CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

22-262

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

CLINICAL PHARMACOLOGY REVIEW

NDA:	22-262
Type/Category:	505(b)(1)
Brand Name:	Lo Seasonique™ (pending)
Generic Name:	Levonorgestrel (LNG) + Ethinyl Estradiol (EE)
Relevant INDs:	IND 60,399 and IND 63,735
Indication:	Prevention of Pregnancy
Dosage Form:	Immediate Release Tablets
Route of Administration:	Oral
Dosing Regimen and Strength:	84 days of LNG 0.1 mg / EE 0.02 mg followed by 7 days of EE 0.01 mg (91 day regimen)
Sponsor:	Duramed Pharmaceuticals, Inc.
OCP Division:	Division of Clinical Pharmacology 3
OND Division:	Division of Reproductive and Urologic Products (DRUP)
Submission Dates:	December 26, 2007 (original) April 3, 2008 (revised PLR label draft)
Reviewer:	Chongwoo Yu, Ph.D.
Team Leader:	Myong-Jin Kim, Pharm.D.

TABLE OF CONTENTS

1 EXECUTIVE SUMMARY

Duramed Pharmaceuticals Inc. submitted a New Drug Application (NDA) 22-262 for Lo Seaonique™ (LNG 0.1 mg / EE 0.02 mg tablets and EE 0.01 mg tablets) immediate release tablets under Section 505(b)(1). Lo Seasonique™ is a 91 day extended-cycle oral contraceptive (OC) indicated for the prevention of pregnancy in women who elect to use this product as a method of contraception. It utilizes 84 days of combination of LNG 0.1 mg / EE 0.02 mg tablets followed by 7 days of EE 0.01 mg tablet monotherapy. Extended-cycle OCs are proposed to reduce or eliminate the withdrawal bleeding that occurs once every 28 days in traditional combined OCs.

In 2003, the first extended-cycle OC regimen, Seasonale® (84 days of LNG 0.15 mg / EE 0.03 mg, followed by 7 days of placebo, NDA 21-544, Duramed) was approved. Subsequently, another extended-cycle OC regimen, Seasonique® (84 days of LNG 0.15 mg / EE 0.03 mg, followed by 7 days of EE 0.01 mg) was approved in 2006 (NDA 21-840, Duramed). Seasonique® incorporated the identical 84 day active combination pill period as Seasonale®, but the 7 day placebo period was replaced by 7 days of EE 0.01 mg monotherapy. The Sponsor believes that increased ovarian suppression with the addition of EE during the usual 7-day hormone free interval (HFI) may minimize fluctuation in estradiol levels and improve cycle control. Furthermore, the Sponsor believes that the elimination of placebo may enhance the level of hormonal suppression or allow the onset of hormonal suppression to occur sooner, while minimizing hormonal fluctuations. Duramed submitted NDA 21-921 to market Lo Seasonale™, a lower dose of extended-cycle OC compared to Seasonale® (84 days of LNG 0.1 mg / EE 0.02 mg followed by 7 days of placebo), but withdrew its application for consideration in 2006.

The combination tablets of Lo Seasonique™ are manufactured using the same formulation, manufacturing process and components as those approved for the presently available Barr/Duramed generic product Lessina® (ANDA # 75,803, LNG 0.1 mg / EE 0.02 mg tablets and placebo tablets, approved on May 20, 2002) except for the color of the non-functional film coating. According to the FDA guidance for industry on SUPAC-IR solid dosage forms, this is classified as a Level 1 change as it consists of color change of the non-functional film coating that is unlikely to affect the drug performance. The EE 0.01 mg tablet formulation of Lo Seasonique™ is identical to the marketed Seasonique® formulation. Lessina®, the AB2 rated generic product of Levlite® (NDA # 20-860, approved on July 13, 1998), contains 21 combination tablets followed by 7 placebo tablets.

The Sponsor has submitted the study report of a bioequivalence (BE) study of Levlite® and Lessina® (Study 99027: LNG 0.1 mg / EE 0.02 mg combination tablet). The BE study report was submitted as documentation of single-dose pharmacokinetics (PK) of Lo Seasonique™. The BE study and bioanalytical method validation reports were previously reviewed by the Office of Generic Drugs (OGD). The Sponsor is relying on the distribution, metabolism, and excretion profiles of Lessina® and Seasonique®.

The safety and efficacy of Lo Seaonique™ for the prevention of pregnancy were evaluated in a single pivotal multicenter, open-label clinical trial, Study DR-PSE-309, conducted under IND 63,735. Study DR-PSE-309 was conducted with the to-be-marketed formulation of Lo Seasonique™ (Lessina®'s combination tablet formulation except for the color change of the non-functional film coating and the marketed Seasonique® formulation for the EE tablets). Study DR-PSE-309 was a one-year, single-arm study that treated a total of 2,185 women.

1.1 RECOMMENDATIONS

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.

1.2 PHASE IV COMMITMENTS

None

1.3 SUMMARY OF CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FINDINGS

Lo Seasonique™ is manufactured using the same formulation, manufacturing process and components as those approved for the presently available Barr/Duramed generic product Lessina® except for the color of the non-functional film coating. According to the FDA guidance for industry on SUPAC-IR solid dosage forms, this is classified as a Level 1 change as it consists of color change of the non-functional film coating that is very unlikely to affect the drug performance. Per the Chemistry reviewer, appropriate chemistry documentation was submitted to fulfill the documentation requirement.

Single Dose PK of LNG 0.1 mg / EE 0.02 mg Combination Tablet: Study 99027

A randomized, open label, single dose, two-period crossover BE study was conducted in 30 healthy females under fasted conditions to determine the single dose BA of Lo Seasonique™ and to demonstrate the BE of the LNG 0.1 mg / EE 0.02 mg combination tablets Lessina® (Lo Seasonique™) relative to those of Levlite®. Tablets were administered as 3 units of LNG 0.1 mg / EE 0.02 mg tablets. Tables 1 and 2 summarize the plasma Lo Seasonique™ PK parameters of LNG and EE, respectively, following a single dose.

Table 1: Summary of Plasma LNG PK Parameters following a Single Dose of Lo Seasonique™

PK Parameters	Arithmetic Mean	SD
C_{max} (ng/ml)	6.00	1.63
T_{max} (hr)	1.55	0.57
AUC_{0-t} (ng·hr/ml)	64.28	23.41
AUC_{0-inf} (ng·hr/ml)	76.38	24.86
$t_{½}$ (hr)	28.48	8.71
k_{el} (1/hr)	0.0266	0.0083

* Treatment: 3 x LNG 0.1 mg / EE 0.02 mg tablets; t: time of the last measurable concentration; N=30

Table 2: Summary of Plasma EE PK Parameters following a Single Dose of Lo Seasonique™

PK Parameters	Arithmetic Mean	SD
C_{max} (pg/ml)	122.75	39.45
T_{max} (hr)	1.83	0.67
AUC_{0-t} (pg·hr/ml)	1127.21	341.82
AUC_{0-inf} (pg·hr/ml)	1335.83	365.30
$t_{½}$ (hr)	17.49	7.44
k_{el} (1/hr)	0.0431	0.0102

* Treatment: 3 x LNG 0.1 mg / EE 0.02 mg tablets; t: time of the last measurable concentration; N=30

The effect of food on the BA of Lo Seasonique™ tablets following oral administration has not been evaluated. This statement was added to the proposed label accordingly. The phase 3 clinical trial (Study DR-PSE-309) was conducted regardless of food intake.

Reviewer:
Chongwoo Yu, Ph.D.
Division of Clinical Pharmacology 3
Office of Clinical Pharmacology

Concurrence:
Myong-Jin Kim, Pharm.D., Team leader
Division of Clinical Pharmacology 3
Office of Clinical Pharmacology

2 QUESTION BASED REVIEW

2.1 General Attributes

Q1. What are the nomenclature, molecular structure, molecular function, and molecular weight of the drug substance?

Chemical name and structure:

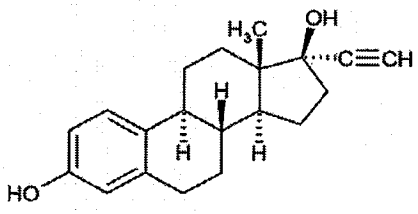
ETHINYL ESTRADIOL:

1. 19-Norpregna-1,3,5(10)-trien-20-yne-3,17-diol,(17α)-
2. 19-Nor-17α-pregna-l,3,5(10)-trien-20-yne-3,17-diol

CAS #: 57-63-6

USAN: ethinyl estradiol

Molecular Structure:



Molecular Formula: $C_{20}H_{24}O_2$

Molecular Weight: 296.40

LEVNORGESTREL:

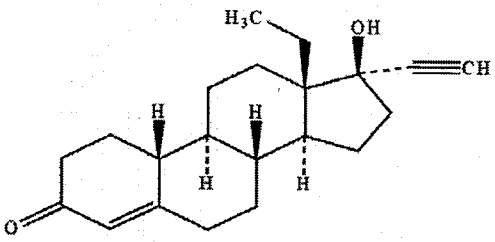
18,19-Dinorpregn-4-en-20-yn-3-one, 13-ethyl-17-hydroxy-, (17α)-(−)-. Or

(−)-13-Ethyl-17-hydroxy-18,19-dinor-17α-pregn-4-en-20-yn-3-one (USP)

CAS #: [797-63-7]

USAN: Levonorgestrel, USP

Molecular Structure:



Molecular Formula: $C_{21}H_{28}O_2$

Molecular Weight: 312.45

Q2. What are the components and composition of the Lo Seasonique™ final product?

The quantitative composition of each component of the drug product is shown in Table 3 below:

Table 3: Quantitative Composition of Each Component of the Drug Product

Levonorgestrel and Ethinyl Estradiol Tablets, USP 0.1mg/0.02mg (0028):

Ingredient	mg/Tablet	w/w (%)	IIG Limit (mg)
Levonorgestrel, USP (Micronized)	0.1	(b) (4)	
Ethinyl Estradiol, USP (Micronized)	0.02		
Anhydrous Lactose, NF	(b) (4)	(b) (4)	
Hydroxypropyl Methylcellulose USP	(b) (4)		
Microcrystalline Cellulose, NF	(b) (4)		
Starch, NF (Corn Starch)	(b) (4)		
(b) (4)			
Magnesium Stearate, NF			
(b) (4)			
(b) (4)			
Total Theoretical Tablet Weight			

Ethinyl Estradiol Tablets USP, 0.01mg (0556)*:

Ingredient	mg/Tablet	w/w (%)	IIG Limit (mg)
Ethinyl Estradiol, USP (Micronized)	0.01	(b) (4)	
Anhydrous Lactose, NF	(b) (4)	(b) (4)	
(b) (4)			
Microcrystalline Cellulose, NF	(b) (4)		
Magnesium Stearate, NF			
(b) (4)			
(b) (4)			
Total Theoretical Tablet Weight			

*Please note that this is the same as approved in NDA 21-840

Q3. How is the Lo Seasonique™ formulation and regimen different from Lessina® or Seasonique®?

Seasonique® contains 84 combination tablets (LNG 0.15 mg / EE 0.03 mg) followed by 7 EE 0.01 mg tablets. Lessina® (ANDA # 75-803, approved on May 20, 2002), the AB2 rated generic product of Levlite® (NDA # 20-860, approved on July 13, 1998), contains 21 combination tablets (LNG 0.1 mg / EE 0.02 mg) followed by 7 placebo tablets. The to-be-marketed formulation of Lo Seasonique™ contains 84 combination tablets that are manufactured using the same formulation, manufacturing process and components as those approved for Lessina® combination tablets except for the color of the non-functional film coating. According to the FDA guidance for industry on SUPAC-IR solid dosage forms, this is classified as a Level 1 change as it consists of the color change of the non-functional film coating that is unlikely to affect the drug performance. Per the Chemistry reviewer, appropriate chemistry documentation was submitted to fulfill the documentation requirement. The formulation of the 7 EE 0.01 mg tablets is identical to that of Seasonique®.

The Sponsor is relying on the distribution, metabolism, and excretion profiles on Lessina® and Seasonique®.

Q4. What is the proposed mechanism of action?

OCs lower the risk of becoming pregnant primarily by suppressing ovulation. Other possible mechanisms may include cervical mucus changes that inhibit sperm penetration and endometrial changes that reduce the likelihood of implantation.

Q5. What are the proposed indication, dosage, and route of administration?

Lo Seasonique™ is a combined hormonal contraceptive indicated for the prevention of pregnancy in women. Lo Seasonique™ consists of 84 orange, embossed tablets containing LNG 0.1 mg and EE 0.02 mg, and 7 yellow, embossed tablets containing EE 0.01 mg. One tablet is to be taken orally the same time every day.

2.2 General Clinical Pharmacology and Biopharmaceutics

Q6. What Clinical Pharmacology and Biopharmaceutics related information have been submitted to support this NDA?

This submission contains the following:

- Draft labeling in PLR format
- Quality overall summary and information on drug substances and drug products
- Bioequivalence study report – single dose PK of LNG/EE combination tablets
- Dissolution profile comparison
- Bioanalytical method validation report
- Clinical summary and study report
- Sponsor's response regarding food effect on Lo Seasonique™ BA

The BE study report that included bioanalytical method validation report was previously reviewed by OGD and found it acceptable. The Sponsor is relying on the distribution, metabolism, and excretion profiles of Lessina® and Seasonique®.

Q7. What are the clinical trial formulation and the to-be-marketed formulation?

Lo Seasonique™ combination tablets are manufactured using the same formulation, manufacturing process and components as those approved for Barr/Duramed's generic product Lessina® (ANDA # 75-803, approved on May 20, 2002) except for the color of the non-functional film coating. The study report of the phase 3 clinical trial, Study DR-PSE-309, stated that orange combination tablets and yellow EE tablets were used in the study. The color of Lessina®'s combination tablet is pink. Thus, the to-be-marketed formulation of Lo Seasonique™ was used in the phase 3 clinical trial, Study DR-PSE-309.

Q8. What are the PK parameters of Lo Seasonique™ following a single dose administration?

A randomized, open label, single dose, two-period crossover BE study was conducted in 30 healthy females under fasted conditions to determine the single dose BA of Lo Seasonique™ and to demonstrate the BE of the LNG 0.1 mg / EE 0.02 mg combination tablets Lessina® (Lo Seasonique™) relative to those of Levlite®. Tablets were administered as 3 units of LNG 0.1 mg / EE 0.02 mg tablets.

Tables 4 and 5 summarize the plasma Lo Seasonique™ PK parameters of LNG and EE, respectively, following a single dose.

Table 4: Summary of Plasma LNG PK Parameters following a Single Dose of Lo Seasonique™

PK Parameters	Arithmetic Mean	SD
C_{max} (ng/ml)	6.00	1.63
T_{max} (hr)	1.55	0.57
AUC_{0-t} (ng·hr/ml)	64.28	23.41
AUC_{0-inf} (ng·hr/ml)	76.38	24.86
$t_{½}$ (hr)	28.48	8.71
k_{el} (1/hr)	0.0266	0.0083

* Treatment: 3 x LNG 0.1 mg / EE 0.02 mg tablets; t: time of the last measurable concentration; N=30

Table 5: Summary of Plasma EE PK Parameters following a Single Dose of Lo Seasonique™

PK Parameters	Arithmetic Mean	SD
C_{max} (pg/ml)	122.75	39.45
T_{max} (hr)	1.83	0.67
AUC_{0-t} (pg·hr/ml)	1127.21	341.82
AUC_{0-inf} (pg·hr/ml)	1335.83	365.30
$t_{½}$ (hr)	17.49	7.44
k_{el} (1/hr)	0.0431	0.0102

* Treatment: 3 x LNG 0.1 mg / EE 0.02 mg tablets; t: time of the last measurable concentration; N=30

Q9. Did the Sponsor use validated bioanalytical assays to generate the study data?

Yes. In Study 99027, a liquid chromatography - tandem mass spectrometry (LC-MS/MS) assay was used to measure LNG and a gas chromatography – mass spectrometry (GC-MS) assay was used to measure EE as necessary. These assays were validated and have successfully met the acceptance criteria outlined in the FDA Guidance to Industry entitled "Bioanalytical Method Validation".

	LNG	EE
Dynamic Range	0.2-20.3 ng/ml	5.0-499.0 pg/ml
LLOQ	0.2 ng/ml	5.0 pg/ml

During the study, the correlation coefficients (r) were $\geq$ 0.9973 for LNG and the coefficients of determination (r^2) $\geq$ 0.998 for EE and the linearity of the analytical methods have been demonstrated successfully.

The inter-batch precision, as measured by the coefficient of variation (CV), for LNG and EE ranged between 5.81-8.27% and 2.08-7.91%, respectively. The inter-batch accuracy of LNG and EE ranged between 91.60-99.68% and 92.80-100.25%, respectively. The intra-batch precision for LNG and EE ranged between 3.18-9.52% and 1.02-11.67%, respectively. The intra-batch accuracy of LNG and EE ranged between 92.44-105.00% and 92.65-111.43%, respectively.

Plasma samples received from the clinical division were stored at -20 °C for a maximum of 51 and 96 days for LNG and EE, respectively, prior to sample analysis. The validated stability of plasma samples stored at -20 °C is at least 239 days for LNG and at least 156 days for EE.

Q10. Was the effect of food on the BA of Lo Seasonique™ tablets evaluated?

No. The Sponsor was asked to address the food effect on Lo Seasonique™'s BA based on available information or literature in the filing communication (74-day letter). In response to the Division's request, the Sponsor has submitted their response on April 3, 2008. The Sponsor's justification of not

evaluating food effect was based on the extensive marketing and regulatory history on LNG/EE OC products, the published study (Boyd *et al.*, 2003) showing no effect of food on the extent of absorption of EE, and the indirect support from the phase 3 clinical trial conducted with Lo Seasonique™ regardless of food intake in which food did not affect its safety or efficacy. Accordingly, the Sponsor has added a statement to the proposed label indicating that food effect of Lo Seasonique™ was not evaluated. It is noted that there are food effect study results of other approved combination OC products such as Loestrin® 24 Fe, Yasmin®, and Yaz® containing other progestins and EE showing food affecting the BA of the OC hormones. However, there is no literature found reporting food effect on LNG/EE combination OCs.

5 Page(s) Withheld

_____ Trade Secret / Confidential (b4)

_____ Draft Labeling (b4)

__X____ Draft Labeling (b5)

_____ Deliberative Process (b5)

Appendix

A.1. Individual Study Review

A.1.1. BE Study: 99027

RANDOMIZED OPEN LABEL, 2-WAY CROSSOVER, BIOEQUIVALENCE STUDY OF BARR LABORATORIES, INC. (USA) AND BERLEX LABS (USA) LEVLITE™ LEVONORGESTREL-ETHINYL ESTRADIOL 0.10 mg-0.02 mg TABLETS ADMINISTERED AS 3 x 0.10 mg-0.02 mg TABLETS IN HEALTHY ADULT FEMALES UNDER FASTING CONDITIONS

Protocol No:	99027
Principal Investigator:	Eric Masson, Pharm.D.
Clinical Study Center:	Anapharm Inc., Sainte Foy, Quebec, Canada
Clinical Study Dates:	April 20, 1999 – May 18, 1999
Analytical Study Facility:	(b) (4)
Analytical Study Dates:	May 25, 1999 – July 25, 1999

OBJECTIVE

The primary objective of the study was to assess the BE of Barr/Duramed Inc.'s LNG 0.1 mg / EE 0.02 mg combination tablet (Lessina®, ANDA # 75-803, approved on May 20, 2002) compared with Berlex Inc.'s LNG 0.1 mg / EE 0.02 mg combination tablet (Levlite®, currently owned by Bayer Healthcare, NDA # 20-860, approved on July 13, 1998) following a single dose of LNG 0.30 mg / EE 0.06 mg (3 tablets per dose) in healthy females under fasting conditions.

STUDY DESIGN, TREATMENT, AND SUBJECTS

A randomized, open label, single dose, two-period crossover BE study was conducted at (b) (4) between April 20, 1999 - May 18, 1999. All subjects were screened within 28 days prior to study enrollment. A total of 35 female subjects were enrolled in the study and 30 subjects completed the study. All subjects were Caucasian females. Subjects ranged in age from 18 to 35 years with a mean of 28 and SD of 5. The mean height was 164.2 cm (range of 154-177.5 cm, SD 5.8), and the mean weight was 61.8 kg (range of 48.4-74.5 kg, SD 7.0).

The subjects were confined in the clinic from at least 10 hr before dosing until after the 24 hr sample collection. Subjects observed a 10 hr overnight fast before dosing and 4 hours after dosing. Subjects were orally administered with 3 tablets of test or reference products. The drug products were administered with 240 ml of water at room temperature. Water was not permitted for 2 hr before and 2 hr after dosing. Standard meals were provided at appropriate times thereafter. Subjects were to remain in an upright position (sitting or standing) for 4 hrs after the study drug was administered. There was a 28 day washout period between treatment periods.

Treatments are listed below:

- **Test**: Lessina® combination (LNG 0.1 mg / EE 0.02 mg) tablet (Batch # 109659R01, Expiration date: N/A, Manufacturing date: March 23, 1999)
- **Reference**: Levlite® combination (LNG 0.1 mg / EE 0.02 mg) tablet (Lot # W80234, Expiration date: June, 2000)

PHARMACOKINETIC EVALUATION

Blood sampling

Blood samples were obtained at pre-dose and at 0.5, 1, 1.25, 1.5, 1.75, 2, 2.5, 3, 4, 6, 8, 10, 12, 16, 24, 36, 48, 72, and 96 hrs post-dose. A total of 40 blood samples were drawn during the study for drug analysis. Plasma was prepared and stored at or below -20 °C until analysis.

Analytical method

A liquid chromatography - tandem mass spectrometry (LC-MS/MS) assay was used to measure LNG and a gas chromatography - mass spectrometry (GC-MS) assay was used to measure EE as necessary. These assays were validated and have successfully met the acceptance criteria outlined in the FDA Guidance to Industry entitled "Bioanalytical Method Validation".

	LNG	EE
Dynamic Range	0.2-20.3 ng/ml	5.0-499.0 pg/ml
LLOQ	0.2 ng/ml	5.0 pg/ml

Table 6: Back-calculated LNG Standard Concentrations from Each Calibration Curve

Batch Number	Nominal Concentrations (ng/mL)							
	0.20	0.41	2.03	4.06	8.12	10.20	15.20	20.30
01AEX	(b) (4)							
02AEX-1								
02AEX-2								
03AEX-1								
03AEX-2								
04AEX-1								
04AEX-2								
05AEX-1								
05AEX-2								
N:	9	8	9	9	9	8	9	9
Mean:	0.20	0.42	2.12	4.03	8.05	10.16	15.25	19.49
SD(±):	0.01	0.02	0.10	0.22	0.26	0.34	0.67	0.42
CV(%):	5.00	4.76	4.72	5.46	3.23	3.35	4.39	2.15
% Nominal:	100.00	102.44	104.43	99.26	99.14	99.61	100.33	96.01

O: Value outside acceptance range (% Nominal ±15%)
RCS: Rejected Calibration Standard

Table 7: Back-calculated EE Standard Concentrations from Each Calibration Curve

Run Number	Nominal Concentrations (pg/mL)							
	5.00	10.00	50.00	99.70	199.00	299.00	399.00	499.00
02AEI 03AEI-1 03AEI-2 04AEI 05AEI 06AEI 08AEI	(b) (4)							
N	5	7	7	7	7	7	7	7
Mean	4.71	10.64	48.82	99.03	200.64	299.79	398.03	498.95
SD(±)	0.35	0.38	2.50	2.47	3.58	6.21	10.12	11.37
CV(%)	7.43	3.57	5.12	2.49	1.78	2.07	2.54	2.28
% Nominal	94.20	106.40	97.64	99.33	100.82	100.26	99.76	99.99

A: Poor chromatography
B: Unacceptable internal standard response
RCS: Rejected Calibration Standard

During the study, the correlation coefficients (r) were ≥ 0.9973 for LNG and the coefficients of determination (r^2) ≥ 0.998 for EE and the linearity of the analytical methods have been demonstrated successfully.

The inter-batch precision, as measured by the coefficient of variation (CV), for LNG and EE ranged between 5.81-8.27% and 2.08-7.91%, respectively. The inter-batch accuracy of LNG and EE ranged between 91.60-99.68% and 92.80-100.25%, respectively. The intra-batch precision for LNG and EE ranged between 3.18-9.52% and 1.02-11.67%, respectively. The intra-batch accuracy of LNG and EE ranged between 92.44-105.00% and 92.65-111.43%, respectively.

Plasma samples received from the clinical division were stored at -20 °C for a maximum of 51 and 96 days for LNG and EE, respectively, prior to sample analysis. The validated stability of plasma samples stored at -20 °C is at least 239 days for LNG and at least 156 days for EE.

For LNG, the dynamic range was 0.2-20.30 ng/ml, with a LLOQ of 0.2 ng/ml. Quality Control (QC) samples of 0.69, 6.93, and 13.90 ng/ml were analyzed with each run and had CVs less than or equal to 8.27%.

For EE, the dynamic range was 5.0-499.0 pg/ml, with a LLOQ of 5.0 pg/ml. QC samples of 15.0, 159.0, and 318.0 pg/ml were analyzed with each run and had CVs less than or equal to 7.91%.

DATA ANALYSIS

Pharmacokinetic Analysis

PK parameters (AUC_{0-t}, AUC_{0-inf}, $AUC_{t/inf}$, C_{max}, T_{max}, $t_{½}$, and k_{el}) were determined from LNG and EE plasma concentration-time data using the actual times of sample collection.

Statistical Analysis

The analysis of variance (ANOVA) was performed on untransformed T_{max}, $t_{½}$, and k_{el} and ln-transformed AUC_{0-t}, AUC_{0-inf}, C_{max}. The ANOVA model included sequence, subjects nested within sequence, period, and formulation as factors. The significance of the sequence effect was tested using subjects nested within sequence as the error term. All other main effects were tested using the residual error (error mean square).

90% confidence intervals (CI) for the difference between drug formulation least square means (LSM) were calculated for the ln-transferred AUC_{inf}, AUC_{last}, and C_{max}. The 90% CIs are expressed as a percentage relative to the LSM of the reference formulation. Ratio of means were calculated using the LSM for log-transformed AUC_{inf}, AUC_{last}, and C_{max}. Ratio of means are expressed as a percentage of the LSM for the reference formulation.

Safety Evaluations and Adverse Events

Safety evaluation included vital signs (i.e., pulse rate and blood pressure measurements), physical exam, ECG, laboratory tests, and adverse events monitoring. A urine pregnancy test (HCG), a urine drug screen, and an alcohol breath test were performed at the check-in of period 1 and 2 for each subject. No serious adverse events were reported during the study. Two subjects were withdrawn from the study due to positive urine drug screen and two subjects were withdrawn from the study due to adverse events unrelated to the study medication. One subject was withdrawn from the study due to positive pregnancy test.

PHARMACOKINETIC RESULTS

For both analytes, the AUC and C_{max} were similar for the test (Lessina®) and reference (Levlite®) preparations. The 90% CIs for the mean ratio of the logarithmic transformed were within the BE range of 80-125%.

Figure 1: Mean Plasma Concentration of LNG over Time following Single Dose Administration of 3 of LNG 0.1 mg / EE 0.02 mg Combination Tablets from Lessina® (test) and Levlite® (reference) (N=30).

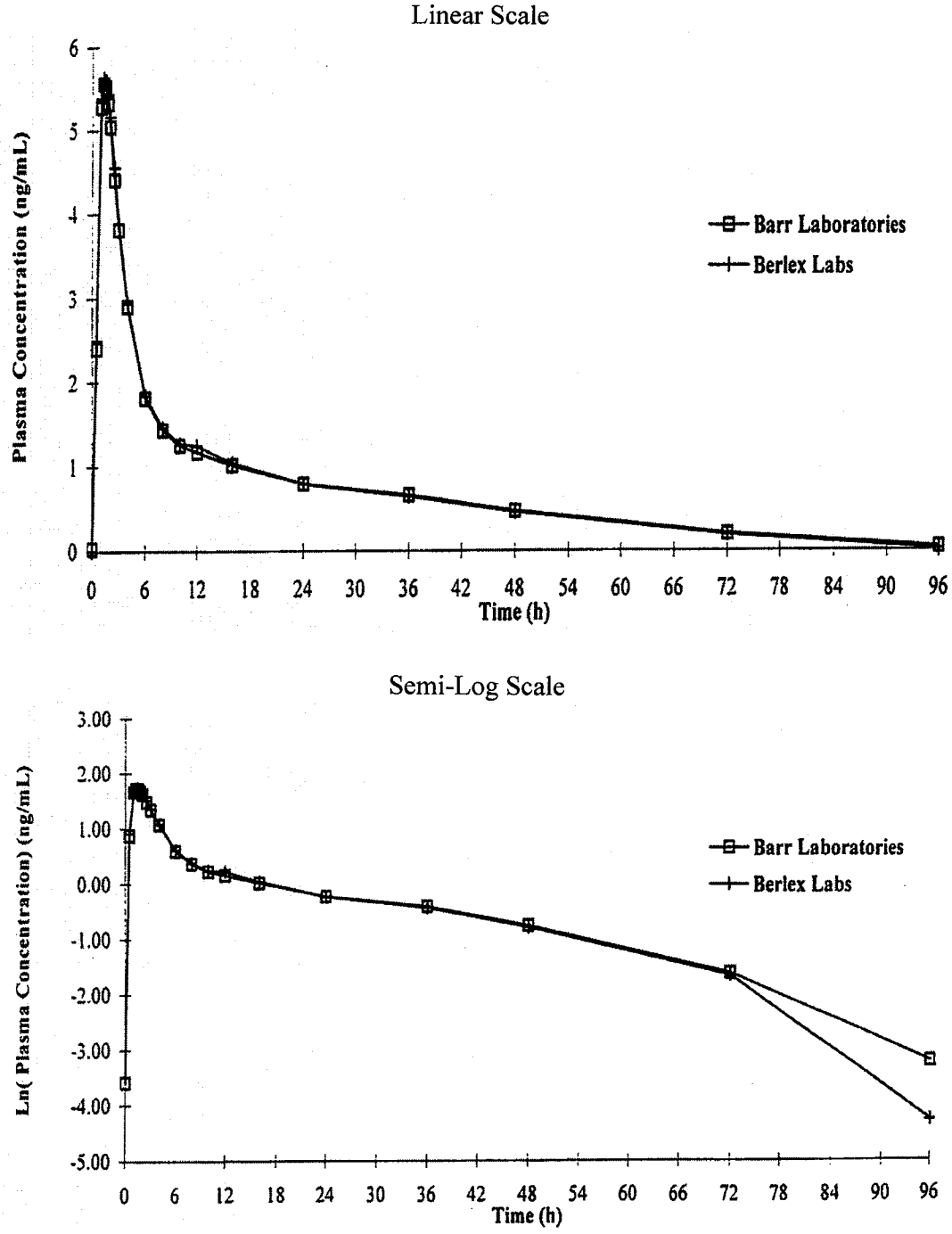


Figure 2: Mean Plasma Concentration of EE over Time following Single Dose Administration of 3 of LNG 0.1 mg / EE 0.02 mg Combination Tablets from Lessina® (reference) and Levlite® (Test).

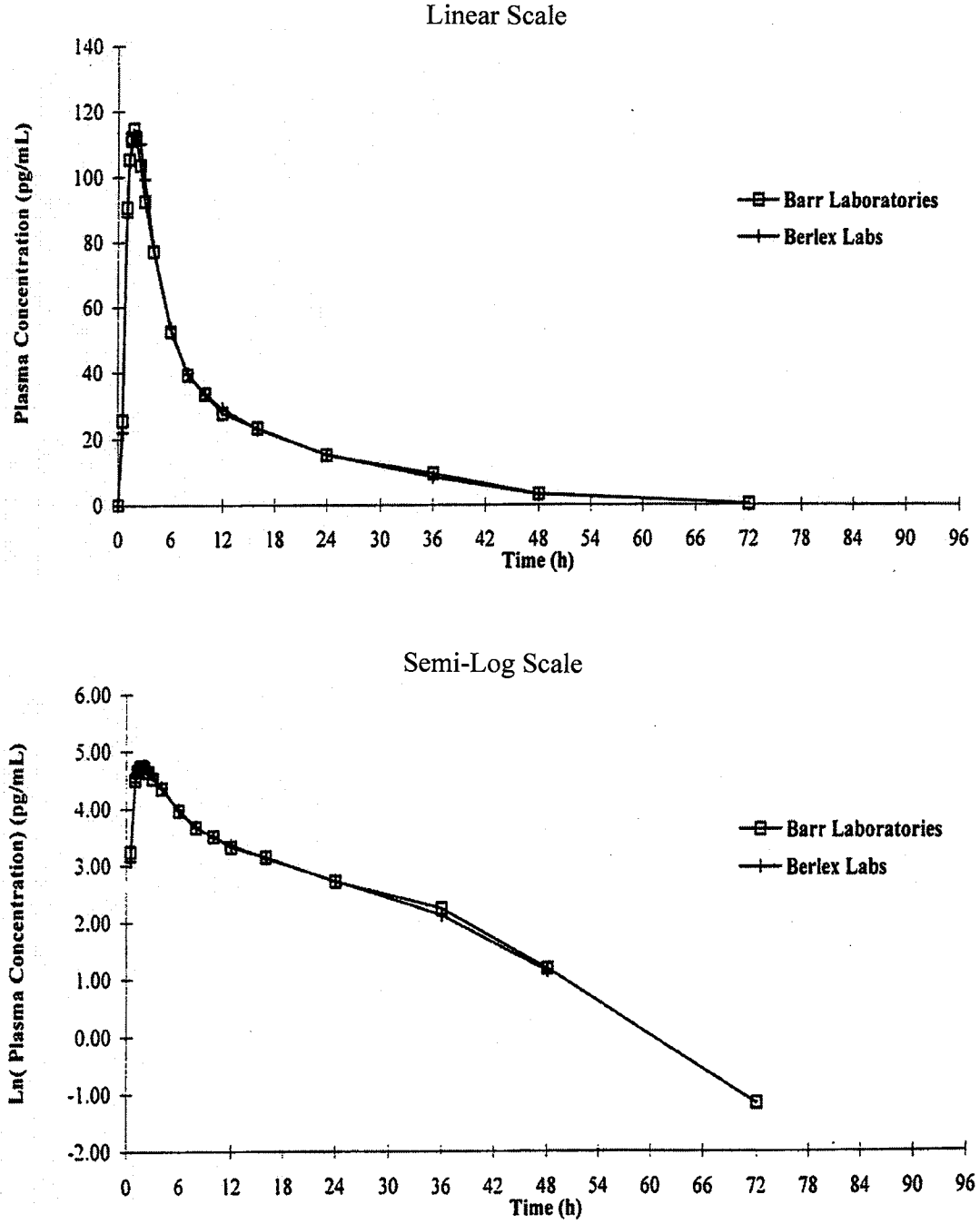


Table 8 summarizes the plasma LNG PK parameters and statistical comparison for Treatment A and B. The 90% CI for the difference between the arithmetic means of C_{max} and the AUCs were within the range of 80-125%.

Table 8: Summary of Plasma LNG PK Parameters and Statistical Comparison for Treatment A and B

Parameters		Test (Barr Laboratories (A)) Mean	±	SD	CV (%)	Reference (Berlex Labs (B)) Mean	±	SD	CV (%)
AUC_{0-t}	(ng.h/mL)	64.28	±	23.41	36.41	63.44	±	24.09	37.98
AUC_{0-inf}	(ng.h/mL)	76.38	±	24.86	32.54	75.14	±	23.96	31.89
$AUC_{\%inf}$	(%)	83.26	±	6.20	7.45	83.37	±	7.95	9.54
C_{max}	(ng/mL)	6.00	±	1.63	27.12	6.05	±	1.77	29.22
T_{max}	(h)	1.55	±	0.57	36.41	1.43	±	0.46	32.37
K_{el}	(h^{-1})	0.0266	±	0.0083	31.32	0.0270	±	0.0078	28.91
$T_{½ el}$	(h)	28.48	±	8.71	30.59	28.01	±	8.89	31.72

Barr Laboratories (A) vs Berlex Labs (B)

	AUC_{0-t}	AUC_{0-inf}	C_{max}
Ratio[1]	100.83%	100.90%	99.32%
90 % Geometric C.I.[2]	93.79 % to 108.39 %	95.03 % to 107.13 %	93.65 % to 105.34 %

[1] Calculated using least-squares means according to the formula: $e^{(\text{Barr Laboratories (A) - Berlex Labs (B)})} \times 100$
[2] 90% Geometric Confidence Interval using ln-transformed data

Table 9 summarizes the plasma EE PK parameters and statistical comparison for Treatment A and B. The 90% CI for the difference between the arithmetic means of C_{max} and the AUCs were within the range of 80-125%.

Table 9: Summary of Plasma EE PK Parameters and Statistical Comparison for Treatment A and B

Parameters		Test (Barr Laboratories (A)) Mean	±	SD	CV (%)	Reference (Berlex Labs (B)) Mean	±	SD	CV (%)
AUC_{0-t}	(pg.h/mL)	1127.21	±	341.82	30.32	1136.36	±	336.25	29.59
AUC_{0-inf}	(pg.h/mL)	1335.83	±	365.30	27.35	1308.12	±	346.69	26.50
$AUC_{\%inf}$	(%)	83.80	±	6.97	8.32	86.37	±	6.23	7.21
C_{max}	(pg/mL)	122.75	±	39.45	32.14	125.01	±	37.96	30.36
T_{max}	(h)	1.83	±	0.67	36.43	2.03	±	0.70	34.59
K_{el}	(h^{-1})	0.0431	±	0.0102	23.61	0.0491	±	0.0126	25.67
$T_{½ el}$	(h)	17.49	±	7.44	42.55	15.29	±	5.26	34.41

Barr Laboratories (A) vs Berlex Labs (B)

	AUC_{0-t}	AUC_{0-inf}	C_{max}
Ratio[1]	98.96%	102.02%	97.87%
90 % Geometric C.I.[2]	93.45 % to 104.80 %	95.96 % to 108.48 %	92.21 % to 103.87 %

[1] Calculated using least-squares means according to the formula: $e^{(\text{Barr Laboratories (A) - Berlex Labs (B)})} \times 100$
[2] 90% Geometric Confidence Interval using ln-transformed data

CONCLUSION

In conclusion, the test (Lessina®) preparation is BE to the reference (Levlite®) drug preparation under fasting conditions. It is noted that the Division of Bioequivalence, Office of Generic Drug has found this study acceptable during their review in May, 2000.

A.2. Clinical Pharmacology Filing Memo

Office of Clinical Pharmacology *New Drug Application Filing and Review Form*			
General Information About the Submission			
	Information		Information
NDA Number	22-262	Brand Name	Lo Seasonique
OCP Division	DCP3	Generic Name	Levonorgestrel (LNG)/Ethinyl Estradiol (EE)
Medical Division	DRUP	Drug Class	Contraceptive
OCP Reviewer	Chongwoo Yu, Ph.D	Indication(s)	Prevention of pregnancy
OCP Team Leader	Myong Jin Kim, Pharm. D.	Dosage Form	Tablet
		Dosing Regimen	84 days of LNG 100 µg / EE 20 µg followed by 7days of 10 µg of EE (91 day regimen)
Date of Submission	December 26, 2007	Route of Administration	Oral
Estimated Due Date of OCP Review	August 26, 2008	Sponsor	Duramed Pharmaceuticals, Inc.
PDUFA Due Date	October 26, 2008	Priority Classification	Standard
Division Due Date	October 5, 2008		

Clin. Pharm. and Biopharm. Information				
	"X" if included at filing	Number of studies submitted	Number of studies reviewed	Critical Comments if any
STUDY TYPE				
Table of Contents present and sufficient to locate reports, tables, data, etc.	x			
Tabular Listing of All Human Studies	x			
HPK Summary	x			
Labeling	x			
Reference Bioanalytical and Analytical Methods	x			
I. Clinical Pharmacology				
Mass balance:				
Isozyme characterization:				
Blood/plasma ratio:				
Plasma protein binding:				
Pharmacokinetics (e.g., Phase I) -				
Healthy Volunteers-				
single dose:				
multiple dose:				
Patients-				
single dose:				
multiple dose:				
Dose proportionality -				
fasting / non-fasting single dose:				
fasting / non-fasting multiple dose:				
Drug-drug interaction studies -				
In-vivo effects on primary drug:				
In-vivo effects of primary drug:				
In-vitro:				
Subpopulation studies -				
ethnicity:				
gender:				
pediatrics:				

geriatrics:				
renal impairment:				
hepatic impairment:				
PD:				
Phase 2:				
Phase 3:				
PK/PD:				
Phase 1 and/or 2, proof of concept:				
Phase 3 clinical trial:				
Population Analyses -				
Data rich:				
Data sparse:				
II. Biopharmaceutics				
Absolute bioavailability:				
Relative bioavailability -				
solution as reference:				
alternate formulation as reference:				
Bioequivalence studies -				
traditional design; single / multi dose:		1		Single-dose, fasting BE study
replicate design; single / multi dose:				
Food-drug interaction studies:				
Dissolution:				
(IVIVC):				
Bio-wavier request based on BCS				
BCS class				
III. Other CPB Studies				
Genotype/phenotype studies:				
Chronopharmacokinetics				
Pediatric development plan				
Literature References		0		
Total Number of Studies		1		

Filability and QBR comments

	"X" if yes	Comments
Application filable?	x	**No comments.**
Comments sent to firm?		
QBR questions (key issues to be considered)	1. Is the proposed label adequate?	
Other comments or information not included above		
Primary reviewer Signature and Date		
Secondary reviewer Signature and Date		

* An Optional Intra-Division Clinical Pharmacology Briefing was held on Thursday, April 24, 2008. The attendees are as follows: HY Ahn, M-J Kim, S Apparaju, D Tran, L Lee, H Kim, J-I Lee, L Soule, and R Orleans.

Filing Memo

Clinical Pharmacology Review

NDA: 22-262
Compound: Lo Seasonique (Levonorgestrel (LNG)/Ethinyl Estradiol (EE))
Sponsor: Duramed Pharmaceuticals, Inc.

Date: 2/6/2008
Reviewer: Chongwoo Yu, Ph.D.

Introduction:

Lo Seasonique™ (LNG 0.1 mg / EE 0.02 mg tablets and EE 0.01 mg tablets), formerly known as DP3 Lo 84/10, is a 91-day extended regimen oral contraceptive (OC) indicated for the prevention of pregnancy in women who elect to use this product as a method of contraception. It utilizes 84 days of combination of LNG 0.1 mg / EE 0.02 mg tablets followed by 7 days of EE 0.01 mg tablet monotherapy.

In 2003, the Division has approved the first extended-cycle OC regimen, Seasonale® (NDA 21-544, approved on September 5, 2003) consisting of 84 days of LNG 0.15 mg / EE 0.03 mg, followed by 7 days of placebo. In 2006, Seasonique® was approved (NDA 21-840, approved on May 26, 2006). Seasonique® incorporated the identical 84 day active combination pill period as Seasonale®, but the 7 day placebo period was replaced by 7 days of EE 0.01 mg monotherapy. NDA 21-921 for Lo Seasonale™ which consists of 84 days of LNG 0.1 mg / EE 0.02 mg followed by 7 days of placebo was withdrew in 2006 due to the high Pearl Index number (4.58).

Lo Seasonique™ utilizes the same formulation as the presently available Barr product Lessina® (ANDA 75-803, approved on May 20, 2002) which contains LNG 0.1 mg / EE 0.02 mg USP tablets and EE 0.01 mg tablets except for the color of the non-functional film coating. The EE 0.01 mg tablet formulation is identical to marketed Seasonique® formulation. Lessina® is a AB2 rated generic product of Levlite® (NDA 20-860, approved on July 13, 1998).

Per Sponsor, the safety and efficacy of Lo Seasonique™ for prevention of pregnancy has been demonstrated in a single pivotal multicenter, open-label clinical trial, DR-PSE-309, conducted under IND 63,735. DR-PSE-309 is a one-year, single-arm study that treated a total of 2,185 women. According to the Sponsor, Lo Seasonique™ demonstrated a level of efficacy and safety that is consistent with what has been observed for other approved low-dose combination oral contraceptive products.

Bioavailability:

No new data is provided. The sponsor relies exclusively on literature or known properties of Levlite®.

ADME (Absorption, Distribution, Metabolism, and Excretion):

No new data is provided. The sponsor relies exclusively on literature or known properties of Levlite®.

Drug-drug interactions:

No new data is provided. Interactions between EE and other drugs have been reported in the literature. No formal drug-drug interaction studies were conducted by the sponsor.

Special population:

No new data is provided. The sponsor did not conduct studies in any special population.

Clinical vs. to-be-marketed formulation:

Lo Seasonique™ utilizes the same formulation as the presently available Barr product Lessina® (ANDA #75-803, approved on May 20, 2002) which contains LNG 0.1 mg / EE 0.02 mg tablets and EE 0.01 mg tablets except for the color of the non-functional film coating. The EE 0.01 mg tablet formulation is identical to marketed Seasonique® formulation (NDA 21-840, approved on May 26, 2006). Lessina® is a AB2 rated generic product of Levlite® (NDA 20-860, approved on July 13, 1998). In Section 9.4.2, the protocol of DR-PSE-309 states that eighty-four orange, embossed tablets, each containing LNG 0.1 mg / EE 0.02 mg and 7 yellow, embossed tablets, each containing 0.01 mg of EE were used in the study. One combination tablet was to be taken each day for 84 days followed by 7 days of EE tablets in 91-day cycles repeated consecutively for approximately one year (four 91-day cycles). The drug used in the trials can be identified by color. Orange/yellow tablets indicate that Lo Seasonique™ was used in Study DR-PSE-309. Lessina® combination tablets were pink and the EE tablets were white.

Bioequivalence (BE) Study

A single-dose, fasting BE study was conducted between Lessina® and Levlite® 21 day regimen tablets under ANDA 75-803 and was found to be acceptable. The waiver request on the 28 day regimen tablets was found to be acceptable by the Office of Generic Drugs (OGD).

Method validation:

No new data is provided. Analytical methods that were used in the BE study were validated.

Food Effect:

No new data is provided. No studies were done to look at the effect of food.

Recommendation:

The Office of Clinical Pharmacology/Division of Clinical Pharmacology 3 finds that the Clinical Pharmacology section for NDA 22-262 is fileable.

Comments for sponsor:

- *Please resubmit the study report of bioequivalence study comparing the currently-marketed Lessina®, which is the same formulation as the to-be-marketed Lo Seasonique™, to the currently-marketed Levlite® to by February 29, 2008.*
- *Please resubmit your draft label for the Absorption part under Section 12.3 Pharmacokinetics using the data obtained from the single-dose, fasting BE study was conducted between Lessina® and Levlite®.*
- *Please address food effects on Lo Seasonique™. This can be based on available information or literature.*

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

/s/

Chongwoo Yu
5/13/2008 03:15:00 PM
BIOPHARMACEUTICS

Myong-Jin Kim
5/20/2008 09:03:35 AM
BIOPHARMACEUTICS

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING CHECKLIST FOR A NEW NDA/BLA

NDA Number: 22-262 **Applicant:** Duramed Pharmaceuticals, Inc. **Stamp Date:** December 26, 2007

Drug Name: Lo Seasonique **NDA Type:**

	Content Parameter	Yes	No	Comment
Criteria for Refusal to File (RTF)				
1	Has the sponsor submitted bioequivalence data comparing to-be-marketed product(s) and those used in the pivotal clinical trials?	x		Request to resubmit bioequivalence study reports comparing Lessina® to Levlite®
2	Has the sponsor provided metabolism and drug-drug interaction information?		x	Relies on literature.
Criteria for Assessing Quality of an NDA				
	Data			
3	Are the data sets, as requested at the earlier meeting (e.g.: Pre-NDA meeting), submitted in the appropriate format (e.g. CDISC)?			NA
4	If applicable, are the pharmacogenomic data sets submitted in the appropriate format?			NA
	Studies and Analyses			
5	Has the Sponsor made an appropriate attempt to determine the reasonable dose individualization strategy for this product (i.e., appropriately designed and analyzed dose-ranging or pivotal studies)?			NA
6	Did the sponsor follow the scientific advice provided regarding matters related to dose selection?			NA
7	Are the appropriate exposure-response (for desired and undesired effects) analyses conducted and submitted in a format as described in the Exposure-Response guidance?			NA
8	Is there an adequate attempt by the sponsor to use exposure-response relationships in order to assess the need for dose adjustments for intrinsic/extrinsic factors that might affect the pharmacokinetic or pharmacodynamics?			NA
9	Are the pediatric exclusivity studies adequately designed to demonstrate effectiveness, if the drug is indeed effective?			NA
10	Did the sponsor submit all the pediatric exclusivity data, as described in the WR?			NA
11	Is the appropriate pharmacokinetic information submitted?	x		BE study comparing Lessina® to Levlite®