CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 21-098

MEDICAL REVIEW(S)

Medical Officer's Review of NDA 21-098
(Complete Response to Approvable Letter and Supplemental Clinical Information)

NDA:	21-098
Sponsor:	Berlex Laboratories, Inc.
Type of submission:	Complete response to Approvable Letter of July 10, 2000 and supplemental clinical information
Drug (generic name):	Drospirenone (DRSP) and ethinyl estradiol (EE)
Proposed trade name:	Yasmin
Proposed indication:	Prevention of pregnancy
Dosing regimen:	3 mg drospirenone (DRSP) and 30 µg ethinyl estradiol (EE) by once daily oral tablet for 21 days followed by a 7-day drug-free interval
Date(s) of this submission:	Primary submission: November 6, 2000 Requested supplemental data and analyses: January 5, 2001; February 12, 2001; March 9, 2001; March 12, 2001; March 16, 2001; March 28, 2001, and April 9, 2001
Date review completed:	April 13, 2001
Reviewer:	Scott E. Monroe, MD Medical Officer, DRUDP

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BACKGROUND

Regulatory History

NDA 21-098 was submitted on May 14, 1999. On March 17, 2000 Berlex Laboratories was sent an Approvable Letter. The Letter stated that Berlex would need to provide the following additional information:

1. Provide final study results of the effects of Yasmin in renally-impaired patients.
2. Provide additional information relating to the effects of Yasmin on serum potassium levels in women receiving drugs such as ACE inhibitors that are known to reduce renal tubular secretion of potassium.

This information was requested because drospirenone (DRSP, the progestogen in Yasmin) is a new molecular entity that has anti-mineralocorticoid activity (similar to that of spironolactone); consequently, drospirenone has the potential to increase serum potassium levels, particularly in women with impaired renal function or in women receiving treatment with other medications that have been shown to increase serum potassium levels.

In response to the Approvable Letter, Berlex submitted the following additional information in May 2000:

1. An analysis of serum potassium data from Study No. 98106, a Phase II study designed to assess the potential for developing hyperkalemia in postmenopausal women who were co-administered the combination drug product containing drospirenone 3 mg/estradiol 1 mg for 14 days and the ACE inhibitor enalapril (Amended Study Report, Date: May 5, 2000).
2. Clinical data from Study No. 303063, a Phase II study designed to assess the effects of administration of 3 mg of drospirenone for 14 days on serum potassium concentrations in female volunteers with impaired or normal renal function (Study Report No. B682, May 5, 2000).

On July 10, 2000, Berlex was issued a second Approvable Letter for NDA 21-098. The Approvable Letter included the following requests:

1. "Additional clinical studies must be performed to assess the risk of hyperkalemia in women using Yasmin 28 Tablets."
2. Provide further information regarding the following Phase IV commitments:
   a) An educational outreach program for health care providers and patients focusing upon the contraindications of using Yasmin in patients with renal and hepatic impairment and in patients predisposed to hyperkalemia;
   b) A surveillance program to evaluate inappropriate prescribing of Yasmin;
   c) Use of a database to evaluate all patients prescribed Yasmin for adverse outcomes that might be a consequence of hyperkalemia; and
   d) Monitor pregnancy outcomes from women exposed to Yasmin for signals of developmental toxicity.

On September 25, 2000, Berlex met with the Division of Reproductive and Urologic Drug Products (DRUDP) to present and discuss their planned complete response to the Approvable Letter of July 10, 2000. At the meeting, Berlex reviewed previously submitted data from relevant clinical studies, presented new data from 2 clinical studies not previously submitted to the DRUDP, and provided further information about their proposal to satisfy the requested Phase IV commitments.

The 2 new clinical studies were:

1. Protocol 97036D: a study comparing treatment with Yasmin to that of placebo in women suffering from premenstrual syndrome (PMS) or premenstrual dysphoric disorder (PMDD) and
2. Protocol 96097A: a study comparing the effects of administration of 17B-estradiol (E2) plus 1 of 4 doses of DRSP to those of E2 alone on hot flashes and the endometrium in post menopausal women.

Based on the information provided in the premeeting briefing document (dated September 11, 2000) and the information presented at the meeting, Berlex was informed that safety reports for the 2 additional studies, along with the other requested information, could be submitted as a complete response to the July 10 Approvable Letter (see September 25, 2000 Meeting Minutes for further details).

Documents Considered in the Present Review

1. Briefing Package (dated September 11, 2000) for the September 25, 2000 Meeting (Vol. A35-1 of NDA 21-098).
2. November 6, 2000 Complete Response containing the following:
   a) Safety Report for Protocol 97036D: "A Multicenter, Double-Blind, Randomized, Placebo-Controlled, Parallel-Group Study to Evaluate the Efficacy of a Monophasic Oral Contraceptive Preparation, Containing Drospirenone 3 mg and Ethinyl Estradiol 30 μg, in the Treatment of Premenstrual Syndrome (PMS) and Premenstrual Dysphoric Disorder (PMDD);"
   b) Safety Report for Protocol 96097A: "A Multicenter, Double-Blind, Randomized Comparison of Continuous Oral Estradiol-Drospirenone Combinations and Continuous Oral Estradiol Examining the Effect on the Endometrium, Symptoms, and Bleeding Patterns in Postmenopausal Women;"
   c) A description of the proposed activities to fulfill the requested Phase IV commitments;
   d) Revised Labeling for Yasmin; and
   e) A Safety Update including approved European Union labeling for Yasmin.
3. Additional statistical analyses and information submitted at the request of the medical reviewer and or statistician on January 5, 2001, February 12, 2001, March 9, 2001, March 12, 2001, March 16, 2001, March 27, 2001, and April 9, 2001.
4. Primary Medical Review (dated 15 Feb 2000) of original NDA 21-098.
5. Medical Review (dated 6 June 2000) of Supplemental Clinical Data.
6. Memorandum from Dr. Throckmorton, Oct 10, 2000.
7. Schering Study Reports 9370 and 9371 (Phase I clinical studies of the tolerability and pharmacology of DRSP).
8. Four-Month Safety Update submitted on March 27, 2001.

Medical review of the above clinical studies and clinical data focused on the effects of treatment with DRSP on serum potassium concentrations and cardiovascular adverse events that might be a consequence of hyperkalemia. Efficacy issues were not reviewed.

CLINICAL PROTOCOL NO. 97036D

Study Title

"A Multicenter, Double-Blind, Randomized, Placebo-Controlled, Parallel-Group Study to Evaluate the Efficacy of a Monophasic Oral Contraceptive Preparation, Containing Drospirenone 3 mg and Ethinyl Estradiol 30 µg, in the Treatment of Premenstrual Syndrome (PMS) and Premenstrual Dysphoric Disorder (PMDD)"

Study Objectives

The objectives of this study were to evaluate the efficacy and safety of cyclic administration of 3 mg of DRSP and 30 µg of ethinyl estradiol (EE) in the treatment of premenstrual syndrome (PMS) and premenstrual dysphoric disorder (PMDD).

Study Design

This was a multicenter, double-blind, randomized, placebo-controlled, parallel-group study. Subjects who qualified for the study were randomly assigned in a 1:1 ratio to either DRSP/EE treatment or placebo.

Study Population

Inclusion Criteria Included

1. Women with PMS/PMDD according to the University of California at San Diego diagnostic criteria.
2. Women, 18 to 40 years of age, who were otherwise healthy.
3. Women who had not used an oral contraceptive for at least 3 months prior to enrollment in the qualification phase.
4. Women with regular menstrual cycles for the 3-month period preceding enrollment into the qualification phase. Menstrual cycle length must have been between 25 and 34 days.

Exclusion Criteria Included

1. Any formal counseling relationship and/or use of medication for PMS including, but not limited to, hormones, bromocriptine, gonadotropin-releasing hormone agonists, vitamin B6 (> 100 mg), anxiolytics, and antidepressants during the 3-month period prior to enrollment in the qualification phase.
2. Medical status or medical history that included conditions that were generally accepted as contraindications for the use of hormonal contraceptives.
3. Smoking of more than 10 cigarettes/day.
4. Over 30 years of age and a current smoker.
5. A systolic blood pressure of > 140 mm Hg or a diastolic blood pressure of > 90 mm Hg (in the sitting position) or currently receiving any treatment for hypertension.
6. Evidence of malignancy or active heart, lung, kidney, liver, endocrinologic, neurologic, psychiatric, gastrointestinal, or immunologic disease.
7. An abnormal baseline laboratory value that was considered clinically significant and suggested specific organ dysfunction.
8. Diabetes mellitus or known to have had an abnormal glucose tolerance test during pregnancy.
9. Received or was receiving Accutane® (isotretinoin) tablets within 30 days or was currently receiving phenobarbital, phenytoin, or rifampin.

Treatments

Active treatment consisted of tablets containing DRSP 3 mg/EE 30 µg (equivalent to Yasmin). Subjects in the active treatment group took a daily tablet of DRSP/EE for 21 consecutive days followed by a daily inactive tablet for 7 days (a 28-day treatment cycle). Subjects assigned to placebo took identical appearing tablets that were also dispensed in packets containing 28 tablets.

Study Conduct and Clinical Study Procedures

Overview of Study

The study was composed of 3 phases: screening, qualification, and treatment.

Screening phase. Women initially were screened for PMS/PMDD according to the University of California at San Diego (UCSD) diagnostic criteria. Those women who also met the inclusion criteria, which was established by questioning, entered the qualification phase after giving informed consent.

Qualification phase. The qualification phase included 2 observational cycles of prospective recording of PMS/PMDD symptoms. Subjects kept a daily record of PMS/PMDD symptoms. Only those who still met (1) the UCSD diagnostic criteria for PMS/PMDD and (2) the criteria for PMS/PMDD based on the daily Calendar of Premenstrual Experiences (COPE) scores after completion of the 2 run-in cycles, entered the Treatment Phase.

Treatment phase. Subjects who qualified for treatment were randomly assigned to 3 months of treatment (three 28-day treatment cycles) with either DRSP/EE or matching placebo. Upon completion of the initial 3-month treatment period, subjects were asked to continue their blinded treatment for an additional 3 months (Extended Treatment Phase).

Safety Assessments

Safety assessments included a medical history and physical examination prior to the onset of treatment (at Study Visit 3), and on-treatment or post treatment physical examinations at Study Visit 9 (3-9 days after completion of Treatment Cycle 3, all subjects) and at Study Visit 12 (3-9 days after completion of Treatment Cycle 6, only those subjects who entered the Extended Treatment Phase). Blood specimens for the measurement of serum chemistries and complete blood count (CBC) were to be obtained prior to treatment and at Study Visits 9 and 12. Subjects were to be questioned about the occurrence of adverse events and the use of concomitant medications at each clinical visit beginning with Study Visit 6 (Day 1-4 of Treatment Cycle 1).

Laboratory Measurements

Blood specimens for measurement of serum chemistries and CBCs were analyzed at a central laboratory [redacted]. According to the final study report,

> "The presence of hemolysis was determined visually by the laboratory assistant or technologist as the serum samples were being organized into loads. Slightly hemolyzed specimens were analyzed, and the results were reviewed by the technologist. Changes of greater than approximately 20% from the previous results were indicative of hemolysis interference. If no previous result was available, rejection due to hemolysis was at the discretion of the reviewing technologist. Severely hemolyzed specimens were not analyzed.
>
> In addition, potassium values between 6.0 and 7.3 mEq/L were suspicious for extended cellular contact, except when these values correlated with previous results. Microscopic demonstration of greater than 10 red blood cells per high-power field (RBCs/HPF) was indicative of prolonged cellular contact. In this case, the values for potassium, LDH, glucose, and phosphorous were rejected."

Medical Officer's Comments

- The procedures that were followed in this Study and Study 96097A to exclude the reporting of elevated serum potassium values that may have been a result of hemolysis or "extended cellular contact" (reported by Berlex to be standard laboratory procedures for the Central Laboratory) also may exclude elevated potassium values that are a result of true clinical hyperkalemia; consequently, these screening procedures have the potential to adversely affect the validity of the clinical trial.
- The sponsor was asked to provide a listing of all samples that were collected for serum chemistry determinations and for which a serum potassium value was not reported. The sponsor reported in the communication of January 5, 2001 that there were 19 instances in which a chemistry blood sample was obtained but no potassium value was reported. In 16 of the 19 instances, a potassium value was not reported because an electrolyte group was not ordered (n=10) or insufficient or no specimen was received by the Central Laboratory (n=6). Among the remaining 3 specimens, a potassium value was not reported for 1 specimen (DRSP/EE group) because it was received beyond the stability date and for 2 specimens because of hemolysis (one specimen from each of the treatment groups).

Disposition and Demographics of Subjects

Disposition of Subjects

A total of 259 women (129 DRSP/EE group; 130 placebo group) at 23 centers received one or more doses of Study Drug and were evaluable for safety. Subject disposition is shown in Table 1.

Table 1. Disposition of Subjects

Disposition	Number (%) of Subjects	
	DRSP/EE	Placebo
Treated (Evaluated for Safety)	129 (100)	130 (100)
Completed 3 Cycles of Treatment	83 (64.3)	98 (75.4)
Completed 6 Cycles of Treatment	39 (30.2)	52 (40.0)
Reason for Discontinuation of Study drug		
Adverse Event	30 (23.3)	12 (9.2)
Lack of Efficacy	1 (0.8)	2 (1.6)
Protocol Deviation	1 (0.8)	3 (2.3)
Withdrawal of Consent	8 (6.2)	10 (7.7)
Other	9 (7.0)	13 (10.0)
Total Discontinued	49 (38.0)	40 (30.8)

Modified from Text Table 2, pg 43, Vol. 1, Nov. 6, 2000 submission.

The percentage of subjects who completed 3 and 6 treatment cycles was higher in the placebo group. Conversely, the percentage of subjects who discontinued treatment because of an adverse event was higher in the DRSP/EE group (23.3%) than in the placebo group (9.2%).

Demographic and Other Baseline Characteristics

The majority of subjects were Caucasian (85%) and ranged in age from 19 to 41 years of age (mean age: 32.5 years) and in weight at baseline from 43.2 to 148.2 kg (mean weight: 69.6 kg). There were no statistically significant differences between treatment groups in demographic variables. Table 2 presents summary demographic data.

Table 2. Summary Statistics for Demographic Data

Variable		DRSP/EE	Placebo
Race			
	Caucasian	110 (85.3%)	110 (84.6%)
	Black	10 (7.8%)	13 (10.0%)
	Hispanic	5 (3.9%)	3 (2.3%)
	Asian	1 (0.8%)	1 (0.8%)
	Other	3 (2.3%)	3 (2.3%)
Age (years)			
	Mean ± Standard Deviation	32.6 ± 5.1	32.5 ± 5.4
	Median	33.0	33.0
	Range	20.0 – 41.0	19.0 - 40.0
Baseline weight (kg)			
	Mean ± Standard Deviation	68.0 ± 14.2	71.2 ± 20.3
	Median	65.9	65.7
	Range	45.9 – 129.3	43.2 - 148.2

Modified from Text Table 3, pg 44, Vol. 1, Nov. 6, 2000 submission.

Concomitant Medication with Potential to Affect Potassium Excretion

The sponsor stated that a total of 120 subjects, 62 (48.1%) DRSP/EE subjects and 58 (44.6%) placebo subjects) were taking nonsteroidal anti-inflammatory drugs (NSAIDs) excluding aspirin products at some time during the clinical trial. No subjects were taking an ACE inhibitor.

Serum Potassium Concentrations and Changes from Baseline Values

One hundred fifteen (115) subjects in each of the treatment groups had a baseline and one or more post baseline serum potassium measurements, either on-treatment or post treatment. Serum potassium concentrations ranged from . ——— ,mEq/L in the placebo group and from ———— ——— Eq/L in the DRSP/EE group (normal range: 3.4 to 5.4 mEq/L). Mean (±SD) changes from baseline for serum potassium concentrations (expressed in terms of both the average and the maximum post baseline change) are summarized in Table 3. The mean changes from baseline in the DRSP/EE treatment group were no greater than those in the placebo group.

Table 3. Mean Changes from Baseline in Serum Potassium Concentrations (mEq/L) (Subjects with Both Baseline and Post Baseline Data)

Treatment Group	Number of Subjects	Baseline Mean ± SD	Change From Baseline in	
			Post Baseline Average Value Mean ± SD	Post Baseline Maximum Value Mean ± SD
Placebo	115	4.15 ± 0.34	0.02 ± 0.38	0.11 ± 0.41
DRSP/EE	115	4.18 ± 0.36	0.00 ± 0.39	0.05 ± 0.40

Modified from Text Table 15, pg 55, Vol. 1, Nov. 6, 2000 submission.

Two subjects (one in each group) had a post baseline serum potassium ≥ 5.5 mEq/L (see Table 4). (Hyperkalemia, in this review, is defined as a serum potassium concentration ≥ 5.5 mEq/L in accordance with the Sponsor's definition). Both subjects were reported to have used NSAIDs at some time during the clinical trial. One subject in the DRSP group had a serum potassium value (3.3 mEq/L) that was below the lower limit of the normal range.

Table 4. Subjects with Serum Potassium Levels ≥ 5.5 mEq/L

Subject Number	Treatment Group	Serum Potassium, mEq/L	
		Baseline	Post Baseline Maximum
3607117	DRSP 3 mg/ EE 30 µg	4.5	5.5
3615019	Placebo	4.0	5.5

The Sponsor also reported on the potential effects of concomitant use of NSAIDs on serum potassium concentrations. Table 5 summarizes the maximum potassium changes from baseline in both the DRSP/EE and placebo groups for all subjects, subjects who used NSAIDs, and subjects who did not use NSAIDs. The use of NSAIDs did not appear to have any effect on the maximum observed post baseline changes in serum potassium concentrations.

Table 5. Maximum Potassium Changes from Baseline (Percent of Subjects in Each Interval)

Treatment	Change from Baseline (mEq/L)	On-Treatment or Post Treatment Period		
		All subjects	No Use of NSAIDs	Used NSAIDs
DRSP/EE		N=115	N=55	N=60
	≤-1.0	1%	0%	2%
	-1.0 to ≤-0.1	43%	40%	45%
	-0.1 to ≤ 0.1	20%	26%	15%
	0.1 to ≤ 1.0	37%	35%	38%
	> 1.0	0%	0%	0%
Placebo		N=115	N=58	N=57
	≤-1.0	1%	2%	0%
	-1.0 to ≤-0.1	28%	24%	32%
	-0.1 to ≤ 0.1	23%	26%	19%
	0.1 to ≤ 1.0	48%	48%	47%
	> 1.0	1%	0%	2%

Based on data in revised Text Table 16, March 16, 2001 submission.

Medical Officer's Comments

- There were no findings in this clinical trial that indicated cyclic treatment with a combination drug product containing 3 mg DRSP and 30 µg EE (Yasmin) increased serum potassium concentrations in healthy, reproductive-aged women. The mean (±SD) change in serum potassium from baseline, based on the post baseline maximum potassium value, was numerically lower in subjects treated with DRSP/EE (0.05 mEq/L [±0.40]) than in subjects treated with placebo (0.11 mEq/L [±0.41]). Serum potassium levels ≥ 5.5 mEq/L (defined as hyperkalemia) occurred in 1 subject in each treatment group. Both of these subjects had post baseline maximum potassium values of 5.5 mEq/L.
- These findings must be interpreted with some caution, however, because of (1) the relatively small number of women treated with DRSP/EE and (2) problems with study design. Since this study was not specifically designed to assess the effects of treatment with DRSP/EE on serum potassium, only 1 or 2 post baseline potassium measurements were obtained from each subject. In addition, many of the post baseline blood samples for potassium measurements were obtained when a subject was not actually receiving DRSP/EE. These off-treatment samples were obtained either during the final 7 days of a 28-day treatment cycle (the days on which subjects were not receiving active Study Drug) or several days after the last dose of active Study Drug at the final study visit.
- The number of subjects in the DRSP/EE group who had measurements of serum potassium while receiving active Study Drug was not provided by the Sponsor in the original Safety Report;

consequently, the Sponsor was asked to provide information regarding the time between the day on which serum potassium was measured and the subject's last dose of DRSP/EE. Based on this information, the medical reviewer determined that a total of 56 serum potassium measurements from 48 of the 129 DRSP/EE subjects were obtained from subjects who had (1) taken at least one dose of DRSP/EE ≥ 24 hours prior to the potassium measurement and (2) had taken their last dose of DRSP/EE no more than 72 hours prior to the potassium measurement.

- There did not appear to be an effect of use of NSAIDs on serum potassium concentrations (Table 5). The significance of this observation, however, is uncertain as NSAID use (frequency and dosage) varied among subjects, and serum potassium concentrations may, or may not have been measured while a subject was actually using an NSAID. In addition, the sponsor appeared to have applied different definitions for NSAID use, apparently including the use of aspirin-containing products and OTC use in some analyses and not including their use in other analyses.

Selected Cardiovascular Adverse Events

The Sponsor, with the assistance of academic consultants, identified 6 cardiovascular adverse events (AEs) that could potentially be associated with hyperkalemia. These adverse events were arrhythmia, bradycardia, tachycardia, dizziness, palpitations, and syncope. Three (2.3%) subjects in the DRSP/EE group and 5 (3.9%) subjects in the placebo group experienced one or more of these cardiovascular AEs. The reported incidence of these specified cardiovascular adverse events is listed in Table 6. Two subjects in the DRSP/EE group with palpitations and 1 subject in the placebo group with dizziness were terminated prematurely because of these adverse events.

Table 6. Incidence of Selected Cardiovascular Adverse Events

		Selected Cardiovascular Adverse Event					
		Arrhythmia	Bradycardia	Dizziness	Palpitation	Syncope	Tachycardia
Treatment Group	N	N (%)	n (%)	n (%)	n (%)	n (%)	n (%)
DRSP/EE *	129	0 (0)	0 (0)	0 (0)	3 (2.3)	0 (0)	1 (0.8)
Placebo	130	0 (0)**	0 (0)	3 (2.3)	2 (1.5)	0 (0)	0 (0)

N = number of subjects randomized and treated; n = number of subjects with event.
* One subject in the DRSP/EE group experienced both palpitations and tachycardia.
** One subject in the placebo group was reported to have developed an arrhythmia with an onset date > 60 days after completion of treatment.
Modified (see ** above) from Table 13, pg 112, Vol. 1, Nov. 6, 2000 submission.

Medical Officer's Comments

- The number of subjects experiencing these selected cardiovascular adverse events (events considered by the sponsor as potentially caused by hyperkalemia) was numerically lower in the DRSP/EE group (n=3) than in the placebo group (n=5). None of these subjects was reported to have had a serum potassium value ≥ 5.5 mEq/L. Although these adverse events may be associated with hyperkalemia, they are more likely to be a result of other factors. Therefore, the incidence of these cardiovascular adverse events is of limited value in identifying subjects with hyperkalemia.

Adverse Events

All Adverse Events. A total of 101 (78.3%) DRSP/EE- and 96 (73.8%) placebo-treated subjects reported at least 1 adverse event. The incidence of adverse events was comparable between DRSP/EE- and placebo-treated subjects for most body systems. The exceptions were nervous system, digestive system, skin, and cardiovascular system due primarily to an increased incidence of headaches, nausea, breast pain, and migraine headaches, respectively, in the DRSP/EE-treated subjects (see Table 7).

Table 7. Body Systems Most Frequently Affected by Adverse Events and Adverse Events Reported More Frequently in DRSP/EE Subjects

Body System (Preferred Term)	DRSP/EE N=129 n (%)	Placebo N=130 n (%)
Any Event	101 (78.3)	96 (73.8)
Body as a Whole	32 (24.8)	33 (25.4)
Cardiovascular	10 (7.8)	5 (3.8)
(Migraine)	6 (4.7)	0 (0.0)
Digestive	34 (26.4)	25 (19.2)
(Nausea)	25 (19.4)	12 (9.2)
Nervous	42 (32.6)	28 (21.5)
(Headache)	30 (23.3)	17 (13.1)
Respiratory	33 (25.6)	36 (27.7)
Skin	22 (17.1)	8 (6.2)
(Breast pain)	15 (11.6)	1 (0.8)
Urogenital	26 (20.2)	28 (21.5)

N = number of subjects randomized and treated; n = number of subjects with event.
From Table 13, pg 112, Vol. 1, Nov. 6, 2000 submission.

Treatment-related adverse events. A total of 72 (55.7%) DRSP/EE- and 49 (37.7%) placebo-treated subjects experienced adverse events reported as related to Study Drug (events classified as possibly, probably, or definitely related to Study Drug).

Intensity of adverse events. Thirty-seven (37, 28.7%) DRSP/EE- and 19 (14.6%) placebo-treated subjects reported adverse events that were considered "severe" in intensity. Adverse events most often classified as severe in the DRSP/EE-treated subjects were headache (7.8% of DRSP/EE subjects; 3.1% of placebo subjects), nausea (6.2% of DRSP/EE subjects; 0.8% of placebo subjects), and breast pain (4.7% of DRSP/EE subjects; 0% of placebo subjects).

Serious adverse events and deaths. No deaths occurred during the study. Five subjects (3 DRSP/EE-treated subjects and 2 placebo-treated subjects) experienced 1 or more serious adverse events (SAEs). In the opinion of the investigators, the SAEs experienced by the 3 DRSP-treated subjects had no relationship to Study Drug. The SAEs reported for the DRSP/EE subjects were tuberculosis, recurrent facial paralysis, and basal cell carcinoma, each in one subject.

Premature terminations due to adverse events. A total of 30 (23.3%) DRSP/EE-treated subjects and 12 (9.2%) placebo-treated subjects were withdrawn from the Study due to an adverse event. Adverse events resulting in discontinuation of Study Drug and occurring with an incidence of > 2% in the DRSP/EE-treated subjects included nausea (4.7%), headache (3.1%), breast pain (3.1%), menstrual disorder (3.1%), depression (2.3%), and hostility (2.3%). Adverse events resulting in discontinuation of Study Drug in the placebo group and occurring with an incidence of > 2% included nausea (2.3%) and amenorrhea (2.3%).

Clinical Laboratory Assessments

Blood Chemistries

Changes in blood chemistry values from the normal range at baseline to values above or below the limits of the normal range at the final Study Visit were not frequent and, in general, were not significantly different between the DRSP/EE and placebo treatment groups.

Hematology Parameters

Changes in hematology values from the normal range at baseline to values above or below the limits of the normal range at the final Study Visit were not frequent and, in general, were not significantly different between the 2 treatment groups.

Medical Officer's Comments

- The percentage of subjects reporting one or more adverse event was numerically higher in the DRSP/EE group (78.3%) than in the placebo group (73.8%). Adverse events that occurred with a higher frequency in the DRSP/EE group included headache, nausea, and breast pain/tenderness – adverse events frequently associated with the use of oral contraceptives. The percentage of subjects withdrawn from the Study due to an adverse event also was higher in DRSP/EE-treated subjects (23.3%) than in placebo-treated subjects (9.2%). This difference was due in large part to the occurrence of those adverse events listed above that are commonly associated with the use of oral contraceptives. Changes in serum chemistry values and hematology values were either comparable between the 2 groups or those expected in women using oral contraceptives. In summary, there were no new general safety findings that would impact on the overall safety assessment of Yasmin.

CLINICAL PROTOCOL NO. 96097A

Study Title

"A Multicenter, Double-Blind, Randomized Comparison of Continuous Oral Estradiol-Drospirenone Combinations and Continuous Oral Estradiol, Examining the Effect on the Endometrium, Symptoms, and Bleeding Patterns in Postmenopausal Women."

Study Objectives

The primary objective of this study was to evaluate the safety, by analysis of protection against hyperplasia in postmenopausal women, of thirteen 28-day treatment cycles of 4 different combinations of DRSP/17B-estradiol (E2) administered daily compared with daily E2 alone. Secondary objectives included evaluation of the effects of each of the combinations of DRSP/E2 compared to E2 alone on: (1) endometrial morphology and bleeding patterns, (2) metabolic and hemostatic laboratory parameters, (3) the frequency and severity of hot flushes, and (4) relief of urogenital symptoms.

Study Design and Treatment

The study was conducted in accordance with a multicenter, double-blind, randomized, parallel group design. Postmenopausal women, with or without menopausal symptoms, who satisfied the inclusion/exclusion criteria were randomly assigned to 1 of 5 treatment groups (4 regimens of daily DRSP/E2 and 1 regimen of daily E2 alone) and were treated for up to 1 year.

Study Population

Inclusion Criteria (Partial listing)

A postmenopausal woman was potentially eligible for enrollment if she met the following criteria:

1. Age ≥ 45 and ≤ 75 years.
2. Intact uterus and diagnostically valid negative endometrial biopsy or, if inadequate tissue, endometrial thickness < 5 mm on vaginal ultrasound.
3. Amenorrhea for ≥ 12 months or, if amenorrhea < 12 month duration but ≥ 6 months, serum estradiol levels must be < 20 pg/mL and serum follicle stimulating hormone (FSH) level must be > 50 units/L.

Exclusion Criteria (Partial listing)

A postmenopausal woman was not eligible for enrollment if any of the following were identified:

1. Baseline endometrial biopsy containing endometrial polyp alone or simple hyperplasia or worse.
2. Abnormal Pap smear suggestive of low grade squamous intraepithelial lesion (LGSIL) or worse.
3. Baseline ultrasound with abnormality that would preclude estrogen therapy.
4. Abnormal, clinically significant findings during gynecological examination that might in the opinion of the Investigator worsen under hormone treatment.
5. Severe systemic disease that might interfere with the conduct of the study or the interpretation of the results.
6. Any disease or condition that compromised the function of the body systems and could result in altered absorption, excessive accumulation, impaired metabolism, or altered excretion of the study medication.
7. Idiopathic thrombophlebitis or thromboembolic disorders within the last 3 years that were unrelated to estrogen therapy or a history of these conditions at any time with previous estrogen therapy.
8. Hypertension: sitting systolic blood pressure ≥ 160 mm Hg or sitting diastolic blood pressure ≥ 95 mm Hg at rest.
9. Known or suspected malignant or premalignant disease, including malignant melanoma (excluding other successfully treated skin cancers).
10. History of sex steroid-dependent malignancy.
11. Insulin-dependent diabetes mellitus.
12. Current significant liver dysfunction or disease.
13. Abnormal baseline laboratory values that were considered to be clinically significant.
14. Fasting baseline cholesterol ≥ 300 mg/dL, triglycerides ≥ 300 mg/dL, or glucose ≥ 140 mg/dL.

Treatments

Five oral treatment regimens, one consisting of E2 alone and four consisting of E2 plus different doses of DRSP, were studied (see Table 8). Tablets containing Study Drugs were similar in appearance to preserve blinding and were supplied by the Sponsor in investigational blister packages suitable for double-blind administration. Each blister pack contained 28 tablets. Subjects were to take one tablet daily for thirteen 28-day treatment cycles (364 days).

Table 8. Study Treatments

Group	E2 (mg)*	DRSP (mg)
1	1.0	–
2	1.0	0.5
3	1.0	1.0
4	1.0	2.0
5	1.0	3.0

* 17B-Estradiol

Study Conduct and Study Procedures

Overview of Study

Postmenopausal women were evaluated at the screening visit (Visit 1) to determine if they satisfied the inclusion/exclusion criteria. Screening procedures included medical history, physical and gynecologic examinations, mammography, vaginal ultrasonography, endometrial biopsy, serum chemistries and CBC. At the baseline visit (Visit 2), which occurred within 4 weeks after screening, subjects were randomized to their treatment assignment and provided with blinded Study Drug. The one year treatment period was divided into thirteen 28-day treatment cycles. Subsequent clinic visits were scheduled at the end of Cycle 1 (Visit 3), Cycle 3 (Visit 4), Cycle 7 (Visit 5), Cycle 10 (Visit 6), and Cycle 13 (Visit 7, end of treatment). Subjects were instructed to remain on their usual diets. Throughout the study, subjects were to record on diary cards the number and severity of daily hot flushes and weekly urogenital symptoms. Subjects were permitted to take, with a few exceptions, any concomitant medications as medically warranted.

Safety Assessments

Safety assessments included the following procedures both at screening (Visit 1) and at the end of treatment (generally end of Cycle 13): (1) medical history (screening visit only); (2) physical examination (also performed at the end of Cycle 7); (3) mammography; (4) endometrial biopsy; and (5) transvaginal ultrasonography (also performed at the end of Cycle 7). Blood specimens for the measurement of serum chemistries, lipids and hematology parameters were obtained at screening (Visit 1), at the end of Cycle 7 (Visit 5), and at the end of Cycle 13 (Visit 7). At each clinical visit, the subject's blood pressure was recorded, and she was questioned about the occurrence of adverse events and the use of concomitant medications.

Laboratory Measurements

Blood specimens for serum chemistries, CBC, and differential were analyzed at a central laboratory [redacted]. Similar screening procedures, as described for Study No. 97036D, were employed by the central laboratory to avoid the reporting of serum potassium values from blood samples that demonstrated signs of hemolysis or that were suspicious for "extended cellular contact."

Medical Officer's Comments

- The procedures that were followed in this Study to exclude the reporting of elevated serum potassium values resulting from improper sample processing may also exclude elevated potassium values that are a result of true clinical hyperkalemia; consequently, the laboratory screening/exclusion procedures have the potential to adversely affect the validity of the observations concerning changes in serum potassium levels in subjects treated with DRSP.
- The Sponsor was asked to provide a listing of all samples that were collected for serum chemistry determinations and for which a serum potassium value was not reported. The Sponsor reported in the communication of March 12, 2001, 52 instances in which a chemistry blood sample was obtained without a reported potassium value. In 11 of the instances, a potassium values was not reported because the test was not ordered (n=2), insufficient or no specimen was received by the Central Laboratory (n=8), or an incorrect specimen type was collected (n=1). Among the remaining 41 specimens, a potassium value was not reported for 8 specimens (1 from each of 8 subjects) because the specimens were received beyond the stability date and for 33 specimens (1 from each of 33 subjects) because of hemolysis. Table 9 summarizes by treatment group the number of samples for which a potassium value was not reported because of hemolysis or "prolonged cell contact."

Table 9. Number of Blood Specimens not Analyzed for Potassium Because of Hemolysis or Prolonged Cell Contact

Treatment Group	Total	Hemolyzed	Prolonged cell contact
E2 1 mg	8	8	0
E2 1 mg/DRSP 0.5 mg	12	7	5
E2 1 mg/DRSP 1.0 mg	8	7	1
E2 1 mg/DRSP 2.0 mg	4	3	1
E2 1 mg/DRSP 3.0 mg	9	8	1

Data from March 12, 2001 communication.

- Not reporting potassium values for these samples would have little, if any effect on the analyses of mean potassium values and the analyses of mean changes from baseline, but could mask individual instances of hyperkalemia. None of the subjects (with one exception) with blood samples that were not analyzed for potassium because of hemolysis or prolonged cell contact reported any the cardiovascular adverse events considered to be potentially related to hyperkalemia.

Disposition and Demographics of Subjects

Disposition

A total of 1142 subjects at 53 clinical centers received at least 1 dose of Study Drug and were evaluable for safety. Of these subjects, 297 (26%) prematurely withdrew form the Study. The number and percentage of these subjects are listed by treatment group and reason for withdrawal in Table 10. The largest percentage of subjects prematurely withdrawing form the Study because of an adverse event was observed in the E2 treatment group (23.5% of subjects).

Table 10. Disposition of Subjects

Disposition	Number (%) of Subjects				
	E2 1 mg	E2 1 mg + 0.5 mg DRSP	E2 1 mg + 1 mg DRSP	E2 1 mg + 2 mg DRSP	E2 1 mg + 3 mg DRSP
Treated	226	227	231	227	231
Premature Withdrawal	77 (34.1)	48 (21.2)	62 (26.8)	54 (23.8)	56 (24.2)
Adverse Event	53 (23.5)	29 (12.8)	35 (15.2)	39 (17.2)	33 (14.3)
Lack of Efficacy	1 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Protocol Deviation	6 (2.7)	4 (1.8)	9 (3.9)	6 (2.6)	5 (2.2)
Withdrawal of Consent	10 (4.4)	11 (4.9)	9 (3.9)	3 (1.3)	11 (4.8)
Other	7 (3.1)	4 (1.8)	9 (3.9)	6 (2.6)	7 (3.0)

From Table 3, pg 179, Vol. 20, Nov. 6, 2000 submission.

Demographic and other baseline characteristics

Of the 1142 subjects evaluable for safety, the mean age was 55.7 years with a range of 42 to 75 years (Table 11). The majority of subjects were Caucasian (92.4%) with Blacks and Hispanics each comprising 2.6% of the subjects. The mean weight of the subjects was 72.7 kg with a range of 44-156 kg. Seventy nine (79) percent of the subjects did not smoke. The 5 treatment groups were well balanced in all categories with the possible exception of race, for which the percentages of Blacks ranged from 1 to 5% across treatment groups.

Table 11. Demographics and Baseline Characteristics

Variable	Statistic	E2 1 mg N = 226	E2 1mg + 0.5 mg DRSP N = 227	E2 1mg+ 1 mg DRSP N = 231	E2 1mg + 2 mg DRSP N = 227	E2 1mg + 3 mg DRSP N = 231
Age (yrs)	Mean	55.4	56.0	55.9	55.2	55.8
	Range	44-75	42-74	45-75	44-74	45-75
Race	Caucasian	209 (93%)	210 (93%)	204 (88%)	216 (95%)	216 (94%)
	Black	3 (01%)	7 (03%)	12 (05%)	4 (02%)	4 (02%)
	Hispanic	6 (03%)	5 (02%)	9 (04%)	3 (01%)	7 (03%)
	Other	8 (03%)	5 (02%)	6 (03%)	4 (02%)	4 (02%)
Wt (kg)	Mean	71.2	71.9	72.8	72.7	74.3
	Range	46-156	46-120	44-134	45-136	46-136

Data from Table 4, pg 180, Vol. 20, Nov. 6, 2000 submission.

Extent of exposure to Study Drug

The duration of treatment, defined as number of days from the first dose to the last dose of study medication, was comparable across treatment groups. The mean treatment durations ranged from 297.2 days to 310.8 days with the overall mean duration being 304.2 days.

Concomitant Medications (Potassium Sparing)

The reported use of selected medications that might affect serum potassium concentrations (e.g. potassium sparing diuretics, NSAIDs, and angiotensin-converting enzyme (ACE) inhibitors) is summarized in Table 12. Of these medications, 205 (18%) subjects used NSAIDs, and a total of 419 (36.7%) subjects used NSAIDs or aspirin (ASA) containing compounds. Twenty five (2.2%) subjects used ACE inhibitors. Of the 5 (0.4%) subjects using potassium sparing diuretics, none used a drug product containing spironolactone.

Table 12. Concomitant Use of Selected Medications

Medication	N (%)
ACE Inhibitors	25 (2.2)
NSAIDs (including aspirin and aspirin containing compounds)	419 (36.7)
NSAIDs	205 (18.0)
Aspirin and Aspirin Containing Compounds	272 (23.8)
Heparin	1 (0.1)
Spironolactone, Aldactone, Aldactazide	0 (0.0)
Potassium sparing diuretics (excluding spironolactone)	5 (0.4)

From Text Table 6, pg 24, Vol. 19, Nov. 6, 2000 submission.

Medical Officer's Comments

- Data presented in Table 12 are those provided by the Sponsor in the submission of November 6, 2000. During the course of subsequent communications with the Sponsor concerning specific data analyses, the Sponsor's definition of "use of NSAIDs during the study" was broadened to include all subjects who reported using NSAIDs (both prescription and OTC use) and aspirin (ASA) containing products at any time during the Study; consequently, the listed number of "NSAID users" in some of the analyses included later in this review is higher than those listed in Table 12. This change in definition, however, does not have a material effect on the interpretation of the findings from this Study as discussed later in this review.

Serum Potassium Concentrations and Changes from Baseline Values

A total of 1091 subjects had both a baseline and one or more post baseline (either on-treatment or post treatment) measurements of serum potassium. Mean, minimum, and maximum serum potassium concentrations in each of the treatment groups at baseline, Visit 5, and Visit 7 are listed in Table 13. Serum potassium values (normal range: 3.4 to 5.4 mEq/L) ranged from [illegible] treatment observation in a subject in the E2/DRSP 0.5 mg group) [illegible] one baseline value in the E2 alone group and one on-treatment value in the E2/DRSP 0.5 mg group). Mean changes in potassium concentrations from baseline at Visits 5 and 7 also are listed in Table 13. Mean changes from baseline ranged from –0.07 mEq/L in the E2 group at Visit 5 to 0.01 mEq/L in the E2/DRSP 3 mg group at Visit 7.

Table 13. Serum Potassium (mEq/L) by Treatment and Visit (All Subjects)

			Visit 5 — End of Cycle 7 —		Visit 7 End of cycle 13 (Termination)	
Treatment	Statistic	Baseline	Value	Change	Value	Change
E2 1mg	N	227	177	177	205	205
	Mean	4.39	4.32	-0.07	4.33	-0.05
	Min					
	Max					
E2 1mg + DRSP 0.5 mg	N	227	185	185	204	204
	Mean	4.33	4.29	-0.05	4.32	-0.00
	Min					
	Max					
E2 1mg + DRSP 1 mg	N	230	178	178	210	210
	Mean	4.34	4.30	-0.04	4.30	-0.03
	Min					
	Max					
E2 1mg + DRSP 2 mg	N	226	180	180	206	206
	Mean	4.38	4.39	-0.01	4.36	-0.02
	Min					
	Max					
E2 1mg + DRSP 3 mg	N	232	186	186	208	208
	Mean	4.31	4.31	0.00	4.33	0.01
	Min					
	Max					

Data from Table 7, submission of March 9, 2001.

The effects of treatment with E2 alone or E2/DRSP on serum potassium also was assessed in terms of the mean post baseline average change and the mean post baseline maximum change from baseline (Table 14). The mean post baseline average changes ranged from –0.05 mEq/L in the E2-treated subjects to 0.00 mEq/L in the E2/DRSP 3 mg treated subjects. The mean post baseline maximal changes ranged from 0.06 mEq/L in the E2-treated subjects to 0.14 mEq/L in the E2/DRSP 0.5 mg treated subjects.

Table 14. Mean (±SD) Changes from Baseline in Serum Potassium (mEq/L) (All Subjects with Both Baseline and Post Baseline Data)

Treatment Group	Number of Subjects	Baseline Mean ± SD	Change From Baseline in	
			Post baseline Average Value Mean ± SD	Post baseline Maximum Value Mean ± SD
E2 1 mg	219	4.38 ± 0.45	-0.05 ± 0.41	0.06 ± 0.41
E2 + 0.5 mg DRSP	216	4.32 ± 0.37	-0.01 ± 0.40	0.14 ± 0.42
E2 + 1.0 mg DRSP	222	4.33 ± 0.39	-0.03 ± 0.39	0.10 ± 0.44
E2 + 2.0 mg DRSP	215	4.39 ± 0.43	-0.02 ± 0.40	0.13 ± 0.42
E2 + 3.0 mg DRSP	219	4.32 ± 0.41	0.00 ± 0.42	0.13 ± 0.44

From Table 1 and Table 2, submission of March 9, 2001

Table 15 shows the number and percentage of subjects whose serum potassium concentrations were ≥ 5.5 mEq/L. (Hyperkalemia in this study, as before, was defined as a serum potassium ≥ 5.5 mEq/L.) Post baseline data are shown separately for (1) all subjects, (2) subjects who used an NSAID or ACE inhibitor (Sponsor's initial classification), and (3) subjects who used an NSAID, an ACE inhibitor, or an aspirin containing product (Sponsor's modified and broadened classification).

Table 15. Number (%) of Subjects With Serum Potassium Values ≥ 5.5 mEq/L

	Baseline		Post Baseline					
	All Subjects		All Subjects		Using NSAID or ACE Inhibitor *		Using NSAID, ACE Inhibitor, or Aspirin **	
Treatment Group	N	≥ 5.5 mEq/L n (%)	N	≥ 5.5 mEq/L n (%)	N	≥ 5.5 mEq/L n (%)	N	≥ 5.5 mEq/L n (%)
E2 1 mg	227	5 (2.2)	219	4 (1.8)	45	0 (0.0)	117	2 (1.7)
E2 1 mg/DRSP 0.5 mg	227	3 (1.3)	217	4 (1.9)	41	0 (0.0)	117	2 (1.7)
E2 1 mg/DRSP 1.0 mg	230	3 (1.3)	223	6 (2.7)	45	1 (2.2)	117	2 (1.7)
E2 1 mg/DRSP 2.0 mg	226	2 (0.9)	216	6 (2.8)	43	1 (2.3)	107	3 (2.8)
E2 1 mg/DRSP 3.0 mg	232	0 (0.0)	220	0 (0.0)	43	0 (0.0)	111	0 (0.0)
Total	1142	13 (1.1)	1095	20 (1.8)	217	2 (0.9)	569	9 (1.6)

N = total number of subjects; n = number of subjects in the category.
* Sponsor's original definition of NSAID and ACE inhibitor usage; data from submission of November 6, 2000.
** Sponsor's revised and broader definition of NSAID and ACE inhibitor usage, including use of aspirin products; data from sponsor's submission of March 9, 2001.

Table 16 lists by treatment group the subjects who had post treatment serum potassium values ≥ 5.5 mEq/L. The highest reported post baseline value was 6.1 mEq/L. A total of 20 (1.8%) subjects had a post baseline serum potassium measurement ≥ 5.5 mEq/L. The number of subjects with post baseline potassium values ≥ 5.5 mEq/L ranged from 0 in the E2/DRSP 3 mg group to 6 in each of the E2/DRSP 1 mg and E2/DRSP 2 mg groups.

Table 16. Subjects with Post Baseline Serum Potassium ≥ 5.5 mEq/L

Treatment	Subject No.	Serum Potassium, mEq/L	
		Baseline	Post Baseline Maximum
E2 1 mg	9715021	5.5	5.5
" "	9716035	5.0	5.5
" "	9720011	5.3	5.6
" "	9721007	5.2	5.6
E2 + 0.5 mg DRSP	9701005	4.7	5.5
" "	9708008	5.3	6.1
" "	9709041	4.1	5.5
" "	9718010	5.5	5.7
E2 + 1.0 mg DRSP	9707016	4.9	5.6
" "	9716036	5.0	5.7
" "	9718005	4.5	5.5
" "	9734007	5.0	5.6
" "	9736043	4.0	5.5
" "	9752010	5.1	5.8
E2 + 2.0 mg DRSP	9707002	5.2	5.5
" "	9709015	4.6	5.9
" "	9709020	4.0	5.7
" "	9709043	5.3	5.5
" "	9715022	4.9	5.6
" "	9752002	4.4	5.5
E2 + 3.0 mg DRSP	None	—	—

From Listing 16, pgs 2306-2323, Vol. 95, Nov. 6, 2000 submission.

Medical Officer's Comments

- Although DRSP was co-administered with 1 mg E2 (instead of 30 µg EE, the estrogen in Yasmin), the study provides information that is relevant to the safety assessment of Yasmin. Data obtained from the subjects with baseline and post baseline potassium values that were enrolled in the E2/DRSP 3 mg group (n=215) and the E2/DRSP 2 mg group (n=219) are most relevant. Although the daily dose of DRSP in the E2/DRSP 2 mg group is less than that in Yasmin (i.e., 3 mg DRSP), the monthly exposure to DRSP in this group (2 mg x 28 days) is very similar to that in women receiving Yasmin (3 mg x 21 days) for prevention of pregnancy.
- There did not appear to be a clinically significant effect of DRSP on serum potassium concentrations in any of the DRSP treatment groups in this population of generally healthy postmenopausal women. Twenty (20) subjects had post baseline serum potassium concentrations above the upper range of normal (≥ 5.5 mEq/L). Two of these 20 subjects also had a pretreatment baseline serum potassium value ≥ 5.5 mEq/L. The numbers of subjects in each treatment group with normal baseline potassium values and with post baseline potassium values ≥ 5.5 mEq/L are shown in Table 17. The highest reported post baseline value was 6.1 mEq/L in a single subject in the E2/DRSP 0.5 mg group. None of these subjects had an increased serum creatinine. The absence of any post baseline potassium values ≥ 5.5 mEq/L in the E2/DRSP 3.0 mg group suggests that the slightly increased number of subjects in the E2/DRSP 1.0 mg and E2/DRSP 2.0 mg treatment groups, relative to the E2 treatment group, is probably not a direct consequence of treatment with DRSP.

Table 17. Number of Subjects with a Normal Baseline Potassium and a Post Baseline Potassium ≥ 5.5 mEq/L

Treatment Group	Number
E2 1 mg	3 *
E2 1 mg/DRSP 0.5 mg	3 **
E2 1 mg/DRSP 1.0 mg	6
E2 1 mg/DRSP 2.0 mg	6
E2 1 mg/DRSP 3.0 mg	0

* A 4th subject had an elevated serum potassium at both baseline and on-treatment (the same value).
** A 4th subject had an elevated serum potassium at baseline that increased further during the post baseline period.

- A more sensitive analysis to detect a small effect of treatment with DRSP on serum potassium concentrations is, in most instances, to determine the mean and/or maximum on-treatment change from baseline, an analysis similar to that summarized in Table 14. The Sponsor was asked to repeat the analyses presented in Table 14, including only those subjects who were still receiving Study Drug or were within 24 hours of their final dose at the time that their serum potassium levels were determined (Table 18). The outcome of this reanalysis was very similar to that of the Sponsor's original analysis; however, there appeared to be a small, dose-related increase in the means of the average post baseline changes in serum potassium, ranging from -0.08 mEq/L (E2 group) to 0.00 mEq/L (E2/DRSP 3 mg group). Such a change in serum potassium would be in agreement with the known pharmacology of DRSP. In addition, the means of the maximum post baseline potassium values for the DRSP treatment groups (range: 0.06 to 0.10 mEq/mL) were all higher than the post baseline mean of the E2 group (-0.01 mEq/mL), again suggesting a small effect of DRSP on serum potassium concentrations.

Table 18. Mean (±SD) Changes from Baseline in Serum Potassium (mEq/L) (Only Subjects with Post Baseline Blood Samples Obtained on-Treatment)

Treatment Group	Number of Subjects	Baseline Mean ± SD	Change From Baseline in	
			Average Post Baseline Value (Mean ± SD)	Maximum Post Baseline Value (Mean ± SD)
E2 1 mg	190	4.39 ± 0.46	-0.08 ± 0.42	-0.01 ± 0.42
E2 + 0.5 mg DRSP	190	4.34 ± 0.37	-0.04 ± 0.40	0.06 ± 0.42
E2 + 1.0 mg DRSP	186	4.32 ± 0.39	-0.02 ± 0.40	0.07 ± 0.43
E2 + 2.0 mg DRSP	187	4.39 ± 0.43	-0.01 ± 0.40	0.10 ± 0.42
E2 + 3.0 mg DRSP	196	4.32 ± 0.41	0.00 ± 0.43	0.09 ± 0.44

From Tables 3 and 4, March 9, 2001 submission.

- The Sponsor also reanalyzed the on-treatment serum potassium data separately for subjects who did, or did not, use an NSAID or ACE inhibitor during their participation in the Study. The reported mean on-treatment serum potassium changes from baseline were similar in both groups of subjects (Table 19). One can not conclude, however, from this observation that the use of an NSAID (or an ACE inhibitor) in women receiving DRSP has no effect on serum potassium as the power to detect a difference was low for several reasons. In the present Study, the Sponsor did not control for the extent of NSAID use, only 2 post baseline serum potassium measurements were obtained, and potassium concentrations were not always measured during the period of actual NSAID use. Furthermore, subjects who were co-administered an ACE inhibitor and E2/DRSP in Study 98106 (a study specifically designed to investigate changes in serum potassium concentrations) exhibited a mean 0.22 mEq/L increase in serum potassium from baseline compared to no increase in subjects receiving only E2/DRSP.

Table 19. Mean (±SD) Changes from Baseline in Serum Potassium (mEq/L) (Subjects with Post Baseline Blood Samples Obtained on-Treatment)

Treatment	Number of Subjects		Mean Change from Baseline (mEq/L)			
			Average Post Baseline Value		Maximum Post Baseline Value	
	No NSAID or ACE Inhibitor	Used NSAID or ACE Inhibitor*	No NSAID or ACE	Used NSAID or ACE	No NSAID or ACE	Used NSAID or ACE
E2 1 mg	88	102	-0.12	-0.05	-0.03	0.01
E2 + 0.5 mg DRSP	85	105	-0.04	-0.05	0.05	0.06
E2 + 1.0 mg DRSP	89	97	-0.02	-0.02	0.07	0.06
E2 + 2.0 mg DRSP	92	95	-0.02	0.00	0.09	0.11
E2 + 3.0 mg DRSP	96	100	-0.01	0.01	0.07	0.10

* Based on the Sponsor's revised and broadened definition of use of NSAIDs
From Tables 3 and 4, March 9, 2001 submission

- Fourteen (14) subjects were reported to have had one or more serum potassium values below the lower limit of the normal ranges (< 3.4 mEq/L) as summarized in Table 19a. Three subjects in the E2/DRSP 1 mg group and 1 subject in the E2/DRSP 3 mg group had a single reported potassium value of < 3.0 mEq/L. There was no apparent relationship between the dose of DRSP and the number of subjects with normal baseline potassium values and a post baseline value < 3.4 mEq/L (hypokalemia).

Table 19a. Number of subjects with hypokalemia (potassium < 3.4 mEq/L) *

	E2 alone	E2 plus 0.5 mg DRSP	E2 plus 1 mg DRSP	E2 plus 2 mg DRSP	E2 plus 3 mg DRSP
Baseline < 3.4 mEq/L	1	0	1**	0	3
Baseline ≥ 3.4 mEq/L with post baseline < 3.4 mEq/L	2	4	1	0	2

* Reported either as an adverse event and/or in the laboratory data listings.
** Subject also had 1 on-treatment potassium value that was the same as her baseline value.

Selected Cardiovascular Adverse Events

The Sponsor also determined the incidence of 6 cardiovascular adverse events that could potentially be associated with hyperkalemia: arrhythmia, bradycardia, dizziness, palpitations, syncope, and tachycardia. The total number of subjects reporting one or more of these adverse events as well as the number of subjects reporting each of these adverse events in the 5 treatments group is shown in Table 20. The number of subjects reporting one or more adverse events ranged from 6 subjects in the E2/DRSP 3 mg group to 13 in the E2/DRSP 1 mg group. The total number of these selected cardiovascular adverse events ranged from 7 events in the E2/DRSP 0.5 mg group to 15 events in the E2/DRSP 1 mg group.

Table 20. Frequency of Selected Cardiovascular Adverse Events

Treatment Group	N*	N**	Selected Cardiovascular Adverse Event					
			Arrhythmia n *** (%)	Bradycardia n (%)	Dizziness N (%)	Palpitation n (%)	Syncope n (%)	Tachycardia n (%)
E2 1 mg	226	8	0 (0.0)	0 (0.0)	7 (3.1)	3 (1.3)	1 (0.4)	0 (0.0)
E2/DRSP 0.5 mg	227	7	0 (0.0)	0 (0.0)	3 (1.3)	2 (0.9)	1 (0.4)	1 (0.4)
E2/DRSP 1 mg	231	13	2 (0.9)	0 (0.0)	10 (4.3)	0 (0.0)	0 (0.0)	3 (1.3)
E2/DRSP 2 mg	227	12	2 (0.9)	1 (0.4)	5 (2.2)	2 (0.9)	0 (0.0)	2 (0.9)
E2/DRSP 3 mg	231	6	0 (0.0)	0 (0.0)	6 (2.6)	0 (0.0)	0 (0.0)	2 (0.9)

N * = total number of subjects at risk; N ** = total number of subjects experiencing one or more of the cardiovascular adverse events, n *** = number of subjects experiencing the specific adverse event.
From Nov. 6, 2000 submission, Vol. 20, Table 8 and Cardiovascular AE Listing.

Medical Officer's Comments

- There was no apparent association between the incidence of subjects experiencing one or more of these cardiovascular adverse events and the dose of DRSP. Overall, 8 of 226 subjects (3.5%) in the E2 group and 38 of 916 subjects (4.1%) in the DRSP groups experienced one or more of these adverse events. The number of subjects was highest in the E2/DRSP 1 mg and the E2/DRSP 2 mg groups (13/231 and 12/227, respectively) and lowest in the E2/DRSP 3 mg group (6/231). Attempting to determine the incidence of hyperkalemia by means of these selected adverse events, however, is of limited value because of both low specificity and low sensitivity. Although these adverse events may be associated with hyperkalemia, they are more likely to be a result of other factors (low specificity). In addition, cardiovascular symptoms of hyperkalemia are generally not apparent at serum potassium concentrations < 6.5 mEq/L (low sensitivity).
- Treatment with Study Drug was discontinued in 7 of these 46 subjects, either entirely or in part because of one or more of these cardiovascular adverse events (Table 21).

Table 21. Selected Cardiovascular Adverse Events Associated with Discontinuation of Study Drug

Treatment Group	Subject No.	Adverse Event	Closest Serum Potassium	
			mEq/L	Days prior to/after AE
E2 1 mg	24027	Dizziness/Palpitations	4.2	7 days prior to onset of AE
E2 + 0.5 mg DRSP	8035	Tachycardia	4.1	During AE *
E2 + 1.0 mg DRSP	36005	Arrhythmia/Tachycardia	4.0	During AE
E2 + 2.0 mg DRSP	9015	Dizziness	5.9	3 days prior to onset of AE
" "	31014	Palpitations	4.4	Possibly during AE
E2 + 3.0 mg DRSP	17018	Dizziness/Tachycardia	4.1	8 days after end of AE
" "	26005	Dizziness	4.6	> 60 days prior to onset of AE

* Value provided in supplemental submission of 12 March 2001, pg 3.

- Only one of these 7 subjects (Subject No. 9015, E2/DRSP 2 mg group, adverse event of dizziness) was reported to have had an elevated serum potassium value (5.9 mEq/L). This value was obtained on December 28, 2000, 3 days prior to the subject's second episode of dizziness. Study Drug was discontinued on December 31. The subject's serum potassium 7 days later was 4.9 mEq/L. The absence of reported hyperkalemia in the other subjects is of limited significance, however, since 3 (and possibly 4) of the other 6 subjects did not have a serum potassium determination at the time of the adverse event.

Adverse Events

A total of 995 (87.1%) of the 1142 subjects in the study reported at least 1 adverse event. Table 22 summarizes by treatment group the number and percentage of subjects experiencing adverse events.

In this Table, adverse events are classified as all adverse events, treatment-related adverse events, severe adverse events, serious adverse events, and adverse events resulting in withdrawal from the Study.

Table 22. Summary of Adverse Events by Treatment Group

	Number (%) of Subjects				
Type of Adverse Event (AE)	E2 1 mg N = 226	E2 1mg + 0.5 mg DRSP N = 227	E2 1mg + 1 mg DRSP N = 231	E2 1mg + 2 mg DRSP N = 227	E2 1mg + 3 mg DRSP N = 231
All AEs	204 (90%)	197 (87%)	202 (87%)	196 (86%)	196 (85%)
Treatment Related AE	144 (64%)	129 (57%)	125 (54%)	136 (60%)	124 (54%)
Severe AEs	47 (21%)	32 (14%)	39 (17%)	35 (15%)	36 (16%)
Serious AEs	7 (3%)	8 (4%)	8 (4%)	5 (2%)	9 (4%)
AEs Resulting in Withdrawal	53 (24%)	29 (13%)	35 (15%)	39 (17%)	33 (14%)

From Nov. 6, 2000 submission, Vol. 20, Tables 8, 10, 11, 12, and 13.

All Adverse Events. The percentage of subjects experiencing an adverse event varied slightly across the treatment groups and ranged from 85% in the E2/DRSP 3 mg group to 90% in the E2 group. Overall, breast pain was the most frequently reported adverse event, occurring in 229 (20.1%) subjects. Other adverse events that were reported at a frequency of more than 10% were upper respiratory infection (15.8%), vaginal bleeding (14.7%), and abdominal pain (10.8%). The percentages of subjects reporting specific adverse events, based on preferred terms, were generally comparable among subjects receiving E2/DRSP or E2 alone. However, the adverse events of endometrial disorder, endometrial hyperplasia, leukorrhea, and peripheral edema were reported more frequently in subjects receiving E2 alone while breast pain was reported more frequently in subjects receiving E2/DRSP.

Treatment-related adverse events. A total of 658 (57.6%) subjects experienced adverse events related to treatment. Among the treatment groups, those subjects receiving E2 alone reported the highest percentage (64%) of drug related adverse events. Breast pain (19.6%), vaginal bleeding (14.3%), abdominal pain (7.6%), and endometrial adverse events (7.2%, preferred terms of endometrial disorder, hyperplasia, or neoplasm) were the most frequently reported adverse events across all treatment groups. All but breast pain (more frequent in the E2/DRSP groups) were reported more frequently in the E2-treated subjects.

Premature terminations due to adverse events. No subject in any of the treatment groups died. A total of 17% of subjects discontinued Study Drug because of an adverse event. A greater percentage of subjects in the E2 group (24%) terminated prematurely due to an adverse event than in any of the E2/DRSP groups (13% to 17%). The most frequently reported adverse events associated with premature terminations were vaginal bleeding (4.7%) and endometrial adverse events (3.2%) (both more frequent in the E2 group) and breast pain (2.3%) (more frequent in the E2/DRSP groups). One subject (E2/DRSP 1 mg group) developed a deep vein thrombosis and was terminated from the Study.

Medical Officer's Comments

- There were no new general safety findings that would impact on the overall safety assessment of Yasmin.

Ongoing Phase III Clinical Trial

Medical Officer's Comments

- Although these are preliminary data from an ongoing Study, they provide additional information about the effects of treatment with 3 mg DRSP in combination with EE in young women using DRSP/EE for prevention of pregnancy. Table 23 summaries these preliminary data. These data suggest that 3 mg of DRSP has a small effect on serum potassium concentrations, and they are in agreement with data described previously in this review.

Table 23. Serum Potassium Values (mEq/L) at Baseline and during Treatment Cycle 1

Statistic	Baseline	Treatment Cycle 1	Change from Baseline
Mean (±SD)	4.2 (±0.3)	4.3 (±0.3)	0.06 (±0.34)
Median	4.2	4.3	0.10
Min			
Max			

Calculations performed by Medical Officer.

PHASE I CLINICAL PHARMACOLOGY STUDIES

These studies were previously reviewed during the primary review of NDA 21-098 (March 2000). In the present review, only changes in serum potassium concentrations are addressed.

Study ME89092/KI89093 (Report No. 9371)

Title. "Investigation of the Tolerability and Influence on Hormonal Regulation during a 5-Day Treatment with 10 mg Drospirenone in 6 Healthy Postmenopausal Women."

Methods. This was a randomized, single-blind, placebo-controlled, parallel-group study in healthy postmenopausal women. The Study was conducted at a single center in Germany. A total of 12 women (49-73 years of age) were randomized to receive either 10 mg DRSP or placebo (6 subjects in each group) for 5 consecutive days. Blood and urine specimens were collected at various times throughout the study to evaluate (1) changes in serum chemistries and hematology parameters, (2) changes in hormonal regulation including the renin-angiotensin-aldosterone system, and (3) pharmacokinetics. Blood specimens for the measurement of serum potassium by flame photometry were obtained prior to treatment and on Treatment Days 2, 3, 4, and 5 (2 hours after the final dose of DRSP). All 12 subjects completed the Study.

Results. Mean, minimum, and maximum serum concentrations of potassium in each of the treatment groups at each of the sampling times are shown in Table 23. One subject in the placebo group and no subjects in the DRSP group had a post baseline potassium value ≥ 5.5 mEq/L.

Table 23. Serum Potassium (mEq/L) during Administration of Placebo or DRSP

			Treatment Period			
Treatment	Statistic	Baseline	Day 2	Day 3	Day 4	Day 5
Placebo	Mean	4.41	4.49	4.62	4.43	4.46
	Min					
	Max					
10 mg DRSP	Mean	4.36	4.52	4.36	4.34	4.69
	Min					
	Max					

From NDA 21-098, Vol. 1.57, pg I-121 and I-122.

The effects of treatment with DRSP on serum potassium concentrations also were assessed in terms of the mean post baseline average changes and the mean post baseline maximum changes from baseline (Table 24). The mean post baseline average changes and maximal changes were very similar in the 2 treatment groups.

Table 24. Mean (±SD) Changes from Baseline in Serum Potassium (mEq/L)

Treatment Group	Baseline Mean ± SD	Change From Baseline in	
		Post baseline Average Value Mean ± SD	Post baseline Maximum Value Mean ± SD
Placebo	4.41 ± 0.23	0.10 ± 0.35	0.42 ± 0.52
10 mg DRSP	4.36 ± 0.07	0.12 ± 0.31	0.45 ± 0.20

From Sept. 21, 2000 Briefing Package, pg 26.

Study 89015 (Report No. 9370)

Title. "Placebo Controlled Single Blind Group Comparison (N=6 Per Group) of Systemic Tolerability, the Influence on Hormonal Regulation and of Drug Plasma Levels After a Single Oral Administration of 10, 25, 50, and 100 Mg of Drospirenone to Healthy Male Volunteers."

Methods. Thirty healthy men (22-41 years of age) each received a single dose of one of 4 dosages of DRSP or placebo. The dosages of DRSP were 10 mg, 25 mg, 50 mg, or 100 mg administered as an aqueous suspension. Six volunteers were assigned to each treatment group. Blood and urine specimens were collected per protocol to assess changes in (1) serum chemistries including potassium concentrations, (2) selected hormone levels, (3) the renin-angiotensin-aldosterone system, and (4) excretion of sodium and potassium. Blood samples for the measurement of serum potassium concentrations by flame photometry were collected prior to dosing with Study Drug and at 3, 8, and 24 hours after dosing.

Results. Mean, minimum, and maximum serum concentrations of potassium in each of the treatment groups at each of the sampling times are shown in Table 25. Only one subject (a subject treated with placebo) had a post treatment potassium value ≥ 5.5 mEq/L.

Table 25. Serum Potassium (mEq/L) Before and After a Single Dose of Study Drug

Treatment	Statistic	Baseline	Post Dosing Period 3 hrs	8 hrs	24 hrs
Placebo	Mean	4.69	4.23	4.41	4.60
	Min				
	Max				
10 mg DRSP	Mean	4.45	4.38	4.11	4.60
	Min				
	Max				
25 mg DRSP	Mean	4.39	4.59	4.24	4.54
	Min				
	Max				
50 mg DRSP	Mean	4.30	4.31	4.13	4.36
	Min				
	Max				
100 mg DRSP	Mean	4.48	4.19	4.32	4.31
	Min				
	Max				

From NDA 20-098, Vol. 1.55, pg I-112 to I-116.

The effects of treatment with DRSP on serum potassium concentrations also were assessed in terms of the mean post baseline average changes and the mean post baseline maximum changes from baseline (Table 26). The mean post baseline average changes ranged from –0.28 mEq/L in the placebo group to 0.07 mEq/L in the DRSP 25 mg group. The mean post baseline maximal changes ranged from -0.01 mEq/L in the placebo group to 0.31 mEq/L in the DRSP 25 mg group.

Table 26. Mean (±SD) Changes from Baseline in Serum Potassium (mEq/L)

Treatment Group	Baseline Mean ± SD	Change From Baseline in Post baseline Average Value Mean ± SD	Post baseline Maximum Value Mean ± SD
Placebo	4.96 ± 0.42	-0.28 ± 0.25	-0.01 ± 0.20
10 mg DRSP	4.45 ± 0.13	-0.09 ± 0.22	0.24 ± 0.33
25 mg DRSP	4.39 ± 0.24	0.07 ± 0.21	0.31 ± 0.35
50 mg DRSP	4.30 ± 0.12	-0.03 ± 0.18	0.28 ± 0.47
100 mg DRSP	4.48 ± 0.31	-0.21 ± 0.29	0.03 ± 0.28

From Sept. 21, 2000 Briefing Package, pg 26.

Medical Officer's Comments

- Both of these Phase I studies were appropriately designed to assess the tolerability and acute effects of DRSP on several homeostatic regulatory systems. Study ME89092, in which 12 postmenopausal women were treated for 5 days with either 10 mg DRSP (3.3 times the dose of DRSP in Yasmin) or placebo, showed little, if any, effect of DRSP on serum concentrations of potassium. In Study 89015, average post baseline mean serum potassium changes from baseline or average post baseline peak serum potassium changes from baseline in the 10, 25, and 50 mg DRSP treatment groups ranged from approximately 0.19 to 0.35 mEq/L higher than those in the placebo group. In the 100 mg DRSP treatment group (the highest dose studied), however, the average mean and peak post baseline changes were approximately 0.07 mEq/L and 0.04 mEq/L higher, respectively, than those in the placebo group and less than those in any of the other DRSP treatment groups; consequently, it is uncertain if the increases observed in the

10, 25 and 50 mg DRSP treatment groups reflect a true effect of DRSP. No subject in either study who received DRSP had a post baseline value ≥ 5.5 mEq/L.

- Although Study ME89092 indicated that a dose of DRSP several fold greater than that in Yasmin did not have a demonstrable effect on serum potassium in healthy women, there are several limitations of this study. Among these are (1) only 6 subjects were treated with DRSP and (2) the treatment period was for only 5 days. Steady state levels of DRSP may not be reached for up to 10 days, consequently, serum concentrations of DRSP on the morning of Treatment Day 5, the time of the final serum potassium measurement in Study ME89092, are likely to have been less than 3 fold those achieved in women using Yasmin for prevention of pregnancy.

SAFETY UPDATE (Reporting Period: March 17, 2000 to March 1, 2001)

The sponsor provided separate Safety Updates for the periods March 17, 2000 to July 10, 2000 (November 6, 2000 submission) and July 10, 2000 to March 1, 2001 (March 27, 2001 submission).

In the introduction to the Safety Update submitted on March 27, 2001, Berlex stated the following:

> "…. this report refers only to new data obtained during the reporting period. These additional data are relatively few; therefore, only serious or potentially serious adverse events (AE), an unusually high frequency of a less serious event, subjects who died, subjects who failed to complete a clinical study due to an AE are described…."
>
> "It was concluded that there is no new safety information learned about DRSP 3 mg and EE 0.030 mg Tablets that may reasonably affect the statement of Contraindications, Warnings and Adverse Reactions in the DRAFT Labeling."

Serious adverse events in clinical trials
Two SAEs (lactose intolerance and depression) were reported in an ongoing Phase III clinical trial comparing Yasmin to another combination oral contraceptive in subjects with acne. The study blind has not been broken; neither SAE was considered to be related to Study Drug. A third SAE (erysipelas, assessed as not related to Study Drug) was reported for a subject receiving 3 mg DRSP/20 µg EE (Yasmin 20) in another ongoing clinical study.

Unusually high frequency of a less serious event in clinical trials
The sponsor stated that there was not an unusually high frequency of a less serious event in any of the studies that were ongoing during the reporting period.

Subjects who died due to an adverse event in a clinical trial
No subjects died in the studies that were ongoing during the reporting period.

Subjects who discontinued due to an adverse event in a clinical trial
There were no discontinuations due to adverse events in studies ongoing during the reporting period.

Commercial marketing experience and foreign regulatory actions

Countries in which the drug has been approved. Labeling for DRSP 3 mg and EE 30 µg Tablets was approved through the Mutual Recognition Process at the beginning of August 2000 for the European Union (EU), as well as Norway and Iceland. National marketing authorizations have been issued for the following countries based on this labeling: Austria, Belgium, Denmark, Finland, France, Germany, Greece, Iceland, Ireland, Italy, Luxembourg, Norway, Portugal, Spain, Sweden, and the United Kingdom. DRSP 3 mg/EE 30 µg Tablets were launched in Germany, Belgium, Luxembourg, Denmark, Iceland, Norway, and Sweden during the reporting period. National marketing authorizations have also been issued for the following countries outside of the EU: Colombia, Czech Republic, Estonia, and Switzerland.

Medical Officer's Comments

- The sponsor previously reported that DRSP 3 mg/EE 30 µg tablets had been approved for marketing in the Netherlands on March 7, 2000. Approved EU labeling lists "severe renal insufficiency or acute renal failure" as a contraindication to the use of Yasmin. European Union labeling also includes the following wording under both "special warnings and precautions for use" and "interactions with other medicinal products and other forms of interactions:" A similar statement should be added to US labeling.

  "Women using Yasmin and concomitant medications with the potential to increase serum potassium such as ACE-inhibitors, angiotensin-II-receptor-antagonists, aldosterone antagonists, potassium-sparing diuretics or NSAIDs used for long-term treatment should be tested for serum potassium during the first treatment cycle."

Reports from foreign regulatory agencies or foreign affiliates. The Sponsor stated that there were no reports of, or analyses of, AEs or warning letters sent to physicians resulting from marketing or other experience with DRSP 3 mg/EE 30 µg Tablets.

Spontaneous reports from foreign marketing experience
Since the launch of Yasmin (also known as Petibelle) in November 2000, 1 death (presumably due to a myocardial infarct or pulmonary embolus) and serious adverse events (SAEs) in 7 women have been reported.

Nonfatal Serious Adverse Events. Four of the 7 subjects experienced nonfatal SAEs that were reported as thrombotic or thromboembolic in nature. Brief histories for these subjects are as follows:

1) A 22 year old women switched from an unknown oral contraceptive to Yasmin and after 1 week suffered a stroke (posterior cerebral infarct). The woman had previously had 3 to 4 migraine attacks with associated transient hemiparesis yearly that had been treated with sumatriptan. After a migraine attach in December 2000, she was treated with rizatriptan. Her headache resolved but the hemiparesis and visual disturbance persisted, and she was diagnosed as having had a stroke.
2) A 35 year old women reported severe dizziness, a fast heart rate, and pain in her leg 8 days after the start of Petibelle. She had previously used an oral contraceptive for 5 years. Petibelle was discontinued. Her clinical exam was normal and she recovered without any treatment. The gynecologist did not suspect a venous thrombosis or a pulmonary embolism, but on query could not exclude them as the cause of this woman's clinical symptoms.
3) After 3 days of using Petibelle, a woman with bronchial carcinoma and a history of 20 years of oral contraceptive use, developed a venous thrombosis in her leg.
4) A 22 year old woman changed from the oral contraceptive Diane-35, which she had used for about 5 years, to Yasmin in December 2000. In January 2001, she developed a deep venous thrombosis in her leg. Thrombolysis was performed.

The other 3 subjects experienced SAEs described as (1) migraine, (2) syncope, hypertension, and dizziness, and (3) pancreatitis, respectively.

Death. A 47 year old, markedly obese ("weight >> 100 kg and short stature") woman started Petibelle in January 2001. She had no recent history of oral contraceptive use but had received Prosiston (norethisterone acetate 6 mg/EE 30 µg) for 7-10 days to initiate menses just prior to starting Petibelle. On February 21 (during the second cycle of use), she developed dyspnea and was taken to

the hospital. An echocardiogram showed signs of "chronic cor pulmonale and possible hypertrophy of the right ventricle. The ECG showed "no signs of hyperkalemia." The woman died on February 22 due to "cardiovascular failure with hypoxic brain damage." (Sponsor's statements in communication of April 9, 2001). The cause of death on the death certificate was "myocardial infarct" although a pulmonary embolus could not be ruled out since an autopsy was not performed.

Medical Officer's Comments

- The sponsor's communication of April 9, 2001 was the source of most of the information regarding this woman's death. In that communication, the Sponsor noted that the attending physician "definitely excluded hyperkalemia as a cause of death." Although it was not reported if this woman was a smoker, her age and weight would be expected to increase her risk for a cardiovascular adverse event while using an oral contraceptive.
- In pivotal and supportive Phase III clinical trials with Yasmin (Study 92052 [European Pivotal Study], Study 96049 [US Pivotal Study], and Study 93044 [European Supportive Study]), approximately 2400 women were treated with Yasmin over 27,000 treatment cycles. In these studies there was 1 reported death, 1 reported pulmonary embolus (suspected) in a 32 year old women 3 weeks after a cholecystectomy, and 2 cases of thrombophlebitis (per the original medical review by D. Hixon, March 2000). The death occurred in a 28 year old woman who, after taking Yasmin for 5 months, died suddenly of a cardiac arrest. Autopsy findings revealed a severe post-streptococcal myocarditis. In the 2 previously unreported clinical trials described in this review (Studies 97036 and 96097), 1 case of deep venous thrombosis and no deaths or pulmonary emboli were reported. The overall reported frequencies of these serious adverse events in clinical trials with Yasmin are comparable to those reported for other combination oral contraceptives.
- The Sponsor has reported that approximately [redacted] cycles of Yasmin and Petibelle have been sold in Germany since its launch in November 2000. The Sponsor estimates that, based on sales and prescribing practices in Germany, 214,000 women have been exposed to Yasmin for at least 2 months (428,000 cycles of exposure). The Medical Reviewer (using slightly different assumptions) estimates that exposure to Yasmin during the period from November 1, 2000 through February 15, 2001 is 275,000 cycles or approximately 21,000 treatment years. Based on the reported incidence of 4.1 venous thromboembolic events (VTEs)/10,000 years of oral contraceptive use, one might expect 8.6 VTEs to have occurred in Yasmin users since its launch in Germany.
- It is difficult at this time to assess the overall significance of the reported thrombotic or thromboembolic adverse events in women using Yasmin in Germany as the reporting period covers only a 4 month interval and there is likely to be underreporting of such events. Additional post marketing safety data obtained over a longer period would help to clarify the significance of these adverse events.

Reports from literature

The Sponsor states that a review of the literature disclosed no new information that would impact on safety labeling.

REVISED LABELING FOR YASMIN

The Approvable Letter of July 10, 2000 was based, in part, upon labeling agreed to by both Berlex and DRUDP. Based on information provided in the November 6, 2000 Complete Response, Berlex has made modifications to the label in the following sections:

Contraindications and **Warnings** sections

"Renal insufficiency" was changed to "Severe renal insufficiency"

Interactions with Drugs that Have the Potential to Increase Serum Potassium

The reference to a potential interaction with NSAIDs was deleted (see lined through text below):

Such drugs include ACE inhibitors ——— ; potassium-sparing diuretics, heparin, and aldosterone antagonists. ———

Medical Officer's Comments

- The labeling changes proposed by Berlex are not supported by new data, and therefore, should not be accepted. The submission of November 6, 2000 does not contain any new information about the potential effects of Yasmin on serum potassium concentrations in renally-impaired women. Although both Study 97036D and Study 96097A included data from women who used NSAIDs, the study designs do not preclude the possibility that a woman using an NSAID concurrently with Yasmin may develop hyperkalemia. Design limitations included (1) a maximum of 2 post baseline serum potassium measurements, (2) variable duration of usage and different dosages of NSAIDs, (3) not requiring that blood samples be obtained during the period of actual NSAID use, and (4) the limited number of subjects who received 3 mg DRSP and had on-treatment measurements of serum potassium (approximately 250 subjects). Therefore, the original (or equivalent) wording regarding the potential interaction of NSAIDs with Yasmin should remain in the label.
- A statement to check serum potassium concentrations in women who are chronically using medications that may reduce the renal excretion of potassium (similar to the statement that appears in the European Union labeling described previously) should be added to US labeling.

PROPOSAL FOR FULFILLING PHASE IV COMMITMENTS

In the Complete Response submitted on November 6, 2000, Berlex has proposed a Phase IV program that consists of 2 components: (1) an educational outreach program; and (2) an active surveillance program to determine (a) the inappropriate prescribing of Yasmin, (b) occurrence of clinical events potentially related to hyperkalemia with use of Yasmin, and (c) the monitoring of pregnancies that occur during the use of Yasmin for the occurrence of congenital malformations.

Educational Outreach Program.

The primary objective of this program will be to educate health care providers (physicians, nurse practitioners, nurses, and pharmacists) on the appropriate patients to whom Yasmin can be prescribed so that use in the at-risk patient is minimized. This information will be provided via several venues including the Berlex sales force and CME programs (lunches, grand rounds, symposia, etc.). The Sponsor proposes to measure the success of these educational programs by tracking prescribing patterns (monitored quarterly) and to modify the educational program as warranted.

Surveillance Program

Overview. The objectives of the surveillance program are to determine (1) the inappropriate prescribing of Yasmin, (2) the occurrence of clinical events potentially related to hyperkalemia in women using Yasmin, and (3) the monitoring of pregnancies that occur during the use of Yasmin for the occurrence of congenital malformations. To achieve these objectives, Berlex will utilize a large database maintained by ——— to follow relevant patient cohorts over 3 years. Specified outcomes will be monitored quarterly. Events that are identified will be confirmed by chart review with findings for each incident summarized in a full case-report.

Database. The sponsor states that ——— has a large research database that captures health care events on — illion of its subscribers. Approximately 800,000 of these subscribers are women, 20-40 years of age. Berlex estimates that Yasmin users captured in the ' ——— database will represen. — of all users in the United States. Berlex also estimates that over the 3 year

surveillance period, approximately 360,000 woman-months of Yasmin use will accrue in women represented in the database.

Methods. The project will be initiated at the time of the US launch of Yasmin. Data collection will continue for 3 years. The study cohort will be comprised of a control group and Yasmin users in a 2:1 ratio. Cases of death, hospitalization, arrhythmia, and other criteria yet to be defined, as well as any care attributed to otherwise unexplained hyperkalemia and electrolyte disturbances (based on disease and procedure codes) will be identified. Pregnancies in the study cohort also will be identified and outcomes determined.

Outcomes Assessment. Cases of potentially inappropriate prescribing will be identified by examining pharmacy claims data for Yasmin prescriptions among women with diagnostic codes and services compatible with renal or hepatic dysfunction. The occurrence of clinical events potentially related to hyperkalemia, hospitalizations, and deaths will be identified and reported in relation to Yasmin or other contraceptive use status, providing a risk (events per 1000 users) and the incidence rate (events per 1000 woman-months). For each event that meets the appropriate criteria, a medical chart review will be conducted and a narrative history will be prepared. The incidence of pregnancies in the study cohort and their outcomes also will be reported. To allow all breakthrough pregnancies to reach term and to allow for the assessment of any abnormal infant outcomes, this aspect of the surveillance program will be continued through 18 months beyond the end of the formal 3 year surveillance period.

Medical Officer's Comments

- The overall program outlined by Berlex to fulfill the requested Phase IV objectives described in the Approvable Letter of July 10, 2000 appears to be appropriate. The Sponsor has proposed both an educational outreach program to minimize inappropriate prescribing of Yasmin and a surveillance program to monitor (1) the inappropriate prescribing of Yasmin, (2) occurrence of clinical events potentially related to hyperkalemia during use of Yasmin, and (3) the monitoring of pregnancies that occur during the use of Yasmin for the occurrence of congenital malformations.
- The surveillance program is described in moderate detail and appears to be feasible. The power of the surveillance program will depend, in part, on the number of women represented in the database who actually use Yasmin. If the sponsor's estimates are correct, the program should be adequately powered. It is not clear from the proposal if the monitoring procedures will capture most hospitalizations and hospital-related medical care.
- Less detail is provided by the Sponsor concerning the design and implementation of the educational outreach program. Education of physicians and health care providers is one of the most important aspect of the Phase IV program and must be given high priority. Specific limits of inappropriate prescribing of Yasmin, well below the estimated oral contraceptive use of 1.4 renally-impaired and 5.6 hepatically-impaired oral contraceptive users/10,000 oral contraceptive users (data provided by Sponsor), should be established. It also is not clear as to how the Sponsor will accurately determine inappropriate prescribing patterns outside of the United Healthcare system.
- The educational outreach program must also stress the importance of spontaneous reporting by healthcare providers of serious adverse events in Yasmin users. The reporting of serious adverse events by healthcare providers outside of the United Healthcare system is of particular importance. The Sponsor should devise procedures to facilitate this process.
- Although the proposal indicates that data will be collected quarterly, the proposal does not clearly state the frequency with which reports will be provided to the FDA. There should be quarterly reporting to the FDA as well. Reports should include line listings, summary tables, and relevant narratives.
- A more detailed review of the Sponsor's phase IV proposal is provided by OPDRA (C. McCloskey, MD, MPH, March 23, 2001).

- The sponsor also reported in the Safety Update of March 27, 2001 that an epidemiological study entitled "The European Active Surveillance Study on Oral Contraceptive Prescribing Practice, Benefits, and Safety" began in February 2001 and will end early in 2006. This is a physician based, multinational study with a primary objective of comparing incidence rates of adverse events in women using Yasmin to those in women using other oral contraceptives. The combined cohort (Yasmin and other oral contraceptive users) is expected to include 30,000 women and 887,000 treatment cycles

MEDICAL OFFICER'S SUMMARY OF FINDINGS AND RECOMMENDATIONS

New information submitted in response to the Approvable Letter of July 10, 2000 included (1) safety data from 2 clinical trials not previously submitted to NDA 21-098, (2) a description of the Sponsor's proposed Phase IV Program, (3) revised labeling, and (4) a brief safety update.

Summary of New Clinical Findings

Study 97036D

Methods. Reproductive-aged women with PMS or PMDD were treated with either 3 mg DRSP + 30 µg EE (Yasmin) or placebo. One hundred twenty nine (129) subjects received DRSP/EE and 130 subjects received placebo. Each treatment cycle consisted of treatment for 21 days with blinded Study Drug (DRSP/EE or placebo) followed by 7 days of treatment with inactive tablets. In the DRSP/EE group, a total of 83 and 39 subjects completed 3 and 6 treatment cycles, respectively. A blood sample for the measurement of serum chemistries (including serum potassium concentration) was to be obtained at baseline and at the end of Treatment Cycles 3 and 6.

Findings. The mean changes in post baseline average and maximum serum potassium concentrations, relative to baseline, were similar in both the DRSP/EE and placebo treatment groups. The highest post baseline serum potassium value reported in each treatment group was 5.5 mEq/L. The number of subjects with any of 6 cardiovascular adverse events identified by the sponsor as potentially related to hyperkalemia (i.e., arrhythmia, bradycardia, dizziness, palpitations, syncope, and tachycardia) was similar in the DRSP/EE group (n=3) to that in the placebo group (n=5). None of these subjects was reported to have had hyperkalemia.

Study 96097A

Methods. Postmenopausal women, with or without menopausal symptoms, who satisfied the inclusion/exclusion criteria were randomly assigned to 1 of 5 treatment groups (1 mg E2 alone or 1 mg E2 plus 0.5 mg, 1 mg, 2 mg, or 3 mg of DRSP). Subjects were to receive once daily treatment for one year (thirteen 28-day treatment cycles). The number of subjects that received one or more doses in the 5 treatment groups ranged from 226 (E2 alone) to 231 (E2/DRSP 1 mg and E2/DRSP 3 mg). A blood sample for the measurement of serum chemistries (including serum potassium concentration) was to be obtained at baseline and at the end of Treatment Cycle 7 (Study Day 196) and Cycle 13 (Study Day 364).

Findings. The mean changes in post baseline average and maximum serum potassium concentrations, relative to baseline, in the four DRSP/E2 treatment groups were similar to, or slightly greater than those in the E2 alone treatment group (relative mean potassium increases of ≤ 0.12 mEq/L compared to E2 alone). Eighteen subjects had a baseline serum potassium < 5.5 mEq/L (below the upper limit of the normal range) and a post baseline value ≥ 5.5 mEq/L. The highest post baseline serum potassium value reported was 6.1 mEq/L (one subject in the E2/DRSP 0.5-mg group).

Number of subjects with post baseline serum potassium values ≥ 5.5 mEq/L*

E2 alone	E2 plus 0.5 mg DRSP	E2 plus 1 mg DRSP	E2 plus 2 mg DRSP	E2 plus 3 mg DRSP
3	3	6	6	0

* Includes only subjects with baseline serum potassium levels of < 5.5 mEq/L.

Forty-six subjects had one or more cardiovascular adverse events that could potentially be related to hyperkalemia as summarized below.

Number of subjects in respective group reporting selected cardiovascular adverse events*

E2 alone	E2 plus 0.5 mg DRSP	E2 plus 1 mg DRSP	E2 plus 2 mg DRSP	E2 plus 3 mg DRSP
8	7	13	12	6

* Includes arrhythmia, bradycardia, dizziness, palpitations, syncope, and tachycardia.

In summary, in these healthy postmenopausal women receiving daily E2/DRSP for up to one year, there were (1) small increases (≤ 0.12 mEq/L) in mean post baseline serum potassium concentrations in subjects treated with E2/DRSP compared to those treated with E2 alone and (2) no apparent dose-related increases in selected cardiovascular adverse events potentially related to hyperkalemia.

Limitations of Study Findings

Neither Study 97036D nor Study 96097A was specifically designed to assess the effects of treatment with DRSP on serum potassium concentrations. Therefore, the information obtained from these studies regarding changes in serum potassium concentrations in women treated with DRSP and adverse events potentially related to hyperkalemia must to be interpreted with some caution.

- In both studies, only 1 or 2 post baseline serum potassium measurements were obtained.
- In Study 97036D, only approximately 48 of the 129 subjects treated with DRSP/EE had a serum potassium measurement either during or within 72 hours of dosing with active Study Drug.
- In both studies, serum samples that appeared to be hemolyzed or that had "prolonged contact with RBCs" were excluded from analysis by the [redacted]. Although these screening procedures will exclude elevated potassium values that are a result of inappropriate specimen processing, they also may exclude elevated potassium values that are a result of true clinical hyperkalemia.
- The 6 adverse events identified by the Sponsor as potentially related to hyperkalemia (arrhythmia, bradycardia, dizziness, palpitations, syncope, and tachycardia) are neither specific for hyperkalemia nor sensitive indicators of mild to moderate hyperkalemia.

Summary of Safety Update

Since the launch of Yasmin (also known as Petibelle) in Europe in November 2000, 1 death (presumably due to a myocardial infarction or pulmonary embolus) in a 47 year old obese woman during her second treatment cycle and nonfatal serious adverse events (SAEs) in 7 women were reported in users of commercially available Yasmin/Petibelle. The nonfatal SAEs in 4 of the 7 women were ischemic or thromboembolic in nature. These were (1) one case of a posterior cerebral infarct in a woman also using rizatriptan for the treatment of migraine headaches, (2) two cases of peripheral venous thrombosis (one in a woman with bronchial carcinoma), and (3) one case of relatively nonspecific symptoms that could possibly have been a result of a venous thrombosis and pulmonary embolus (neither of which was documented and for which no treatment was provided).

- It is difficult to assess at the present time the overall significance of the 5 thromboembolic or ischemic adverse events that have been reported in woman using commercially available Yasmin. They are infrequent, but not unexpected adverse events associated with the use of oral contraceptives. Only 1 of the 4 nonfatal thrombotic events was both well documented and occurred in a woman without other significant risk factors (use of rizatriptan in one woman and bronchial carcinoma in another woman). Although the reported frequency of these events since the launch of Yasmin is less than that reported in several epidemiological studies (4.1/10,000 years of use), the rate of underreporting to the Sponsor is not known. The short reporting period (4 months since product launch) further complicates interpreting the significance of these ischemic or thromboembolic events.

Overall Risk/Benefit Assessment

- Yasmin is a combination oral contraceptive product that contains the progestogen drospirenone (DRSP). Drospirenone is a new molecular entity that has both progestational and anti-mineralocorticoid activity and little, if any, estrogenic, androgenic, or glucocorticoid activity. The clinical development program included 2 pivotal and 1 supportive Phase III clinical trials and more than 30 additional supportive clinical studies. In these studies more than 2,700 subjects were treated with 3 mg DRSP/30 µg EE (Yasmin). Approximately 1,900 subjects completed at least 13 cycles of use with a total cycle use in excess of 30,000. Yasmin was shown to be efficacious in preventing pregnancy with an overall Pearle index of approximately 0.55. The safety profile of Yasmin in these clinical studies appeared to be comparable to those of other approved combination oral contraceptive products. One death (attributed to a post streptococcal myocarditis) and one case of pulmonary embolus were reported in the studies included in the NDA submission.

- The sponsor claims that the overall pharmacological properties of DRSP (anti-mineralocorticoid activity and low androgenicity) may provide some benefits over other progestogens presently in clinical use. These potential benefits include a lower incidence of fluid-retention-related and androgen-related adverse events. To date, however, these potential benefits of DRSP have not been demonstrated in adequate clinical trials. Although the anti-mineralocorticoid activity of DRSP may be beneficial in some circumstances, it also has the potential to induce hyperkalemia in women with impaired capacity to excrete potassium due to intrinsic renal disease or concomitant use of other drugs that may reduce renal potassium excretion (e.g., NSAIDs, ACE inhibitors, potassium sparing diuretics). The Sponsor reports that DRSP is approximately 8-fold more potent than spironolactone in terms of anti mineralocorticoid activity. The suggested daily clinical dose of spironolactone ranges from 25 to 200 mg/day (PDR, 2001 edition). A daily dose of 3 mg of DRSP is therefore comparable to the lowest daily recommended dose of spironolactone.

- The medical reviewer for the original NDA for Yasmin (submitted in May 1999) found no evidence of clinically significant, Yasmin-associated hyperkalemia in the studies submitted at that time. Subsequent to the original NDA, the sponsor submitted data from 2 small clinical studies to assess the effects of DRSP on serum potassium in women with (1) mild or moderate renal impairment and (2) women using an ACE inhibitor for control of hypertension as well as safety data from the 2 additional studies described in detail in this review. In these studies, treatment with DRSP alone or in combination with EE or E2 was shown to have either no effect or a small effect on serum concentrations of potassium. These findings are to be expected based on the known pharmacology of DRSP. It must be appreciated, however, that the clinical studies conducted with Yasmin were not, in general, designed to investigate the effects of DRSP on potassium homeostasis; consequently, they must be interpreted with some degree of caution (see previous comments by Medical Reviewer under "Limitations of Study Findings").

- It is possible that under a specific set of conditions a woman using Yasmin for prevention of pregnancy will experience a clinically serious adverse event as a consequence of hyperkalemia. However, based on presently available data, the likelihood of this appears to be acceptably low and can be further reduced through (1) appropriate labeling and (2) education of healthcare providers as to women who should not receive Yasmin (Phase IV commitment). Lastly, the Sponsor reports that the number of women using of oral contraceptives who also have either renal or hepatic disease is presently low (i.e., 1.43 women with renal disease and 5.6 women with hepatic disease per 10,000 oral contraceptive users, based on data obtained from the New England Insurer Research Database). The Phase IV educational program for healthcare providers should reduce further the use of Yasmin in this population at greater risk for developing hyperkalemia.

- The significance of the one reported death (from a myocardial infarct or pulmonary embolus) and the 4 nonfatal thrombotic or ischemic adverse events is uncertain at this time. Of these 5 serious adverse events, however, only one was well documented or occurred in the absence of other factors know to increase the risk of a thrombotic or ischemic event.
- A review of thromboembolic adverse events reported to the FDA for the first post approval year for 8 different combined oral contraceptive products revealed 8 such events (range: 0 events to 4 events depending upon the product). Since DRSP has not previously been used in a contraceptive product and is not closely related to any progestogen presently used in a contraceptive product, additional post marketing safety information would be helpful in assessing the significance of the serious adverse events reported in women using commercially available Yasmin in Germany.

Medical Officer's Overall Recommendations

1. Approval of Yasmin for the prevention of pregnancy is recommended pending the Sponsor's (a) providing additional post marketing safety data, (b) acceptance of the labeling changes described below, and (c) adequately addressing the outstanding Phase IV issues listed below. The sponsor has otherwise adequately addressed each of the issues in the approvable letter of July 10, 2000.

2. The sponsor should provide an updated Safety Report for the period through June 1, 2001. Such a reporting period will provide for 6 months of on-market use of Yasmin and an additional month for collection of the safety information.

3. The following labeling changes should be made:

   a) The Sponsor has proposed the following labeling changes: (1) changing "renal insufficiency" to "severe renal insufficiency" in the Contraindications and Warnings Sections and (2) deleting the reference to NSAIDs in the Drug Interaction Section. Neither of these changes is warranted based on the clinical data submitted to date by the Sponsor.

   b) A statement advising that serum potassium concentrations should be checked in women using Yasmin and another medication that may reduce renal excretion of potassium should be added to the approved labeling. The following or similar wording would be suitable:

      "Women using Yasmin and concomitant medications with the potential to increase serum potassium such as ACE-inhibitors, angiotensin-II-receptor-antagonists, aldosterone antagonists, potassium-sparing diuretics or NSAIDs used for long-term treatment should be tested for serum potassium during the first treatment cycle."

4. The proposed Phase IV program, with some modifications as listed below, adequately addresses the issues listed in the Approvable Letter of July 10, 2000. In additional to the program already proposed, the sponsor will need to:

   a) Provide to the FDA quarterly surveillance and educational training status reports containing line listings, summary tables, and relevant subject narratives,

   b) Ensure that the surveillance program based on the United Healthcare database will identify Yasmin users who are hospitalized, receive emergency treatment, or who experience other serious adverse events,

   c) Educate healthcare providers to the importance of reporting all serious adverse events (especially cardiac events) that occur in Yasmin users,

   d) Provide healthcare providers with a mechanism to facilitate the reporting of serious adverse events in Yasmin users, and

   e) Set acceptable limits for inappropriate prescribing of Yasmin and describe the corrective actions that will be taken if the limits are exceeded.

_____ _____

Scott E. Monroe, MD Date
Medical Officer, DRUDP

Cc: NDA 21-098
HFD-580
S. Allen, D Shames, D Hixon, S. Monroe, J Best

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

/s/

Scott Monroe
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MEDICAL OFFICER

Dena Hixon
5/11/01 04:30:59 PM
MEDICAL OFFICER

JUN 2 1 2000

Medical Officer's Review of NDA (Supplemental Clinical Information)

NDA:	21-098
Sponsor:	Berlex Laboratories, Inc.
Type of submission:	Supplemental clinical information in support of original NDA filing
Drug (generic name):	Drospirenone and ethinyl estradiol
Proposed trade name:	Yasmin
Proposed indication:	Prevention of pregnancy
Dose and route of administration:	3 mg of drospirenone (DRSP) and 30 µg of ethinyl estradiol (EE) by a once daily oral tablet for 21 days followed by a 7 day drug-free interval
Date(s) of this submission:	April 20, May 4, and May 8, 2000
Date(s) submission received:	April 24, May 5, and May 9, 2000
Date review completed:	June 16, 2000
Reviewer:	Scott E. Monroe, MD Medical Officer, DRUDP

BACKGROUND

On March 17, 2000 Berlex Laboratories was sent an Approvable Letter for NDA 21-098. Berlex was also informed that before their application could be approved, it would be necessary for them to address the following:

1. Provide final study results of the effects of Yasmin in renally impaired patients;
2. Provide additional information relating to the effects of Yasmin on serum potassium levels in women receiving drugs such as ACE inhibitors that are known to reduce renal tubular secretion of potassium;
3. Provide revised draft labeling that specifically addressed items 1 and 2 above; and
4. Provide a safety update.

Items No. 1 and 2 were requested because drospirenone has antimineralocorticoid activity (similar to that of spironolactone), and therefore, has the potential to increase serum potassium levels, particularly in women with impaired renal function or in women receiving treatment with other medications that have been shown to increase serum potassium levels.

This review is based on the following information submitted by Berlex Laboratories in response to the Approvable Letter of March 17:

- Final statistical analysis of serum potassium data from Study No. 98106 –"A double blind, randomized, 2-parallel groups study to evaluate the potential for developing hyperkalemia when the hormone replacement therapy combination drug product drospirenone/estradiol is co-administered with an ACE inhibitor in postmenopausal women." Report date: April 12, 2000; Amended Report Date: May 5, 2000.

- Final Clinical Study Report (No. B682) for Protocol No. 303063 – "Open-label study to assess the effect of 3 mg drospirenone (DRSP) on serum potassium and to evaluate the pharmacokinetics of DRSP in female volunteers with impaired or normal renal function after repeated oral administration over 14 days." Report date: May 5, 2000.
- Abbreviated Safety Update (Reporting period: January 16, 2000 to March 17, 2000). Submission date: May 4, 2000; supplemental information provided on June 16, 2000.

CLINICAL PROTOCOL NO. 98106

Study Title

"A double blind, randomized, 2-parallel groups study to evaluate the potential for developing hyperkalemia when the hormone replacement therapy combination drug product drospirenone/estradiol is co-administered with an ACE inhibitor in postmenopausal women."

Study Objectives

The primary objective of this study was to evaluate the potential for developing hyperkalemia during treatment with both an angiotensin converting enzyme (ACE) inhibitor (enalapril) and the drug combination DRSP/estradiol (E_2).

Study Design and Treatment

This was a Phase I, single center, double blind, randomized, placebo controlled, 2-group, parallel study. Twenty-four (24) subjects receiving treatment with an ACE inhibitor (enalapril, 20 mg/day) for hypertension, who met all study entry criteria, were to be randomly assigned to once daily oral treatment for 14 days with either a placebo tablet or a tablet containing 3 mg of DRSP and 1 mg of E_2. The study drug combination used in this clinical trial differed from that of Yasmin as it contained 1 mg of E_2 instead of 30 μg of ethinyl estradiol.

Study Population.

Inclusion Criteria Included

1. Generally healthy postmenopausal (natural or surgical) women, 45-75 years of age, who were receiving treatment with enalapril (10 mg bid) for mild hypertension beginning least 7 days prior to the onset of treatment with study drug and throughout the clinical trial;
2. Screening serum potassium between 3.5 and 4.5 mEq/L;
3. Screening creatinine clearance (based on the Cockcroft-Gault formula) > 60 mL/min;
4. Serum estradiol levels of ≤ 20 pg/mL and serum FSH levels of ≥ 40 mIU/mL; and
5. Essentially normal serum chemistry and hematology values.

Exclusion Criteria Included

1. A significant history of pulmonary, cardiovascular (other than mild hypertension), renal, hepatic, gastrointestinal, gall bladder/biliary, hematologic, endocrine, neurologic, or psychiatric disease;
2. Conditions that are generally considered to be contraindications (absolute or relative) to the use of hormonal contraceptives or estrogen replacement therapy including current smoking, migraine accompanied by disturbance in sensory perception or locomotion, Pap smear showing evidence of epithelial cell abnormality, vaginal bleeding of unknown etiology, and history of thromboembolic disorders or thrombophebitis;
3. Previous diagnosis of cancer other than minor skin lesions successfully treated;
4. Subjects who received (a) within 60 days prior to start of the study any drug known to induce or inhibit liver enzymes, broad-spectrum antibiotics, or any investigational drug or (b) within 30 days prior to start of study drug any sex hormone.

Clinical Study Procedures and Study Conduct

The study was conducted at a single center (Division of Clinical Pharmacology, University of Miami). Although most study procedures were conducted in an outpatient facility, subjects were studied in an inpatient facility for two 24-hour periods to permit frequent blood sampling. The inpatient assessments occurred between Pretreatment Day 1 and Treatment Day 1 and between Treatment Days 14 and 15.

The effect of treatment with DRSP/E_2 on serum potassium concentrations, compared to that of placebo, was assessed by (a) the area under the 24-hr concentration time curve ($AUC_{0\text{-}24\ hr}$) and Cmax for serum potassium prior to and on the final day of treatment with study drug and (b) by every other day single measurements of serum potassium (also referred to as "safety assessments" in the protocol) during the treatment period. The blood-sampling schedule for assessment of serum potassium concentrations is summarized in Table 1.

Table 1. The blood sampling schedule for assessment of serum potassium concentrations.

Type of Sample	Screen	Pretreatment		Treatment Period							
Day:		-2	-1	2	4	6	8	10	12	14	15
Single AM sample	X	X		X	X	X	X	X	X		X
24-hr samples[A]			X							X	

[A] Sampling times occurred at: 0, 2, 4, 6, 8, 10, 12, 18, and 24 hours

During the period of inpatient blood sampling and monitoring, a 24-hr urine was collected for the measurement of sodium, potassium, creatinine, and calcium. Blood samples for the measurement of creatinine, plasma renin activity (PRA), aldosterone and sodium were also obtained. (Data from these assessments were not provided in this abbreviated report).

Analytical Methods for Determination of Serum Potassium Concentrations

Single AM samples (safety samples). Potassium concentrations in these samples were determined using an ion selective electrode method a[illegible]

These samples were analyzed on the day of collection, typically within 4 to 6 hours from their being sent for analysis. The normal reference range for serum potassium using this method was reported by the Sponsor to be 3.5-5.3 mEq/L.

Twenty-four (24)-hr AUC samples. Potassium concentrations in these samples were determined using a validated atomic absorption assay at [illegible]. For each subject, samples from the pretreatment and end-of-treatment collections were analyzed on the same day. Normal reference ranges for this assay have not been established since the procedure is not routinely used for clinical diagnostic purposes. The Sponsor stated, however, that the assay had been validated in accordance with FDA guidelines on bioanalytical method validation.

Protocol-Defined Statistical Analysis for Serum Potassium Concentrations

The primary protocol-defined analysis for assessing the possible effects of DRSP on serum potassium concentrations was based on a comparison of the $AUC_{0\text{-}24\ hr}$ and Cmax values in the placebo and DRSP/E_2 treatment groups on the final day of treatment, adjusted for respective pretreatment values. Serum potassium levels in the DRSP/E_2 and the placebo treatment groups were to be declared bioequivalent if the 90% confidence limits for the $AUC_{0\text{-}24\ hr}$ and Cmax potassium ratios for (DRSP/Æ$_2$)/(placebo) were contained within the limits of 0.8 and 1.25.