Table 24 Demographics, ITT, PITT and Safety Cohorts

Protocol DR-PSE-309	ITT Cohort (N=1,950)	PITT Cohort (N=1,735)	Safety Cohort (N=2,185)
Age (yrs)			
Mean	27.7	26.4	27.7
Median	26.8	25.9	26.7
Weight (lbs)			
Mean	159.1	159.3	158.7
Median	149	149	148
Body Mass Index (kg/m^2)			
Mean	26.8	26.8	26.7
Median	25.1	25.1	25.0
Race			
African-American	224 (11.5%)	200 (11.5%)	256 (11.7%)
Asian	32 (1.6%)	31 (1.8%)	36 (1.6%)
Caucasian	1,458 (74.8%)	1,288 (74.2%)	1,627 (74.5%)
Hispanic	194 (9.9%)	177 (10.2%)	218 (10.0%)
Other	42 (2.2%)	39 (2.2%)	48 (2.2%)
Smoking Status			
Current Smoker	348 (17.8%)	350 (20.2%)	398 (18.2%)
Past Smoker	353 (18.1%)	301 (17.3%)	388 (17.8%)
Non-Smoker	1,249 (64.1%)	1,084 (62.5%)	1,399 (64.0%)
Prior OC Usage			
Unknown	5 (0.3%)	5 (0.3%)	5 (0.2%)
Continuous User[1]	1,190 (61.0%)	1,049 (60.5%)	1,297 (59.4%)
Prior User[2]	554 (28.4%)	493 (28.4%)	644 (29.5%)
Fresh Start[3]	201 (10.3%)	188 (10.8%)	239 (10.9%)

[1] Had history of OC use within six months prior to enrollment
[2] Had history of OC use, but not within six months prior to enrollment
[3] Had no prior history of OC use
Source: NDA 22-262, Clinical Study Report (CSR), Adapted from Tables 7, 8, and 9, Pages 61-63

Medical Reviewer's Comments

- *Almost 75% of all treated patients in this study were Caucasian.*
- *The fact that all enrolled subjects were required to be fluent in English could account for the smaller percentages of Asian and Hispanic study subjects.*
- *The number of fresh starts was quite low (10%) compared to prior and continuous users. This tends to bias the study population to those women who have had fewer problems with OCs and/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.*
- *The mean age of the women in this study was 27 years, with a mean weight of approximately 160 lbs and a mean BMI of approximately 27.*

7.2.1.2 Extent of exposure (dose/duration)

The extent of drug exposure during the study is listed in Table 25.

Table 25 Extent of Exposure, Safety Cohort

Study DR-PSE-309	Lo Seasonique (N=2185)	
Months on Study	N	%
≤1	55	2.5
>1-2	80	3.7
>2-3	112	5.1
>3-4	191	8.7
>4-5	81	3.7
>5-6	52	2.4
>6-7	147	6.7
>7-8	42	1.9
>8-9	30	1.4
>9-10	108	4.9
>10-11	10	0.5
>11-12	20	0.9
>12	1257	57.5
Completed Study[1]	1249	57.2

[1]Subjects with four complete cycles
Source: NDA 22-262, CSR, Adapted from Table 35, Page 81

Medical Reviewer's Comments

- *The above table lists calendar months of exposure to study drugs. Of the 1,257 subjects listed as having > 12 months of exposure to Lo Seasonique, 1,249 fully completed treatment. This exceeds the FDA recommended subject exposure of 200 women for ≥ 12 months in order to adequately assess safety.*
- *Of the 2,185 subjects who began the study, 1,249 (57.2%) remained in the study to completion.*

7.2.2 Description of Secondary Clinical Data Sources Used to Evaluate Safety

No secondary clinical sources were used to evaluate safety for this NDA review.

7.2.3 Adequacy of Overall Clinical Experience

An adequate number of subjects were exposed to the study drug for an adequate duration of time in order to evaluate the safety and efficacy of this product.

7.2.4 Adequacy of Special Animal and/or In Vitro Testing

No special animal and/or in-vitro testing was indicated or required.

7.2.5 Adequacy of Routine Clinical Testing

The routine clinical testing for this NDA was adequate. No special metabolic, clearance and interaction workup was required for this NDA.

7.2.6 Adequacy of Metabolic, Clearance, and Interaction Workup

Not applicable.

7.2.7 Adequacy of Evaluation for Potential Adverse Events for Any New Drug and Particularly for Drugs in the Class Represented by the New Drug; Recommendations for Further Study

The data submitted to the NDA was adequate for the evaluation for potential adverse events. No recommendations for further study are necessary.

7.2.8 Assessment of Quality and Completeness of Data

The quality and completeness of data provided in the submission is adequate and complete.

7.2.9 Additional Submissions, Including Safety Update

The 120-day Safety Update Report was received on April 25, 2008. Further information on 11 of the pregnancies which occurred during Study DR-PSE-309 was provided. Nine subjects reported no pregnancy or neonatal complications. Two patients were lost to follow-up.

The 120-day Safety Update Report also contains a follow-up of two ongoing serious adverse events. One patient reported a resolved right tibial fracture and a second patient, who had never started study medication, was being followed for invasive ductal carcinoma of the breast.

No further safety data was provided for Lo Seasonique. The drug is not marketed in Europe and there are no further clinical trials being conducted in this country.

7.3 Summary of Selected Drug-Related Adverse Events, Important Limitations of Data, and Conclusions

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

- The Clinical Study Report for the primary clinical trial (DR-PSE-309) was submitted for review. In this study, a total of 1,249 subjects completed one year of treatment with Lo Seasonique. This exceeds the minimum Division recommendation of 200 women completing one year of treatment to adequately demonstrate OC safety.
- There were no deaths or VTEs reported in Study DR-PSE-309.
- The most common adverse event during the trial was headache, which occurred in 730 subjects (33%). The reason for the high occurrence of headache with Lo Seasonique is unclear. Headache or migraine was the cause of study discontinuation in only 23 subjects (1.1%), however.
- A significant adverse event related to the use of Lo Seasonique was unanticipated bleeding and/or spotting. During Study DR-PSE-309, 9.6% of subjects discontinued, at least in part, due to bleeding and/or spotting.

- 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 primary study that there are significant problems with anemia in those subjects taking Lo Seasonique. Mean hematocrit and hemoglobin values remained stable during the study.
- There were no notable changes in vital signs (i.e., systolic and diastolic blood pressure, heart rate, weight or temperature) over time within or between the treatment groups.
- There were no new signals of unexpected serious adverse events related to the use of Lo Seasonique.

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.

7.4 General Methodology

7.4.1 Pooling Data Across Studies to Estimate and Compare Incidence

The single phase 3 clinical trial submitted to this NDA does not provide an opportunity to pool data. There is extensive clinical information available regarding LNG/EE dosing formulations so that pooled data across studies is not required for evaluation of safety and efficacy of this drug. Exploration for predictive factors was also not required for evaluation of safety and efficacy.

7.4.1.1 Explorations for drug-demographic interactions

The product is intended for reproductive age women only. The pharmacologic class is well characterized. There have been no apparent differences based on race or ethnicity in regard to the safety or efficacy of OCs.

8 ADDITIONAL CLINICAL ISSUES

8.1 Dosing Regimen and Administration

There is no clinical issue with the dosing regimen and administration of Lo Seasonique.

Lo Seasonique is a low dose 91-day extended cycle oral contraceptive. One tablet is taken orally every day for 91 days followed by the next package of 91 days tablets. Patients are cautioned in

the Patient Package Insert (PPI) to take the pill at the same time every day. The Applicant did not conduct a single-dose crossover food effect study.

Medical Reviewer's Comments

- *LNG/EE combination OCs have been used extensively in the US without any labeling instructions regarding the administration with respect to food. There has been no evidence to date of any clinical concern regarding differences in absorption between the fasting and fed states.*
- *The primary trial for Lo Seasonique contained in this NDA did not specify how the product should be taken with respect to food.*

8.2 Drug-Drug Interactions

No drug-drug interaction studies were performed for this NDA application. Class labeling for OCs includes a section on drug-drug interactions, which will be included in the Lo Seasonique label.

8.3 Special Populations

This product is recommended for use only in women of childbearing age. No other special populations were studied. There is no evidence in the current medical literature that the safety or efficacy of OCs is significantly affected by race.

8.4 Pediatrics

All applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

The Applicant has requested a full waiver of all pediatric studies because, according to class labeling, the safety and efficacy of LNG/EE combination tablets have been established in all women of reproductive age. Similarly, the safety and efficacy profile of Lo Seasonique is expected to be the same for post-pubertal adolescent females less than 18 years of age as it is for females older than 18 years of age. A partial waiver is therefore recommended. This partial waiver is based on extrapolation from the large body of existing data which provides evidence that combination OCs are as safe and effective in postpubertal females as they are in other women of reproductive age.

8.5 Advisory Committee Meeting

No Advisory Committee meeting was indicated or held.

8.6 Literature Review

No literature review was performed.

8.7 Postmarketing Risk Management Plan

The Applicant did not provide a postmarketing risk management plan. Standard post-marketing surveillance (AERS) is recommended to further monitor the efficacy and safety of Lo Seasonique.

8.8 Other Relevant Materials

Not applicable.

9 OVERALL ASSESSMENT

9.1 Conclusions

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 affected 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.

Annual Hormone Exposure
Extended-cycle oral contraception regimens inherently expose women to a higher total annual dose of both LNG and EE than conventional 28 day oral contraceptive regimens containing equivalent amounts. As shown in Table 26, the total annual dose of both active ingredients in Lo Seasonique falls within the range of other approved combination oral contraceptives containing LNG and EE.

Table 26 Total Annual Exposure to EE and LNG

	Levlite	Nordette	Lybrel	Seasonale	Seasonique	Lo Seasonique
EE dose/combination tablet (mg)	0.02	0.03	0.02	0.03	0.03	**0.02**
LNG dose/combination tablet (mg)	0.10	0.15	0.09	0.15	0.15	**0.10**
EE dose/tablet (mg)	0	0	0	0	0.01	**0.01**
# of active tablets/cycle	21	21	28	84	91	**91**
# of cycles/year	13	13	13	4	4	**4**
# of active tablets/year	273	273	364	336	364	**364**
Total EE/year (mg)	5.46	8.19	7.28	10.08	10.36	**7.0**
Total LNG/year (mg)	27.3	40.95	32.76	50.4	50.4	**33.6**

Source: NDA 21-840, Integrated Summary of Benefits and Risks, Adapted from Table 5.

Medical Reviewer's Comments

- *The substitution of unopposed EE 10 mcg monotherapy for placebo tablets given for four seven-day periods has already been evaluated and approved as part of the Seasonique regimen.*
- *The total annual dose of EE in the Lo Seasonique regimen is 7.0 mg per year, which is lower than many approved OC products. Recently approved Lybrel, an OC containing LNG 90 mcg/EE 20 mcg taken daily for one year, exposes a patient to 7.28 mg per year of EE. This is approximately 280 mcg or 4% more EE per year than Lo Seasonique.*
- *The total annual dose of LNG found in Lo Seasonique is also lower than many approved OC products.*

9.2 Recommendation on Regulatory Action

Approval of Lo Seasonique™ for prevention of pregnancy is recommended based on the Applicant's demonstration of an acceptable Pearl Index and an acceptable safety profile.

9.3 Recommendation on Postmarketing Actions

Standard post-marketing surveillance (AERS) is recommended to further monitor the safety of Lo Seasonique.

9.3.1 Risk Management Activity

No specific risk management steps are warranted based on presently available data.

9.3.2 Required Phase 4 Commitments

No phase 4 commitments are required or recommended.

9.3.3 Other Phase 4 Requests

No other phase 4 requests are recommended.

9.4 Labeling Review

The Applicant originally proposed the trade name of Lo Seasonique. Although they did not object to the proposed name, the Division of Medication Error Prevention and Analysis (DMEPA) has suggested that the position of the prefix Lo immediately preceding rather than following the root name may help in distinguishing Lo Seasonique from Seasonique. In addition, DMEPA suggested eliminating the space between the modifier, "Lo," and the root name to avoid misinterpretation with a net quantity since Lo can resemble the number "10".

Medical Reviewer's Comments

- *The Applicant has recently notified the Division of its acceptance of the suggestions made by DMEPA. The name of the product will be "LoSeasonique."*
- *The LoSeasonique label was submitted in the format prescribed by the Physician Labeling Rule (PLR), and, if approved, would represent the first PLR label for an OC.*
- *Consults on the proposed label were obtained from the Study Endpoints and Labeling Development Team, the Division of Risk Management and the Division of Drug Marketing, Advertising and Communication.*

The primary objectives of the new PLR OC label are to increase the utility of the label by making it more concise and focused.

Major changes from prior OC labels will include:

- (b) (4)
- Description of the bleeding profile demonstrated with Lo Seasonique, particularly the frequency and duration of unscheduled bleeding
- 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.

Agreement has been reached with the Applicant on labeling. The carton/container labeling submitted by the Applicant, as revised in accord with comments by DMEPA and the CMC reviewer, is also acceptable.

9.5 Comments to Applicant

There are no additional comments that need to be communicated to the Applicant.

10 APPENDIX

Combination Oral Contraceptives containing Ethinyl Estradiol/Levonorgestrel Approved in the United States

NDA #	Proprietary Name/ Applicant	Approval Date	EE strength (mg)	LNG strength (mg)	Generic/ #/Applicant/year
16-672 16-806	Ovral Ovral-28 Wyeth Ayerst	1968	0.05	0.25*	Ogestrel 075406/SCS/1999
17-612 17-802	Lo/Ovral Lo/Ovral-28 Wyeth Ayerst	1976	0.03	0.15**	Low-Ogestrel-21/28 075288/Watson/1999 Cryselle /075480/Duramed Pharm/2001
18-668/ 18-782	Nordette-21 Nordette-28 Wyeth Ayerst	5/10/82	0.03	0.15	Portia-21/ 075866/Barr Labs/2002 Levora-21/28/073592/ 073594/Watson/1993
19-192 19-190	Triphasil 21 Triphasil 28 Wyeth Ayerst	11/01/84	0.03 0.04 0.03	0.05 0.125 0.075	Trivora-21/28/074538 Watson/1997 Enpresse-21/28/075809 Duramed Pharm/2001
20-683	Alesse 21 Alesse 28 Wyeth Ayerst	3/27/97	0.02	0.10	Lessina-21/28/075803 Barr/2002 Aviane-21/28/075796 Duramed Pharm/2001
20-860	Levlite Berlex	7/13/98	0.02	0.10	
20-946	Preven Gynetics	9/01/98	0.05	0.25	
Extended Cycle Combination Oral Contraceptives					
21-544	Seasonale Barr Labs	9/05/03	0.03	0.15	
21-840	Seasonique Barr Labs	5/2006	0.02	0.10	
21-864	Lybrel Wyeth	5/2007	0.02	0.09	

Source: Medical Reviewer compilation from various sources
(*) Ovral (and its generic equivalent, Ogestrel 0.5/50) contains 0.5 mg d,l-norgestrel of which 0.25 mg is the active progestin levonorgestrel.
(**) Lo/Ovral (and its generic equivalents, Low-Ogestrel and Cryselle) contains 0.3 mg d,l- norgestrel, of which 0.15 mg is the active progestin levonorgestrel.

LIST OF INVESTIGATORS, Study DR-PSE-309

Site#	Investigator	City	State
001	(b) (6)		NC
002			KS
003			FL
004			NJ
005			CO
006			WA
007			PA
008			TX
009			GA
010			KY
011			CA
012			NJ
013			FL
014			AZ
015			NJ
016			FL
017			AZ
018			NC
019			TX
020			FL
021			OH
022			WA
023			CA
024			TX
025			OK
026			WA
027			OR
028			WA
029			NJ
030			GA
031			NE
032			MO
033			FL
034			CO
035			TX
036			ID
037			OH
040			AZ
041			NC
042			FL
043			PA
044			PA
045			IL
046			MO
047			KS
048			CT

049	-	-	-
050	(b) (6)		PA
051			FL
052			-
053			CO
054			VA
055			AL
056			FL
057			AZ
058			VA
059			NY

10.1 Review of Individual Study Reports

This NDA submission consisted of only one primary clinical trial, which is reviewed in the body of this document.

10.2 Line-by-Line Labeling Review

The Applicant has submitted acceptable labeling, which will be attached to the Approval letter.

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

/s/

Ronald Orleans
10/24/2008 03:07:53 PM
MEDICAL OFFICER

Lisa Soule
10/24/2008 03:28:40 PM
MEDICAL OFFICER
I concur with Dr. Orleans' conclusions and recommendation.

CLINICAL FILING CHECKLIST FOR A NEW NDA/BLA

NDA Number: 22-262 **Applicant: Duramed Pharm.** **Stamp Date: 26-Dec-07**

Drug Name: Lo Seasonique **NDA Type: Standard Review** **Padufa Goal Date: 26-OCT-08**

	Content Parameter	Yes	No	NA	Comment
FORMAT/ORGANIZATION/LEGIBILITY					
1.	Identify the general format that has been used for this application, e.g. electronic CTD.			X	eCTD but not Global Summit Review enabled
2.	On its face, is the clinical section of the application organized in a manner to allow substantive review to begin?	X			Well organized.
3.	Is the clinical section of the application indexed (using a table of contents) and paginated in a manner to allow substantive review to begin?	X			
4.	For an electronic submission, is it possible to navigate the application in order to allow a substantive review to begin (*e.g.*, are the bookmarks adequate)?	X			
5.	Are all documents submitted in English, or are English translations provided when necessary?	X			
6.	On its face, is the clinical section of the application legible so that substantive review can begin?	X			
LABELING					
7.	Has the applicant submitted draft labeling in electronic format consistent with 21 CFR 201.56[1] and 201.57 (or 21 CFR Subpart C for OTC products), current divisional and Center policies, and the design of the development package?	X			Section 1.14.1
SUMMARIES					
8.	Has the applicant submitted all the required discipline summaries (*i.e.*, Module 2 summaries)?	X			Chemistry submitted but no non-clinical summary included
9.	Has the applicant submitted the integrated summary of safety (ISS)?			X	Only one phase 3 study included in the submission
10.	Has the applicant submitted the integrated summary of efficacy (ISE)?			X	Only one phase 3 study included in the submission
11.	Has the applicant submitted a benefit-risk analysis for the product?	X			
12.	Indicate if the Application is a 505(b)(1) or a 505(b)(2). If Application is a 505(b)(2) and if appropriate, what is the reference drug?			X	Application filed as a 505(b)(1)
DOSE					
13.	If needed, has the sponsor made an appropriate attempt to determine the correct dosage and schedule for this product (*i.e.*, appropriately designed dose-ranging studies)? Study Number: Study Title: Sample Size: Arms: Location in submission:			X	Dose ranging studies are not necessary for this product..
EFFICACY					
14.	On its face, do there appear to be the requisite number of	X			

[1] http://www.access.gpo.gov/nara/cfr/waisidx_01/21cfr201_01.html

CLINICAL FILING CHECKLIST FOR A NEW NDA/BLA

	Content Parameter	Yes	No	NA	Comment
	adequate and well-controlled studies in the application? Pivotal Study #1 DR-PSE-309 Indication: Oral Contraceptive Pivotal Study #2 N/A Indication: N/A				
15.	Do all pivotal efficacy studies appear to be adequate and well-controlled within current divisional policies (or to the extent agreed to previously with the applicant by the Division) for approvability of this product based on proposed draft labeling?	X			Division commented on statistical plan for the primary study on 10/16/2007.
16.	Do the endpoints in the pivotal studies conform to previous Agency commitments/agreements? Indicate if there were not previous Agency agreements regarding primary/secondary endpoints.	X			Pearl Index calculations
17.	Has the application submitted a rationale for assuming the applicability of foreign data to U.S. population/practice of medicine in the submission?			X	
SAFETY					
18.	Has the applicant presented the safety data in a manner consistent with Center guidelines and/or in a manner previously requested by the Division?	X			
19.	Has the applicant submitted adequate information to assess the arythmogenic potential of the product (*e.g.*, QT interval studies, if needed)?			X	
20.	Has the applicant presented a safety assessment based on all current worldwide knowledge regarding this product?			X	
21.	For chronically administered drugs, have an adequate number of patients (based on ICH guidelines for exposure[2]) been exposed at the dose (or dose range) believed to be efficacious?	X			-At least 200 subjects completing 13 cycles -Minimum of 10,000 28-day cycles
22.	For drugs not chronically administered (intermittent or short course), have the requisite number of patients been exposed as requested by the Division?			X	
23.	Has the sponsor submitted the coding dictionary[3] used for mapping investigator verbatim terms to preferred terms?	X			
24.	Has the sponsor adequately evaluated the safety issues that are known to occur with the drugs in the class to which the new drug belongs?	X			
25.	Have narrative summaries been submitted for all deaths and adverse dropouts (and serious adverse events if requested by the Division)?	X			
OTHER STUDIES					
26.	Has the applicant submitted all special studies/data requested by the Division during the pre-submission			X	

[2] For chronically administered drugs, the ICH guidelines recommend 1500 patients overall, 300-600 patients for six months, and 100 patients for one year. These exposures MUST occur at the dose or dose range believed to be efficacious.

[3] The "coding dictionary" consists of a list of all investigator verbatim terms and the preferred terms to which they were mapped. It is most helpful if this comes in as a SAS transport file so that it can be sorted as needed; however, if it is submitted as a PDF document, it should be submitted in both directions (verbatim -> preferred and preferred -> verbatim).

CLINICAL FILING CHECKLIST FOR A NEW NDA/BLA

	Content Parameter	Yes	No	NA	Comment
	discussions with the sponsor?				
27.	For Rx-to-OTC switch and direct-to-OTC applications, are the necessary consumer behavioral studies included (*e.g.*, label comprehension, self selection and/or actual use)?			X	
PEDIATRIC USE					
28.	Has the applicant submitted the pediatric assessment, or provided documentation for a waiver and/or deferral?	X			Module 1.9.1
ABUSE LIABILITY					
29.	If relevant, has the applicant submitted information to assess the abuse liability of the product?			X	
FOREIGN STUDIES					
30.	Has the applicant submitted a rationale for assuming the applicability of foreign data in the submission to the U.S. population?			X	
DATASETS					
31.	Has the applicant submitted datasets in a format to allow reasonable review of the patient data?	X			
32.	Has the applicant submitted datasets in the format agreed to previously by the Division?	X			
33.	Are all datasets for pivotal efficacy studies available and complete for all indications requested?	X			
34.	Are all datasets to support the critical safety analyses available and complete?	X			
35.	For the major derived or composite endpoints, are all of the raw data needed to derive these endpoints included?	X			
CASE REPORT FORMS					
36.	Has the applicant submitted all required Case Report Forms in a legible format (deaths, serious adverse events, and adverse dropouts)?	X			
37.	Has the applicant submitted all additional Case Report Forms (beyond deaths, serious adverse events, and adverse drop-outs) as previously requested by the Division?	X			
FINANCIAL DISCLOSURE					
38.	Has the applicant submitted the required Financial Disclosure information?	X			Module 1.3.4
GOOD CLINICAL PRACTICE					
39.	Is there a statement of Good Clinical Practice; that all clinical studies were conducted under the supervision of an IRB and with adequate informed consent procedures?	X			Module 5.3.5.1 Clinical Study Report Page 27
CONCLUSION					
40.	From a clinical perspective, is this application fileable? If not, please state why.	X			Application is fileable

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

Reviewing Medical Officer Date

CLINICAL FILING CHECKLIST FOR A NEW NDA/BLA

Clinical Team Leader Date

Background

Trade names become confusing.

- Seasonique is Seasonale with EE instead of placebo.
- Lo Seasonique is Lo Seasonale with EE instead of placebo.

Seasonale: (PI=1.98)

- NDA 21-544 approved 9/2003
- 84-days of 150 LNG/30 EE followed by 7 days of placebo (5:1 ratio)

Lo Seasonale: (b) (4)

- NDA 21-921
- 84-days of 100 LNG /20 EE (5:1 ratio) followed by 7 days placebo
- Withdrawn in 2006. (b) (4)

Seasonique: (PI=1.77)

- NDA 21-840 approved 5/2006
- First 91-day regimen.
- 84-days of 150 LNG /30 EE (5:1 ratio) followed by 7 days of 10 mcg EE
- 2200 women treated for up to four 91-day cycles
- 1100 completed one year of treatment
- 17,000 28-day cycles of exposure
- Endometrial biopsies done on 119 subjects

Lo Seasonique: (PI=2.44 or 2.15 depending; compliant use PI=1.77)

- Second 91-day regimen
- 84-days of 100 LNG /20 EE (5:1 ratio) followed by 7 days of 10 mcg EE
- One multi-center, single arm clinical trial
- 2,185 subjects were treated and 1,249 subjects completed four 91-day cycles (16,237 women-years).
- Total exposure was 6,442 91-day cycles or 20,937 28-day cycles
- Satisfies criteria of at least 200 subjects completing 13 cycles and minimum of 10,000 28-day cycles
- Applicant states that advantages are "potential for improved safety profile" and that the additional EE may help suppress ovarian function and improve BTB.
- Study design: Four 91-day cycles and a 4-week follow-up period
- Safety: 7000 mcg annual EE exposure (Seasonique is 10,360 mcg/year); No deaths or VTEs reported. No endometrial biopsies were done. Relying on Seasonique data.
- 8.4% discontinued the study because of bleeding.

Lybrel: (PI=2.38)

- Continuous 365 day regimen of 90 mcg LNG/20 mcg EE

Ortho-TriCyclen Lo: (PI=2.67)

CLINICAL FILING CHECKLIST FOR A NEW NDA/BLA

(b) (4)

[redacted]

DR-PSE-309: Median Number of Days of Reported Bleeding and/or Spotting (Based on Daily Diary) - Subjects With at Least One Complete Cycle of Treatment (ITT)

Cycle	Bleeding		Spotting Only		Unsched. Bleeding (Day 1-84)		Unsched. Spotting Only (Day 1-84)	
	91-day	28-day	91-day	28-day	91-day	28-day	91-day	28-day
1	7	2.2	11	3.4	**5**	1.3	10	2.5
2	4	1.2	7	2.2	**1**	0.3	5	1.3
3	3	0.9	5	1.5	**0**	1.0	4	1.0
4	4	1.2	4	1.2	**0**	0.8	3	0.8

Total Days of Unscheduled Bleeding and/or Spotting per Cycle (Complete Cycles Only) – All Treated Subjects With at Least One Complete Cycle of Treatment for Study SEA 301

Drug	Cycle	N	Mean	Median	Mean / Median per Subject-Month [A]
SEA-301					
Seasonale	1	385	16.4	14.0	4.1 / 3.5
	2	331	12.3	7.0	3.1 / 1.8
	3	296	10.8	6.0	2.7 / 1.5
	4	262	9.1	4.0	2.3 / 1.0
	(b) (4)				
Seasonale Lo					
Levlite	1	225	2.8	2.0	
	2	215	1.9	1.0	
	3	211	2.0	1.0	
	4	195	2.0	1.0	
	5	189	1.8	1.0	
	6	186	1.7	1.0	
	7	173	1.7	1.0	
	8	172	1.7	1.0	
	9	171	1.8	1.0	
	10	166	1.7	1.0	
	11	154	1.1	1.0	
	12	153	1.7	1.0	
	13	148	1.8	1.0	

[A] Obtained by multiplying the 91-day cycle result by the factor (21/84) "to adjust" for the difference in cycle length compared to a 28-day convention cycle.

Source: NDA 21-921, ISS, Page 83, and FDA reviewer's calculation of the means.