (0.6)	14 (0.6)
Investigator discretion	3 (0.1)	3 (0.1)

Source: Medical Team Leader review of NDA 22-262, Table 3.

Division Director's Comments

- *The differences between the DRUP analysis and that of the Applicant are small and do not impact on the interpretation of the safety data.*
- *According to the medical Team Leader, the 226 subjects withdrawn due to "patient request for withdrawal" included:*
    - *97 due to bleeding*
    - *46 due to personal reasons (e.g., not sexually active, noncompliance, disliked not having monthly period, not otherwise specified)*
    - *45 due to inconvenience (e.g., moving, insufficient time)*
    - *23 due to desire for pregnancy*
    - *15 due to adverse events or non-bleeding health complaint*
- *The percentage of subjects who withdrew because of an adverse event (11.6%) was not excessive for a one year contraceptive clinical trial. Withdrawals due to adverse events are discussed further in Section 8.3.*
- *According to the primary Medical Reviewer "the overall discontinuation rate for LoSeasonique was 42.8%. This percentage is similar to other extended cycle OCs. Seasonale (NDA 21-544) had an overall discontinuation rate in the Safety cohort of 40.6% and Seasonique (NDA 21-840) had a discontinuation rate in the Safety cohort of 50.3%. The discontinuation rate for the recently approved Lybrel was 56.8%."*
- *The size of the safety database is acceptable for the proposed product. For a new contraceptive product that is based on a previously approved progestin (e.g., LNG) and estrogen (e.g., EE), DRUP generally requires a minimum database that includes (1) the equivalent of 10,000 x 28-day cycles of treatment and (2) 200 subjects completing one year of treatment. Both of these criteria were exceeded in Study DR-PSE-309.*

8.2 Deaths and Other Serious Adverse Events

There were no deaths in the clinical development program for LoSeasonique. There were 39 serious adverse events (SAEs) reported by 35 subjects in Study DR-PSE-309. The Applicant reported that 2 of these SAEs resulted in discontinuation of the subject from the trial (i.e., illicit drug use [not related to study drug] and headache with a syncopal episode [possibly related to study drug]). The medical Team Leader, however, identified 3 additional cases (excluding those related to pregnancy) in which the subject also appeared to have been terminated prematurely from study participation for reasons related to a SAE. These were one case each of (1) non-resolution of a pneumo-mediastinum associated with exacerbation of asthma (not related), (2) cholecystitis (possibly related), and (3) Tylenol overdose and depression (possibly related).

Division Director's Comments

- *There were no cases of deep venous thrombosis or pulmonary embolus in this trial. Thromboembolic events are a serious risk associated with the use of COCs.*
- *The total number of subjects with SAEs (35/2185 [1.6%] and the specific SAEs in this trial of one-year duration do not raise any concerns about the overall safety of LoSeasonique.*

8.3 Discontinuations for Adverse Events

Based on the Applicant's analysis, 253 of 2,185 subjects (11.6%) terminated prematurely because of an adverse event (AE). MedDRA System Organ Class (SOC) terms that were associated with subject discontinuations of $\geq$ 0.5% and the most commonly reported AEs within each of the SOC terms are listed in Table 4. The SOCs with the highest number of subject discontinuations because of an adverse event and the numbers of subjects discontinuing were Reproductive System and Breast Disorders (n=117), Psychiatric Disorders (n=39), Nervous System Disorders (n=26), and Skin and Subcutaneous Tissue Disorders (n=23).

Table 4 Adverse Events Associated with Subject Discontinuations

MedDRA System Organ Class (SOC) Preferred Term	Number (N) (% of 2,185 Safety Subjects)	
	N	%
Reproductive System and Breast Disorders-Total	**117**	**(5.4)**
Metrorrhagia	70	(3.2)
Menorrhagia	19	(0.9)
Vaginal Hemorrhage	16	(0.7)
Breast Tenderness	4	(0.2)
Dysmenorrhea	3	(0.1)
Uterine Hemorrhage	1	(0.1)
Menstruation Irregular	1	(0.1)
Psychiatric Disorders-Total	**39**	**(1.8)**
Mood Swings	11	(0.5)
Depression	10	(0.5)
Nervous System Disorders-Total	**26**	**(1.2)**
Headache	15	(0.7)
Migraine	8	(0.4)
Skin and Subcutaneous Tissue Disorders-Total	**23**	**(1.1)**
Acne	12	(0.6)
Alopecia	4	(0.2)
Pigmentation Disorder	2	(0.1)
Gastrointestinal Disorders-Total	**19**	**(0.9)**
Nausea	12	(0.6)
Abdominal Pain	3	(0.1)
Investigations-Total	**18**	**(0.8)**
Weight Gain	11	(0.5)
Blood Pressure Increased	6	(0.3)
Blood Triglycerides Increased	1	(0.1)
General Disorders -Total	**14**	**(0.6)**
Irritability	9	(0.4)
Chest Pain	2	(0.1)
Fatigue	2	(0.1)

Source: Modified from primary Medical Review of NDA 22-262, Table 10.

Division Director's Comments

- *The types of adverse events associated with discontinuation from Study DR-PSE-309 and the numbers of subjects reporting them are consistent with those observed in prior one-year clinical trials for hormonal contraceptives.*
- *As would be expected in a clinical trial of a COC with an extended dosing cycle, adverse events related the abnormal uterine bleeding were the most common cause of subject discontinuations. Subject discontinuations related to unacceptable bleeding patterns are discussed further in Section 8.4.*

8.4 Uterine Bleeding

Subjects completed a paper diary that recorded the occurrence of uterine spotting or bleeding, in addition to use of study drug, any other medications, or the use of contraception other than study drug. Approximately one-half of the subjects were provided with a diary that was to be completed on a once weekly basis. The remainder of the subjects were provided with a diary in which information was to be recorded each day. The Applicant provided the uterine

bleeding data separately for each cohort of diary users. The following definitions for uterine bleeding were used:

- Spotting: Not requiring use of either pads or tampons.
- Bleeding: Requiring use of pads and/or tampons.

Spotting/bleeding was characterized as "scheduled" if it occurred during the 7-day interval in which subjects were taking the EE-alone tablets and as "unscheduled" if it occurred during the 84 days on which subjects were taking LNG/EE tablets. Unscheduled spotting/bleeding is likely to be more troublesome to subjects because it is unpredictable.

Table 5 summarizes the number of days of scheduled spotting and/or bleeding (spotting/bleeding that occurred on Treatment Days 85-91) for each 91-day treatment cycle. Data listed in the Table are limited to that from (1) subjects who maintained daily diaries and (2) cycles for which complete data (i.e., approximately 91 days of cycle data) were available.

Table 5 Number of Days with Scheduled Spotting and/or Bleeding per 91-Day Treatment Cycle

Treatment Cycle	N	Mean	Minimum	Q1*	Median	Q3*	Maximum
1	848	3.1	0	0	3	5	7
2	728	2.8	0	0	3	5	7
3	656	2.5	0	0	2	5	7
4	574	2.7	0	0	3	5	7

* Q1/Q3 = Quartile 1 and Quartile 3, respectively.
Source: Final Report for Study DR-PSE-309, p 642, Table 171.

Division Director's Comment

- *The mean number of days of scheduled bleeding or spotting was fairly consistent across treatment cycles and ranged from 2.5 to 3.1 days per 91-day treatment cycle.*

Table 6 summarizes the number of days of unscheduled spotting and/or bleeding (spotting/bleeding that occurred on Treatment Days 1-84) for each 91-day treatment cycle. Data listed in this Table also are limited to that from (1) subjects who maintained daily diaries and (2) cycles for which complete data (i.e., approximately 91 days of cycle data) were available).

Table 6 Number of Days with Unscheduled Spotting and/or Bleeding per 91-Day Treatment cycle

Treatment Cycle	N	Mean	Minimum	Q1*	Median	Q3*	Maximum
1	848	21.5	0	7	17	31.5	84
2	728	14.3	0	3	10	22	76
3	656	11.7	0	1	7	18	71
4	574	10.0	0	0	6	15	65

* Q1/Q3 = Quartile 1 and Quartile 3, respectively.
Source: Final Report for Study DR-PSE-309, p 639, Table 165.

Division Director's Comments

- *Unscheduled bleeding/spotting appeared to decrease with the duration of treatment, although it is possible that subjects with more frequent spotting/bleeding withdrew early from the study. Regardless of the basis for the change over time, the mean and median number of days with spotting and/or bleeding during Treatment Cycle 4 was reduced by approximately 50% from that reported for Treatment Cycle 1.*
- *According to the medical Team Leader, among the subjects whose reason for discontinuation was listed as "adverse event," 108 discontinued because of complaints related to vaginal bleeding. The medical Team Leader also stated in her review that among the discontinuation categories of "patient request" and "other," there were an additional 101 cases that involved bleeding-related reasons. Therefore, a total of 209 (9.6%) subjects in Study DR-PSE-309 discontinued, at least in part, due to a bleeding/spotting-related concern.*
- *The primary Medical Reviewer stated in his review that "mean end of study changes from baseline in hemoglobin and hematocrit were negligible and not clinically significant."*
- *Because it is not possible to determine in advance if the bleeding pattern associated with the use of LoSeasonique (as well as that for other extended cycle COCs) will be acceptable to a specific woman, labeling will need to delineate clearly the bleeding profile reported for women using LoSeasonique in the clinical trial.*

8.5 Overall Assessment of Safety

The overall safety profile for LoSeasonique, based on the data obtained in Study DR-PSE-309, appears to be comparable to that for other COCs approved for marketing in the U.S. The safety data from Study DR-PSE-309 do not raise any new safety concerns regarding LoSeasonique beyond those that are well know to be associated with the use of COCs. Among the safety issues of greatest concern are those related to a serious venous thromboembolic event (VTE) such as a deep venous thrombosis or a pulmonary embolism. Although the total exposure to LoSeasonique in Study DR-PSE-309 (approximately 20,000 x 28-day equivalent treatment cycles) was not adequate to estimate accurately the risk of a serious VTE in users of the drug product, there were no reports of a serious VTE among the users of LoSeasonique.

The uterine bleeding pattern associated with the use of LoSeasonique may not be acceptable to some women, and these women may discontinue use of the product. Unfortunately, there is no way to predict in advance whether a woman will find the bleeding profile to be acceptable or not. Labeling will therefore need to clearly address this matter.

The primary Medical Reviewer made the following statements in his review:

> *"Based on the data reviewed, Lo Seasonique was associated with an acceptable overall safety profile and generally appeared to be well tolerated. The incidence rate of observed adverse events was consistent with what has been previously observed with other low dose oral contraceptive regimens, with the possible exception of the high incidence of nausea. Patterns of reported unscheduled bleeding and unscheduled spotting decreased after the first 91-day cycle. Changes in laboratory results for chemistry, lipids, hematology and urinalysis were small and consistent with what has been observed in similar oral contraceptive regimens"*

"Review of the safety data provided in this NDA supports the safety of Lo Seasonique when used for prevention of pregnancy."

Division Director's Comment

- *Women who use LoSeasonique for prevention of pregnancy will be exposed to more LNG and EE than women who use a COC containing 0.1 mg LNG/0.02 mg EE with a traditional 28-day dosing cycle. However, women who use LoSeasonique will be exposed to less LNG and EE than women who use Seasonale or Seasonique (approved COCs with extended dosing cycles) or Nordette (a 28-day COC that contains 21 tablets of 0.15 mg LNG/0.03 mg EE) and its generic equivalents. The safety profiles for these previously approved products are acceptable, and it is anticipated that the safety profile for LoSeasonique will be comparable.*

9. ADVISORY COMMITTEE MEETING

This Application was not presented to an Advisory Committee (AC) because the Division did not believe that AC guidance was needed to make a regulatory decision concerning the approvability of the Application. In January 2006, the Advisory Committee for Reproductive Health Products (ACRHP) discussed oral contraceptive products. Among the areas of focus, was an extensive discussion of acceptable efficacy for oral contraceptive products and their labeling. The recommendations from the January 2006 meeting have been fully considered in (1) the review of this Application and (2) the Division's decision regarding the approvability and labeling of LoSeasonique tablets.

10. PEDIATRICS

The Applicant requested a waiver of pediatric studies. The Pediatric Review Committee (PeRC) granted a partial waiver for pre-menarcheal children because they are not at risk for pregnancy. The remainder of the PREA requirement for pediatric studies has been fulfilled by extrapolation. Decades of clinical experience with a wide variety of oral hormonal contraceptives support DRUP's expectation that the efficacy and safety of LoSeasonique in postmenarcheal adolescents, like that of other previously approved oral contraceptives, will not differ from that in young adult women.

11. OTHER RELEVANT REGULATORY ISSUES

Site inspections by the Division of Scientific Investigation were not requested by the primary review team because no sites appeared to be outliers in terms of adverse event reporting, pregnancies, or dropouts.

The Applicant submitted financial disclosure information for all investigators; only 3 investigators had disclosable information and 2 of the 3 enrolled fewer than (b) (6) subjects. The third investigator enrolled (b) (6) subjects and reported receiving an honoraria of ≤ $15,000. His site reported (b) (6) This site does not appear to be an outlier with respect to these important outcomes.

12. LABELING

The Applicant proposed the trade name Lo Seasonique. The Division of Medication Error Prevention and Analysis (DMEPA) found this trade name acceptable, with a recommendation that the space between "Lo" and "Seasonique" be eliminated to minimize the chance that "Lo" will be omitted, thus causing confusion with the approved product Seasonique. The Applicant agreed to make this revision.

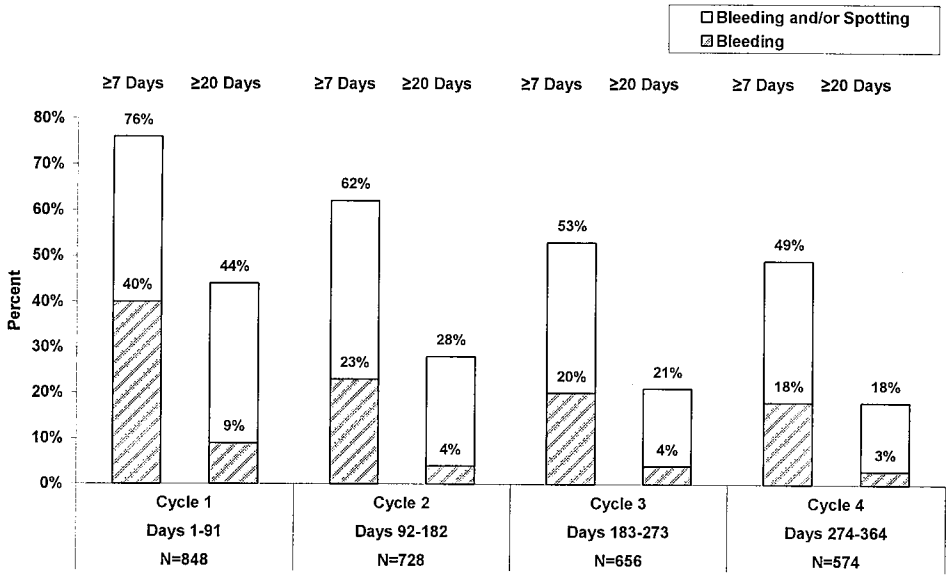
The label for LoSeasonique was submitted in the format prescribed by the Physician Labeling Rule (PLR). The label for LoSeasonique will be the first approved label for a COC using the new PLR format. During the review process, consultations on the proposed label were obtained from the Study Endpoints and Labeling Development Team, the Division of Risk Management (DRISK) and the Division of Drug Marketing, Advertising and Communication (DDMAC). Their comments were incorporated into the label as deemed appropriate by DRUP. The major changes from previous labels for COCs include:

- (b) (4)
- Clear description of the efficacy population and inclusion of the 95% confidence interval for the Pearl Index value
- Further revision of the "Information for Patient" section to provide a more focused discussion of what a user needs to know about the use of this product.

Additional issues specifically relevant to the safe and effective use of LoSeasonique, which are addressed in labeling include:

- Addition of specific adverse reaction data from the clinical trial, including adverse reactions leading to discontinuation from the trial, and common adverse reactions.
- Discussion of only a "Sunday start," as this was the method used exclusively in the clinical trial.
- Description of the bleeding profile demonstrated with LoSeasonique in Study DR-PSE-309. This information is provided in both a table and figure format to assist both healthcare providers and patients in deciding if LoSeasonique might be an appropriate contraceptive choice. The following figure is contained in the to-be-approved labeling:

Figure 1. Percent of Women Taking LoSeasonique who Reported Unscheduled Bleeding and/or Spotting (Based on Daily Diaries)



Carton and container labeling was reviewed by DMEPA and the CMC reviewer. These were revised by the Applicant in accordance with their recommendations.

Final acceptable labeling for LoSeasonique was received from the Applicant on October 24, 2008.

13. DECISION/ACTION/RISK BENEFIT ASSESSMENT

13.1 Regulatory Action

The Applicant has provided sufficient information for me to conclude that LoSeasonique, when used in accordance with approved product labeling, will be a safe and effective oral contraceptive product. Based on the safety and efficacy data submitted in support of NDA 22-262 and the agreed to product labeling submitted by the Applicant on October 21, 2008 (carton labeling) and October 24, 2008 (package insert), LoSeasonique will be approved for the indication of "for use by women to prevent pregnancy."

13.2 Risk/Benefit Assessment

Safety considerations. The overall safety profile for LoSeasonique, based on the data obtained in Study DR-PSE-309, appears to be comparable to that for other COCs approved for marketing in the U.S. These safety data do not raise any safety concerns regarding LoSeasonique beyond those that are well known to be associated with the use of COCs. Of note, there were no reports of a serious VTE (e.g., deep venous thrombosis or pulmonary

embolus) among the users of LoSeasonique in Study DR-PSE-309. The bleeding profile associated with the use of LoSeasonique may not be acceptable to some women, but does not otherwise pose a safety concern. Labeling will clearly describe the bleeding profile that has been reported in users of LoSeasonique.

Efficacy considerations. The Applicant has submitted an acceptable clinical trial database supporting the efficacy for this low-dose extended cycle COC. Based on 36 on-treatment pregnancies and a total of 17,068 completed 28-day cycle equivalents for subjects ≤ 35 years of age during which no backup contraception was used, the Pearl Index value was calculated by the FDA statistician to be 2.74 (95% Confidence Interval: 1.92, 3.78). Approved labeling provides this information regarding the clinical trial findings. While the Pearl Index value for LoSeasonique is somewhat higher, possibly reflecting slightly reduced efficacy, than that for previously approved low dose COCs, the product provides for a lower dose option for women who wish to use a COC with an extended dosing cycle.

Overall Risk/Benefit Assessment. The overall risk/benefit profile for LoSeasonique is acceptable for an oral contraceptive product. LoSeasonique will be a lower dosage COC product than currently available for those women who wish to use a COC with an extended dosing cycle (i.e., 91-day cycle) for prevention of pregnancy.

13.3 Recommendation for Postmarketing Risk Management Activities

No postmarketing risk management activities are warranted or requested beyond that of the approved product labeling and routine pharmacovigilance monitoring.

13.4 Recommendation for other Postmarketing Study Commitments

No postmarketing study commitments are warranted or requested.

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
10/24/2008 05:45:56 PM
MEDICAL OFFICER

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
10/24/2008 05:51:05 PM