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APPLICATION NUMBER:

21-840

**CLINICAL PHARMACOLOGY AND
BIOPHARMACEUTICS REVIEW(S)**

Clinical Pharmacology Memo

Date: 5-22-06

NDA #: 21-840 (Complete Response, Date March 27, 2006)

Drug Product: Seasonique (levonorgestrel/ethinyl estradiol)

Indication: Contraception

Subject: Concurrence of Clinical Pharmacology Review and Label

NDA 21840 was originally reviewed by Dr. Julie Bullock. This memo documents my concurrence of the label submitted in the complete response.

Ameeta Parekh, Ph.D.
Team Leader, Clinical Pharmacology (DCP3)

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Ameeta Parekh
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BIOPHARMACEUTICS

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Clinical Pharmacology and Biopharmaceutics Review

NDA	21,840
Submission Date	October 21, 2004
Brand Name	Seasonique™
Generic Name	Levonorgestrel (LNG)/Ethinyl Estradiol (EE) and Ethinyl Estradiol (EE)
Reviewer	Julie M. Bullock, Pharm.D.
Team Leader	Ameeta Parekh, Ph.D.
OCPB Division	Division of Pharmaceutical Evaluation II
ORM Division	Division of Reproductive & Urologic Drug Products
Sponsor	Duramed
Submission Type; Code	000
Dosing regimen	Once Daily
Indication	Prevention of pregnancy

OCPB Briefing on 05/27/05 attended by: Hank Malinowski, Ameeta Parekh, Stephan Ortiz, Sandhya Apparaju, John Hunt, Ron Orleans, Shelly Slaughter & June Komura.

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1 Executive Summary

The subject of this submission is a 91-day treatment cycle of a combination oral contraceptive (COC) with the indication of the prevention of pregnancy. Each 91-day treatment cycle includes 84 combination tablets containing both levonorgestrel (0.15 mg) and ethinyl estradiol (0.03 mg), and 7 tablets containing only ethinyl estradiol (0.01 mg).

In this NDA, the sponsor has submitted three pivotal bioavailability/bioequivalence studies. The first study was a multiple dose 91-day pharmacokinetic safety study in 30 subjects with LNG/EE (0.15/0.03) for 84 days and 0.03 mg EE for 7 days. The second study was a single dose crossover BE study in 30 subjects to test the blue combination LNG/EE to-be-marketed Seasonique™ tablet formulation to the white LNG/EE clinical trial tablet formulation. The third study was a SD crossover relative BA study in 18 subjects under fasting conditions to test that the 0.03 mg EE yellow clinical trial tablet formulation was BE to an equal dose of an EE containing oral solution.

Two Phase III Clinical studies were submitted. The first study evaluated the efficacy and safety of the 91-day extended regimen COC for 1 year (4 91-day cycles). Two doses were studied; LNG/EE (0.15/0.03) for 84 days and either 0.03 mg EE or 0.01 mg EE for 7 days. The second study evaluated the efficacy for prevention of pregnancy in woman and safety by obtaining endometrial biopsies of COC regimes using EE during the pill free interval. Three test products were used:

- 84 day LNG 0.15/EE 0.03 mg + 7 day 0.03 mg EE,
- 84 day LNG 0.15/EE 0.03 mg + 7 day 0.01 mg EE,
- 25 day LNG 0.15/EE 0.03 + 3 day 0.03 EE.

One reference (Nordette® 21 day LNG 0.150/EE 0.03 mg + 7 day placebo) product was given for 1 year. The sponsor seeks approval of only the Seasonique™ 0.15/0.03 mg 84 day LNG/EE plus 7 day 0.01 mg EE strength.

The to-be-marketed formulation of Seasonique™ is similar to the sponsors extended cycle oral contraceptive Seasonale® (NDA 21-544). Each Seasonale® 91 day regimen includes 84 combination tablets containing 0.15/0.03 mg LNG/EE and 7 placebo tablets. The Seasonique™ and Seasonale® COC tablet formulations are identical to each other except for the color of the film coating. The formulation of Seasonale® is identical to the approved ANDA 75-866 product, Portia™, (generic equivalent of Nordette® 0.15/0.03 mg LNG/EE).

1.1 Recommendations

The Office of Clinical Pharmacology and Biopharmaceutics/Division of Pharmaceutical Evaluation II (OCPB/DPE-II) has reviewed NDA 21-820 submitted on October 21, 2004. The overall Human Pharmacokinetic Section is *acceptable*.

Julie M. Bullock, Pharm.D.

Ameeta Parekh, Ph.D., Team Leader

2 Summary of Clinical Pharmacology and Biopharmaceutics Findings

Seasonique™ is a novel 91-day COC containing 84 days of combination LNG/EE 0.15/0.03mg tablets and 7 days of 0.01 EE tablets. Seasonique™ is identical in dosage to the approved 91-day COC Seasonale®, except for the 7 days of 0.01 EE for which Seasonale® has placebo tablets.

A multiple dose study, a BE, and a BA study were reviewed. In vitro dissolution was also submitted for the product to compare the clinical trial formulation and the to-be-marketed formulation. The in vitro dissolution for the LNG/EE tablet showed an f_2 of <50 therefore the sponsor performed a BE study between the TBM and CT formulation of the combination LNG/EE tablet.

Study 10216207 assessed the pharmacokinetic profile of one Seasonique™ regimen at key points across an entire 91 day extended cycle regimen. PK samples were drawn on Day 1, 21, 84 and 91. The Seasonique™ regimen studied in this trial was the LNG/EE 0.15/0.03 mg tablets and EE 0.03 mg tablets. The study confirmed that increasing the duration of uninterrupted combination oral contraceptive treatment from the conventional 21 days to 84 days does not result in any further accumulation of drug.

Seasonique™ is proposed to be marketed as 84 blue active tablets and 7 yellow EE tablets. However, the clinical studies were dosed with white active tablets and white EE tablets. The only difference in formulations between the proposed commercial blue and yellow tablets and the clinical white tablets is the color coat, blue versus white for the combination tablet, and yellow versus white for the EE tablet. This difference did not affect the rate and the extent of LNG and EE absorption as demonstrated in the BE study 10416204.

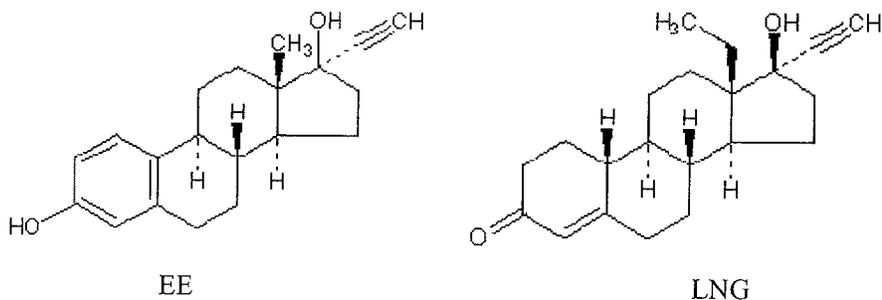
3 Question Based Review

3.1 General Attributes

What are the highlights of the chemistry and physico-chemical properties of the drug substance, and the formulation of the drug product?

Physico-chemical properties

- Structural formula:



- Established name: Levonorgestrel, USP (LNG), Ethinyl estradiol, USP (EE)
- Molecular Weight: 312.45 (LNG); 296.41 (EE)

- Molecular Formula: $C_{21}H_{28}O_2$ (LNG); $C_{20}H_{24}O_2$
- Chemical Name: (-)-13-Ethyl-17-hydroxy-18,19-dinor-17 α -pregn-4-en-yn-3-one (LNG); 19-Norpregna-1,3,5(10)-trien-20-yne-3,17-diol, (17 α)- (EE)

Drug Formulation

TABLE 1: Levonorgestrel/Ethinyl Estradiol tablets clinical trial (CT) and to-be-marketed (TBM) formulation comparisons

Components	Seasonique™ CT	Seasonique™ TBM	Seasonale®
Levonorgestrel, USP (mg)	0.15	0.15	0.15
Ethinyl Estradiol, USP (mcg)	0.03	0.03	0.03
Microcrystalline Cellulose, NF			
Anhydrous Lactose			
Magnesium Stearate			
Tablet Diameter (Core)			
Tablet Weight (Core)			
Coated Tablet Weight			
coating color	white	blue	pink

TABLE 2 Ethinyl Estradiol (EE) tablets clinical trial (CT) and to-be-marketed (TBM) formulation comparisons.

Components	EE CT (0.01 mg)	EE TBM (0.01 mg)	EE CT (0.03 mg)
Ethinyl Estradiol, USP (mcg)	0.01	0.01	0.03
Microcrystalline Cellulose			
Anhydrous Lactose			
Magnesium Stearate			
Tablet Diameter (Core)			
Tablet Weight (Core)			
Coated Tablet Weight			
coating color	white	yellow	white

The Seasonique™ CT formulation is identical to that of the Seasonique™ TBM formulation except for the color of the film coating. The Seasonique™ LNG/EE TBM formulation has a blue film coating as the CT formulation was white. The EE tablet CT formulation was white and the EE TBM formulation is yellow. The LNG/EE Seasonique™ TBM and CT formulations are identical to the TBM formulation of Seasonale® except for color of the film coating

What is the proposed mechanism of drug action and therapeutic indications?

Combinational hormonal contraceptives act by suppression of gonadotropins. The primary mechanism of action is inhibition of ovulation. Other alterations include changes in cervical mucus that inhibit sperm penetration and endometrial changes that reduce the likelihood of implantation.

The addition of the 7 day EE monotherapy phase _____

What is the proposed dosage and route of administration?

The proposed indication is the prevention of pregnancy. The dosage of Seasonique™ is one blue LNG/EE tablet daily for 84 consecutive days, followed by 7 days of yellow EE tablets.

3.2 General Clinical Pharmacology

To compare the relative BA of the Seasonique™ TBM formulation with the formulation used in the clinical study, a randomized, single-dose, two-way crossover study in 30 healthy female adult subjects was conducted. Subjects were randomized to receive a single oral dose of two 0.15/0.03mg LNG/EE tablets after an overnight fast.

The 90% CI for the difference between test (Seasonique™ TBM) and reference (CT formulation) least squares means for the parameters AUC_{0-t} , $AUC_{0-\infty}$, and C_{max} using ln-transformed data for LNG and EE were within 80-125%. Therefore a single dose of two LNG/EE 0.15/0.03mg tablets of the Seasonique™ CT formulation were bioequivalent under fasting conditions.

TABLE 3: Comparisons of ln transformed LNG/EE results

	Least Squares Means		90 % CI
	TBM	CT	TBM vs. CT
Levonorgestrel			
AUC_{0-t} (ng hr/mL)	63.75	65.92	0.898 - 1.042
AUC_{inf} (ng hr/mL)	70.49	71.07	0.911 - 1.079
C_{max} (ng/mL)	5.59	5.56	0.936 - 1.077
Ethinyl Estradiol			
AUC_{0-t} (pg hr/mL)	1385.67	1380.19	0.971 - 1.038
AUC_{inf} (pg hr/mL)	1476.54	1475.43	0.967 - 1.036
C_{max} (pg/mL)	147.63	147.99	0.951 - 1.046

TABLE 4: Pharmacokinetic Parameters of LNG/EE following single oral doses of two tablets of 0.15/0.03 mg LNG/EE Seasonique™ TBM formulation

	LNG			EE	
	Mean ¹ ± SD	CV%		Mean ¹ ± SD	CV%
AUC_{0-t} (ng hr/mL)	80.25 ± 86.97	108.4	AUC_{0-t} (pg hr/mL)	1453.3 ± 474.96	32.7
$AUC_{0-\infty}$ (ng hr/mL)	93.08 ± 102.20	109.8	$AUC_{0-\infty}$ (pg hr/mL)	1553.67 ± 525.96	33.9
C_{max} (ng/mL)	6.05 ± 3.01	49.7	C_{max} (pg/mL)	157.9 ± 65.98	41.8
T_{max} (hr)	1.5 ± 0.52	35.7	T_{max} (hr)	1.5 ± 0.46	29.9
k_{el} (hr ⁻¹)	0.022 ± 0.006	27.9	k_{el} (hr ⁻¹)	0.04 ± 0.009	21.1
$T_{1/2}$ (hr)	34.39 ± 10.64	30.96	$T_{1/2}$ (hr)	17.5 ± 3.98	22.8

¹ Arithmetic mean

Do PK parameters change with time following chronic dosing?

A single-treatment, multiple dose, steady state PK study in 30 normal healthy female adult subjects was conducted to assess the pharmacokinetic profile of one Seasonique™ regimen at key points across an entire 91 day extended cycle regimen. PK samples were drawn on Day 1, 21, 84 and 91. The Seasonique™ regimen studied in this trial was the LNG/EE 0.15/0.03 mg tablets and EE 0.03 mg tablets. The study confirmed that increasing the duration of

Parameter	Ethinyl Estradiol							
	Test Product				Reference Product			
	N	Mean	SD	CV%	N	Mean	SD	CV%
AUC 0-t (pg-hr/ml)	17	769.41	214.07	27.82	17	771.11	192.13	24.92
AUCinf (pg-hr/ml)	17	815.46	217.31	26.65	17	921.93	195.89	23.83
Cmax (pg/ml)	17	97.78	29.67	30.35	17	101.89	28.70	28.17
Tmax (hour)	17	1.12	0.37	33.28	17	1.08	0.30	27.76
Ke (1/hour)	17	0.0398	0.01	28.53	17	0.0432	0.01	28.31
Elimhalf (hour)	17	19.35	7.79	40.28	17	18.04	8.33	46.18

**Ethinyl Estradiol
(LN-TRANSFORMED DATA)**

Parameter	*Geometric Mean		Confidence Intervals
	Test: Ethinyl Estradiol Tablets, USP 0.03 mg	Reference: Ethinyl Estradiol, USP	
C _{max}	94.27	98.44	(87.72, 104.53)
AUC _{0-t}	742.51	747.42	(92.92, 106.21)
AUC _{inf}	788.89	798.32	(92.39, 105.69)

* Geometric means based on least square means of ln-transformed values.

The 90% confidence intervals about the ratio of the geometric means for C_{max}, AUC_{0-t} and AUC_{inf} were within the 80%-125% limits concluding that EE 0.03mg tablet is bioequivalent to the EE oral solution under fasting conditions.

3.2.2 Exposure-Response Information

What are the characteristics of the exposure response relationships (dose-response, concentration-response) for efficacy?

Comment: No formal exposure response relationships were studied in Phase III. No measurements of study drug concentrations were made during the studies.

Two pivotal clinical studies were conducted to assess the safety and efficacy of Seasonique™; the doses studied are outlined below.

- PSE-301: Four 91-day cycles (1 year) study in 2000 patients
 - 84/30 regimen: 84 days LNG/EE 0.150/0.03mg, 7 days EE 0.03mg
 - 84/10 regimen: 84 days LNG/EE 0.150/0.03mg, 7 days EE 0.01mg
- PSE-302: 91 day endometrial biopsy study in 372 patients
 - 84/30 regimen: 84 days LNG/EE 0.150/0.03mg, 7 days EE 0.03mg
 - 84/10 regimen: 84 days LNG/EE 0.150/0.03mg, 7 days EE 0.01mg
 - 25/30 regimen: 24 days LNG/EE 0.150/0.03mg, 3 days EE 0.03mg
 - Nordette®: 21 days LNG/EE 0.150/0.03mg, 7 days placebo

Only study PSE-301 had the primary endpoint as prevention of pregnancy as determined by the Pearl Index. Study PSE-301 had co-primary endpoints of safety using results of endometrial biopsy, and it also studied the prevention of pregnancy using the Pearl Index.

In study PSE-301 for the 84/10 regimen the annualized rate of pregnancy (Pearl Index) was 1.27 (based on a total of 5125 28-day cycles) for treated patients with at least one complete cycle of treatment with an additional exclusion of those cycles where patients had used other birth control methods. Without the exclusion of other birth control methods the Pearl Index was 0.92. When used as directed, the Seasonique™ 84/10 is >99% effective in preventing pregnancy.

The 91-day 84/30 regimen for which approval is not being sought, also demonstrated a high degree of efficacy with respect to prevention of pregnancy. The Pearl Index in the principal analysis with an additional exclusion of those cycles where patient had used another birth control method was 2.74 (based on a total of 4748 28-day cycles of exposure). A Pearl Index of 1.95 was calculated when no exclusions towards other birth control methods was applied.

Both the Seasonique™ 84/30 and 84/10 regimens had a high incidence of inter menstrual bleeding (80%) during the first two months of therapy. Menorrhagia was reported at a higher incidence for the 84/30 regimen compared to the 84/10 regimen. In both cases Seasonique™ had higher incidences of inter menstrual bleeding and menorrhagia than the two 28-day regimen studied in PSE-302. However, by the third 91-day Seasonique™ 84/10 or 84/30 cycle the patterns of scheduled and unscheduled bleeding and or spotting are comparable to the 28-day Nordette regimen and are superior to the marketed 91-day product Seasonale® according to the sponsors reports.

Comment: The sponsor has provided no explanation as to why the Seasonique™ 84/10 regimen was chosen for approval over the 84/30. Both products seen to have similar efficacy and safety profiles and therefore pursuing the lowest dose of 0.01 mg estrogen during the 7 day period is justifiable from the Agency's standpoint.

3.3 Intrinsic Factors (renal, hepatic)

No formal studies to evaluate the effect of race or hepatic or renal disease on the disposition of Seasonique™ have been conducted. Literature suggests that ethinyl estradiol clearance in renal failure patients was found to be decreased relative to normal healthy women.

Comment: Other LNG/EE products have performed no formal studies for race or renally or hepatically impaired patients. Their labels include the generic statements of; "No formal studies have been conducted to study the effect of (race, renal impairment, hepatic impairment) on the pharmacokinetic of ...".

3.4 Extrinsic Factors (DDI)

No formal drug-drug interactions were preformed. The sponsor will use the FDA class labeling for DDIs in their label. The class labeling covers the known interactions with anti-infective agents, anti-HIV protease inhibitors, herbal products, CYP3A4 inhibitors, and other drugs that are altered pharmacokinetically by estrogens.

Comment: For more information see the label.

3.5 General Biopharmaceutics

Both active pharmaceutical ingredients LNG and EE are USP grade material and are manufactured by ~~_____~~ and ~~_____~~ respectively. Seasonique™ LNG/EE and EE tablets are manufactured, packaged, and tested by Barr Laboratories, Inc., and Duramed Pharmaceuticals, Inc. Both Duramed Pharmaceuticals, Inc., and Barr Laboratories, Inc., are subsidiaries of Barr Pharmaceuticals, Inc.

3.5.1 Formulation

What are the differences between the clinical formulation and to be marketed formulation?

The Seasonique™ CT formulation is identical to that of Seasonique™ TBM formulation except

for the color of the film coating. The Seasonique™ LNG/EE CT tablet has a white film coating, whereas the Seasonale® LNG/EE TBM tablet formulation has a blue film coating. The EE CT tablet has a white film coating, whereas the EE TBM tablet has a yellow film coating (refer to Drug Formulation section).

3.5.2 Absolute Bioavailability

3.5.3 Food Effect

No food effect study was performed.

Comment: The other LNG/EE products have not performed formal food effect studies. A search of the literature found no published food effect studies with LNG/EE combination tablets.

3.5.4 In Vitro Dissolution

Dissolution testing profile testing was conducted on the LNG/EE combination tablets and on the EE tablets.

Levonorgestrel/Ethinyl Estradiol Tablets

All of the dissolution profiles were conducted in accordance with the USP 23 monograph for levonorgestrel/ethinyl estradiol tablets with modified sample times.

Equipment: Apparatus II (paddles)
Temperature: 37 ± 0.5 °C
Rotation Speed: 75 rpm
Medium: 5 ppm Tween 80 in Water
Volume: 500 mL
Time Intervals: 15, 30, 45, 60, 90 minutes

FIGURE 1: Mean dissolution profiles of LNG/EE tablets. Batch No. 205554001 (Seasonique™ TBM), Batch No. 200313001R (Seasonique™ CT).

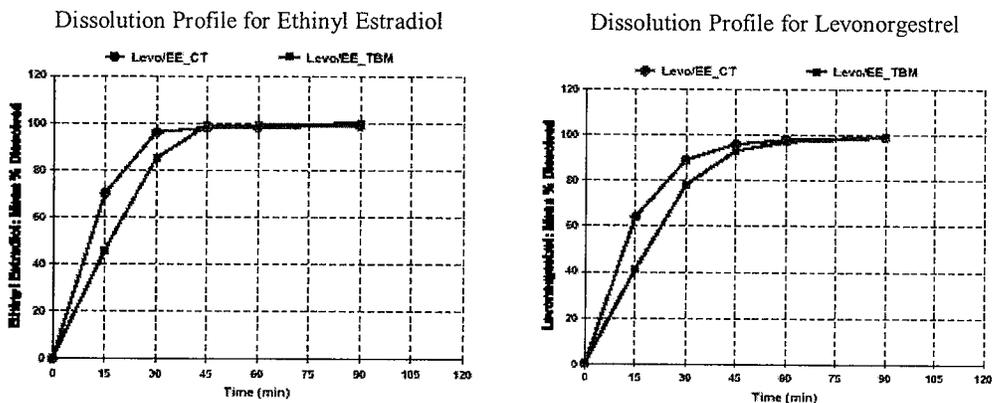


TABLE 7: Summary of *In Vitro* Dissolution Studies: Levonorgestrel(LNG)/Ethinyl Estradiol(EE)

Study Ref. No.	Product ID/ Batch No.	Dosage Form	No. of Dosage Units	Analyte	Collection times				
					Mean % Dissolved (range)				
					15 min	30 min	45 min	60 min	90 min
ARD RPT 1224	Seasonique™ TBM/ 205554001	Film-Coated Tablet	12	LNG	41 (34-55)	78 (71-90)	93 (91-97)	97 (95-100)	99 (97-101)
				EE	46 (38-59)	85 (78-94)	99 (98-101)	99 (98-100)	100 (98-102)
	Seasonique™ CT/ 200313001R	Film-Coated Tablet	12	LNG	64 (50-74)	89 (83-93)	96 (94-98)	98 (96-100)	99 (97-102)
				EE	70 (57-81)	96 (89-103)	98 (95-103)	98 (91-102)	99 (95-104)

The f2 factor for LNG and EE was 47 and 46 respectively which does not ensure sameness between the products. These differences in the dissolution profiles of the combination tablet prompted the bioequivalence study to prove the two products bioequivalence. The sponsor concluded that the dissolution method may be overly discriminatory for the LNG/EE combination tablets.

Ethinyl Estradiol

All of the dissolution profiles were conducted in accordance with the USP 23 monograph for levonorgestrel and ethinyl estradiol tablets, with sample collection times modified.

Equipment: Apparatus II (paddles)

Temperature: 37 ± 0.5 °C

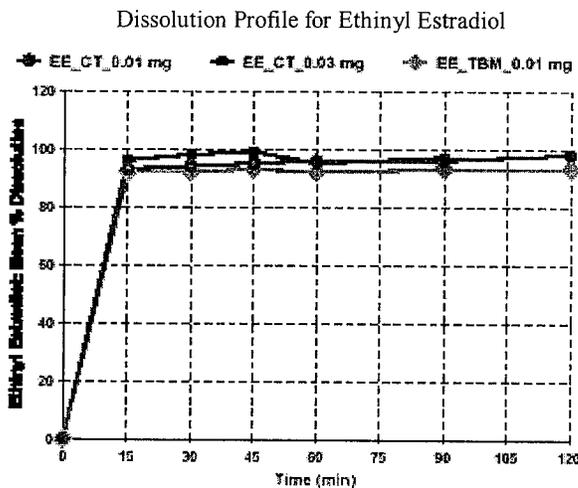
Rotation Speed: 75 rpm

Medium: 5 ppm Tween 80 in Water

Volume: 500 mL

Time Intervals: 15, 30, 45, 60, 90, 120 minutes

FIGURE 2: Mean dissolution profiles of EE tablets. Batch No. 205564001R (EE TBM), Batch No. 200323001R (EE CT 0.01mg), Batch No. 100291001R (EE CT 0.03 mg).



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TABLE 8: Summary of *In Vitro* Dissolution Studies: Ethinyl Estradiol (EE)

Study Ref. No.	Product ID/ Batch No.	Dosage Form	No. of Dosage Units	Analyte	Collection Mean % Dissolved (range) times					
					15 min	30 min	45 min	60 min	90 min	120 min
ARD_RPT_1227	EE TBM/ 205564001R 0.01 mg yellow	Film-Coated Tablet	12	EE	92 (89-94)	92 (89-95)	93 (90-95)	92 (90-94)	93 (90-95)	93 (90-98)
ARD_RPT_1227	EE CT/ 200323001R 0.01 mg white	Film-Coated Tablet	12	EE	93 (90-96)	94 (92-97)	95 (91-99)	96 (91-99)	96 (91-99)	98 (95-101)
ARD_RPT_1227	EE CT/ 100291001R 0.03 mg white	Film-Coated Tablet	12	EE	96 (92-102)	98 (93-102)	99 (96-102)	95 (92-99)	97 (93-99)	-

The f2 factor between EE 0.01 mg tablets was 74 which concludes similarity between the TBM formulation and the CT formulation of the EE 0.01 mg tablets

3.6 Analytical Section

TABLE 9: Bioanalytical Methods specification and performance

	Analyte				
	Levonorgestrel (LN)		Ethinyl Estradiol (EE)		
BA/BE Study Number	10216207	10416204	10216207	10416204	R00-570
Bioanalytical Report Number	AA00127-2	AA21280-1	AA00127-1	AA21280-2	25912-1
Type of Biological Fluid	Plasma				
Assay Method	LC-MS/MS				
Internal Standard					
Lower Limit of Quantitation					
Assay Range					
Mean Recovery	97%	97%	67%	67%	60%
Internal Standard Recovery	110%	110%	61%	61%	61%
Validation QC Samples					
Interday Precision					
Interday Accuracy					
Validation QC Samples					
Intraday Precision					
Intraday Accuracy					
Bioanalysis QC Samples					
Interday Precision					
Interday Accuracy					

All assays for levonorgestrel and ethinyl estradiol were performed and validated by

4 Detailed Labeling Recommendations

CLINICAL PHARMACOLOGY

Mode of Action

Combination oral contraceptives act by suppression of gonadotropins. Although the primary mechanism of this action is inhibition of ovulation, other alterations include changes in the cervical mucus (which increase the difficulty of sperm entry into the uterus) and changes in the endometrium (which reduce the likelihood of implantation).

Pharmacokinetics

Absorption:

Distribution:

The apparent volume of distribution of levonorgestrel and ethinyl estradiol are reported to be approximately 1.8 L/kg and 4.3 L/kg, respectively. Levonorgestrel is about 97.5 - 99% protein-bound, principally to sex hormone binding globulin (SHBG) and, to a lesser extent, serum albumin. Ethinyl estradiol is about 95 - 97% bound to serum albumin. Ethinyl estradiol does not bind to SHBG, but induces SHBG synthesis, which leads to decreased levonorgestrel clearance. Following repeated daily dosing of combination levonorgestrel/ethinyl estradiol oral contraceptives, levonorgestrel plasma concentrations accumulate more than predicted based on single-dose kinetics, due in part, to increased SHBG levels that are induced by ethinyl estradiol, and a possible reduction in hepatic metabolic capacity.

Metabolism:

Following absorption, levonorgestrel is conjugated at the 17 β -OH position to form sulfate and to a lesser extent, glucuronide conjugates in plasma. Significant amounts of conjugated and unconjugated 3 α ,5 β -tetrahydrolevonorgestrel are also present in plasma, along with much smaller amounts of 3 α ,5 α -tetrahydrolevonorgestrel and 16 β -hydroxylevonorgestrel. Levonorgestrel and its phase I metabolites are excreted primarily as glucuronide conjugates. Metabolic clearance rates may differ among individuals by several-fold, and this may account in part for the wide variation observed in levonorgestrel concentrations among users.

First-pass metabolism of ethinyl estradiol involves formation of ethinyl estradiol-3-sulfate in the gut wall, followed by 2-hydroxylation of a portion of the remaining untransformed ethinyl estradiol by hepatic cytochrome P-450 3A4 (CYP3A4). Levels of CYP3A4 vary widely among individuals and can explain the variation in rates of ethinyl estradiol hydroxylation. Hydroxylation at the 4-, 6-, and 16- positions may also occur, although to a much lesser extent than 2-hydroxylation. The various hydroxylated metabolites are subject to further methylation and/or conjugation.

Excretion:

About 45% of levonorgestrel and its metabolites are excreted in the urine and about 32% are excreted in feces, mostly as glucuronide conjugates. The terminal elimination half-life for levonorgestrel after a single dose of Seasonique™ was about 34 hours.

Ethinyl estradiol is excreted in the urine and feces as glucuronide and sulfate conjugates, and it undergoes enterohepatic recirculation. The terminal elimination half-life of ethinyl estradiol after a single dose of Seasonique™ was found to be about 18 hours.

SPECIAL POPULATIONS

Race

No formal studies on the effect of race on the pharmacokinetics of Seasonique™ were conducted.

Hepatic Insufficiency

No formal studies have been conducted to evaluate the effect of hepatic disease on the pharmacokinetics of Seasonique™. However, steroid hormones may be poorly metabolized in patients with impaired liver function.

Renal Insufficiency

No formal studies have been conducted to evaluate the effect of renal disease on the pharmacokinetics of Seasonique™.

Drug-Drug Interactions

See PRECAUTIONS section – Drug Interactions.

Drug Interactions

Changes in contraceptive effectiveness associated with co-administration of other products

a. Anti-infective agents and anticonvulsants

Contraceptive effectiveness may be reduced when hormonal contraceptives are co-administered with antibiotics, anticonvulsants, and other drugs that increase the metabolism of contraceptive steroids. This could result in unintended pregnancy or breakthrough bleeding. Examples include rifampin, barbiturates, phenylbutazone, phenytoin, carbamazepine, felbamate, oxcarbazepine, topiramate, and griseofulvin. Several cases of contraceptive failure and breakthrough bleeding have been reported in the literature with concomitant administration of antibiotics such as ampicillin and tetracyclines. However, clinical pharmacology studies investigating drug interaction between combined oral contraceptives and these antibiotics have reported inconsistent results.

b. Anti-HIV protease inhibitors

Several of the anti-HIV protease inhibitors have been studied with co-administration of oral combination hormonal contraceptives; significant changes (increase and decrease) in the plasma levels of the estrogen and progestin have been noted in some cases. The safety and efficacy of combination oral contraceptive products may be affected with co-administration of anti-HIV protease inhibitors. Healthcare providers should refer to the label of the individual anti-HIV protease inhibitors for further drug-drug interaction information.

c. Herbal products

Herbal products containing St. John's Wort (*hypericum perforatum*) may induce hepatic enzymes (cytochrome P450) and p-glycoprotein transporter and may reduce the effectiveness of contraceptive steroids. This may also result in breakthrough bleeding.

Increase in plasma levels of estradiol associated with co-administered drugs

Co-administration of atorvastatin and certain combination oral contraceptives containing ethinyl estradiol increase AUC values for ethinyl estradiol by approximately 20%. Ascorbic acid and acetaminophen may increase plasma ethinyl estradiol levels, possibly by inhibition of conjugation. CYP 3A4 inhibitors such as itraconazole or ketoconazole may increase plasma hormone levels.

Changes in plasma levels of co-administered drugs

Combination hormonal contraceptives containing some synthetic estrogens (e.g., ethinyl estradiol) may inhibit the metabolism of other compounds. Increased plasma concentrations of cyclosporin, prednisolone, and theophylline have been reported with concomitant administration of combination oral contraceptives. Decreased plasma concentrations of acetaminophen and increased clearance of temazepam, salicylic acid, morphine and clofibrac acid, due to induction of conjugation have been noted when these drugs were administered with combination oral contraceptives.

5 Appendices

5.1 Population PK Analysis

None

5.2 Individual Study Review

5.2.1 Study 10216207: Multiple Dose Steady State Study

Objective

To evaluate the single and steady state pharmacokinetics of DP3 (0.15/0.03 mg LNG/EE and 0.03 mg EE) tablets (Barr Laboratories, Inc.) in healthy female, adult subjects.

To monitor hormone levels during the study and for 48 days following the final dose.

Subjects

Of the 30 subjects who enrolled, 28 subjects completed the study

Ages ranged from 19 to 51 (mean age 30). Individual weight variation was not more than $\pm 20\%$ from normal for height and weight for body frame with two exceptions (+3 and +4 lbs for 20% at screening in two subjects).

Design

Open Label, single treatment, multiple dose, steady state, pharmacokinetic study.

On Day 1 through 84, subjects were required to take one 0.15/0.03mg LNG/EE tablet. On Days 1, 21, and 84 the tablet was administered with 240 mLs of water by the study staff after an overnight fast of at least 10 hours. During the outpatient portions of the study, subjects were required to self-administered the study drug and report the date and time of each dose in a dosing diary.

On days 85 through 91, subjects were required to take one 0.03 mg EE tablet. On Day 91 the tablet was administered with 240 mLs of water after an overnight fast of at least 10 hours. During the outpatient portions, the subject was required to self-administer the study drug and record the date and time of each dose in a dosing diary.

During the confinement periods (Days 1, 21, 84 and 91), standardized, caffeine-free meals or snacks were served.

Subjects were requested to refrain from certain concomitant medication use during the study. They were also instructed to abstain from any products containing alcohol, caffeine, or grapefruit within 48 hours prior to dosing on Study Days 1, 21, 84 and 91. During the confinement periods the use of tobacco was prohibited from one hour prior until for hours post dosing and for 30 minutes prior to any vital sign measurement.

Treatments

Days 1-84: 1 x 0.150/0.03 mg levonorgestrel/ethinyl estradiol tablets, USP; Batch No. 100311002R; Manufacture Date 11/15/2001

Days 85-91: 1 x 0.03 mg ethinyl estradiol tablet, USP; Bach No. 100291001R; Manufacture Date 9/05/01

- Cmin on Day 18, 19, 20, and 21 are comparable confirming that steady-state plasma concentration is reached on or before Day 19. No accumulation occurs as Cmin on Day 21, 84 and 91 are also comparable.
- EE 0.03 mg tablets have similar PK characteristics as the combination LNG/EE 0.150/0.03mg tablets.

TABLE 11: Study 10216207 Mean \pm SD PK parameters for EE

	Day 1	Day 21	Day 84	Day 91
N	30	30	28	27/28
AUC ₀₋₂₄ (pg·h/ml)	509.28 \pm 171.99	837.10 \pm 271.17	791.49 \pm 214.95	867.52 \pm 277.57
AUC ₀₋₉₆ (pg·h/ml)				1235.87 \pm 415.45
AUC _{inf} (pg·h/ml)				1327.30 \pm 432.87
Cmax (pg/ml)	69.78 \pm 25.89	99.58 \pm 31.30	91.27 \pm 32.46	102.32 \pm 50.40
Cmin (pg/ml)		14.66 \pm 6.45	14.49 \pm 5.27	15.45 \pm 6.92
% Fluctuation		572 \pm 247	446 \pm 211	558 \pm 203
Tmax* (h)	1.33	1.33	1.67	1.33
Ke (1/h)				0.041 \pm 0.011
T _{1/2} (h)				17.93 \pm 4.29
Vd (L/kg)				10.41 \pm 2.93
Cl (L/hr)				26.79 \pm 8.59

*median

Conclusions

For both LNG and EE the pharmacokinetic parameters estimated after Day 21 dosing were essentially similar to the estimates obtained after dosing on Day 84 (for LNG) and after dosing on Day 84 and Day 91 (for EE). Steady state levels of LNG/EE during longer dosing duration of DP3 are similar to the steady state levels observed for a typical 21 day combination contraceptive regimen.

5.2.2 Study 10416204: Relative BA of LNG/EE tablets

Objective

To compare the relative bioavailability of the test formulation of Levonorgestrel/Ethinyl Estradiol with the reference formulation of Levonorgestrel/Ethinyl Estradiol in healthy, female, subjects.

Subjects

Of the 30 subjects who enrolled 29 completed the study. The subjects were healthy, non-tobacco-using females between the ages of 19 and 51 (mean 31) years and had a body mass index within 19 to 30 kg/m² inclusive (mean BMI 24.5). The majority of the subjects were Hispanic and Black. Only one Caucasian participated in the study

Design

Randomized, single dose, two-way, crossover study.

Subjects received the test and reference treatments following an overnight fast of at least 10

Parameter	Least Squares means ¹		Test/Ref Ratio ²	Power ³	90% Confidence Interval ⁴	
	Test	Reference			Lower	Upper
Ln-Transformed Data						
AUC _{0-t} (ng hr/mL)	63.75	65.92	0.96	>0.99	0.8980	1.0420
AUCinf (ng hr/mL)	70.49	71.07	0.99	0.98	0.9110	1.0790
Cmax (ng/mL)	5.59	5.56	1.00	>0.99	0.9360	1.0770

1 Least Squares geometric means for ln-transformed data

2 Test/Ref Ratio calculated as Test mean divided by Reference mean

3 Power to detect a difference of 20% (original data) or a ratio of 1.25 (ln-transformed data).

4 Confidence interval on the ratio.

TABLE 13: Study 10416204 Ethinyl Estradiol pharmacokinetic results (N=29)

Parameter	Least Squares means ¹		Test/Ref Ratio ²	Power ³	90% Confidence Interval ⁴	
	Test	Reference			Lower	Upper
AUC _{0-t} (pg hr/mL)	1450.11	1453.14	0.99	>0.99	0.9632	1.0326
AUCinf (pg hr/mL)	1543.49	1556.56	0.99	>0.99	0.9511	1.0320
Cmax (pg/mL)	157.46	158.06	0.99	>0.99	0.9434	1.0490
Tmax (h)	1.54	1.52	1.01	0.98	0.9399	1.0910
Ke (1/h)	0.0413	0.0407	1.01	>0.99	0.9614	1.0685
Thalf (h)	17.48	18.10	0.96	0.98	0.8873	1.0446
Ln-Transformed Data						
AUC _{0-t} (pg hr/mL)	1385.67	1380.19	1.00	>0.99	0.9714	1.0376
AUCinf (pg hr/mL)	1476.54	1475.43	1.00	>0.99	0.9668	1.0358
Cmax (pg/mL)	147.63	147.99	0.99	>0.99	0.9510	1.0463

5 Least Squares geometric means for ln-transformed data

6 Test/Ref Ratio calculated as Test mean divided by Reference mean

7 Power to detect a difference of 20% (original data) or a ratio of 1.25 (ln-transformed data).

8 Confidence interval on the ratio.

Conclusions

The new formulation of 0.15/0.03mg Levonorgestrel/Ethinyl Estradiol Tablets are bioequivalent to the clinical trial formulation of 0.15/0.03mg Levonorgestrel/Ethinyl Estradiol tablets.

5.2.3 Study R00-570

Objective

To compare the relative bioavailability of Ethinyl Estradiol Tablets to an Ethinyl Estradiol Oral Solution in healthy female subjects under fasting conditions.

Subjects

Seventeen of 18 Healthy female volunteers completed the study. Mean age was 24.2 years of age.

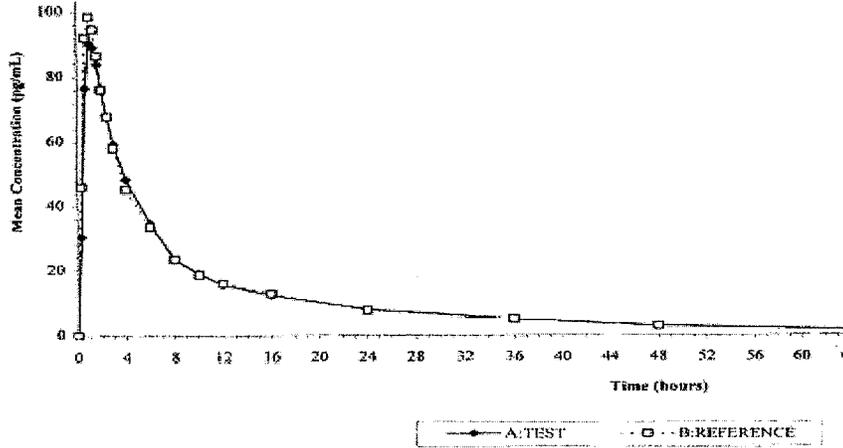
Design

Randomized, single-dose, two-way crossover study in healthy female subjects under fasting

Parameter	Least Squares Mean ¹		% Ratio	90% Confidence Interval ²	
	Test	Reference		Lower	Upper

² Confidence interval on the ratio.

FIGURE 3: Mean Plasma Ethinyl Estradiol Concentrations



Conclusions

Ethinyl Estradiol Tablets 0.03mg is bioequivalent to the Ethinyl Estradiol Oral Solution when administered under fasting conditions.

5.3 Cover Sheet and OCPB Filing/Review Form

Please see DFS review posted by Julie Bullock, Pharm.D.

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Julie Bullock
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Ameeta Parekh
8/17/2005 09:28:52 AM
BIOPHARMACEUTICS

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Office of Clinical Pharmacology and Biopharmaceutics
New Drug Application Filing and Review Form

General Information About the Submission

	Information		Information
NDA Number	21-840	Brand Name	Seasonique™
OCPB Division (I, II, III)	DPE II (HFD 870)	Generic Name	levonogestrel/ethinyl estradiol tablets 0.15/0.03 mg and ethinyl estradiol tablets 0.01mg
Medical Division	DRUDP (HFD 580)	Drug Class	Oral Contraceptives
OCPB Reviewer	Julie Bullock, Pharm.D.	Indication(s)	Prevention of pregnancy
OCPB Team Leader	Ameeta Parekh, Ph.D.	Dosage Form	Tablet
OCPB Pharmacometrics Reviewer		Dosing Regimen	Once Daily
Date of Submission	10/21/2004	Route of Administration	Oral
Estimated Due Date of OCPB Review	7/19/2005	Sponsor	Duramed Pharmaceuticals Inc.
PDUFA Due Date	8/19/2005	Priority Classification	N/A
Division Due Date			

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) -				
<i>Healthy Volunteers-</i>				
single dose:				
multiple dose:				
<i>Patients-</i>				
single dose:	X	1		PK drawn on Day 1, 21, 84 and 91 giving SD and MD data
multiple dose:	X			
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:	X	2		
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:	X	1		
alternate formulation as reference:				
Bioequivalence studies -				
traditional design; single / multi dose:	X	1		single dose
replicate design; single / multi dose:				
Food-drug interaction studies:				
Dissolution:	X	2		
(IVVC):				
Bio-wavier request based on BCS				
BCS class				
III. Other CPB Studies				
Genotype/phenotype studies:				
Chronopharmacokinetics				
Pediatric development plan				
Literature References				
Total Number of Studies	5			

Filability and QBR comments

	"X" if yes	Comments
Application fileable?	X	Reasons if the application is not fileable (or an attachment if applicable) For example, is clinical formulation the same as the to-be-marketed one?
Comments sent to firm?		Comments have been sent to firm (or attachment included). FDA letter date if applicable.
QBR questions (key issues to be considered)		
Other comments or information not included above		
Primary reviewer Signature and Date		
Secondary reviewer Signature and Date		

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Filing Memo

Clinical Pharmacology and BioPharmaceutics Review

NDA: 21-840
Compound: Seasonique Tablets (Levonorgestrel/Ethinyl Estradiol and Ethinyl Estradiol)
Sponsor: Duramed
Filing Date: 12/20/2004
Reviewer: Julie M. Bullock, Pharm.D.

Background:

This NDA includes the data from two Phase II clinical trials, two pivotal BA/BE studies and one supportive SD/MD pharmacokinetic study performed with the Seasonique product. The sponsor made reference to their NDA product Seasonale[®] (NDA 21-544 approved 9/5/2003). Seasonique is proposed to be marketed as 84 blue active tablets containing 0.3 mg LNG/0.1 mg EE, and 7 tablets containing 0.1mg EE. The only difference in formulation between the clinical trial formulation and the to-be-marketed formulations is their color. The clinical trial formulations for both the LNG/EE tablet and the EE tablet were white, while the TBM tablets are blue and yellow respectively.

Pharmacokinetic Studies

-Conducted in healthy, non-pregnant, female subjects

- Pivotal BA/BE studies
 - Study 10416204: A randomized, single dose, two-way crossover BE study under fasting conditions to compare the LNG/EE blue TBM Seasonique tablet formulation to that of the white LNG/EE Clinical Trial formulation.
 - Study R00-570: A randomized, single dose, two-way crossover BA study under fasting conditions to demonstrate that the 0.03 mg EE CT formulation is BA to the reference EE oral solution
 - Study 10216207: Single treatment, multiple dose, steady state PK study to characterize the PK profile the 0.15/0.03 mg LNG/EE tablets and 0.03mg EE tablets at key points across an entire 91 day extended cycle regimen. PK was drawn on Days 1, 21, 84 and 91

Clinical Studies

- A randomized, multicenter, trial to evaluate the efficacy and safety of two dose levels (LNG 0.15mg/EE 0.03mg + EE 0.03 and LNG 0.15/EE 0.03 mg + EE 0.01 of extended OC therapy for 12 consecutive months (4 cycles).
- A randomized, multicenter trial to evaluate the efficacy for prevention of pregnancy in women and safety by obtaining endometrial biopsies of 4 OC therapies.
 - LNG 0.15 mg/EE 0.03mg x 84 days, followed by EE 0.03mg x 7 days
 - LNG 0.15 mg/EE 0.03mg x 84 days, followed by EE 0.01 mg x 7 days
 - LNG 0.15 mg/EE 0.03mg x 25 days, followed by EE 0.03 mg x 3 days
 - Nordette[®]: LNG 0.15/EE 0.03 mg x 21 days followed by placebo tablets x 7 days

The sponsor provided the following:

1. Human Pharmacokinetics and Bioavailability section summary, full study reports and proposed labeling
2. Drug formulation
3. Bioanalytical methods
4. In-vitro dissolution data
5. A list of references

6. Sponsor states that the to-be-marketed Seasonique formulation is bioequivalent to the clinical trial Seasonique formulation

Recommendation

The Office of Clinical Pharmacology and Biopharmaceutics/Division of Pharmaceutical Evaluation II find that the Human Pharmacokinetics and Bioavailability section for NDA 21-840 is fileable.

Julie M. Bullock, Pharm.D.

Date

Ameeta Parekh, Ph.D., Team Leader

Date

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Julie Bullock
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Ameeta Parekh
12/20/04 11:53:42 AM
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