CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-544

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

Clinical Pharmacology and Biopharmaceutics Review Division of Pharmaceutical Evaluation II	
NDA:	**21-544**
Brand Name:	**Seasonale**
Generic Name:	**Levonorgestrel (LNG)/Ethinyl Estradiol (EE)**
Sponsor:	**Barr Laboratories Inc.**
Relevant IND(s):	**60,399**
Date of Submission:	**05-AUG-2002**
Type of Submission:	**Original NDA**
Code:	**3S**
Formulation:	**Oral**
Strength:	**LNG 0.15 mg/EE 0.03 mg**
Indication:	**Prevention of Pregnancy**
Reviewer:	**Myong-Jin Kim, Pharm.D.**
Team Leader:	**Ameeta Parekh, Ph.D.**
OCPB Division:	**DPE-II**
OND Division:	**Reproductive & Urologic Drug Products**

1. EXECUTIVE SUMMARY

Seasonale® is a novel 91-day combination oral contraceptive (COC) for the prevention of pregnancy when administered as a 91-day regimen consisting of 84 consecutive days of active tablets followed by 7 consecutive days of placebo tablets. Each Seasonale tablet contains levonorgestrel (LNG) 0.15 mg and ethinyl estradiol (EE) 0.03 mg. The sponsor's rationale for developing Seasonale was to reduce the frequency of scheduled withdrawal bleeding in addition to prevention of pregnancy.

In support of this NDA, the sponsor submitted one clinical study (SEA-301), and two pivotal and three supportive BA/BE studies under Section 505(b)(2). Pivotal clinical study, SEA-301, was a Phase III, four-arm, parallel, randomized, multi-center, open-label study to assess the safety and efficacy of two different strength test products, Seasonale and Seasonale Ultra-Lo (0.10/0.02 mg LNG/EE). The sponsor seeks approval of only the Seasonale 0.15/0.03 mg LNG/EE strength.

The to-be-marketed formulation of Seasonale (Seasonale TBM) is identical to the sponsor's approved ANDA 75-866 product, Portia™, (generic equivalent of Nordette® 0.15/0.03 mg LNG/EE; approved on May 23, 2002). The sponsor made a cross-reference to their ANDA and

submitted a bioequivalence study (Study 99028) which compared Portia and Nordette®-21/28 (NDA 18-668, NDA 18-782). Thereby, the sponsor relied on the previous findings of safety and effectiveness of the conventional 28-day regimen for Nordette®-28 in addition to the findings from the pivotal clinical study.

The sponsor also submitted a bridging study (Study 10216206) which compared the proposed Seasonale TBM formulation and the formulation used in the clinical study (Seasonale CT). The only difference in formulations between the Seasonale TBM and the Seasonale CT formulations was the

Based on the results of these two bioequivalence studies, Seasonale TBM formulation is bioequivalent to both the reference listed drug Nordette, and to the Seasonale CT formulation used in the clinical study, SEA-301.

1.1 Recommendation

The Office of Clinical Pharmacology and Biopharmaceutics/Division of Pharmaceutical Evaluation II (OCPB/DPE-II) has reviewed NDA 21-544 submitted on August 5, 2002. The overall Human Pharmacokinetic Section is *acceptable*. Labeling comments outlined in the labeling section have been accepted by the sponsor.

Myong-Jin Kim, Pharm.D.

RD initialed by Ameeta Parekh, Ph.D., Team Leader _____

FT signed by Ameeta Parekh, Ph.D., Team Leader _____

2. TABLE OF CONTENTS

Terms & Abbreviations

ANOVA.....Analysis of Variance
BE.....Bioequivalence
CI.....Confidence Interval
COC.....Combination Oral Contraceptive
EE.....Ethinyl Estradiol
GC/MS.....Gas Chromatography/Mass Spectrophotometry
HPLC.....High Performance Liquid Chromatography
LNG.....Levonorgestrel
LSM.....Least-Squares Means
NCI.....Negative Chemical Ionization
NLT.....Not Less Than
PK.....Pharmacokinetics
PD.....Pharmacodynamics
Seasonale CT.....Seasonale Clinical Trial Formulation
Seasonale TBM.....Seasonale To-Be-Marketed Formulation

3. SUMMARY OF CPB FINDINGS

Seasonale® is a novel 91-day COC (0.15/0.03 mg LNG/EE) for the prevention of pregnancy when administered as 84 consecutive days of active tablets followed by 7 consecutive days of placebo tablets. The sponsor's rationale for developing Seasonale was to reduce the frequency of scheduled withdrawal bleeding in addition to prevention of pregnancy.

Two pivotal BE studies, Study 10216206 and Study 99028, were reviewed. Three supportive BA/BE studies (Studies 99027, 10216205, 10116208) were not reviewed for the following reasons:

1) Study 99027 is a BE study of Seasonale Ultra-Lo (0.10/0.02 mg LNG/EE) and Berlex 's approved Levlite (0.10/0.02 mg LNG/EE). The sponsor seeks approval of only the Seasonale 0.15/0.03 mg LNG/EE strength.
2) Study 10216205 and Study 10116208 are the relative BA studies of sponsor's two experimental formulations of Seasonale.

Seasonale is proposed to be marketed as 84 pink active tablets and 7 white placebo tablets where the pink active tablets are identical to Barr's generic tablets, Portia (generic equivalent of Nordette® 0.15/0.03 mg LNG/EE). However, Seasonale clinical study, SEA-301, was dosed with [redacted] active tablets (Seasonale CT). The only difference in formulations between the proposed commercial pink tablet and the clinical [redacted] tablet was the [redacted] and this difference did not affect the rate and the extent of LNG and EE absorption as demonstrated in the BE study (Study 10216206).

The 90% CI for the difference between formulation LSM for the parameters AUC_{0-t}, $AUC_{0-\infty}$, and C_{max} using ln-transformed data for LNG and EE were within 80 to 125 % (Study 10216206). Therefore, a single dose of two LNG/EE 0.15/0.03 mg tablets of the Seasonale TBM formulation and a single dose of two LNG/EE 0.15/0.03 mg tablets of the Seasonale CT formulation were concluded to be bioequivalent under fasting conditions.

Study 10216206 (BE Study of Seasonale TBM and Seasonale CT Tablets):

Table 1. Comparisons of LNG/EE results (Seasonale TBM vs. Seasonale CT).

	LNG			EE		
	LSM		90 % CI (ratio of LSM)	LSM		90 % CI (ratio of LSM)
	Seasonale TBM	Seasonale CT	Seasonale TBM vs. Seasonale CT	Seasonale TBM	Seasonale CT	Seasonale TBM vs. Seasonale CT
AUC_{0-t}	55.96 ng•hr/mL	58.69 ng•hr/mL	0.90 – 1.01 (0.95)	1262 pg•hr/mL	1209 pg•hr/mL	1.01 – 1.09 (1.04)
$AUC_{0-\infty}$	60.24 ng•hr/mL	63.09 ng•hr/mL	0.90 – 1.01 (0.96)	1336 pg•hr/mL	1297 pg•hr/mL	1.00 – 1.07 (1.03)
C_{max}	5.45 ng/mL	5.67 ng/mL	0.91 – 1.01 (0.96)	138 pg/mL	125 pg/mL	1.03 – 1.18 (1.10)

Following single oral doses of two 0.15/0.03 mg LNG/EE tablets, the C_{max} of LNG was 5.63 ± 1.45 ng/mL and occurred approximately 1.4 hours post-dose. The terminal plasma elimination half-life of LNG was approximately 30 hours. For EE, the C_{max} was 144.5 ± 45.4 pg/mL, the T_{max} was around 1.6 hours and the terminal elimination half-life was about 15 hours.

It should be noted that the sponsor did not evaluate the effect of food on the rate and the extent of LNG/EE absorption after Seasonale administration.

4. QUESTION-BASED REVIEW

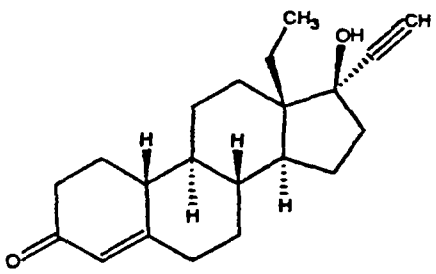
4.1 General Attributes

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

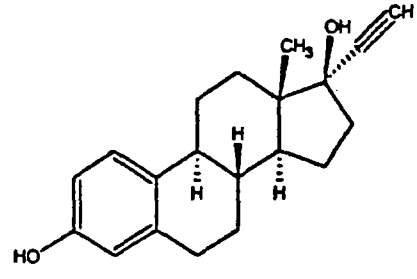
Physico-chemical properties

- Structural formula:

LNG



EE



- Established Name: Levonorgestrel, USP (LNG); Ethinyl estradiol, USP (EE)
- Molecular Weight: 312.4 (LNG); 296.4 (EE)

- Molecular Formula: $C_{21}H_{28}O_2$ (LNG); $C_{20}H_{24}O_2$ (EE)
- Chemical Name: d(-)-13 beta-ethyl-17-alpha-ethinyl-17-beta-hydroxygon-4-en-3-one (LNG); 19-nor-17α-pregna-1,3,5(10)-trien-20-yne-3,17-diol (EE)

Drug Formulation

Table 2. Drug Product Formulation Comparison

Components	Seasonale® CT	Seasonale® TBM	Portia™
Levonorgestrel, USP (Micronized)	0.15	0.15	0.15
Ethinyl Estradiol, USP (Micronized)	0.03	0.03	0.03
[redacted]			
[redacted]			
Hydroxypropyl Methyl Cellulose [redacted] USP	[redacted]		
Microcrystalline Cellulose, NF	[redacted]		
Anhydrous Lactose, NF [redacted]	[redacted]		
Magnesium Stearate, NF	[redacted]		
Tablet Diameter (Core)	[redacted]		
Tablet Weight (Core)	[redacted]		
[redacted] Weight	[redacted]		
Coated Tablet Weight	85 mg	85 mg	85 mg
[redacted]	[redacted]	pink	pink
Biostudy Batch*	104371007R	109921001T	109929R01
Where used (biostudy protocol #)	10116208 10216205 10216206	10216206	99028
Active tablet batches (pill pack batches) used in Study SEA-301	104379R01 (190240001) 104370001R (19024002R) 104371004R (19024100:R)		
Active tablet batches (pill pack batches) used in Study SEA-301A	104371005R (190241003R)		

*Only batches that were dosed in the bioequivalence studies are listed.

The pink active tablet and white placebo tablet formulations and manufacturing processes for Seasonale TBM and Portia are identical. The Seasonale CT formulation is identical to that of Seasonale TBM/Portia formulation except for the color of the film coating. The Seasonale CT has a [redacted] film coating, whereas Seasonale TBM/Portia formulation has a pink film coating. All of the formulations tested were [redacted]

The code debossed on the tablets of Portia and the Seasonale TBM products are as follows:

1) Seasonale TBM active tablets are debossed with "S" on the top and "62 ~ on the bottom
2) Portia active tablets are debossed with "B" on the top and "922" on the bottom
3) Seasonale TBM placebo tablets are debossed with "S" on the top and "~.97" on the bottom
4) Portia placebo tablets are debossed with "B" on the top and "208" on the bottom

Comments:

- The sponsor conducted a BE study to link the Seasonale TBM and Seasonale CT formulations (Study 10216206).
- Comparative dissolution profiles for the differences in debossing are not necessary.

2. What is the proposed mechanism of action?

Combination hormonal 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 the endometrium (which reduce the likelihood of implantation).

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

The proposed indication is prevention of pregnancy in women who elect to use this product as a method of contraception. The dosage of Seasonale is one pink active tablet daily for 84 consecutive days, followed by 7 days of white inert tablets.

4.2 General Clinical Pharmacology

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

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

Table 3. Comparisons of LNG/EE results (Seasonale TBM vs. Seasonale CT).

	LNG			EE		
	LSM		90 % CI (ratio of LSM)	LSM		90 % CI (ratio of LSM)
	Seasonale TBM	Seasonale CT	Seasonale TBM vs. Seasonale CT	Seasonale TBM	Seasonale CT	Seasonale TBM vs. Seasonale CT
AUC_{0-t}	55.96 ng•hr/mL	58.69 ng•hr/mL	0.90 – 1.01 (0.95)	1262 pg•hr/mL	1209 pg•hr/mL	1.01 – 1.09 (1.04)
$AUC_{0-\infty}$	60.24 ng•hr/mL	63.09 ng•hr/mL	0.90 – 1.01 (0.96)	1336 pg•hr/mL	1297 pg•hr/mL	1.00 – 1.07 (1.03)
C_{max}	5.45 ng/mL	5.67 ng/mL	0.91 – 1.01 (0.96)	138 pg/mL	125 pg/mL	1.03 – 1.18 (1.10)

Table 4. Pharmacokinetic parameters of LNG/EE following single oral doses of 2 x 0.15/0.03 mg LNG/EE tablets (Seasonale TBM).

LNG			EE		
PK Parameters	Arithmetic Mean ± SD (range)	CV %	PK Parameters	Arithmetic Mean ± SD (range)	CV %
AUC_{0-t} (ng•hr/mL)	60.83 ± 25.56 (20.28 – 121.09)	42.0	AUC_{0-t} (pg•hr/mL)	1306.9 ± 361.1 (722.0 – 2299.2)	27.6
$AUC_{0-\infty}$ (ng•hr/mL)	64.95 ± 25.79 (21.81 – 125.83)	39.7	$AUC_{0-\infty}$ (pg•hr/mL)	1379.6 ± 319.9 (887.7 – 2403.3)	23.2
C_{max} (ng/mL)	5.63 ± 1.45	25.7	C_{max} (pg/mL)	144.5 ± 45.4	31.4
T_{max} (hr)	1.36 ± 0.28 (1.00 – 2.00)	20.3	T_{max} (hr)	1.64 ± 0.45 (1.00 – 3.00)	27.5
k_{el} (hr^{-1})	0.025 ± 0.008 (0.015 – 0.052)	32.1	k_{el} (hr^{-1})	0.047 ± 0.011 (0.031 – 0.077)	22.6
$T_{1/2}$ (hr)	29.75 ± 8.27 (13.41 – 46.78)	27.8	$T_{1/2}$ (hr)	15.44 ± 3.18 (9.05 – 22.43)	20.6

Comments:

- The mean plasma PK parameters of Seasonale reported in the labeling (see Table 1 of the label under the section of "**Pharmacokinetics**") are revised based on the PK data from Study 10216206 (see Table 4 above).

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

Pivotal clinical study, SEA-301, was conducted to assess the safety and efficacy of two different strength test products, Seasonale (0.15/0.03 mg LNG/EE), and Seasonale Ultra-Lo (0.10/0.02 mg LNG/EE). However, the sponsor seeks approval of only the Seasonale 0.15/0.03 mg LNG/EE strength. Seasonale Ultra-Lo is not being considered for approval. In the clinical study, there were 8 on-treatment pregnancies with a Pearl Index (PI) of 4.07 in the Seasonale Ultra-Lo treatment group whereas Seasonale resulted 4 on-treatment pregnancies with a PI of 1.98. A PI of 1.98 was considered acceptable for Seasonale (see Medical Officer's Review).

Do PK parameters change with time following chronic dosing?

The pharmacokinetics of LNG and EE after administration of Seasonale as a 91-day regimen consisting of 84 consecutive days of active tablets followed by 7 consecutive days of placebo tablets have not been evaluated by the sponsor. The sponsor stated in the original NDA submission that because of the extensive scientific literature on the PK of LNG and EE, a steady state PK study on Seasonale was not conducted. However, the sponsor submitted Protocol No. 444-03 proposing to assess the PK of Seasonale following multiple doses. This proposed protocol was submitted to the Agency in May 2003.

Kuhnz W *et al* found that steady state of LNG is reached approximately on Day 18 after multiple dose administration of LNG/EE 0.15 mg/0.03 mg (a total treatment period of 3 months, 21 days of active tablets followed by 7 days of placebo tablets per each cycle). SHBG levels increased during treatment cycles 1 and 3 by about 37 % and 65 %, respectively, as compared to

pretreatment values and reached steady state at about Day 18. Therefore, the authors concluded that the steady state concentrations of LNG are related to changes in protein binding of LNG. A moderate increase in SHBG (up to 50 %) over pretreatment levels did not seem to cause marked changes in the protein-binding pattern of LNG. However, the total binding capacity in serum is increased, thus contributing to the observed increase in total drug levels. There was no difference between the AUC values of EE on Day 25 of cycles 1 and 3 (Contraception 1992;46:455-469). No long-term changes in steady-state PK were observed between cycles 1 and 3 when a conventional triphasic LNG/EE COC was dosed for 3 full cycles confirming that indeed steady state is reached within 21 days (Kuhnz W et al. Contraception 1994;50:563-79).

4.3 Biopharmaceutics

Both active pharmaceutical ingredients, LNG and EE, are USP grade material and are manufactured by Barr Laboratories, Inc. Seasonale active and placebo tablets are manufactured, packaged and tested by Barr Laboratories, Inc..

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

The Seasonale CT formulation is identical to that of Seasonale TBM formulation except for the color of the film coating. The Seasonale CT has a film coating, whereas Seasonale TBM formulation has a pink film coating (refer to Drug Formulation section).

4.4 Analytical Section

	LNG		EE	
Study No.	99028	10216206	99028	10216206
Type of Biological Fluid	Plasma	Plasma	Plasma	Plasma
Assay Method				
Assay				
Sensitivity (LOQ)				
Recovery				
Linearity				
Range				
QC Sample				
Inter-Assay Precision				
Inter-Assay Accuracy				
QC Sample				
Intra-Assay Precision				
Intra-Assay Accuracy				

For Study 99028, intra-assay precision (and accuracy ( ) were less than at LOQ of g/mL (LNG). Inter- and intra-assay precision of EE at LOQ of g/mL were and respectively. Intra-assay accuracy was The dilution standards prepared at a LNG concentration of g/mL were diluted in plasma ir and dilutions. The yielded precision and accuracy were dilution), lilution), and dilution), dilution) respectively.

Comments:
The analytical methods are acceptable. Both accuracy and precision are within acceptable values.

***In vitro* Dissolution**

Comparative *in-vitro* dissolution profile testing on the test and reference (products prior to conducting its pivotal BE studies) was done. All of the dissolution profiles were conducted in accordance with the USP 23 monograph for LNG and EE tablets with modified sample collection 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, and 90 minutes

In-Vitro Dissolution Specification:

LNG	NLT [redacted] (Q)	@ 45 minutes
EE	NLT [redacted] Q)	@ 45 minutes

Comments:

- Initially, the sponsor proposed the dissolution specification of NLT [redacted] Q) at 60 minutes for LNG and EE. The dissolution profile data (Table 5; biostudy batches, 109929R01, 109921001T, 10437100R) of Seasonale showed that greater than [redacted] of LNG and EE were dissolved by 60 minute sampling time. Therefore, the sponsor's proposed dissolution specifications of NLT [redacted] Q) at 60 minutes for LNG and EE were deemed to be wide.
- Based on the dissolution profile data of three biostudy batches and in consultation with the CMC reviewer, the following specifications were recommended to the sponsor (May 7, 2003 teleconference):

  LNG: NLT [redacted] (Q) at 30 minutes
  EE: NLT [redacted] Q) at 30 minutes

- In response, the sponsor submitted the stability data at 30 and 45 minutes (Table 6; batches, 200622002R, 109921001T, 104370002R) and proposed NLT [redacted] Q) at 45 minutes for LNG and EE (CMC Amendment dated May 14, 2003). Based on the dissolution profile data of three biostudy batches (109929R01, 109921001T, 10437100R) and two stability batches (200622002R, 109921001T), the specifications of NLT [redacted] Q) at 45 minutes for LNG and EE were proposed by the FDA (concurrence of the CMC reviewer and the OCPB DPEII management on May 20, 2003) and the sponsor accepted the specifications on May 23, 2003.

Figure 1. Mean dissolution profiles of LNG/EE tablets, USP, 0.150 mg/0.030 mg Batch No. 109929R01 (Portia) by Barr Lab. Inc. versus Nordette® (LNG/EE tablets, USP 0.150 mg/0.030 mg) Lot No. 9978271 by Wyeth Lab Inc.

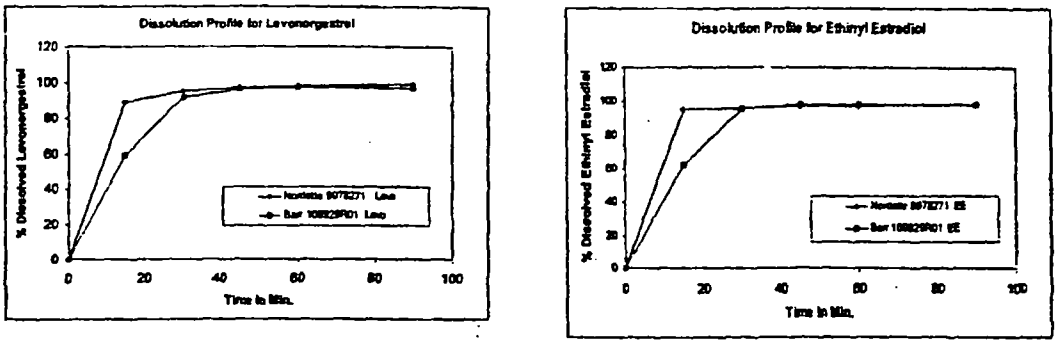


Figure 2. Mean dissolution profiles of LNG/EE tablets: Batch No. 109921001T (Seasonale TBM), Batch No. 104371007R (Seasonale CT).

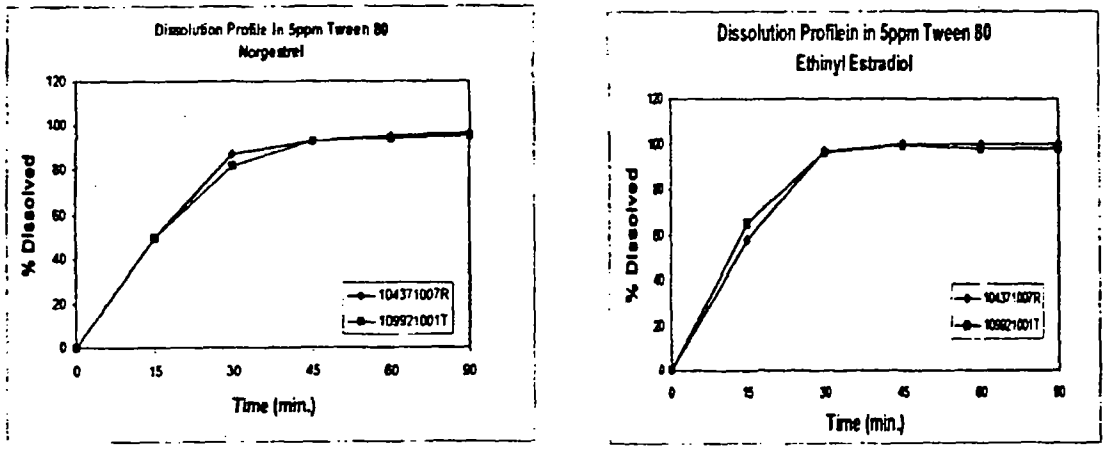
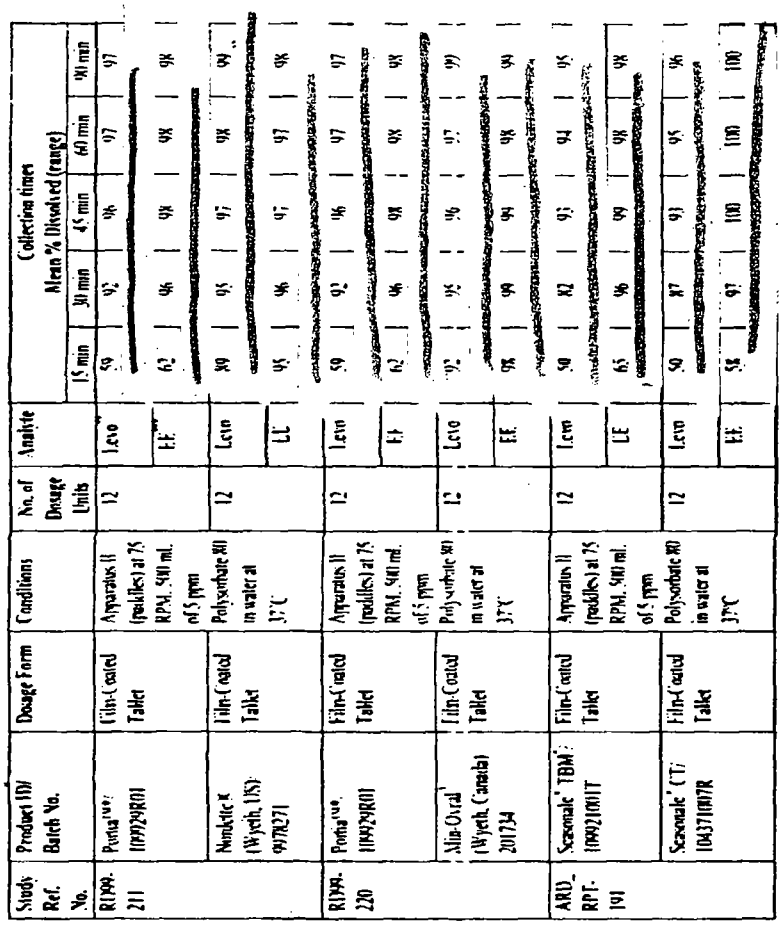


Table 5. Summary of In-Vitro Dissolution Studies



Study Ref. No.	Product ID/ Batch No.	Dosage Form	Conditions	No. of Dosage Units	Analyte	Collection times Mean % Dissolved (range) 15 min	30 min	45 min	60 min	90 min
R1999-211	Portia™ (199929R01)	Film-Coated Tablet	Apparatus II (paddles) at 75 RPM, 500 mL of 5 ppm Polysorbate 80 in water at 37°C	12	Levo	59	92	96	97	97
					EE	62	96	98	98	98
	Nordette® (Wyeth, USA) 9978271	Film-Coated Tablet		12	Levo	80	95	97	98	99
					LE	95	96	97	97	98
R1999-220	Portia™ (199929R01)	Film-Coated Tablet	Apparatus II (paddles) at 75 RPM, 500 mL of 5 ppm Polysorbate 80 in water at 37°C	12	Levo	59	92	96	97	97
					EE	62	96	98	98	98
	Min-Ovral® (Wyeth, Canada) 201734	Film-Coated Tablet		12	Levo	92	95	96	97	99
					EE	98	99	99	98	99
ARD-RPT-191	Seasonale® TBM: (199921001T	Film-Coated Tablet	Apparatus II (paddles) at 75 RPM, 500 mL of 5 ppm Polysorbate 80 in water at 37°C	12	Levo	90	82	93	94	95
					LE	65	96	99	98	98
	Seasonale® (TM: (104370002R	Film-Coated Tablet		12	Levo	90	87	93	95	96
					EE	58	97	100	100	100

Table 6. In-Vitro Dissolution Data of the Stability Lots (at 30 and 45 minutes).

Tab	200622002R				200622002R				199921001T				104370002R			
	EE		LEVO		EE		LEVO		EE		LEVO		EE		LEVO	
	6M ACC		6M ACC		9M CRT		9M CRT		18M CRT		18M CRT		30M CRT		30M CRT	
	30	45	30	45	30	45	30	45	30	45	30	45	30	45	30	45
1																
2																
3																
4																
5																
6																
AVG	82	88	80	88	79	89	76	88	80	87	79	88	76	80	87	89
MIN																
MAX																
RSD	3.2	1.2	7.1	2.7	5.3	2.3	5.1	1.9	3.5	1.3	2.5	1.2	2.1	2.2	1.5	0.8

5. 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 the endometrium (which reduce the likelihood of implantation).

Pharmacokinetics

Absorption:
No specific investigation of the absolute bioavailability of Seasonale® in humans has been conducted. However, literature indicates that levonorgestrel is rapidly and completely absorbed after oral administration (bioavailability nearly 100%) and is not subject to first-pass metabolism. Ethinyl estradiol is rapidly and almost completely absorbed from the gastrointestinal tract but, due to first-pass metabolism in gut mucosa and liver, the bioavailability of ethinyl estradiol is approximately 43 %.

Table 1: Mean ± SD Pharmacokinetic Parameters Following A Single Dose Administration of Two Tablets of Seasonale® in Healthy Female Subjects Under Fasting Conditions

~~Analyte~~	AUC_t ~~(mean ± SD)~~	C_{max} ~~(mean ± SD)~~	T_{max} ~~(mean ± SD)~~	$T_{1/2}$ ~~(mean ± SD)~~
Levonorgestrel	60.8 ± 25.6 ng*hr/mL	5.6 ± 1.5 ng/mL	1.4 ± 0.3 hours	29.8 ± 8.3 hours
Ethinyl estradiol	1307 ± 361 pg*hr/mL	145 ± 45 pg/mL	1.6 ± 0.5 hours	15.4 ± 3.2 hours

The effect of food on the rate and the extent of levonorgestrel and ethinyl estradiol absorption following oral administration of Seasonale® has not been evaluated.

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 17β-OH position to form sulfate and to a lesser extent, glucuronide conjugates in plasma. Significant amounts of conjugated and unconjugated 3α,5β-tetrahydrolevonorgestrel are also present in plasma, along with much smaller amounts of 3α,5α-tetrahydrolevonorgestrel and 16β-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 Seasonale® was ~~—~~ about — 30 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 Seasonale® was ~~found to be~~ about — 15 hours.

SPECIAL POPULATIONS:

Race
No formal studies on the effect of race on the pharmacokinetics of Seasonale® were conducted.

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

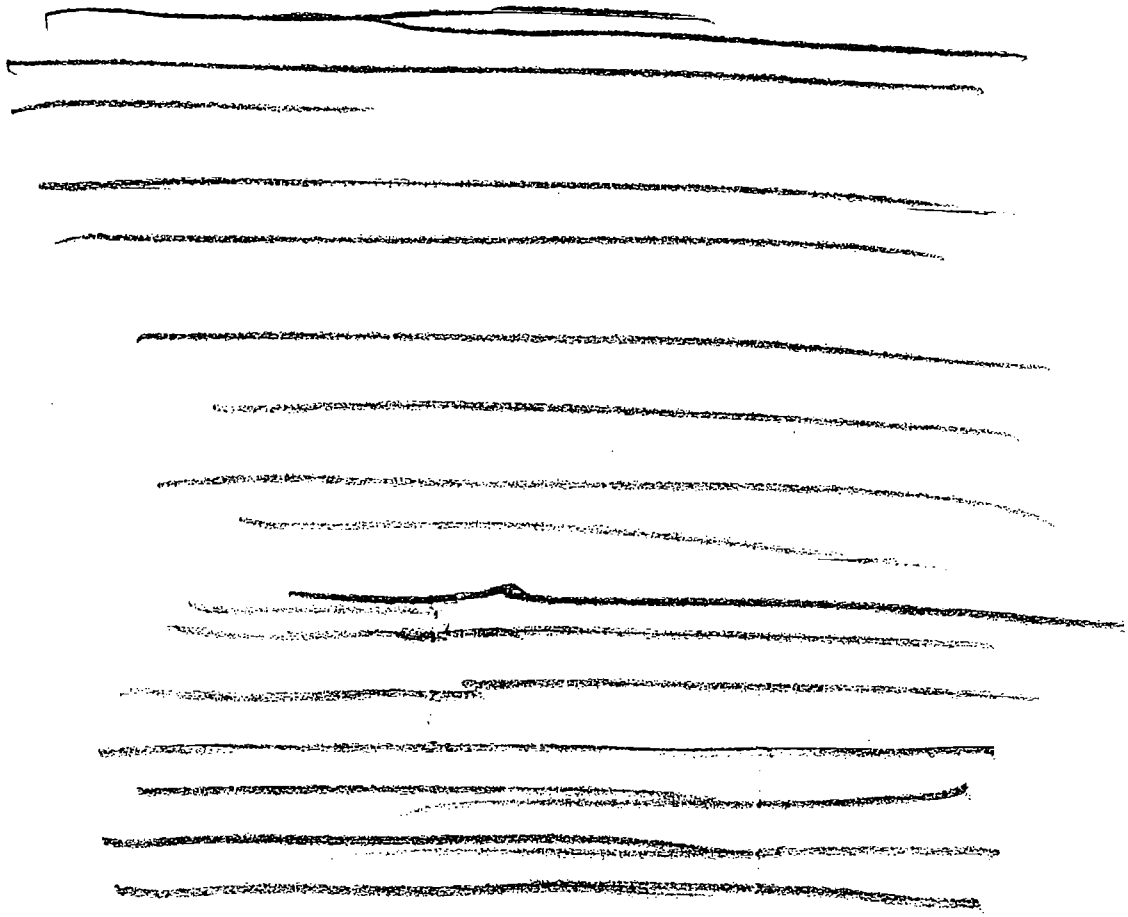
Renal Insufficiency
No formal studies have been conducted to evaluate the effect of renal disease on the pharmacokinetics of Seasonale®.

Drug-Drug Interactions

See "Precautions" section—Drug Interactions

PRECAUTIONS: :

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 clofibric acid, due to induction of conjugation have been noted when these drugs were administered with combination oral contraceptives.

6. APPENDICES

6.1 Individual Study Reviews

1) STUDY 99028:
"Randomized, 3-way crossover, bioequivalence study of Barr Laboratories, Inc. (USA) levonorgestrel-ethinyl estradiol 0.150 mg-0.030 mg tablets (Portia™) and Wyeth-Ayerst Laboratories (USA) Nordette® 0.150 mg-0.030 mg tablets and Wyeth-Ayerst Canada Inc. (Canada) Min-Ovral® 0.150 mg-0.030 mg tablets administered as 2 x 0.150 mg-0.030 mg tablets in healthy adult females under fasting conditions"

Objective:

- To compare the rate and extent of absorption of 0.150/0.030 mg tablets by Barr Laboratories, Inc., (Test) versus Nordette® by Wyeth-Ayerst Laboratories, (Reference A) and Min-Ovral® by Wyeth-Ayerst Canada Inc., (Reference B) as 2 x 0.150/0.030 mg tablets LNG/EE tablets under fasting conditions

Subjects:

- Of 30 healthy Caucasian female subjects who were enrolled, 29 subjects completed the study. One subject, Subject No. 13, was withdrawn from the study prior to Period III dosing due to a positive urine drug screen.

- Ages ranged from 18 to 35 (mean ± SD, 27 ± 6); weights were within 15% of their ideal body weight (weights, 59.5 ± 5.4 kg, 50.3 – 69.6 kg)
- Seven subjects were smokers and the number of cigarettes smoked per day ranged from 10 to 20.

Design:
- A randomized, fasting, single dose, three-treatment crossover study with a washout period of 28 days between treatments
- Subjects were randomized to receive a single oral dose of 2 x 0.03/0.15 mg EE/LNG tablets after an overnight fast of at least 10 hours.
- All doses were administered with 240 mL of room temperature tap water.
- Subjects abstained from food or drinks containing xanthine, grapefruit products, acetaminophen, and alcohol from 48 hours prior to each period until the end of each blood collection period. The use of tobacco was prohibited from one hour prior to and 4 hours post dosing.
- Subjects continued to fast until 4 hours post-dose. On each study day, standardized meals were served at approximately 4, 9, and 13 hours after dosing.
- There was at least 28-day interval between treatments.

Treatments:
Test: 2 x 0.150/0.030 mg LNG/EE tablets, USP; Batch No. 109929R01; Manufacture date 08/10/99 (Portia).
Reference (A): 2 x 0.150/0.030 mg LNG/EE tablets, USP; Batch No. 9978271; Manufacture date 11/00 (Nordette).
Reference (B): 2 x 0.150/0.030 mg LNG/EE tablets, USP; Batch No. 201734; Manufacture date 04/04 (Min-Ovral).

Sample Collection:
- Blood samples were collected for 96 hours post-dose (at pre-dose, 0.5, 1, 1.25, 1.5, 1.75, 2, 2.5, 3, 4, 6, 8, 10, 12, 16, 24, 36, 48, 72, 96 hours) for determination of plasma LNG and EE concentrations.

PK Analysis:
- ANOVA for ln-transformed AUC_{0-t}, $AUC_{0-\infty}$, and C_{max}
- The ANOVA model included sequence, subject within sequence, period and treatment as factors
- Ratio of LSM and 90% CI of the ratio for the ln-transformed parameters AUC_{0-t}, $AUC_{0-\infty}$, and C_{max}

PK Results:
- For both LNG and EE, no statistically significant difference was noted between treatments for $t_{1/2}$ and k_{el} and ln-transformed AUC_{0-t} and $AUC_{0-\infty}$.
- A statistically significant difference was detected between treatments for T_{max} for both LNG/EE, ($p<0.0001$ LNG; $p=0.034$ EE) and for ln-transformed C_{max} for LNG ($p<0.0001$).
- The ratios of LSM and 90% CI of Portia to Nordette formulations were within the acceptance range of 80 % to 125 % for ln-transformed AUC_{0-t}, $AUC_{0-\infty}$, and C_{max} for both LNG and EE.

Table 7. Pharmacokinetic parameters (arithmetic mean ± SD) of LNG following a single oral dose of 2 x 0.150/0.030 mg LNG/EE tablets (Portia vs. Nordette).

LNG				
	Test (Portia)		Reference (Nordette)	
PK Parameters	Mean ± SD (range)	CV %	Mean ± SD (range)	CV %
AUC_{0-t} (ng•hr/mL)	71.78 ± 44.97 (12.15 – 247.70)	62.7	69.01 ± 34.54 (15.98 – 196.20)	50.0
$AUC_{0-\infty}$ (ng•hr/mL)	86.37 ± 59.05 (16.77 – 345.64)	68.4	85.17 ± 51.68 (22.13 – 315.71)	60.7
C_{max} (ng/mL)	6.35 ± 2.27	35.8	5.53 ± 1.53	27.7
T_{max} (hr)	1.32 ± 0.37 (1.00 – 2.50)	28.2	1.80 ± 0.50 (1.00 – 3.00)	27.9
k_{el} (hr^{-1})	0.028 ± 0.010 (0.013 – 0.052)	37.4	0.026 ± 0.008 (0.010 – 0.041)	29.6
$T_{1/2}$ (hr)	28.62 ± 10.60 (13.41 – 52.35)	37.1	29.79 ± 10.94 (16.93 – 70.78)	36.7

Table 8. Pharmacokinetic parameters (arithmetic mean ± SD) of EE following a single oral dose of 2 x 0.150/0.030 mg LNG/EE tablets (Portia vs. Nordette).

EE				
	Test (Portia)		Reference (Nordette)	
PK Parameters	Mean ± SD (range)	CV %	Mean ± SD (range)	CV %
AUC_{0-t} (pg•hr/mL)	1434.6 ± 492.2 (757.4 – 2646.2)	34.3	1380.1 ± 399.5 (775.8 – 2482.4)	29.0
$AUC_{0-\infty}$ (pg•hr/mL)	1650.3 ± 599.1 (927.3 – 3555.4)	36.3	1577.7 ± 442.5 (877.8 – 2897.9)	28.0
C_{max} (pg/mL)	147.1 ± 50.6	34.4	141.5 ± 39.3	27.8
T_{max} (hr)	1.74 ± 0.42 (1.25 – 2.50)	24.1	1.49 ± 0.43 (1.00 – 3.00)	28.9
k_{el} (hr^{-1})	0.045 ± 0.013 (0.013 – 0.068)	28.3	0.045 ± 0.010 (0.024 – 0.065)	22.4
$T_{1/2}$ (hr)	17.22 ± 8.34 (10.24 – 53.67)	48.4	16.48 ± 4.39 (10.60 – 29.04)	26.6

Table 9. Comparisons of LNG/EE results (Portia vs. Nordette)

	LNG			EE		
	LSM		90 % CI (ratio of LSM)	LSM		90 % CI (ratio of LSM)
	Test (Portia)	Reference (Nordette)	Test vs. Reference	Test (Portia)	Reference (Nordette)	Test vs. Reference
AUC_{0-t}	60.86 ng•hr/mL	61.42 ng•hr/mL	0.91 – 1.07 (0.99)	1361 pg•hr/mL	1330 pg•hr/mL	0.98 – 1.07 (1.02)
$AUC_{0-\infty}$	73.57 ng•hr/mL	75.13 ng•hr/mL	0.92 – 1.05 (0.98)	1564 pg•hr/mL	1522 pg•hr/mL	0.98 – 1.07 (1.03)
C_{max}	5.97 ng/mL	5.30 ng/mL	1.06 – 1.20 (1.13)	139 pg/mL	137 pg/mL	0.97 – 1.08 (1.02)

Comments:

- Based on these results, a single dose of two LNG/EE 0.150/0.030 mg tablets of the Portia formulation and a single dose of two LNG/EE 0.150/0.030 mg tablets of the Nordette formulation are concluded to be bioequivalent under fasting conditions.

2) STUDY 10216206:

"The relative bioavailability of two 0.150/0.030 mg LNG/EE tablet formulations under fasting conditions"

Objective:

- To compare the BE of the TBM formulation of 0.15/0.03 mg LNG/EE tablets with the formulation used in the clinical study, SEA-301, under fasting conditions

Subjects:

- Of thirty (30) healthy, female, adult subjects enrolled in the study, a total of 30 subjects completed the BE study.
- The mean age of the subjects was 28 yrs (range, 18 - 51 years) and the mean weight was 137 lbs (range, 100 - 177 lbs). Individual weight variation of the subjects was not more than ± 20% from normal for height and body frame.
- Subjects 35 years of age or older were non-tobacco users for 30 days prior to dosing. Four subjects less than 35 years of age smoked less than one packet of cigarettes a day (2 Caucasians, 2 Hispanics).

Design:

- A randomized, single-dose, two-way, crossover BE study
- Subjects were randomized to receive a single oral dose of 2 x 0.03/0.15 mg EE/LNG tablets after an overnight fast.
- All doses were administered with 240 mL of room temperature tap water.
- Subjects continued to fast until 4 hours post-dose. On each study day, standardized, caffeine-free meals or snacks were served at approximately 4, 9, 13, and 24 (optional release snack) h after dosing. The use of tobacco was prohibited from one hour prior to and 4 hours post dosing and for 30 minutes prior to any vital sign measurement.
- There was a 28-day interval between treatments.

Treatments:
Test (A): 2 x 0.150/0.030 mg LNG/EE tablets, USP; Batch No. 109921001T; Manufacture date 08/29/01 (Seasonale TBM).
Reference (B): 2 x 0.150/0.030 mg LNG/EE tablets, USP; Batch No. 104371007R; Manufacture date 10/01/01 (Seasonale CT).

Sample Collection:

- Blood samples were collected prior to dosing (within one hour before dosing) 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, 96, 120, and 144 hours post dosing.

PK Results:

Table 10. Pharmacokinetic parameters (arithmetic mean ± SD) of LNG following single oral doses of 2 x 0.15/0.03 mg LNG/EE tablets (Seasonale TBM vs. Seasonale CT).

LNG	**Test (Seasonale TBM)**		**Reference (Seasonale CT)**	
PK Parameters	Mean ± SD (range)	CV %	Mean ± SD (range)	CV %
AUC_{0-t} (ng•hr/mL)	60.83 ± 25.56 (20.28 – 121.09)	42.0	62.63 ± 22.65 (17.86 – 136.39)	36.2
$AUC_{0-\infty}$ (ng•hr/mL)	64.95 ± 25.79 (21.81 – 125.83)	39.7	68.52 ± 21.88 (36.06 – 142.10)	31.9
C_{max} (ng/mL)	5.63 ± 1.45	25.7	5.87 ± 1.56	26.5
T_{max} (hr)	1.36 ± 0.28 (1.00 – 2.00)	20.3	1.37 ± 0.36 (1.00 – 2.50)	26.5
k_{el} (hr^{-1})	0.025 ± 0.008 (0.015 – 0.052)	32.1	0.026 ± 0.009 (0.014 – 0.061)	36.2
$T_{1/2}$ (hr)	29.75 ± 8.27 (13.41 – 46.78)	27.8	29.50 ± 8.49 (11.39 – 48.91)	28.8

Table 11. Pharmacokinetic parameters (arithmetic mean ± SD) of EE following single oral doses of 2 x 0.15/0.03 mg LNG/EE tablets (Seasonale TBM vs. Seasonale CT).

EE	**Test (Seasonale TBM)**		**Reference (Seasonale CT)**	
PK Parameters	Mean ± SD (range)	CV %	Mean ± SD (range)	CV %
AUC_{0-t} (pg•hr/mL)	1306.9 ± 361.1 (722.0 – 2299.2)	27.6	1253.5 ± 348.9 (696.2 – 2301.3)	27.8
$AUC_{0-\infty}$ (pg•hr/mL)	1379.6 ± 319.9 (887.7 – 2403.3)	23.2	1341.0 ± 354.2 (729.2 – 2364.4)	26.4
C_{max} (pg/mL)	144.5 ± 45.4	31.4	132.7 ± 44.9	33.8
T_{max} (hr)	1.64 ± 0.45 (1.00 – 3.00)	27.5	1.51 ± 0.42 (1.00 – 2.50)	28.0

k_{el} (hr^{-1})	0.047 ± 0.011 (0.031 – 0.077)	22.6	0.046 ± 0.013 (0.015 – 0.081)	28.4
$T_{1/2}$ (hr)	15.44 ± 3.18 (9.05 – 22.43)	20.6	16.45 ± 6.71 (8.56 – 46.87)	40.8

Table 12. Comparisons of LNG/EE results (Seasonale TBM vs. Seasonale CT).

	LNG			EE		
	LSM		90 % CI (ratio of LSM)	LSM		90 % CI (ratio of LSM)
	Seasonale TBM	Seasonale CT	Seasonale TBM vs. Seasonale CT	Seasonale TBM	Seasonale CT	Seasonale TBM vs. Seasonale CT
AUC_{0-t}	55.96 ng•hr/mL	58.69 ng•hr/mL	0.90 – 1.01 (0.95)	1262 pg•hr/mL	1209 pg•hr/mL	1.01 – 1.09 (1.04)
$AUC_{0-\infty}$	60.24 ng•hr/mL	63.09 ng•hr/mL	0.90 – 1.01 (0.96)	1336 pg•hr/mL	1297 pg•hr/mL	1.00 – 1.07 (1.03)
C_{max}	5.45 ng/mL	5.67 ng/mL	0.91 – 1.01 (0.96)	138 pg/mL	125 pg/mL	1.03 – 1.18 (1.10)

Comments:
The CI for LNG/EE are within the BE acceptable limits of 0.80 – 1.25.

- A single dose of two LNG/EE 0.15/0.03 mg tablets of the Seasonale TBM formulation and a single dose of two LNG/EE 0.15/0.03 mg tablets of the Seasonale CT formulation are bioequivalent under fasting conditions.

6.2 Cover Sheet and OCPB Filing/Review Form

Office of Clinical Pharmacology and Biopharmaceutics

New Drug Application Filing and Review Form

General Information About the Submission

	Information		Information
NDA Number	21-544	Brand Name	Seasonale
OCPB Division (I, II, III)	DPE II	Generic Name	Levonorgestrel/Ethinyl Estradiol
Medical Division	DRUDP	Drug Class	Oral Contraceptive
OCPB Reviewer	Myong-Jin Kim	Indication(s)	Prevention of Pregnancy
OCPB Team Leader	Ameeta Parekh	Dosage Form	Tablet
		Dosing Regimen	0.150 mg/0.030 mg
Date of Submission	05/AUG/02	Route of Administration	Oral
Estimated Due Date of OCPB Review		Sponsor	Barr Laboratories Inc.
PDUFA Due Date	05/SEP/03	Priority Classification	3S
Division Due Date	29/AUG/03		

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:	X	1		
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:	X			
Bioequivalence studies -				
traditional design; single / multi dose:	X	5	2	
replicate design; single / multi dose:				
Food-drug interaction studies:				
Dissolution:	X	1	1	
(IVIVC):				
Bio-wavier request based on BCS				
BCS class				
III. Other CPB Studies				
Genotype/phenotype studies:				
Chronopharmacokinetics				
Pediatric development plan				
Literature References	X		9	
Total Number of Studies				

Filability and QBR comments		
	"X" if yes	Comments
Application filable ?	X	Reasons if the application is not filable (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		

CC: NDA 21-544, HFD-850 (L.Lesko, S.Huang), HFD-580 (G.Willett, S. Monroe), HFD-870 (A. Parekh, H. Malinowski, J. Hunt), CDR (B. Murphy)

CP&B Briefing attendees on May 14, 2003: Drs. S. Al-Habet, D.J. Chatterjee, J. Hunt, Gerald Willett, and A. Parekh.

Filing Memo

Clinical Pharmacology and Biopharmaceutics Review

NDA: 21-544
Compound: Seasonale Tablets (Levonorgestrel/Ethinyl Estradiol)
Sponsor: Bar Research Inc.

Date: 29/AUG/2002
Reviewer: Myong-Jin Kim

Background:

This NDA includes the data from a single Phase III clinical trial, SEA-301, two pivotal BA/BE studies and three supportive BA/BE studies performed with the Seasonale® product. The sponsor made a reference to their ANDA 75-866 product (Portia; approved May 23, 02), bioequivalent to Nordette (LNG/EE tablets, USP 0.150 mg/0.030 mg). Seasonale® is proposed to be marketed as 84 pink active tablets and 7 white placebo tablets where the pink tablets are identical to Barr's generic tablets, Portia. However, Seasonale® clinical study, SEA-301, was dosed with [redacted] active tablets. The only difference in formulations between the proposed commercial pink tablet and the clinical [redacted] tablet is proposed to be the [redacted], pink versus [redacted]

The sponsor intends to market the same pink tablet for its generic Nordette product (Portia) as well as for the Seasonale® NDA, and to cross reference a large part of the ANDA in the Seasonale NDA, specifically sections within Biopharmaceutics.

Pharmacokinetic Studies

-Conducted in healthy, non-pregnant, female subjects
-Randomized, crossover design under fasting conditions
-Single-dose studies

a. Pivotal BA/BE Studies

- **Study 99028:** A BA/BE Study--to compare Barr's generic pink tablets (Portia) to that of Nordette (refer to ANDA 75-866).
- **Study 10216206:** A Bridging BE Study--to compare the SEA-301 clinical trial [redacted] tablets to that of the proposed commercial pink tablets.

b. Supportive BA/BE Studies

Sponsor stated that Studies 10216205 and 10116208 are submitted for completeness only since they were conducted to compare the BA of Seasonale with experimental formulations that were not pursued further for this NDA.

- **Study 99027:** A BE study of Barr and Berlex Labs Levlite LNG/EE 0.10 mg-0.02 mg tablets administered as 3 X 0.10 mg-0.02 mg tablets
- **Study 10216205:** A relative BA study of two 0.150/0.030 mg LNG/EE tablets

- **Study 10116208:** A relative BA study of two 0.150/0.030 mg LNG/EE tablets

Clinical Study – SEA 301 (Phase III Study)

- A four-arm, parallel, randomized, multi-center, open label study to evaluate two dose levels (LNG/EE, 0.150/0.030 and 0.10/0.02) of extended (84 days active + 7 days inactive) OC therapy for 12 consecutive months (4 cycles) and two dose levels (LNG/EE, 0.150/0.030, Nordette, and 0.10/0.02, Levlite) of conventional (21 days active + 7 days inactive) OC for 12 months (13 cycles)

The sponsor provided the following:

1. Human Pharmacokinetics and Bioavailability section summary, full study report, and proposed labeling
2. Drug formulation
3. Bioanalytical methods
4. In-vitro dissolution data
5. A list of references
6. Sponsor states that to-be-marketed Seasonale formulation is bioequivalent to the clinical trial Seasonale formulation (Study SEA-301)

Recommendation:

The Office of Clinical Pharmacology and Biopharmaceutics/Division of Pharmaceutical Evaluation II find that the Human Pharmacokinetics and Bioavailability section for NDA 21-544 is fileable.

/S/

Myong-Jin Kim, Pharm.D. Date

/S/

Ameeta Parekh, Ph.D., Team Leader Date

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

/s/

Myong-Jin Kim
9/3/03 04:30:18 PM
PHARMACOLOGIST

Venkateswar Jarugula
9/3/03 04:42:47 PM
BIOPHARMACEUTICS