

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*  
**21-676**

**MEDICAL REVIEW(S)**

**DIVISION OF REPRODUCTIVE AND UROLOGIC PRODUCTS  
CLINICAL TEAM LEADER MEMORANDUM**

<b>NDA</b>	NDA 21-676/N-000
<b>Type of Application</b>	Original NDA (complete response to Approvable Action)
<b>Applicant</b>	Berlex, Inc. Montville, NJ 07045
<b>Proprietary Drug Name</b>	YAZ
<b>Established Drug Name</b>	Drospirenone 3 mg/ethinyl estradiol 0.02 mg tablets
<b>Drug Class</b>	Progestin and estrogen combination
<b>Indication</b>	Prevention of pregnancy in women
<b>Route of Administration</b>	Oral
<b>Dosage Form</b>	Tablet
<b>Dosage Strength</b>	Drospirenone 3 mg/ethinyl estradiol 0.02 mg per tablet
<b>Dosing Regimen</b>	One drospirenone/ethinyl estradiol tablet daily for 24-consecutive days followed by 4 placebo tablets (a 28-day dosing cycle that is repeated)
<b>CDER Receipt Date</b>	June 16, 2005
<b>PDUFA Goal Date</b>	March 16, 2006 (Based on 3-month extension)
<b>Date of Memorandum</b>	March 16, 2006
<b>Reviewer</b>	Scott E. Monroe, MD Clinical Team Leader/Deputy Director, DRUP

**1. RECOMMENDATIONS**

**1.1 RECOMMENDATION REGARDING APPROVABILITY**

I recommend that drospirenone 3 mg/ethinyl estradiol 0.02 mg tablets (24-day active dosing regimen) be approved for the indication of "*prevention of pregnancy in women who choose to use an oral contraceptive.*"

**1.2 BASIS FOR RECOMMENDATION REGARDING APPROVABILITY (RISK/BENEFIT ANALYSIS)**

My recommendation for approval of drospirenone (DRSP) 3 mg/ethinyl estradiol (EE) 0.02 mg tablets (YAZ) for marketing as a combination oral contraceptive is based on the data provided in the original NDA submitted on October 16, 2003, the Applicant's Complete Response submitted on June 15, 2005, additional information submitted during both review cycles, and final revised labeling submitted on March 16, 2006.

DRSP 3 mg/EE 0.02 mg was shown to have acceptable efficacy (Pearl Index of 1.41, 95% confidence interval [CI]: 0.73-2.47) and an acceptable safety profile for an effective hormonal contraceptive product in the primary clinical trial (Study 303740) submitted in support of this Application. Additional efficacy and safety data were provided by the Applicant from supportive clinical trials with DRSP 3 mg /EE 0.02 mg for (1) prevention of pregnancy (Studies 308020 and 308021) and (2) proposed secondary indications (i.e., treatment of premenstrual dysphoric disorder [PMDD] and acne). There are no preclinical toxicology, chemistry, manufacturing, and controls (CMC), or biopharmaceutical deficiencies.

### 1.3 RECOMMENDATION ON RISK MANAGEMENT STEPS AND/OR PHASE 4 STUDIES

#### 1.3.1 Risk Management Steps



**Labeling.** All contraindications and bolded warnings regarding the risk of hyperkalemia presently included in the approved labeling for Yasmin (the only other oral contraceptive that contains DRSP) as well as other sections unique to labeling for Yasmin are retained in labeling for DRSP 3 mg/EE 0.02 mg tablets (YAZ).

#### 1.3.2 Phase 4 Studies

The Applicant will conduct a large postmarketing, international, prospective, controlled, non-interventional study. The primary objective will be to compare the incidence of serious thrombotic and thromboembolic events in users of DRSP/EE oral contraceptives (both Yasmin [the Applicant's presently marketed product] and YAZ) to the incidence of these events in users of combination oral contraceptives that do not contain DRSP. The study will be conducted in the U.S. and Europe and will recruit \_\_\_\_\_

## 2. BACKGROUND

### 2.1 DESCRIPTION OF PRODUCT

Drospirenone 3 mg/EE 0.02 mg tablets contain less ethinyl estradiol (EE) than the Applicant's currently marketed product Yasmin (DRSP 3 mg/EE 0.03 mg tablets, NDA 21-098). Yasmin was approved in the U.S. on May 11, 2001 for prevention of pregnancy and is currently available in over 40 countries worldwide. Yasmin is the only contraceptive product currently marketed in the U.S. that contains the progestin DRSP. Drospirenone differs from other progestins in combination oral contraceptives in that (1) it is a derivative of 17 $\alpha$ -spironolactone and not of 19-nortestosterone and (2) it has aldosterone-antagonistic properties. In preclinical studies, DRSP also was shown to have anti-androgenic activity and no androgenic, estrogenic, or glucocorticoid activity at the doses that were investigated.

The Applicant's parent company (Schering AG)

One dosing regimen (the subject of this NDA) consists of one daily "active" tablet for 24 days followed by a daily placebo tablet for 4 days. This is the only

dosing regimen for which the Applicant is seeking marketing approval at the present time. In addition to seeking approval for the indication of prevention of pregnancy, the Applicant is seeking marketing approval for the secondary indication of PMDD (NDA 21-873) and plans to seek approval for the secondary indication of treatment of acne. DRSP 3 mg/EE 0.02 mg (24-day active dosing regimen) is not approved in any market, and there presently are no pending marketing applications for the 24-day active dosing regimen outside of the U.S.



## 2.2 REGULATORY HISTORY

The Applicant first submitted NDA 21-676 in October 2003 for the single indication of prevention of pregnancy. In the original NDA submission, the Applicant provided data from 2 non-comparative Phase 3 clinical trials that investigated the safety and efficacy of either the 24-day active dosing regimen (Study 303740) or the 21-day active dosing regimen (Study 303860). Each study included safety and efficacy data from more than 10,000 28-day treatment cycles and from more than 200 women who used DRSP 3 mg/EE 0.02 mg tablets for at least one year. Based on the submitted data, it was concluded by the Division that both the 24-day regimen and the 21-day regimen were effective in preventing pregnancy. Although the Division recommended that the Applicant seek approval for the 21-day active dosing regimen, the Applicant sought approval only for the 24-day dosing regimen. On November 17, 2004, the Division issued an approvable letter for DRSP 3 mg/EE 0.02 mg tablets that stated the following:

*We have completed our review of this application, and it is approvable. Before the application may be approved, however, it will be necessary for you to (1) demonstrate a clinical benefit for the 24-day regimen over that provided by a 21-day regimen to offset the increased potential risk associated with the additional 3 days of drospirenone/ethinyl estradiol or (2) propose a 21-day regimen for consideration. This can be accomplished by any of the following:*

- 1. Provide evidence that the proposed 24-day contraceptive dosing regimen provides a clinical benefit over that provided by a 21-day regimen. This evidence could consist of demonstrating fewer "escape ovulations" with the 24-day regimen compared to the 21-day regimen.*
- 2. Demonstrate that the 24-day regimen is safe and effective for either of the two secondary indications that are presently under investigation, premenstrual dysphoric disorder (PMDD) and acne.*
- 3. Submit an application amendment for the 21-day dosing regimen for the contraceptive indication.*

Following the Approvable Action for DRSP 3 mg/EE 0.02 mg for the indication of prevention of pregnancy in women, the Applicant submitted another NDA on December 22, 2004 (NDA 21-873) for DRSP/EE tablets that included 2 indications: (1) the primary indication of prevention of pregnancy (with cross-reference to NDA 21-676) and (2) a secondary indication for the treatment of symptoms of PMDD. On January 23, 2006, the Division issued an approvable letter for NDA 21-873. The Applicant was informed that approval of NDA 21-873

was contingent upon (1) the Division's determination that additional safety data, which was submitted late in the review cycle for NDA 21-873 (and which could not be reviewed prior to the extended PDUFA goal date) did not adversely impact on the Division's assessment of the safety profile for of DRSP 3 mg/EE 0.02 mg tablets and (2) the Applicant submitting acceptable labeling.

While the review of NDA 21-873 was ongoing, the Applicant submitted on June 15, 2005 a Complete Response to the Approvable Letter for NDA 21-676. The initial Complete Response submission included (1) a Final Report for a Phase 2 pharmacodynamic study (Study 308382) that compared the effectiveness of the 24-day dosing regimen to that of the 21-day dosing regimens in terms of suppression of ovarian activity and (2) a safety update.

### **3. OVERVIEW OF CLINICAL PROGRAM**

In addition to the Final Report for Phase 2 Study 308382 and the initial safety update submitted as the Complete Response, the Applicant subsequently submitted (at the request of the Division) (1) substantial new clinical trial efficacy and safety data for DRSP 3 mg/EE 0.02 mg tablets and (2) updated supportive postmarketing safety data for Yasmin. Additional clinical trial data included (1) a draft Final Report of a Phase 3 trial (Study 308020) that compared the safety and effectiveness of DRSP 3 mg/EE 0.02 mg over seven 28-day treatment cycles to that of Mercilon (a combination oral contraceptive approved in Europe for marketing that contains 0.150 mg desogestrel/0.02 mg EE), (2) supportive efficacy and safety data based on the initial findings from a recently completed large European Phase 3 prevention of pregnancy clinical trial (Study 308021), and (3) supportive safety data from (a) two Phase 3 clinical trials that compared the safety and effectiveness of DRSP/EE to that of placebo for the treatment of acne and (b) two Phase 3 clinical trials that compared the safety and effectiveness of DRSP/EE to that of placebo for the treatment of PMDD. This Memorandum focuses on the findings from Study 303740 (primary efficacy and safety study for the indication of prevention of pregnancy), Phase 2 Study 308382 (suppression of follicular development), and updated supportive postmarketing safety data for Yasmin.

Detailed descriptions of the efficacy and safety findings for DRSP 3 mg/EE 0.02 mg tablets for the indication of prevention of pregnancy are presented in (1) Dr. Willett's primary Medical Review (dated November 16, 2004) of original NDA 21-676 and his primary Medical Review (dated March 14, 2006) of the Complete Response to the Approvable Letter for NDA 21-676 and (2) my previous Team Leader Memorandum (dated November 17, 2004) for original NDA 21-676. Dr. Willett's primary Medical Review of March 14, 2006 also thoroughly discusses the supportive (1) clinical trial safety data from the Phase 3 studies for PMDD and acne and (2) postmarketing safety data for Yasmin.

## **4. EFFICACY FINDINGS**

### **4.1 PHASE 3 EFFICACY STUDIES**

#### **4.1.1 Principal Efficacy Study (Study 303740)**

##### **4.1.1.1 Total Exposure and Demographics**

**Study 303740.** In Study 303740 (the primary study that supported the safety and efficacy of DRSP 3 mg/EE 0.02 mg (24-day active dosing regimen), 1,027 women were exposed to study

drug for up to one year. Total exposure was 11,480 28-day cycles or 883 women-years. Of the 1,027 women exposed to Yasmin, 746 completed the one-year study. The mean age in the intent-to-treat (ITT) population was 24.7 years. The mean BMI was 22.4 kg/m<sup>2</sup>. The ethnicity of the subjects was 87.8% Caucasian, 4.6% Hispanic, 4.3% Black, 1.2% Asian, and 2.1% classified as “other.” The contraceptive methods used and the percentage of subjects using them just prior to their entry into the study were: none (11.0%), combination oral contraceptives (59.7%), condoms (27.1%), IUDs (0.3%), and other (1.9%).

**Team Leader Comments**

- *The majority of the subjects in Study 303740 were Caucasian (87.8%). Although this ethnic distribution is not representative of the ethnicity of American women who are likely to use DRSP 3 mg/EE 0.02 mg, there is no reason to believe that the safety and efficacy of the product is likely to be dependent on race, per se, based on experience with other combination oral contraceptives. However, factors such as obesity and hypertension that may be associated with an increased risk of thrombotic/thromboembolic adverse events may be more prevalent in specific ethnic groups.*
- *The Division has required that clinical trials to support the safety and efficacy of new formulations/dosing regimens for combination oral contraceptives include (1) at least 200 women who are treated for one year and (2) a total of at least 10,000 28-day treatment cycles. Study 303740 meets the Division’s requirements.*

**4.1.1.2 Disposition**

Disposition of the subjects in Study 303740 is presented in Table 1. Seventy-one (71) percent of subjects completed treatment; 6.6% terminated prematurely because of an adverse event.

**Table 1 Disposition of Subjects in Study 303740**

Subject Disposition	n	%
Subjects Enrolled	1049	100.0
Study medication never administered	20	1.9
Completed study	746	71.1
Prematurely terminated	273	26.0
Adverse event	69	6.6
Withdrew consent	34	3.2
Protocol deviation	28	2.7
Subject lost (no further info available)	50	4.8
Pregnancy	11	1.0
Other	80	7.6
Death	1	0.1
Unknown	10	1.0

Source: Table 11 from Final Report for Study 303740.

**4.1.1.3 Efficacy**

The Applicant’s protocol for establishing contraceptive efficacy was similar to other product submissions in this class. The primary efficacy endpoint was the number of “on-treatment” pregnancies. The primary efficacy analysis was based on the Pearl Index (PI), which is the number of “on-treatment” pregnancies per 100 women-years of use. The value for the Pearl

Index in Table 2 is based on (1) the primary Medical Reviewer's assessment of 12 on-treatment pregnancies (all pregnancies for which conception was assessed as occurring after the onset of treatment and within 14 days of the last dose of study drug) and (2) 11,050 28-day treatment cycles. Approximately 430 treatment cycles were excluded from the PI calculation. These cycles were excluded because of (a) the use of backup contraception, (2) the subject being over 35 years of age at entry, or (3) the subject indicating that she was not sexually active during a 28-day cycle.

**Table 2 Efficacy of DRSP 3 mg /EE 0.02 mg Tablets in Women ≤35 Years of Age (Study 303740)**

Total 28-day Cycles of Exposure	Total Number of On-Treatment Pregnancies		Pearl Index **	2-sided 95% Confidence Interval (CI)
	Applicant's Determination	FDA's Determination		
11,050 *	11	12	1.41	0.73; 2.47

\* Calculated by dividing number of days of exposure by "28". Excludes women > 35 years of age, cycles during which back up contraception was used, or cycles not associated with sexual activity

\*\* Pearl Index based on 12 "on-treatment" pregnancies

Source: Modified from Table A, pg 11, primary Medical Review by Dr. Willett for NDA 21-676 (November 16, 2004).

**Team Leader Comment**

- *The day of conception for one pregnancy was estimated as occurring 12 days after the last dose of DRSP/EE. Based on the Division's present policy of including all pregnancies that occur within 14 days of the last dose of study drug, the primary Medical Reviewer (but not the Applicant) considered this as an on-treatment pregnancy.*
- *A Pearl Index of 1.41 is acceptable for a combination oral contraceptive.*

**4.1.2 Supportive Efficacy Studies**

**Study 308020.** The Applicant submitted a draft Final Report for Study 308020, which was a comparative Study of DRSP 3 mg/EE 0.02 mg versus Mercilon for seven 28-day treatment cycles. In the DRSP/EE group, 201 of 229 subjects completed treatment. In the Mercilon group, 196 of 220 subjects completed treatment. There were no pregnancies in the DRSP/EE group, which resulted in a Pearl Index value of 0.0 (upper limit of the 2-sided 95% CI of 3.41). There was one pregnancy in the Mercilon group, which resulted in a Pearl Index value of 0.93 (upper limit of the 2 sided 95% CI of 5.19).

**Study 308021.** Study 308021 was a non comparative efficacy and safety study of DRSP 3 mg/EE 0.02 mg tablets of one year duration. The Applicant submitted efficacy data from this clinical trial, which completed the clinical phase on January 30, 2006. According to the Applicant, there were 5 on-treatment pregnancies among women 35 years of age or less in 13,248 28-day treatment cycles during which no back up contraception was used. Based on these data, the Applicant's calculated a Pearl Index value of 0.49 (two-sided 95% CI of 0.16 and 1.14).

The efficacy findings for Study 308020 and Study 306021 are summarized Table 3.

**Table 3 Efficacy of DRSP 3 mg/EE 0.02 mg Tablets in Supportive Studies 308020 and 308021**

Study Number	Total 28-day Cycles of Exposure	Number of On-Treatment Pregnancies	Pearl Index	2-sided 95% Confidence Interval
308020	1,408*	0	0.0	3.41**
308021	13,248*	5	0.49	0.16; 1.14

\* Excludes cycles during which back-up contraception was used

\*\* Upper limit of 2-sided 95% CI

Source: Submissions of (a) November 22, 2005, final Draft Report for Study 208020, pg 58 and (b) March 9, 2006 (additional information for Study 308021).

### **Team Leader Comments**

- *Because the Division did not review the actual data listings for Study 308021, it is possible that the primary Medical Reviewer would have identified additional on-treatment pregnancies not reported by the Applicant. However, even if several (i.e., up to 5) additional pregnancies were identified during a complete review by the Division of the data, the Pearl Index value would not exceed 1.0.*
- *The findings from both Study 308020 and Study 308021 support the conclusion that DRSP 3 mg/EE 0.02 mg tablets are effective for the prevention of pregnancy.*

### **4.2 PHASE 2 SUPPORTIVE EFFICACY STUDY**

To address the Division's request that approval of the 24-day active dosing regimen of DRSP 3 mg/EE 0.02 mg tablets could be supported by demonstrating a "clinical benefit" or "fewer escape ovulation" with the 24-day regimen, the Applicant submitted Study 308382. This was a single center, double-blind, randomized study of follicular development in 100 women treated with DRSP/EE tablets by either a 24-day active dosing regimen or a 21-day active dosing regimen. Inhibition of follicular development and inhibition of ovulation was assessed by ultrasound monitoring of follicle size and measurement of serum progesterone (P) and 17- $\beta$ -estradiol (E2) concentrations. Ovarian activity was classified according to the Hoogland scoring system that is described in Table 4.

**Table 4 Hoogland Scoring System**

Score	Ovarian Activity	Diameter of FLS (mm)	P (nmol/L) *	E2 (nmol/L)
1	No activity	$\leq 10$	--	
2	Potential activity	$> 10$	--	
3	Non-active FLS	$> 13$	--	$\leq 0.1$
4	Active FLS	$> 13$	$\leq 5$	$> 0.1$
5	LUF	$> 13$ , persisting	$> 5$	$> 0.1$
6	Ovulation	$> 13$ , ruptured	$> 5$	$> 0.1$

FLS = Follicle like structure; LUF = Luteinized unruptured follicle;

\* To convert from nmol/L to ng/mL, multiply by 0.3145

Source: Table 4, pg 25, primary Medical Review by Dr. Willett for NDA 21-676 (March 14, 2006).

The treatment phase consisted of three 28-day cycles, during which subjects received either 24 or 21 days of treatment with DRSP 3 mg/EE 0.02 mg. Frequent measurements of follicle size and hormone levels were carried out during Cycles 2 and 3 to assess ovarian activity. In treatment Cycle 3, the effect of not taking 3 tablets on ovarian activity was investigated to simulate the

clinical situation in which a woman might forget to take 3 consecutive birth control tablets. The ultrasonography and serum hormone level findings for Treatment Cycles 2 and 3 are summarized in Table 5 and Table 6, respectively.

**Table 5 Results of Hoogland Scoring for Treatment Cycle 2**

Hoogland Score and Category	24-Day Regimen N= 52	21-Day Regimen N = 52
1- No activity	45	28
2- Potential activity	5	11
3- Non-active FLS	0	0
4- Active FLS	1	11
5- LUF	0	1
6- Ovulation	0	1
No result	1	0

FLS = Follicle like structure; LUF = Luteinized unruptured follicle;

Source: Table 6, pg 27, primary Medical Review by Dr. Willett for NDA 21-676 (March 14, 2006).

**Table 6 Results of Hoogland Scoring for Treatment Cycle 3**

Hoogland Score and Category	24-Day Regimen N = 52	21-Day Regimen N = 52
1- No activity	27	15
2- Potential activity	8	7
3- Non-active FLS	0	0
4- Active FLS	13	24
5- LUF	0	0
6- Ovulation	1	4
No result	3	2

FLS = Follicle like structure; LUF = Luteinized unruptured follicle;

Source: Table 7, pg 28, primary Medical Review by Dr. Willett for NDA 21-676 (March 14, 2006).

#### **Medical Officer's Comments**

- *In both treatment cycles nearly twice as many subjects in the 24-day regimen compared to the 21-day regimen were classified as having "no activity."*
- *In Cycle 3, there was only one escape ovulation in the 24-day regimen compared to 4 escape ovulations in the 21-day regimen.*

The Applicant utilized a proportional odds model to compare the Hoogland scores across treatment groups (see Table 7). An odds ratio of >1 indicates that the Hoogland scores across treatment groups are different and is compatible with greater ovarian suppression in the 24-day dosing regimen.

**Table 7: Odds Ratios for Treatment Effect in Cycles 2 and 3**

Cycle	Estimated Odds Ratio	95% CI
2	6.91	[2.67;20.49]
3	3.06	[1.44;6.65]

Source: Modified from Table 9, pg 29, primary Medical Review for NDA 21-676 (March 14, 2006).

### **Team Leader Comments**

- *The odds ratios for treatment cycles 2 and 3 were 6.91 and 3.06, respectively.*
- *The lower limit for the respective 95% CI did not cross 1, a finding compatible with a statistically significant treatment effect.*

### **4.3 OVERALL ASSESSMENT OF EFFECTIVENESS**

DRSP 3 mg/EE 0.02 mg tablets (YAZ, 24-day dosing regimen) is effective for prevention of pregnancy. The Pearl Index of 1.41 (95% CI: 0.73-2.47) in Study 303740 (the primary efficacy study in support of this NDA) is well within the acceptable range for a combination oral contraceptive. Data from supportive Study 308020 (Pearl Index value of 0.0) and Study 308021 (Pearl Index value of 0.49) provide additional evidence that DRSP 3 mg/EE 0.02 mg tablets are effective for prevention of pregnancy.

Data obtained from a Phase 2 study (based on the Hoogland scoring system) indicated that the 24-day active dosing regimen produced greater suppression of ovarian follicular development than a 21-day active dosing regimen. Whether this finding would be associated with a reduced pregnancy rate in actual clinical use is not known.

## **5. SAFETY FINDINGS**

The safety component of this Memorandum focuses on serious adverse events that are known to occur in users of combination oral contraceptives or serious adverse events that occurred in clinical trials with DRSP 3 mg/EE 0.02 mg (both the 24- and 21-day dosing regimens). The primary medical reviewer (Dr. G. Willett) has reviewed in detail the safety profile of DRSP 3 mg/EE 0.02 mg in his primary Medical Reviews of November 16, 2004 (original NDA 21-676) and March 14, 2006 (the present submission). Based on the clinical trial information provided by the Applicant in this submission, data previously submitted data to NDA 21-676, and postmarketing safety data from Yasmin, I concur with the primary Medical Reviewer's overall assessment that the reported safety profile for DRSP 3 mg/EE 0.02 mg tablets (24-day dosing regimen) (1) is acceptable for an effective combination oral contraceptive and (2) supports a recommendation for approval for the indication of prevention of pregnancy in women.

### **5.1 CLINICAL TRIAL SAFETY DATA FOR DRSP 3 MG/EE 0.02 MG**

Safety data in this review are current as of the Applicant's (1) last general safety update (data cut-off date of January 23, 2006) and (2) submission of safety data on March 3, 2006 for recently completed Study 308021.

### 5.1.1 Exposure to DRSP 3 mg/EE 0.02 mg Tablets

Subject exposure to DRSP 3 mg/EE 0.02 mg tablets (24 day active dosing regimen) is summarized in Table 8. Total exposure across all studies (including studies conducted for the secondary indications of PMDD and acne) was greater than 28,981 28-day treatment cycles. Exposure to DRSP 3 mg/EE 0.02 mg tablets in Study 303740 (the primary efficacy and safety study) was 11,480 28-day cycles.

**Table 8 Subject Exposure to DRSP 3 mg/EE 0.02 mg Tablets**

Study No.	Purpose of Study	No. Subjects on DRSP/EE	Duration of Treatment (cycles)	Total No. of 28-Day Treatment Cycles	No. of Subjects Treated for 1 yr
303740	Contraception (24-day)	1027	13	11,480	746
301888	Metabolic Effects	29	7	182	0
304049	Treatment of PMDD	231	3	579	0
305141	Treatment of PMDD	54	3	140	0
308020	Cycle control comparative	227	7	1354	0
306996	Treatment of Acne	270	6	~1407*	0
306820	Treatment of Acne	266	6	~1346*	0
308021	Contraception	1,101	13	> 12,493**	961
<b>Subtotal</b>		<b>2,442</b>	<b>NA</b>	<b>&gt; 28,981</b>	<b>1,707</b>

\* = Derived by (#subjects x mean number of days on drug) divided by 28 days

\*\*= Based on 961 subjects completing one year of treatment; the value under-estimates exposure as it does not include treatment cycles from subjects who prematurely discontinued treatment

Source: Modified from Table 38, pg 63, primary Medical Review for NDA 21-676 (March 14, 2006).

### Team Leader Comments

- *To assess the safety of a new hormonal contraceptive product, the Division requires that at least 200 subjects complete one year of treatment and that total exposure include at least 10,000 28-day treatment cycles. Data in support of NDA 21-676 exceed these requirements.*
- *In the original submission for NDA 21-676, total exposure to DRSP 3 mg/EE 0.02 mg (24 day active dosing regimen) included only 11,662 28-day treatment cycles. In the present submission (Complete Response), total exposure data has increased significantly to > 28,981 28-day treatment cycles.*

### 5.1.2 Deaths

Four deaths have been reported in clinical studies of DRSP 3 mg/EE 0.02 mg tablets. Two of the deaths occurred in Study 303740 (the principal contraceptive safety and efficacy Phase 3 study for the 24-day regimen) at the single US study site. One of the deaths, secondary to pesticide poisoning, occurred one month following discontinuation of DRSP/EE. The other death, occurring 3 months after starting DRSP/EE, was secondary to smoke inhalation in a fire. The

other 2 deaths occurred in non-U.S. Study 308021, which was an open label efficacy and safety study of the 24-day regimen for 13 cycles in 1,010 subjects. One of these deaths was secondary to Goodpasture's syndrome; the other death was secondary to murder.

**Team Leader Comment**

- *None of the deaths was assessed as being related to treatment with DRSP/EE by either the Investigators or the FDA primary Medical Reviewer. Based on information provided in the Applicant's submission, I concur with the primary Medical Reviewer.*

**5.1.3 Serious Thrombotic or Thromboembolic Events**

There is a well-known increased risk for thrombotic and thromboembolic adverse events, including pulmonary embolus associated with death, in women who use combination oral contraceptives. In the clinical trials with DRSP/EE tablets, the Applicant reported 2 cases of confirmed pulmonary embolus (both in women using the 21-day regimen).

**Team Leader Comments**

- *The primary Medical Reviewer estimated that the rate of serious venous thromboembolic events (VTEs) in clinical trials with DRSP 3 mg/ EE 0.02 mg is approximately 6.1 per 10,000 women-years of use. This value is based on the 2 reported cases of pulmonary embolus and an estimated total exposure of 42,338 total treatment cycles (includes cycles from both 21- and 24-day active dosing regimens) or 3,257 women-years of exposure. (Exposure data is approximate since data from recently completed Study 308021 have not been fully validated).*
- *According to the primary Medical Reviewer, the rate of 6.1 per 10,000 women-years of use is lower than the VTE rate for the approved product Yasmin in the first year of the postmarketing EURAS Study (approximately 15 cases per 10,000 women-years, see Section 5.2). This rate is also lower than the VTE rate in the postmarketing Prescription-Event Monitoring (PEM) Study for Yasmin carried out in the UK. The VTE incidence rate in the PEM Study was 13.7 cases per 10,000 women-years.*
- *Since both cases of pulmonary embolus occurred in users of the 21-day active dosing regimen, there is no suggestion, based on clinical trial data, that the 24-day regimen poses a greater risk for the development of serious thrombotic adverse events than the 21-day regimen.*

**5.1.4 Adverse Events Leading to Premature Termination of Treatment**

In Study 303740 (principle safety and efficacy study for the 24-day regimen), a total of 125 adverse events in 77 of 1,027 volunteers (7.5%) led to discontinuation of treatment with study medication. The most common adverse events leading to premature discontinuation of treatment were headache in 14 subjects (1.4%), intermenstrual bleeding, and nausea in 7 subjects (0.7%) each, and decreased libido and depression in 6 subjects (0.6%) each. A total of 65 volunteers prematurely discontinued the study medication due to treatment-related adverse events. Table 9 lists the most common adverse events leading to premature discontinuation of treatment and the number of subjects reporting each of them.

**Table 9 Most Common Adverse Events Associated with Premature Discontinuation of Study Medication (Study 303740)**

ADVERSE EVENT	N = 1027	
	AEs	(%)
Headache	14	1.4
Intermenstrual bleeding	7	0.7
Nausea	7	0.7
Libido decreased	6	0.6
Depression	6	0.6
Emotional lability	5	0.5
Vomiting	5	0.5
Dysmenorrhea	5	0.5
Breast pain	4	0.4
Weight gain	4	0.4
Abdominal pain	4	0.4
Rash	3	0.3
Acne	3	0.3
Migraine	3	0.3
Back pain	2	0.2
Asthenia	2	0.2
Abnormal laboratory test	2	0.2
Edema	2	0.2
Sweating increased	2	0.2
Dizziness	2	0.2
Somnolence	2	0.2
Menorrhagia	2	0.2

Source: Table 15, pg 41, Primary Medical Review for NDA 21-676 (March 14, 2006).

### **Team Leader Comment**

- *The adverse events leading to premature discontinuation of treatment in Study 303740 are commonly reported in users of combination oral contraceptives and may lead to drug discontinuation. The percentages of subjects discontinuing treatment because of these adverse events are not increased above those expected in a one year clinical trial for a combination oral contraceptive.*

### **5.1.5 Hyperkalemia**

#### **5.1.5.1 Primary Efficacy and Safety Study (Study 303740)**

Because DRSP possesses anti-mineralocorticoid activity, DRSP 3 mg/EE 0.02 mg has the potential to increase serum potassium concentrations. The primary Medical Reviewer, in his original review of Study 303740 (the principal safety and efficacy Phase 3 study for the 24-day regimen), made the following statement: “All of the elevated potassium levels appeared to represent “pseudohyperkalemia” resulting from hemolysis or transport problems. There was no evidence of true hyperkalemia or any hyperkalemia type of symptomatology found at the time of these elevated values. Repeat testing in each case revealed normal values.”

#### **5.1.5.2 Supportive Safety Studies**

In the Applicant’s Complete Response, additional safety data, including clinical trial data for serum potassium concentrations, were provided. The additional data were obtained from 2 trials

conducted for the secondary indication of treatment of PMDD (Studies 304049 and 305141) and 2 trials conducted for the secondary indication of treatment of acne (Studies 306996 and 306820).

**Studies 304049 and 305141.** In the safety review of the PMDD studies, the primary Medical Reviewer made the following statement: *“A small but increased percent of DRSP/EE subjects as compared to placebo subjects had increases in potassium levels outside of the normal range over the course of treatment. However, these elevated potassium levels were not associated with cardiovascular sequelae in any case, and tended to resolve without discontinuation of DRSP/EE. The overall mean change in potassium level with treatment was minimal and similar to that experienced in the placebo group.”*

**Studies 206996 and 306820.** In his safety review of the acne studies, the primary Medical Reviewer made the following statement: *“The slight increases in potassium appear relatively similar in both the treated and placebo groups. No clinically related symptoms are reported for any of these values.”*

#### **Team Leader Comments**

- *Based on the primary Medical Reviewer’s assessment of the clinical trial data submitted to NDA 21-676, there were no findings that indicated that treatment with DRSP 3 mg/EE 0.02 mg (24-day active dosing regimen) was associated with a significant increase in serum potassium concentrations or produced any clinical symptoms of hyperkalemia.*
- *Based on postmarketing safety reports to date, there is no suggestion that the use of Yasmin (which also contains 3 mg DRSP) has resulted in an increased risk of serious adverse events secondary to hyperkalemia (see Section 5.2.2.2). This observation may be a consequence of approved labeling for Yasmin which contains bolded warnings about the potential risk of hyperkalemia and contraindications to its use that are not included in the labeling for other combination oral contraceptives.*

#### **5.2 SUPPORTIVE SAFETY DATA (POSTMARKETING SAFETY DATA FOR YASMIN)**

The Applicant provided data from two large postmarketing safety surveillance trials for Yasmin, the presently marketed DRSP product.

##### **5.2.1 European Active Surveillance (EURAS) Study**

The European Active Surveillance (EURAS) Study for Yasmin was initiated in March 2001. This surveillance study is part of a European effort to monitor postmarketing safety of combination oral contraceptives with new progestins and/or estrogens. Results from this ongoing study were last formally updated by the Applicant on 15 June 2005. At that time, approximately 59,510 women were enrolled, representing 117,153 women-years of observation, including 34,310 women-years of exposure to Yasmin. The numbers and rates of confirmed thrombotic/thromboembolic adverse event for users of Yasmin, levonorgestrel-based oral contraceptives, and “other” oral contraceptives are listed in Table 10.

**Table 10 EURAS Study – Confirmed Thromboembolic Adverse Events**

Event Category	Yasmin (34,310 WY)			LNG-containing OCs (32,415 WY)			Other OCs (50,428 WY)		
	N	Events Per 10 <sup>4</sup> WY	95% CI	N	Events Per 10 <sup>4</sup> WY	95% CI	N	Events Per 10 <sup>4</sup> WY	95% CI
All VTE & ATE	28	8.2	5.4 – 11.8	25	7.7	5.0-11.4	48	9.5	7.0-12.6
All VTE	25	7.3	4.7 - 10.8	20	6.2	3.8-9.5	42	8.3	6.0-11.3
PE	7	2.0	0.8 – 4.2	5	1.5	0.5-3.6	8	1.6	0.7-3.1
All ATE	3	0.9	0.2 – 2.6	5	1.5	0.5-3.6	6	1.2	0.4-2.6
AMI	0	0.0	0.0 – 1.1	2	0.6	0.1-2.2	4	0.8	0.2-2.0
CVA	3	0.9	0.2 – 2.6	3	0.9	0.2-2.7	2	0.4	0.0-1.4
All Fatal VTE/ATE	0	0.0	0.0 – 1.1	2	0.6	0.1-2.2	0	0.0	0.0-0.7

VTE = venous thromboembolic event, ATE = arterial thromboembolic event, AMI = acute myocardial infarction  
CVA = cerebrovascular accident, WY = women-years

Source: Applicant's 18 Aug 2005 submission (NDA 21-676); Table 5, June 15, 2005 Update for EURAS.

### **Team Leader Comments**

- *These interim results suggest that users of Yasmin do not have a higher rate of thrombotic/thromboembolic events than users of combination oral contraceptives that do not contain DRSP.*
- *On February 28, 2006, the Applicant submitted a brief summary of the final EURAS study findings. A formal report of these findings has not been submitted because the trial has only recently closed and the data are undergoing final verification. The summary report indicated that there have been no significant changes in the point estimates for Yasmin from those listed in Table 10.*
- *Based on the Applicant's full Interim Report submitted in August 2005 and the brief summary update of the final study findings submitted in February 2006, there is no signal that the rate of serious thrombotic adverse events is greater in users of Yasmin than with other combination oral contraceptives.*

### **5.2.2 Ingenix Study**

The U.S. postmarketing surveillance study for Yasmin (Ingenix Study based on the claims database of United Health Care) was initially undertaken to monitor for adverse events related to hyperkalemia. The Ingenix Study was subsequently modified to include monitoring for thrombotic and thromboembolic adverse events.

#### **5.2.2.1 Thrombotic and Thromboembolic Adverse Events**

The analyses for thrombotic and thromboembolic adverse events, based on the Final Report for the Ingenix Postmarketing Study, is presented in Table 11.

**Table 11 Intent-to Treat Incidence Rates of Chart-Confirmed VTE/ATE (Stroke) Outcomes for Yasmin vs. other OC Cohorts (Final Results of Ingenix Postmarketing Study)**

Outcome/Subgroup	Yasmin Cohorts (N=22,429) (PY = 14,540.5)			Other OC Cohorts (N=44,858) (PY = 28,169.2)			RR	95% CI
	N	IR (1)	95% CI	N	IR	95% CI		
All VTE	18	1.2	0.8-1.9	39	1.4	1.0-1.9	0.9	0.5-1.6
Pulmonary embolism	5	0.3	0.1-0.8	12	0.4	0.2-0.7	0.8	0.2-2.5
Venous thrombosis	12	0.8	0.5-1.4	25	0.9	0.6-1.3	1.1	0.5-2.2
Venous thrombosis & pulmonary embolism	1	0.1	0.0-0.3	2	0.1	0.0-0.2	1.0	0.2-18.6
Stroke (2)	1	0.0	0.0-0.2	1	0.0	0.0-0.2	1.9	0.2-152.0

PY = Person-years; IR= Incidence rate; RR= Rate ratio

(1) = Incidence rates expressed as events per 1,000 person-years

(2) = Of ATEs there were also 3 myocardial infarctions reported in the other OC cohort but none in the Yasmin cohort  
Source: Applicant's submission of February 23, 2006 to NDA 21-098 (Yasmin): Table 6 (modified), pg 21, Ingenix Final Report: Dispensing Practices, Health Outcomes, and Pregnancy Outcomes in Women Taking Yasmin and Other Oral Contraceptives: Matched Cohort Analysis of VTE/ATE Outcomes.

#### **Team Leader Comment**

- *The final analysis for the Ingenix Postmarketing Study does not indicate a higher risk for thrombotic or thromboembolic adverse events in users of Yasmin, compared to the risk in users of other combination oral contraceptives.*

#### **5.2.2.2 Hyperkalemia and Related Adverse Events**

Within the matched cohorts of Yasmin and other oral contraceptive (OC) initiators, there was no difference in the risk of hyperkalemia by oral contraceptive exposure status (rate ratio [RR] for Yasmin versus other OC initiators: 0.5; 95% CI: 0.0-4.9) (see Table 12). The rate ratios for possible symptoms of hyperkalemia (syncope, arrhythmia, electrolyte disturbances, myocardial infarction, etc.) also were not statistically significantly different based on type of contraceptive usage.

**Table 12 Incidence Rates of Chart-Confirmed Outcomes for Hyperkalemia and Possibly Related Symptoms (Final Results of Ingenix Postmarketing Study)**

Outcome	Yasmin Initiators N=22,429 Person Years = 14,540.5			Other OC Initiators N=44,858 Person Years =28,169.2			Rate Ratio	95% CI
	N	IR	95% CI	N	IR	95% CI		
Hyperkalemia	1	0.07	0.0-0.4	4	0.14	0.0-0.4	0.5	0.0-4.9
Hospitalization with Hyper- or Hypokalemia	0	0.0	0.0-0.2	7	0.2	0.1-0.5	0.0	0.0-1.3
Other Electrolyte Disturbance	24	1.7	1.1-2.5	52	1.8	1.4-2.4	0.9	0.5-1.5
Other Findings								
Syncope	59	4.1	3.1-5.2	151	5.4	4.5-6.3	0.8	0.6-1.0
Arrhythmia	39	2.7	1.9-3.7	57	2.0	1.6-2.6	1.3	0.9-2.0
Dialysis	0	0.0	0.0-0.2	4	0.1	0.0-0.4	0.0	0.0-2.9
Myocardial Infarction	0	0.0	0.0-0.2	3	0.1	0.0-0.3	0.0	0.0-4.7
Death	3	0.2	0.0-0.6	7	0.2	0.1-0.5	0.8	0.1-3.6

IR = Incidence rate, events per 1,000 person years; CI = Confidence interval

Source: Applicant's submission of February 23, 2006 to NDA 21-098 (Yasmin): Table 6, pg 27 (Modified), Ingenix Final Report: Dispensing Practices, Health Outcomes, and Pregnancy Outcomes in Women Taking Yasmin and Other Oral Contraceptives.

### **Team Leader Comment**

- The incidence rate for arrhythmia was slightly greater in the Yasmin initiators (2.7/1,000 women-years) compared to that in the other OC group (2.0/1,000 women-years) resulting in a rate ratio of 1.3 (95% CI: 0.9 to 2.0). All cases of arrhythmia were individually reviewed by the primary Medical Reviewer who made the following comment in his review: "There is no evidence from analysis of the individual cases that this is due to hyperkalemia. Most of these cases represent pre-existing conditions and in the new events of arrhythmia the level of potassium identified in the chart was within normal limits. In addition, there was no specific EKG finding of hyperkalemia in any of these cases of arrhythmia (peaked T waves, widened QRS or flattened p waves). The safety advisory board also evaluated the arrhythmia cases and identified the preponderance as having a preexisting diagnosis. There is no evidence that Yasmin contributed to the deaths in the Yasmin initiator cohort."*

### **5.3 SUMMARY OF SAFETY ASSESSMENT**

The total number of 28-day treatment cycles with DRSP 3 mg/EE 0.02 mg (24-day dosing regimen) and the number of subjects exposed to the drug for one year in Study 303740 (the primary efficacy and safety study) is acceptable for a new hormonal contraceptive product that does not contain a new molecular entity. The primary Medical Reviewer's estimate of the total exposure to DRSP 3 mg/EE 0.02 mg (the 24-day active dosing regimen), including studies for secondary indications, is > 28,981 28-day treatment cycles with 1,707 subjects completing at least one year of treatment. Based on review of the clinical trial data, the safety profile for DRSP 3 mg/EE 0.02 tablets is acceptable for an effective hormonal contraceptive product.

Safety data from 2 large postmarketing studies do not raise any safety concerns for the Applicant's approved hormonal contraceptive product Yasmin, which also contains DRSP

(DRSP 3 mg/EE 0.03 mg tablets taken for 21 of every 28 days). These postmarketing findings are supportive of the clinical trial safety profile for DRSP 3 mg/EE 0.02 mg tablets (YAZ), which contain the same amount of DRSP and 33% less EE.

## 6. RISK/BENEFIT ASSESSMENT OF DRSP/EE (24-DAY DOSING REGIMEN) FOR PREVENTION OF PREGNANCY

**Efficacy.** Based on the data provided in NDA 21-676, DRSP 3 mg/EE 0.02 mg tablets are effective in preventing pregnancy. In the principal efficacy study (Study 303740), the Pearl Index value was 1.41. In 2 supportive clinical trials, the Pearl Index values were reported to be 0.0 (Study 308020) and 0.49 (Study 308021). All of the Pearl Index values are acceptable for a hormonal contraceptive product.

**Safety.** In my review of the original submission of NDA 21-676, I recommended that the Applicant seek approval of the 21-day active dosing regimen, instead of the 24-day active dosing regimen, because of a potential safety advantage for the 21-day regimen. In the Complete Response (the present Application), additional data supporting the safety of the 24-day active dosing regimen has been provided. These new safety data include data obtained from a Phase 3 comparative contraceptive study (Study 308020), two Phase 3 studies for the secondary indication of treatment of symptoms of PMDD in women who chose to use an oral contraceptive for prevention of pregnancy (Studies 304049 and 305141), and two Phase 3 studies for the secondary indication of treatment of acne in women who chose to use an oral contraceptive for prevention of pregnancy (Studies 306820 and 306996). The safety profile of DRSP 3 mg/EE 0.02 mg tablets in these latter studies was acceptable for an effective hormonal contraceptive.

The Applicant also has provided additional supportive safety data from 2 large postmarketing studies with Yasmin (a combination oral contraceptive that contains the same daily dose of DRSP (i.e., 3 mg) but a higher daily dose of EE (0.03 mg vs. 0.02 mg). Data from these 2 postmarketing studies do not show an increased relative risk for thrombotic or thromboembolic events in women using Yasmin compared to this risk in women using other combination oral contraceptives (see Section 5.2.1 and Section 5.2.2.1). In the Ingenix Study, the potential risk of developing hyperkalemia in women using Yasmin also was investigated. Within the matched cohorts of Yasmin and other oral contraceptive (OC) initiators, there was no difference in the risk of hyperkalemia by oral contraceptive exposure status (rate ratio for Yasmin versus other OC initiators: 0.5; 95% CI: 0.0-4.9) (see Section 5.2.2.2).

Based on the safety data provided in NDA 21-676, the overall safety profile for DRSP 3 mg/EE 0.02 mg tablets (24-day dosing regimen) is acceptable for an effective hormonal contraceptive product.

**Overall Risk/Benefit Assessment.** Although a small potential safety advantage for the 21-day active dosing regimen cannot be excluded, the risk/benefit profile for the 24-day regimen is acceptable for a combination oral contraceptive. Based on the efficacy and safety data in the original Submission of NDA 21-676 and the additional safety data in the Complete Response, I recommend that DRSP 3 mg/EE 0.02 mg tablets (24-day active dosing regimen) be approved for the indication of *“prevention of pregnancy in women who choose to use an oral contraceptive.”*

## 7. LABELING ISSUES

Acceptable labeling was submitted by the Applicant on March 15, 2006. All contraindications and bolded warnings regarding the risk of hyperkalemia presently included in the approved labeling for Yasmin (the only other oral contraceptive that contains DRSP) as well as other sections unique to labeling for Yasmin were retained in labeling for DRSP 3 mg/EE 0.02 mg tablets (YAZ). Labeling otherwise conforms to class labeling recommendations for combination oral contraceptives.

## 8. RECOMMENDATIONS OF NON-MEDICAL DISCIPLINES AND DIVISIONS

### 8.1 TOXICOLOGY AND PRECLINICAL PHARMACOLOGY

The primary Toxicology Reviewer (Krishan Raheja, PhD.) made the following comments and recommendation in his review of March 15, 2006:

*NDA 21-676 originally submitted on 10-17-03 was reviewed on 4-7-04. All pharmacology, ADME, general toxicology, genotoxicity studies, reproductive toxicity studies and carcinogenicity studies reviewed under NDA 21-098 for the approval of Yasmin supported the safety of combination of drospirenone/ethinyl estradiol for the contraception indication. The primary difference between Yasmin and Yasmin 20 (YAZ) is that the reduced amount of ethinyl estradiol in YAZ is complexed with B-cyclodextrin as the EE-B-cyclodextrin clathrate to ensure shelf stability at low concentrations. No new toxicology studies were requested or submitted for NDA 21-676. Labeling for YAZ is similar to that for approval of NDA 21-098 for Yasmin.*

*Recommendation on approvability: Based on review and approval of NDA 21-098 for Yasmin, Pharmacology recommends approval of NDA 21-676 for YAZ. The reduction of ethinyl estradiol dose in the YAZ formulation under NDA 21-676 may further improve the safety.*

### 8.2 CMC AND PRODUCT MICROBIOLOGY

The primary Chemistry Reviewer (Donna Christner, Ph.D.) made the following recommendation in her review (dated September 20, 2005):

*This NDA can be APPROVED from a CMC standpoint pending final acceptable labeling.*

Dr. Christner made the following statement in an Addendum (dated December 11, 2005) to her original CMC Review:

*The original recommendation for NDA 21-676 was that the applications could be approved from a CMC standpoint pending acceptable labeling. Acceptable labeling has been submitted and NDA 21-676 can be approved from a CMC standpoint.*

### 8.3 CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS

The primary Clinical Pharmacology and Biopharmaceutics Reviewer (Julie M. Bullock, Pharm.D.) stated the following in her review (signed December 12, 2005):

*NDA 21-676, YAZ for prevention of pregnancy is acceptable from a Clinical Pharmacology and Biopharmaceutics perspective.*

#### 8.4 STATISTICS

The Statistical Reviewer (Shahla Farr, M.S.) stated the following in the Conclusion of her review of the original NDA submission:

*Based on the data provided by the sponsor, Study A12007 for Drospirenone 3 mg/Ethinyl Estradiol 0.02 mg (YAZ) tablets, 24-day regimen, shows a Pearl index of 1.41 (95% CI: 0.73 to 2.42) based on 12 pregnancies. For Study A15129, for the 21-day regimen, the Pearl index is 0.35 (95% CI: 0.06 to 1.02) based on 3 pregnancies.*

The Statistical Reviewer stated the following regarding Study 308382 (Phase 2 pharmacodynamic study - inhibition of follicular development) in the Conclusion of her review (dated January 18, 2006) of the Complete Response:

*This study lacked a prospective statistical analysis plan and can only be considered to be descriptive. There is an apparent trend that the 24-day regimen might have some benefit over the 21-day regimen. The statistical methods that the sponsor has used seem to be reasonable. This reviewer assessed and re-evaluated the sponsors' results. The findings were similar to that of the Sponsor's.*

*Comparing the results of three different recalculations of the primary efficacy endpoints with the original evaluation, better follicular suppression is indicated with the 24 day regimen compared to the 21 day regimen.*

#### 8.5 DIVISION OF SCIENTIFIC INVESTIGATION

No inspections were requested based on the Complete Response.

#### 8.6 OFFICE OF DRUG SAFETY/DIVISION OF MEDICATION ERRORS AND TECHNICAL SUPPORT

Todd Bridges, R.Ph, Division of Medication Errors and Technical Support (DMETS) made the following comments and recommendations in his review (dated January 24, 2006):

*Since the last review dated July 8, 2005 (ODS Consult#: 04-0013-3 and 04-0013-4, NDA#: 21-873), DMETS has not identified any additional proprietary or established names that have the potential for confusion with YAZ™. However, DMETS continues to have concern with the potential for YAZ™ to be misinterpreted as an abbreviation of Yasmin®. Therefore, DMETS still does not recommend the use of the proprietary name, YAZ™.*

*Additionally, DDMAC finds the proprietary name, YAZ™, acceptable from a promotional perspective.*

DMETS also did not support the use of the trade name "YAZ" during the original review cycle for DRSP 3 mg/EE 0.02 mg tablets. The Division discussed the concerns expressed by DMETS during the original review cycle and again during the present review cycle. The Division acknowledges that there is the possibility that a prescription for Yasmin (with poor legibility) might be misinterpreted as a prescription for YAZ. Should such a dispensing error occur, this will not pose a safety risk for the woman nor will it increase the risk that the woman will experience an unplanned pregnancy.

#### 8.7 DIVISION OF DRUG MARKETING, ADVERTISING, AND COMMUNICATIONS (DDMAC)

C. Kulick (DDMAC) recommended many changes to the proposed label during her initial review of labeling for NDA 21-676 (November 3, 2004) and subsequently during her review of labeling

for NDA 21-873 (combined indications of prevention of pregnancy and treatment of PMDD). All recommendations were reviewed and considered in final labeling.

**8.8 DIVISION OF SURVEILLANCE, RESEARCH, AND COMMUNICATION SUPPORT (DSRCS)**

J. Best, M.S.N., R.N. (DSRCS) made specific and general recommendations regarding the format and simplification of language for the Patient Package Insert in her review of April 2004 and the subsequent review of labeling for NDA 21-873 (April 14, 2005). All recommendations were reviewed and considered. Those which were consistent with present class labeling for combination oral contraceptives were incorporated.

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## CLINICAL REVIEW

Application Type NDA  
Submission Number 21-676  
Submission Code AZ

Letter Date 15 Jun 2005  
Stamp Date 16 Jun 2005  
PDUFA Goal Date 16 Dec 2005 (original)  
16 Mar 2006 (extension)

Reviewer Name Gerald Willett MD  
Review Completion Date 14 Mar 2006

Established Name Drospirenone 3 mg / Ethinyl  
estradiol 0.02 mg  
(Proposed) Trade Name YAZ

Therapeutic Class Hormonal Contraceptive

Applicant Berlex Laboratories

Priority Designation S

Formulation Tablets  
Dosing Regimen One tablet daily (24 days of active  
followed by 4 days of placebo)

Indication Contraception  
Intended Population Women at risk for pregnancy

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## 1 EXECUTIVE SUMMARY

### 1.1 Recommendation on Regulatory Action

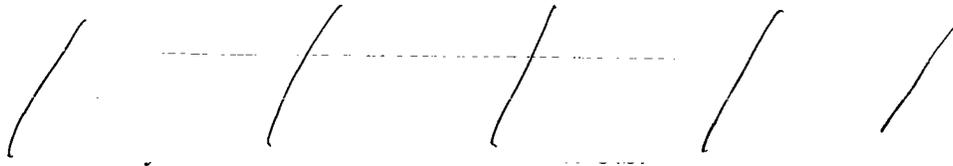
Approval is recommended for YAZ (24-day active dosing regimen of drospirenone 3 mg/ethinyl estradiol betadex 0.020 mg tablets) based on the contraceptive efficacy, comparative ovarian suppression data, and safety data submitted to NDA (21-676) through all review cycles. Additionally the data submitted in the Applicant's complete response (June 15, 2005) supports that a 24-day active dosing regimen of this product shows more ovarian follicular suppression than a comparable 21-day active dosing regimen of this product. Acceptable labeling was submitted on March 9, 2006.

### 1.2 Recommendation on Postmarketing Actions

The proposed risk management activity and postmarketing safety Study are acceptable.

#### 1.2.1 Risk Management Activity

Product labeling will include, in addition to the standard class warnings for combination oral contraceptives, a Bolded Warning (similar to that for Yasmin) that informs healthcare providers and consumers about the risk of hyperkalemia associated with the use of drospirenone.



#### 1.2.2 Required Phase 4 Commitments

In addition to the risk management activities described above, the Applicant has committed to (and has initiated) a large prospective Phase 4 postmarketing safety Study of drospirenone containing OCs called the International Active Surveillance Study of Women taking Oral Contraceptives (INAS OC). The Study has commenced already with patients taking Yasmin. The amended protocol for this surveillance study is found in the Applicant's 18-Aug-2005 submission. This Study is designed in a similar manner to the ongoing European Active Surveillance (EURAS) Study that is assessing vascular adverse events for Yasmin users compared to users of other combination oral contraceptives. These vascular adverse events include deep vein thrombosis, pulmonary embolism, myocardial infarction and cerebrovascular accident. The INAS Study has a U.S. component in addition to a European component prescribing physicians in the US and approximately in Europe). It will compare drospirenone combination oral contraceptives (Yasmin and YAZ) to those which contain other progestagens. The Study will recruit

### 1.3 Summary of Clinical Findings

#### 1.3.1 Brief Overview of Clinical Program

Berlex seeks approval of a second drospirenone (DRSP) based combination oral contraceptive, hereafter referred to as YAZ. This contraceptive contains two-thirds the daily level of ethinyl estradiol (EE) that is found in the Applicant's approved product Yasmin (0.02 mg EE per YAZ tablet compared to 0.03 mg EE per Yasmin tablet) and the same amount of drospirenone (3 mg DRSP) per tablet. The product also differs from Yasmin in that the dosing regimen for YAZ consists of 24 days of active tablets followed by 4 days of placebo tablets compared to 21 days of active tablets followed by 7 days of placebo tablets for Yasmin.

In the first review cycle for prevention of pregnancy with YAZ (conducted under NDA 21-676), the Applicant received an Approvable Action. The Applicant was asked to demonstrate that there was added clinical benefit for the 24-day active dosing regimen compared to a 21-day active dosing regimen. The approvable letter suggesting how this benefit might be demonstrated is found in the regulatory section of this review.

Subsequent to the Approvable Action, the Applicant filed NDA 21-873 for the indication of prevention of pregnancy and the secondary indication of treatment of symptoms of premenstrual dysphoric disorder (PMDD). This review is focused primarily on the portion of NDA 21-676 that consists of the Applicant's Complete Response to the Approvable Action that sought additional data to support the 24-day active dosing regimen of YAZ by demonstrating greater suppression of ovarian function with the 24-day regimen. The Complete Response also includes safety data from 2 additional Phase 3 contraceptive studies and 4 additional Phase 3 clinical trials that support secondary indications for YAZ that the Applicant is seeking. This review also includes summaries of the efficacy and safety findings that were included in the original medical officer's review of NDA-21-676 for prevention of pregnancy.

#### 1.3.2 Efficacy

##### 1.3.2.1 Contraceptive Efficacy

The Applicant's protocol for establishing contraceptive efficacy was similar to that for other product submissions in this class. Over ten thousand 28-day cycles were studied in the 24-day YAZ regimen under protocol 303740. More than 200 women completed 13 cycles of use.

The primary efficacy endpoint was the number of "during treatment" pregnancies defined as all pregnancies with an estimated date of conception after the onset of treatment with Study Drug and through 4 days (Applicant's definition) or 14 days (Division of Reproductive and Urologic Products [DRUP] definition) after the last dose of Study Drug. The primary efficacy analysis was the Pearl Index, which is the number of "during treatment" pregnancies per 100 women-years of use. The efficacy for the 24-day YAZ regimen, expressed in terms of the Pearl Index is

listed in Table A. The value for the Pearl Index in Table A is based on the Medical Officer's determination of the number of "during treatment" pregnancies and exclude (a) cycles where backup contraception was used, (b) cycles for women over age 35, and (c) cycles for women listed as sexually inactive.

**Table A. Efficacy of the 24-day YAZ Regimen of 3 mg DRSP / 0.02 mg EE (Protocol 303740)**

Total days of exposure	Total 28-day cycles of exposure	Total Number Pregnancies		Pearl Index**	2-sided 95% confidence interval
		Applicant's Determination	FDA's Determination		
309,386	11,050 *	11	12	1.41	0.73-2.47

\* Calculated by dividing number of days of exposure by "28".

\*\* Pearl Index based on 12 "during treatment" pregnancies in protocol 303740

Source: Page 11 of Medical Officers Review for YAZ (NDA 21-676), November 16, 2004

### 1.3.2.2. Additional Contraceptive Efficacy Support from Study 308020 Findings

Study 308020 was a comparative Study of the YAZ 24-day regimen versus Mercilon over 7 cycles. There were no pregnancies in the YAZ 24-day regimen group which resulted in a Pearl Index of 0.0 with the upper 2-sided 95% confidence limit of 3.41. The Pearl Index for the Mercilon group based on the 1 pregnancy detected during the Study was 0.93 with the upper 2-sided 95% confidence limit of 5.16.

### 1.3.2.3. Support for 24-Day Active Dosing Regimen Compared to a 21-Day Regimen

The Applicant has shown greater suppression of ovarian activity with the 24-day regimen of 3 mg DRSP/0.02 mg EE compared to a 21-day regimen via Hoogland scoring in protocol 308382. Hoogland scoring assesses ovarian activity in terms of (1) maximal development of ovarian follicles and evidence of ovulation as assessed by sequential ultrasonography and (2) changes in serum concentrations of estradiol and progesterone.

## 1.3.3 Safety

### 1.3.3.1 Primary Safety Data for YAZ

#### 1.3.3.1.1 Exposure

The numbers of subjects exposed to 3 mg DRSP/0.02 mg EE tablets is acceptable. The number of 28-day treatment cycles completed is at least 42,338 (there are a small number of cycles not included from those prematurely discontinuing in study 308021). The number of subjects completing 13 cycles of therapy is 2,145.

#### *1.3.3.1.2 Overall Safety Findings*

In summary, the safety assessment based on all submitted data for subjects treated with YAZ indicates that YAZ has an acceptable safety profile for a highly effective contraceptive product.

#### *1.3.3.1.3 Deaths in Clinical trials with 3 mg DRSP / 0.02 mg EE*

The following information concerning deaths is current through February 2006 (via safety updates of past and ongoing YAZ studies and a separate medical officer request for this information). There were four deaths reported in the clinical studies of YAZ. Two of these deaths occurred in protocol 303740 (YAZ, 24-day regimen) at the single US Study site. Neither of these deaths was related to Study medication. One of the deaths, secondary to pesticide poisoning, occurred one month following discontinuation of Study drug. The other death, occurring three months after starting Study medication, was secondary to smoke inhalation in a fire. The other two deaths occurred in recently completed Study 308021, which is an open label Study of the 24-day regimen for 13 cycles in 1010 volunteers. One of these deaths was secondary to Goodpasture's syndrome and the other death was secondary to murder. Neither of these deaths is attributable to Study drug.

#### *1.3.3.1.4 Serious Thromboembolic Complications and Other SAEs in the Clinical Studies with 3 mg DRSP / 0.02 mg EE Tablets*

There were no reports of serious thromboembolic events in clinical trial subjects receiving the 24-day active dosing regimen of 3 mg DRSP / 0.02 mg EE tablets. There were two confirmed venous thromboembolic (VTE) adverse events (2 cases of pulmonary emboli) in subjects receiving the 21-day active dosing regimen of 3 mg DRSP / 0.02 mg EE tablets (Study 303860). This represents an overall VTE rate of approximately 6.1 per 10,000 women-years for the DRSE/EE product (clinical trial data combined for the 24 and 21-day active dosing regimens) based on an approximate exposure of 42,338 total 28-day treatment cycles or 3,257 women years of exposure. (Exposure data can only be approximated since data from recently completed Study 308021 have not been fully validated).

#### **Medical Officer's Comment**

- *This rate is lower than the VTE rate of the approved product Yasmin in the first year of the EURAS Study (approximately 15 cases per 10,000 women-years of use). This rate is also lower than the VTE rate in the Prescription-Event Monitoring (PEM) Study for Yasmin carried out in the UK. The VTE incidence rate in the PEM Study was 13.7 cases per 10,000 women-years. The overall numbers of other drug related serious adverse events (SAEs) in all of the clinical studies is small, and the adverse events are those that are known to be related to the use of combination oral contraceptives.*

#### *1.3.3.1.5 Discontinuations Due to Adverse Events.*

The discontinuation rate due to adverse events in the 24-day regimen only studies (303740, 301888, 304049, 305141, 306820, 306996, 308020 and 308021) was 6.3% (187 out of 2,941 subjects). The discontinuation rate due to adverse events in the 21-day regimen only studies (305466, 14588, 14523, and 303860) was 6.8% (54 out of 789 subjects).

In the YAZ 24-day regimen pivotal Study (303740), the adverse events contributing to the greatest number of drug-related discontinuations were headache (14 incidents, 1.3% of subjects) followed by intermenstrual bleeding (0.6%), nausea (0.6%), depression (0.6%), decreased libido (0.6%), dysmenorrhea (0.5%), emotional lability (0.5%) and vomiting (0.5%). All of these events are known side effects of combination oral contraceptives.

Headache was also the most common drug-related adverse event seen in Study 303740 reported by 13.3% of subjects, followed by breast pain (6.9%), vaginal moniliasis (6.5%), leukorrhea (5.6%), and nausea/vomiting (4.6%).

#### *1.3.3.1.6 Safety Lab Findings.*

Safety labs were performed in the 24-day regimen protocol (303740). The laboratory analysis from the 24-day regimen Study is sufficient for safety evaluation of 3 mg DRSP / 0.02 mg EE overall. Increased mean levels of lipids (cholesterol and triglycerides) were seen. These findings are comparable to the well-characterized effects of combination oral contraceptives (COCs) on lipids.

Careful potassium monitoring in Study 303740 was performed due to the potential potassium retaining effects of drospirenone. All of the elevated potassium levels identified in the 24-day regimen protocol appeared to represent "pseudohyperkalemia" resulting from hemolysis or transport problems. There was no evidence of true hyperkalemia or any hyperkalemic type symptomatology found at the time of these elevated values. Repeat testing in each case revealed normal values.

The findings of a large Phase 4 cohort claims database Study (the Ingenix Study of Yasmin, see below) and postmarketing reports (AERS) from Yasmin have also provided data that do not show a safety signal regarding an increased the risk of hyperkalemia in women using Yasmin (i.e., 3 mg DRSP /day ).

#### *1.3.3.1.7 Vital Signs, Bleeding Patterns*

Neither the 24-day nor 21-day active dosing regimens produced any significant mean changes in vital signs or body weight. Both the 24-day regimen and the 21-day regimens had acceptable menstrual cycle control data. The incidence of pill-associated amenorrhea and intracyclic bleeding were acceptable for both regimens.

#### *1.3.3.2 Supportive Post Marketing Safety Data based on the Approved Product Yasmin*

The Applicant has provided data from two large ongoing postmarketing safety surveillance trials that support the safety of the presently marketed DRSP product Yasmin.

##### *1.3.3.2.1 EURAS*

The European Active Surveillance Study (EURAS) was initiated for Yasmin in March 2001. This surveillance Study is part of a European effort to perform postmarketing safety assessments for contraceptive formulations with new progestins and/or estrogens. This Study completed on December 31 2005. The final numbers of venous and arterial thromboembolic events was

provided by the applicant in a safety update submitted on February 28, 2006. The Applicant also has provided close estimates, but not the final values, for subject exposure since the final analysis has not been completed. The comparative table (see Table B) shows the thrombotic/thromboembolic adverse event rates for Yasmin, levonorgestrel-based oral contraceptives and “other” oral contraceptives and the exposure estimates. The results demonstrate that in regard to thrombotic/thromboembolic adverse events, Yasmin has similar rates compared to other combination oral contraceptives.

**Table B: EURAS Study: Confirmed Thromboembolic AEs (Number of Events, Incidence, 95% CI)**

Event Category	Yasmin (40,193 WY)			LNG-containing OCs (37,891 WY)			Other OCs (58,575 WY)			Total
	N	Per 10 <sup>4</sup> WY	95% CI	N	Per 10 <sup>4</sup> WY	95% CI	N	Per 10 <sup>4</sup> WY	95% CI	N
All VTE & ATE	33	8.2	5.7-11.5	38	10.0	7.1-13.1	71	12.1	9.5-15.3	142
All VTE	30	7.5	5.0-10.6	28	7.4	4.9-10.7	59	10.1	7.7-13.0	117
Of which PE	7	1.7	0.7-3.6	7	1.8	0.7-3.8	11	1.9	0.9-3.4	25
All ATE	3	0.7	0.2-2.2	10	2.6	1.3-4.8	12	2.0	1.1-3.6	25
Of which AMI	0	0.0	0.0-0.9	6	1.6	0.6-3.4	5	0.9	0.3-2.0	11
Of which CVA	3	0.7	0.2-2.2	3	0.8	0.2-2.3	7	1.2	0.5-2.5	13
All Fatal VTE/ATE	0	0.0	0.0-0.9	3	0.8	0.2-2.3	0	0.0	0.0-0.6	3

VTE = venous thromboembolic event; ATE = arterial thromboembolic event; AMI = acute myocardial infarction; CVA = cerebrovascular accident; WY = women-years

Based on ITT analysis

Exposure data are “close” to final values per the Applicant as final data analysis is ongoing

Source: Applicant’s 28 Feb 2006 submission (NDA 21-676)

### 1.3.3.2.2 Ingenix Study

The US postmarketing surveillance study (Ingenix Study of United Health Care Patients) was initially designed to evaluate the use of Yasmin among women with contraindications or warnings related to its use, to assess compliance of healthcare providers with the recommendation to measure serum potassium in the first cycle of Yasmin among women receiving long-term therapy with drugs that predispose to increased serum potassium, and to assess the occurrence of electrolyte disturbances (particularly hyperkalemia) and related clinical outcomes among women taking Yasmin. A total of 22,429 Yasmin initiators and 44,858 other oral contraceptive (OC) initiators contributed 14,540 and 28,169 person years respectively to the outcome analysis.

Within the matched cohorts of Yasmin and Other OC initiators there was no difference in risk of hyperkalemia by oral contraceptive exposure status rate ratio (RR) for Yasmin versus Other OCs: 0.5, 95% confidence interval (CI): 0.0-4.9). The rate ratio for hyperkalemia was not meaningfully different from the rate ratios for any of the individual surrogate measures of that condition (arrhythmia, syncope, electrolyte disturbance and myocardial infarction) or that of a composite hyperkalemia endpoint comprised of all surrogate measures together (RR=0.9, 95% CI 0.7-1.1).

The Ingenix Study was modified after its inception to also monitor thrombotic and thromboembolic adverse events. The final report of the Ingenix Study (see Table C) shows a

similar risk for Yasmin, compared to other oral contraceptives, for thrombotic and thromboembolic adverse events.

**Table C: Ingenix Study Results (Intent-to Treat Incidence Rates of Chart-Confirmed VTE/ATE Outcomes by Subgroup and Rate Ratios for Yasmin vs. Other OC Cohorts)**

Outcome/Subgroup	Yasmin Cohorts (N=22,429) (PY = 14,540.5)			Other OC Cohorts (N=44,858) (PY = 28,169.2)				
	N	IR <sup>(1)</sup>	95% CI	N	IR	95% CI	RR	95% CI
All VTE	18	1.2	0.8-1.9	39	1.4	1.0-1.9	0.9	0.5-1.6
Pulmonary embolism	5	0.3	0.1-0.8	12	0.4	0.2-0.7	0.8	0.2-2.5
Venous thrombosis	12	0.8	0.5-1.4	25	0.9	0.6-1.3	1.1	0.5-2.2
Venous thrombosis & pulmonary embolism	1	0.1	0.0-0.3	2	0.1	0.0-0.2	1.0	0.2-18.6
Strokes (2)	1	0.0	0.0-0.2	1	0.0	0.0-0.2	1.9	0.2-152.0

PY = Person-years; IR= Incidence rate; RR= Rate ratio

(1) = Incidence rates expressed as events per 1,000 person-years

(2) = Of ATEs there were also 3 myocardial infarctions reported in the other OC cohort but none in the Yasmin cohort

Source: Applicant's 22 Feb 2006 submission of final study report for Ingenix Study

#### 1.3.3.2.3 AERS Reporting and ODS Review

An updated report from the Office of Drug Safety (ODS) based on data in the FDA's AERS database through August 31, 2005 has indicated lower reporting rates of thromboembolic adverse events and deaths for Yasmin since their last assessment approximately one year ago (see Table D). It is anticipated that YAZ will have lower spontaneous reporting rates of these adverse events due to the reduced amount of ethinyl estradiol in this product.

**Table D: Vascular Adverse Events and Deaths for Yasmin in AERS Reporting Data since U.S. Product Launch.**

	Yasmin (May 2001-May 2004)		Yasmin (May 2001-Aug 2005)	
	N	Reporting Rate (per 100,000)	N	Reporting Rate (per 100,000)
Estimated Total Prescriptions	/ / / / /			
Person-Years of Exposure	/ / / / /			
All Embolism & Thrombosis	89	11.9	123	6.5
Pulmonary Embolism	43	5.7	53	2.7
Cerebrovascular Events	16	2.1	23	1.2
Myocardial Infarction	Not assessed		2	0.1
All Deaths	6	0.8	6	0.3

Source: ODS reports of August 31, 2004 and November 1, 2005

#### 1.3.4 Dosing Regimen and Administration

The Applicant has provided additional Phase 2 pharmacodynamic data that indicates that the 24-day active dosing regimen is associated with greater ovarian suppression than is the 21-day

active dosing regimen. The Applicant's proposed dosing regimen is a 3 mg DRSP/0.02 mg EE tablet daily for 24 days followed by 4 days of placebo tablets.

### 1.3.5 Drug-Drug Interactions

As a class, combination oral contraceptives are known for certain drug-drug interactions (rifampin, anticonvulsants, antibiotics, atorvastatin and St. John's Wort. In addition there are potential interactions of the drospirenone component of this combination oral contraceptive with other potassium altering drugs such as ACE inhibitors, angiotensin-II receptor antagonists, potassium-sparing diuretics, potassium supplementation, heparin, aldosterone antagonists and NSAIDs.

The Applicant's hepatic cytochrome enzymes interaction studies with omeprazole, simvastatin and midazolam have not shown any significant interactions.

### 1.3.6 Special Populations

**Gender** - Combination oral contraceptives are intended for the population of women at risk for pregnancy.

**Race** - A small pharmacokinetic Study was performed by the Applicant comparing Japanese and Caucasian women. This Study showed no differences in these two ethnic populations.

The racial distribution for the 24-day regimen in the pivotal trial 303740 was 87.8% Caucasian; 4.6% Hispanic; 4.3% Black; 1.2% Asian and 2.1% other.

Although there are very few non-Caucasians in these studies, there is no evidence from previous combination oral contraceptive NDAs or from the literature to suspect that the safety or efficacy of estrogen/progestin combination oral contraceptives differ based on the race of the user.

**APPEARS THIS WAY  
ON ORIGINAL**

## 2 INTRODUCTION AND BACKGROUND

### 2.1 Product Information

Berlex seeks approval of a second drospirenone (DRSP) based combination oral contraceptive. This contraceptive (hereafter referred to as YAZ) contains two-thirds the daily level of ethinyl estradiol (EE) that is found in the Applicant's approved product Yasmin (0.02 mg EE per tablet in YAZ compared to 0.03 mg EE per tablet in Yasmin) and the same amount of drospirenone (3 mg DRSP) per tablet.

The product also differs from Yasmin in that the dosing regimen consists of 24 days of active tablets followed by 4 days of placebo tablets compared to 21 days of active tablets followed by 7 days of placebo tablets for Yasmin.

Both of these approaches (lower daily ethinyl estradiol doses and extended pill use past 21-days) have been studied recently for combination oral contraceptives. Lowering the ethinyl estradiol should theoretically provide a better safety margin. This was seen when the dose of ethinyl estradiol was lowered in older combination oral contraceptives (containing  $\geq 0.05$  mg ethinyl estradiol) to  $\leq 0.035$  mg of ethinyl estradiol. Proving that lowering ethinyl estradiol to the 0.02 mg range from the 0.03 to 0.035 mg range results in added safety with less thromboembolic disease has been more difficult because it would require huge trials due to the relative rarity of these serious adverse events.

The effort to study more extended regimens with less placebo use is based on ideas related to additional ovarian suppression which theoretically could translate to less unintended pregnancies. Extended therapies may also have the potential for fewer days of premenstrual symptoms.

National approval of the 21-day regimen of 3 mg DRSP / 0.02 mg EE (marketed under the name Yasminelle) was granted in the Netherlands, the Reference Member State, on August 4, 2005. The product has not yet been marketed. (This information is derived from the Applicant's submission of February 28, 2006).

### 2.5 Presubmission Regulatory Activity

In the first review cycle for prevention of pregnancy with YAZ (NDA 21-676), the Applicant received an Approvable Action. The Applicant was asked to demonstrate that there was added clinical benefit for the 24-day active dosing regimen compared to a 21-day active dosing regimen. The Approvable Letter suggesting how this benefit might be demonstrated is provided later in this section of this review.

The present medical review is focused primarily on the portion of NDA 21-676 that consists of the Applicant's Complete Response to the Approvable Action of November 17, 2004. The present review also includes summaries of the efficacy and safety findings that were included in

the medical officer's original review of NDA-21-676 for prevention of pregnancy. Safety updates covering other supportive clinical studies with YAZ for prevention of pregnancy and the secondary indications of PMDD and acne have been reviewed in addition to reports of recently completed and ongoing postmarketing studies of Yasmin.

The content of the Approvable Letter that described the deficiencies of the original submission and the information that would need to be provided to address these deficiencies is provided below:

#### 17 November 2004 Approvable Letter

*We have completed our review of this application, and it is approvable. Before the application may be approved, however, it will be necessary for you to (1) demonstrate a clinical benefit for the 24-day regimen over that provided by a 21-day regimen to offset the increased potential risk associated with the additional 3 days of drospirenone/ethinyl estradiol or (2) propose a 21-day regimen for consideration. This can be accomplished by any of the following:*

*1. Provide evidence that the proposed 24-day contraceptive dosing regimen provides a clinical benefit over that provided by a 21-day regimen. This evidence could consist of demonstrating fewer "escape ovulations" with the 24-day regimen compared to the 21-day regimen.*

#### **Medical Officer's Comment:**

- The Applicant's proposed use of Hoogland scoring which monitors for follicular suppression through multiple determinations (sonography, progesterone and estradiol) is also felt to be acceptable for the comparative Study. Comparative information on the ovarian suppression of both the 24-day and 21-day active dosing regimens was provided. These data were a major component of the Applicant's Complete Response to NDA 21-676 that was submitted on June 15, 2005.*

2. Demonstrate that the 24-day regimen is safe and effective for either of the two secondary indications that are presently under investigation, premenstrual dysphoric disorder (PMDD) and acne.

#### **Medical Officer's Comment:**

- Subsequent to the Approvable Action, the Applicant filed NDA 21-873 for the indication of prevention of pregnancy and the secondary indication of treatment of symptoms of premenstrual dysphoric disorder (PMDD). NDA 21-873 received an Approvable Action on January 23, 2006 primarily because safety data from several supportive clinical trials with YAZ, submitted within 90 days of the PDUFA goal date, had not been reviewed.*

3. Submit an application amendment for the 21-day dosing regimen for the contraceptive indication. The amendment should include acceptable labeling, acceptable financial

disclosure information for the investigators who participated in Study 303860, acceptable CMC information regarding final packaging of the 21-day regimen, and a safety update. You can consider a dosing regimen that includes 7 days of placebo tablets instead of 7 tablet-free days.

Regardless of the option chosen, your submission should also include

r / / / /

Should you continue to pursue approval of the 24-day dosing regimen, your submission should also include a proposal to conduct a large, adequately powered post-marketing surveillance Study to compare the incidence of serious thrombotic and thromboembolic events in users of this product to that in users of other combination oral contraceptives that do not contain drospirenone. This type of Study would not be necessary should you choose to pursue a 21-day dosing regimen.

Labeling remains unresolved. Further discussions regarding this topic will occur in the next review cycle.

When you respond to the above deficiencies, include a safety update as described at 21 CFR 314.50(d)(5)(vi)(b). The safety update should include data from all non-clinical and clinical studies of the drug under consideration regardless of indication, dosage form, or dose level.

**Medical Officer's Comment:**

- *This reviewer felt that the safety and efficacy data from the original submission was sufficient to warranted approval of the 24 day dosing regimen. Others in the Division sought additional reassurances concerning the 24-day regimen since there would be an additional three days of pill use per cycle. The division has approved three other combination oral contraceptives with extended use past 21-days. Mircette has 5 additional days of ethinyl estradiol use. Seasonale has two additional weeks of active pill use every three cycles. Loestrin 24 Fe has been recently approved and has three additional days of active pill use every cycle similar to the presently proposed YAZ product.*
- *In the Applicant's complete response of June 15, 2005 for NDA 21-676, the Applicant chose to provide additional evidence of benefit for the 24-day regimen by providing a final Study report for protocol 308382 that indicates more ovarian suppression with the 24-day regimen compared to the 21-day regimen. Although this Study was not powered or designed to show more escape ovulations than in the 21-day dosing regimen, the division has accepted the design of protocol 308382 (greater ovarian suppression based on the Hoagland's criteria [see Section 6.1.4.2.4]) as providing potential supportive evidence for the justification of the 24 day dosing regimen.*
- *The Applicant has also provided a safety update and commitments in the June 15, 2005 submission to (a)*

*(b) conduct a large, adequately powered post-marketing surveillance Study to compare the incidence of serious thrombotic and thromboembolic events in users of this product to that in users of other combination oral contraceptives that do not contain drospirenone.*

## **2.6 Other Relevant Background Information**

National approval of the 21-day regimen of 3 mg DRSP / 0.02 mg EE (marketed under the name Yasminelle) was granted in the Netherlands, the Reference Member State, on August 4, 2005. The product has not yet been marketed. (This information is derived from the Applicant's submission of February 28, 2006).

## **3 SIGNIFICANT FINDINGS FROM OTHER REVIEW DISCIPLINES**

### **3.1 CMC**

Chemistry recommends approval from a CMC standpoint. The chemistry review indicated that the Applicant has submitted stability data during the first cycle review of NDA 21-676 and requested an expiry of 48 months. In the second review cycle, the sponsor submitted 48 months of stability data. Based on the submitted data, an expiry of 48 months can be granted.

### **3.2 Animal Pharmacology/Toxicology**

Pharmacology (Reviewer Krishan Raheja) recommended approval of YAZ during the first review cycle with the following recommendations:

A. Recommendation on Approvability: Pharmacology recommends approval of NDA 21-676 based on previous finding of safety and prior approval of Yasmin (Berlex NDA 21-098), a contraceptive, which contains 3 mg DRSP and 0.03 mg EE. The present proposed formulation, Yaz has the same indication, i.e., contraception and is administered by the same route, but contains only 0.02 mg of EE compared to 0.03 mg in Yasmin.

B. Recommendation for Nonclinical Studies: Preclinical safety is supported by reference to studies that were submitted to support approval of NDA 21-098 for Yasmin. In addition this NDA (NDA 21-676) contains eight pharmacology reports (AW63, B273, B283, A04834, AQ61, AF46 and AF45), six ADME reports (B206), AV64, B589, B824, A618 and B320) and eight toxicology reports (AG69, B178, B839, AS78, A09791, A09897, A11703 and A11637), which were not previously submitted in NDA 21-098.

## **4 DATA SOURCES, REVIEW STRATEGY, AND DATA INTEGRITY**

### **4.1 Sources of Clinical Data**

The sources of clinical data include:

- Original submission for NDA- 21-676 (16 October 2003) and DRUP reviews
- Original submission of NDA 21-873 for the combined indication of prevention of pregnancy and treatment of symptoms of PMDD (secondary indication)

- Complete response submission (June 15, 2005) for NDA 21-676 that includes:
  1. Follicular suppression Study 308382
  2. Safety updates for 3 mg DRSP / 0.02 mg EE clinical trials (24-day active dosing regimen) not previously reported
  3. Supportive safety updates from Yasmin postmarketing studies (EURAS and Ingenix)
- FDA's Office of Drug Safety reviews from August 31, 2004 and November 1, 2005 of AERS database reporting rates for oral contraceptives including Yasmin
- Additional efficacy and safety information submitted at the request of the Division during the review process. This information was obtained from the Applicant's completed (1) acne studies and (2) comparative Study of YAZ to Mercilon, and a just completed large European open label safety and efficacy Study of YAZ for prevention of pregnancy.

#### **4.2 Tables of Clinical Studies**

The completed clinical studies for 3 mg DRSP / 0.02 mg EE Tablets (24 or 21 day dosing regimens) are listed in Table 1.

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**Table 1 Clinical Studies of 3 mg DRSP/0.02 mg EE Tablets (24 or 21 day dosing regimens)**

Study	Dosing arms/ number of subjects	Description
<b>Phase 1 and Phase 2 Studies</b>		
301780	<ul style="list-style-type: none"> <li>• 3 mg DRSP / 0.02 mg EE betadex Clathrate; n=18</li> <li>• 3 mg DRSP / 0.02 mg EE (free steroid); n= 18</li> <li>• 6 mg DRSP / 0.04 mg EE (oral suspension); n= 18</li> </ul>	Phase 1 Bioavailability Study
300080	<ul style="list-style-type: none"> <li>• 3 mg DRSP / 0.02 mg EE (betadex Clathrate); n=18</li> <li>• 6 mg DRSP, n=6</li> <li>• 3 mg DRSP; n=6</li> <li>• 1 mg DRSP; n=6</li> </ul>	Phase 1 Single dose PK Study in Japan
304326	<ul style="list-style-type: none"> <li>• 3 mg DRSP / 0.02 mg EE (betadex Clathrate); n=18</li> <li>• 6 mg DRSP in 6 subjects</li> <li>• 3 mg DRSP in 6 subjects</li> <li>• 1mg DRSP in 6 subjects</li> </ul>	Phase 1 Single dose PK Study in Germany
305103	3 mg DRSP / 0.02 mg EE in 48 subjects for 21 days	Phase 1 Multi-dose PK Study
303741	3 mg DRSP in 24 subjects over 14 days	Drug interaction Study with simvastatin
306946	3 mg DRSP in 24 subjects over 9 days	Drug interaction Study with midazolam
305466	3 mg DRSP / 0.02 mg EE in 23 subjects over 2-cycles with 21-day regimen	Phase 2 Ovulation inhibition Study
14588	3 mg DRSP / 0.02 mg EE in 30 subjects over 2-cycles with 21-day regimen	Phase 2 Ovulation inhibition Study
308382	3 mg DRSP / 0.02 mg EE: 24-day regimen (n=52) or 21-day regimen (n=52 ) for 3 cycles	To Compare the Effects of 24-Day and. 21-Day Regimens on Suppression of Ovarian Activity
<b>Phase 3 Studies with 24-day regimen (YAZ)</b>		
303740	3 mg DRSP / 0.02 mg EE in 1,027 subjects over 13 cycles with 24-day regimen	Phase 3 Study for safety and efficacy (24-day dosing regimen)
301888	<ul style="list-style-type: none"> <li>• 3 mg DRSP / 0.02 mg EE; 29 subjects over 7-cycles</li> <li>• 0.150 mg desogestrel / 0.02 mg EE in 30 subjects over 7 cycles</li> </ul>	Comparative Phase 3 Study of plasma lipids, hemostatic variables and carbohydrate metabolism
304049	<ul style="list-style-type: none"> <li>• 3 mg DRSP / 0.02 mg EE; n= 231 over 3 cycles</li> <li>• Placebo in 218 subjects over 3 cycles</li> </ul>	Phase 3 Premenstrual Dysphoric Disorder (PMDD) Study
305141	<ul style="list-style-type: none"> <li>• 3 mg DRSP / 0.02 mg EE in 54 subject</li> <li>• Placebo in 49 subjects</li> </ul>	Phase 3 Premenstrual Dysphoric Disorder (PMDD) crossover Study
306820	<ul style="list-style-type: none"> <li>• 3 mg DRSP / 0.02 mg EE; n=266 for 6 cycles</li> <li>• Placebo in 286 subjects for 6 cycles</li> </ul>	Phase 3 Acne Study
306996	<ul style="list-style-type: none"> <li>• 3 mg DRSP / 0.02 mg EE; n=270 for 6 cycles</li> <li>• Placebo in 268 subjects for 6 cycles</li> </ul>	Phase 3 Acne Study
308020	<ul style="list-style-type: none"> <li>• 3 mg DRSP / 0.02 mg EE; n= 229 for 7 cycles</li> <li>• 0.15 mg desogestrel / 0.02 mg EE; n=220 over 7 cycles</li> </ul>	Open comparative Study of YAZ in a 24-day regimen vs Mercilon 2 for 7 cycles in 440 Healthy Female Volunteers" (Draft summary submitted)
308021	3 mg DRSP / 0.02 mg EE 24-day regimen in 1101 subjects for up to 13 cycles	Phase 3 Open Label Safety and Efficacy (961 subjects completed 13 cycles)
<b>Phase 3 Studies with 21-day regimen</b>		
14523	<ul style="list-style-type: none"> <li>• 3 mg DRSP / 0.02 mg EE in 220 subjects over 7 cycles with 21-day regimen</li> <li>• 0.15 mg desogestrel / 0.02 mg EE in 221 subjects over 7 cycles</li> </ul>	Comparative Phase 3 Study of cycle control for the 21-day regimen
303860	3 mg DRSP / 0.02 mg EE in 516 subjects over 26 cycles	Phase 3 Contraceptive Study (21-day regimen)

#### **4.4 Data Quality and Integrity**

Datasets were reviewed to assess accuracy in the summary reports. A biostatistical review of Protocol 308382 (comparative effectiveness in ovarian suppression between the 21 and 24 day active dosing regimens) was performed and is summarized in Section 6.1.5.

#### **4.5 Compliance with Good Clinical Practices**

In regard to **Study Protocol 308382** (comparative effectiveness of the 21 and 24 day active dosing regimens) the Applicant provided the following information:

The Study commenced only after the protocol had been approved by the appropriate ethics committee (EC) and written notification of the approval had been received by Schering AG. The investigator was not to modify or alter this protocol without first obtaining the written agreement of Schering AG. All alterations that were not only of an administrative nature required a formal protocol amendment and were approved by the appropriate EC before the implementation, except where immediate implementation in order to eliminate an imminent hazard to the subject was necessary.

All protocol amendments which were agreed upon were recorded on the standard protocol amendment form provided by Schering AG, and were signed and dated by both the Applicant and the investigator.

The planning and conduct of this clinical Study was subject to national laws. Only when all of the requirements of the appropriate regulatory authority were fulfilled did the Study begin. The Study was conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki and the International Conference on Harmonization (ICH) – Good Clinical Practice (GCP) guidelines.

At the discretion of the Study manager, the entire Study could have been cancelled for medical reasons. In addition, Schering Group retained the right to end the Study for medical-scientific or GCP-relevant reasons. In the event of a premature termination, the investigators, EC, and regulatory authorities were to be informed by the Study manager.

#### **4.6 Financial Disclosures**

This is not required for the follicular suppression Study 308382. The Applicant properly addressed the financial disclosure requirements in the original review cycle for the 24-day regimen studies.

### **5 CLINICAL PHARMACOLOGY**

In the first review cycle, this NDA was found acceptable to the Office of Clinical Pharmacology and Biopharmaceutics.

In this review cycle, Dr. Julie Bullock (primary clinical pharmacology reviewer) made the following recommendation:

*“NDA 21-676, YAZ for Oral Contraception is acceptable from a Clinical Pharmacology and Biopharmaceutics perspective.”*

She also referenced an interaction Study that was discussed in NDA 21-355 (Angeliq):

*“In addition please reference the submission made on March 31, 2005 for NDA 21-355 (Angeliq) which contains a Phase 1 drug-drug interaction Study to evaluate the potential of DRSP to inhibit CYP3A4 using midazolam as a marker substrate for CYP3A4. The review of this Study was completed by Julie Bullock, Pharm. D (Review in DFS). This Study concluded that there is no clinically meaningful interaction between DRSP and midazolam.”*

## **6 INTEGRATED REVIEW OF CONTRACEPTIVE EFFICACY**

### **6.1.4 Efficacy Findings**

The integrated review of efficacy is composed of two main sections. One is the contraceptive efficacy which was thoroughly evaluated in the first review cycle as well as new contraceptive efficacy data submitted during review of the Complete Response. A summary of these findings is presented in this review. The second is the findings of the follicular suppression Study 308382.

#### **6.1.4.1 Contraceptive Efficacy**

##### **24-day Dosing Regimen (Primary Efficacy Data)**

###### **Protocol 303740**

The Applicant's protocol for establishing contraceptive efficacy is similar to other product submissions in this class. Over ten thousand 28-day cycles were studied in Protocol 303740 for the 24-day YAZ regimen. More than 200 women completed 13 cycles of use.

The primary efficacy endpoint was the number of “during treatment” pregnancies defined as all pregnancies with an estimated date of conception after the onset of treatment with Study drug and through 4 days (Applicant's definition) or 14 days (DRUP's definition) after the last dose of Study drug. The primary efficacy analysis was the Pearl Index, which is the number of “during treatment” pregnancies per 100 women-years of use. The efficacy for the 24-day YAZ regimen, expressed in terms of the Pearl Index is listed in Table 2. The value for the Pearl Index in Table 2 is based on the Medical Officer's determination of the number of “during treatment” pregnancies and excludes cycles where backup contraception was used, cycles for women over age 35, and cycles for women listed as sexually inactive.

**Table 2 Efficacy of the 24-day YAZ Regimen of 3 mg DRSP / 0.02 mg EE (Protocol 303740)**

Total days of exposure	Total 28-day cycles of exposure	Total Number Pregnancies		Pearl Index**	2-sided 95% confidence interval
		Applicant's Determination	FDA's Determination		
309,386	11,050 *	11	12	1.41	0.73-2.47

\* Calculated by dividing number of days of exposure by "28"

\*\* Pearl Index based on using 12 "during treatment" pregnancies in protocol 303740

Source: Page 11 of Medical Officers Review for YAZ (NDA 21-676), November 16, 2004

**Life Table Analysis of Contraceptive Efficacy.** Based on the Applicant's determination of 11 "during treatment" pregnancies, the 1 year pregnancy rate according to Kaplan Meier life table analysis, in their original submission was 1.26% with a 95% confidence interval of [0.52%; 2.01%].

Based on the Division's determination of 12 "during treatment" pregnancies, the life table recalculation resulted in a cumulative pregnancy rate of 2.2% [95% CI: 0.2%; 4.2%]

**Medical Officer's Comment:**

- *The increase from 1.26% to 2.2% in the life table analysis resulted because the added 12<sup>th</sup> pregnancy occurred at the end of the Study (day 388) with relatively few remaining subjects*

**Study 308020** – The Applicant submitted a draft Final Report for this Study. In Study 308020 (comparative Study with Mercilon) there were 229 subjects in the YAZ 24-day regimen group and 220 subjects in the Mercilon group. This Study lasted for 7 cycles. In the YAZ 24-day regimen, 201 subjects completed the Study medication. In the Mercilon group 196 subjects completed the Study course. There were no pregnancies in the YAZ group which led to a PI / adjusted PI of 0.0 / 0.0 with the upper 2-sided 95% confidence limit of 3.41 for the PI, and that of 3.49 for the adjusted PI. The PI for the Mercilon group based on the 1 pregnancy detected during the Study was 0.93 with the upper 2-sided 95% confidence limit of 5.16. The adjusted PI was similar, 0.93; with the upper 2-sided 95% confidence limit of 5.19.

**Study 308021** – The applicant submitted preliminary efficacy data from this clinical trial that completed the clinical phase on January 30, 2006. The Applicant reported 5 on-treatment pregnancies among women 35 years of age or less in 13,248 28-day treatment cycles during which back up contraception was not used. Based on the Applicant's preliminary analysis, the Pearl Index value was 0.49 (two-sided 95% confidence interval [0.16; 1.14]) The Kaplan Meier estimate of the pregnancy rate after one year of treatment (last conception date after 322 days of treatment) was 0.50% (95% confidence interval: [0.21%; 0.19%]).

**Medical Officer's Comment:**

- *This additional pregnancy prevention data lends added support to the contraceptive efficacy of YAZ, 24-day regimen.*

**21 Day dosing regimen (Supportive Efficacy Data)**

The following table (Table 3) shows the Pearl Index for the 21-day regimen of YAZ. Protocol 303860 was carried out in a similar fashion to that of protocol 303740.

**Table 3 Efficacy of the 21-day YAZ Regimen of 3 mg DRSP / 0.02 mg EE (Protocol 303860)**

Total days of exposure)	Total 28-day cycles of exposure	Total Number Pregnancies		Pearl Index	2-sided 95% confidence interval
		Applicant's Determination	FDA's Determination		
309,136	11,040	2	3	0.35	0.07-1.04

\* = Calculated by dividing number of days of exposure by "28".

Source: Page 11 of Medical Officers Review for YAZ (NDA 21-676), November 16, 2004

**Medical Officer's Comment:**

- *Differences in the Pearl Index between the two regimens were described in the medical officer review of the original submission. The higher Pearl Index for the 24-day regimen could be partly a result of the different countries involved. Brazil had a disproportionately high number of pregnancies (n=7 with 4 subject failures) in 24-day protocol and Brazil was not part of the 21-day protocol. In addition the 21-day protocol was carried out for 26 months which tends to give better results.*
- *The Pearl Index for the 24-day regimen is acceptable. The information regarding ovarian suppression in the following section shows more ovarian suppression with the 24-day regimen compared to the 21-day regimen.*

**6.1.4.2 Ovarian Suppression with the 24-Day Regimen Compared to the 21-Day Regimen**

The Applicant conducted a Study (protocol 308382) where ovarian suppression was studied using the 24-day regimen compared to the 21-day regimen. The endpoint for this Study was Hoogland scoring (see Table 4 for details) in the second and third cycle of use. The third cycle was conducted using a predefined dosing error of 3 missed tablets on days 1 to 3 of that cycle. Hoogland scoring incorporates more parameters than solely measuring serum progesterone and allows additional follicular measurements through frequent sonographic evaluations.

The Applicant showed that the 24-day regimen was statistically better than the 21-day regimen in producing better suppression of ovarian function.

**Medical Officer's Comment**

- *This reviewer finds the Hoogland scoring to be an acceptable tool for comparing ovarian suppression between the two regimens. The following section focuses on the ovarian suppression efficacy in greater detail.*

*6.1.4.2.1 Title of Study:*

“Single center, double-blind, randomized Study to compare the effect of SH T 00186 D ( 3 mg DRSP / 0.02 mg EE ) on follicular development in a 24-day regimen versus a 21-day regimen in 100 healthy female volunteers in cycle 2 and after intentional dosing errors in cycle 3”

*6.1.4.2.2 Study Objectives:*

The aim of this Study was to compare the effects of 3 mg DRSP / 0.02 mg EE in a 24-day regimen versus a 21-day regimen on follicular growth as assessed by follicular size, as well as the incidence of ovulation in cycle 2 and after predefined dosing errors in both regimens in cycle 3 (i.e., 3 missed tablets on days 1 to 3 of cycle 3). Ovulation inhibition was assessed by ultrasound monitoring of follicle size and analysis of serum hormone levels (follicle-stimulating hormone [FSH], luteinizing hormone [LH], progesterone, and 17-β-estradiol [E2]). Ovarian activity was classified according to the Hoogland scoring system as described below in Section 6.1.4.2.4. Safety parameters assessed were adverse events (AEs), laboratory variables, physical and gynecological examinations including cervical smears, vital signs, and body weight.

*6.1.4.2.3 Study Design:*

The Study was carried out as a single center, double-blind, randomized Study. One hundred subjects were planned with 50 subjects per treatment regimen (24 day regimen or 21 day regimen with 3 mg DRSP / 0.02 mg EE).

In the pretreatment cycle preceding the treatment phase, hormonal contraceptive use was not allowed. The pretreatment cycle started with the first day of bleeding after the screening visit. Follicular growth and ovulation were closely monitored by transvaginal ultrasound (TVU) and serum hormone levels. The subject was admitted to the treatment phase only if the pretreatment cycle was assessed as ovulatory. If ovulation did not occur in the first pretreatment cycle, a second pretreatment cycle could be performed to assess ovulation. If the pretreatment phase was assessed as ovulatory, the subject was randomized to 1 of the 2 treatment groups, in the order of arrival at the center on day 23 of the pretreatment cycle (visit 6).

The treatment phase consisted of 3 cycles, each with 28 treatment days for all subjects. Tablet intake in the first treatment cycle began on the first day of menses. After the third treatment cycle, return to fertility was monitored during a follow-up cycle to demonstrate resumption of ovulation.

Frequent measurements of follicle size and hormone analyses during cycles 2 and 3 were carried out to assess ovarian activity. Since no ovulations took place in the first cycle in previous studies with similar regimens, measurements were only started in treatment cycle 2 in order to assess if a ‘stepwise ripening’ of follicles had occurred. In treatment cycle 3 the effect of initially ‘missed tablets’ on ovarian activity was investigated. Return to fertility, i.e., normal ovarian function was examined in a follow-up cycle.

#### 6.1.4.2.4 Primary Efficacy Analyses and Statistical Methods

Efficacy measurements started in cycle 2, since in previous studies with similar regimen, no ovulation took place in the first treatment cycle.

Transvaginal ultrasonography was to be performed at every visit using a transvaginal probe. Print-outs for documentation were to be taken. They were to be labeled with the subject's initials, examination date, and, if necessary, further information, e.g., right / left side of pelvis.

- The diameter of the largest follicle-like structure per ovary (FLS, i.e., follicles or cystic ovarian structures) was to be documented after calculating the average of the transverse and longitudinal diameters.
- The endometrial thickness (double layer) was to be measured.
- The absence or presence of cervical mucus was to be determined.

At visit 6 (admission to treatment) in the pretreatment cycle, the subject was only admitted to the treatment phase if the follicular diameter reached  $\geq 15$  mm or if ovulation had occurred.

Blood samples (5 mL per sample) for the determination of FSH, LH, progesterone, and E2 were to be taken at the time points displayed in the Study flowcharts. The blood samples were sent to and analyzed by a central laboratory

The blood samples were to be frozen and collected at the Study center and sent to the central laboratory at the end of the Study. To ensure measurements under identical conditions, all samples were measured in 1 batch at the end of the Study. In addition, in some cases progesterone was measured during the course of the Study in order to verify ovulation, but for this no extra blood sample was needed.

A separate blood sample (5 mL) was taken at each sampling time point for DRSP measurements. This measurement offered an additional means to check the treatment compliance of the subjects (diary cards were another means of checking for compliance). Only for those samples where compliance was doubtful, DRSP levels were assessed through a validated method.

Ovarian activity was classified according to Hoogland (Hoogland and Skouby, 1993) once per cycle for cycles 2 and 3, and for the follow-up cycle based on the results of the transvaginal ultrasonography, the serum progesterone, and E2 analyses. The classification was only possible after hormone measurements were available, i.e., after completion of Study the conduct. The Hoogland scores are defined in the following table (Table 4):

**Table 4: Hoogland Scoring System**

Score	Activity	Diameter of FLS (mm)	Progesterone* (nmol/L)	E2 (nmol/L)
1	No activity	≤ 10	--	
2	Potential activity	> 10	--	
3	Non-active FLS	> 13	--	≤ 0.1
4	Active FLS	> 13	≤ 5	> 0.1
5	LUF	> 13, persisting	> 5	> 0.1
6	Ovulation	> 13, ruptured	> 5	> 0.1

FLS = Follicle like structure; LUF = Luteinized unruptured follicle

\* = Conversion from nmol/L to ng/mL - multiply by 0.3145

Source: Page 38 of 5895, Study report A25848 (NDA 21-676)

All subjects who took at least 1 tablet of Study medication and for whom at least 1 observation after dosing was available were included in the full analysis set (FAS). The other subjects were classified as 'listing only' (LOS). This means, their data are presented in the individual subject data listings but were not be included in any statistical analysis. Subjects were analyzed according to the treatment they actually received.

A volunteer of the FAS was included in the per-protocol-set (PPS) provided she had no major protocol deviation which affected the primary efficacy variable. Major protocol deviations were:

- Follicular diameter < 15 mm at visit 6 in pretreatment cycle
- No ovulation in pretreatment cycle based on hormone profile
- Use of steroid hormone-containing medication during the Study, e.g., contraceptives
- Cycles 2 and / or 3 not performed
- 'Morning after pill' taken during cycles 1, 2 or 3.

The primary efficacy variable was the Hoogland score in cycles 2 and 3.

For the efficacy variables, analyses of the FAS and the PPS were performed. The analysis of the PPS was regarded as the primary analysis. For the safety variables only the FAS was analyzed. No interim analysis was planned.

#### 6.1.4.2.5 Secondary Efficacy Analyses

Secondary efficacy variables were the serum concentrations of the endogenous hormones progesterone, E2, LH, and FSH, endometrial thickness, and cervical mucus in cycles 2 and 3.

#### 6.1.4.2.6 Subject Disposition

A total of 128 subjects were screened, of whom 23 failed screening. The reasons for screening failure were 'inclusion / exclusion criteria not met' for 16 subjects, withdrawal of consent for 4 subjects, and 'other' reasons for 3 subjects. These 'other' reasons were as follows: irregular cycle with no menses within 8 weeks after visit 1 (subject no. 322), symptoms of dizziness and paresthesia in fingers in precycle (subject no. 332), and 'cycle too long' (subject no. 418).

Randomization numbers were assigned to 105 subjects, among whom 52 subjects were on the 24-day regimen, and 53 subjects on the 21-day regimen. Study treatment was never administered to 1 subject (1.9%, PID 350) on the 21-day regimen for withdrawal of consent. Treatment was administered to 104 subjects, with 52 subjects on each regimen.

Treatment was prematurely discontinued for 5 subjects (4.8%): these were 3 subjects (5.8%) on the 24-day regimen (PIDs 356 and 381 for withdrawal of consent, and PID 324 for an 'other' reason, i.e., unexpected vacation) and 2 subjects (3.8%) on the 21-day regimen (PID 351 for withdrawal of consent, and PID 326 for an AE, i.e., depressive mood). Study course and Study medication were completed by 99 subjects (95.2% of the FAS), with 49 subjects (94.2%) on the 24-day regimen and 50 subjects (96.2%) on the 21-day regimen.

#### 6.1.4.2.7 Datasets Analyzed

All subjects who took at least 1 tablet of Study medication and for whom at least 1 observation after dosing was available were included in the FAS. Subjects not fulfilling these criteria were classified as 'listing only' (LOS). A subject of the FAS was included in the per protocol set (PPS) provided she had no major protocol deviation which affected the primary efficacy variable.

The FAS consisted of 104 subjects, with 52 subjects on the 24-day regimen and 52 subjects on the 21-day regimen.

The PPS comprised 99 subjects, with 49 subjects on the 24-day regimen and 50 subjects on the 21-day regimen.

The LOS comprised 1 subject assigned to the 21-day regimen who never took any Study medication.

#### 6.1.4.2.8 Demographics

The mean height, weight and BMI for subjects in Study 308382 are listed in Table 5.

**Table 5: Height, Weight and BMI in Study 308382**

	24-Day Regimen		21-Day Regimen	
	Mean	SD	Mean	SD
Derived age [years]	25.6	4.1	25.6	4.4
Height [cm]	170.4	5.8	169.1	6.9
Weight [kg]	64.4	7.3	66.0	9.5
Derived BMI [kg/m <sup>2</sup> ]	22.2	2.5	23.0	2.7

Source: Page 62 of 5895, Study report A25848 (NDA 21-676)

#### **Medical Officer's Comment**

- *The mean age and BMI are comparable between the two treatment groups.*

The majority of subjects (98 subjects or 94.2%) in the FAS were Caucasian, i.e., 49 subjects (94.2%) on both treatment regimens, 2 were Asian (24-day regimen), and 1 was Black (21-day regimen). Three subjects had 'other' ethnicity, specified as half Caucasian, half mix (24-day regimen), a quarter Caucasian, half Black, and a quarter Indian (21-day regimen), and half Black, a quarter Asian, and a quarter Red Indian (21-day regimen).

**Medical Officer's Comment**

- *The imbalance in ethnicity is not considered by this reviewer to be clinically significant in an ovulatory Study such as this one. The Study arms were comparable in other demographic factors (smoking, alcohol consumption, medical history and gynecologic history). Although more women in the 24-day regimen had recently used oral contraceptives than the 21-day regimen there would be no carry over efficacy effect since all women had to establish ovulation prior to be accepted into the treatment phase.*

6.1.4.2.9 Prior and Concomitant Treatments

**Medical Officer's Comment**

- *The dataset MED02.xpt was reviewed. There was no evidence of prior or concomitant medication use that would affect the efficacy analysis.*

6.1.4.2.10 Primary Efficacy Results

Hoogland scoring in cycle 2 and cycle 3 were utilized as the primary efficacy endpoints (see Table 6 and Table 7). The two tables list the numbers of subjects in each of the Hoogland categories for cycle 2 and cycle 3, respectively.

**Table 6: Results of Hoogland Scoring for Treatment Cycle 2 - FAS**

Hoogland Score	24-Day Regimen Total N FAS= 52	21-Day Regimen Total N FAS = 52
1- No activity	45	28
2- Potential activity	5	11
3- Non-active FLS	0	0
4- Active FLS	1	11
5- LUF	0	1
6- Ovulation	0	1
No result	1	0

Source: Page 74 of 5895, Study report A25848 (NDA 21-676)

**Table 7: Results of Hoogland Scoring for Treatment Cycle 3**

Hoogland Score	24-Day Regimen Total N FAS= 52	21-Day Regimen Total N FAS = 52
1- No activity	27	15
2- Potential activity	8	7
3- Non-active FLS	0	0
4- Active FLS	13	24
5- LUF	0	0
6- Ovulation	1	4
No result	3	2

Source: Page 74 of 5895, Study report A25848 (NDA 21-676)

**Medical Officer's Comment**

- *In both cycles nearly twice as many subjects are found in the no activity category in the 24-day regimen compared to the 21-day regimen.*

For both the FAS and PPS, the proportion of subjects with Hoogland scores 1 or 2 in cycle 3 (which had 3 intentionally missed tablets at the beginning of the cycle) was higher for the 24-day regimen compared to the 21-day regimen as shown in Table 8)

**Table 8: Proportion of Subjects with Hoogland Scores of 1 or 2 in Cycle 3 (FAS)**

Treatment	Total No. subjects	No. of Subjects with Scores of 1 or 2	% of Subjects with Scores of 1 or 2	90% CI
24-day	49	35	71.4	[60.81;82.04]
21-day	50	22	44.0	[32.45;55.55]

Source: Page 70 of 5895, Study report A25848 (NDA 21-676)

**Medical Officer's Comment**

- *This proportional assessment in Cycle 3 was also pre-specified in the original protocol. This table comes from the June 15, 2005 submission and does not represent any recalculation base on conservative evaluation of progesterone levels.*

A proportional odds model was fitted for the Hoogland score as an ordinal response (logarithmic- linear or log-linear model). An estimated odds ratio for having a lower Hoogland score of 1 would mean there was no difference in treatment effects between the 24-day and 21-day regimens. The following table (Table 9) shows the odds ratios for treatment effect in cycles 2 and 3 using the full analysis set (FAS). The table includes the initial efficacy odds ratio submitted by the Applicant in the June 15, 2005 submission in addition to recalculations requested the primary medical reviewer. The recalculations are based on excluding more subjects based on low progesterone levels in the baseline period. This reviewer felt that more conservative progesterone analysis should be used to identify "ovulatory" subjects. It is noteworthy that the statistical analysis still showed more ovarian suppression with the 24-day regimen compared to the 21-day regimen.

**Table 9: Full Analysis – Odds Ratios for Treatment Effect in Cycles 2 and 3 (includes Recalculations Based on Excluding Different Levels of Progesterone in Baseline Cycle)**

Baseline Determination	Subjects excluded	Cycle	Estimated Odds Ratio	95% CI
Applicant's initial efficacy table		2	6.91	[2.67;20.49]
		3	3.06	[1.44;6.65]
Recalculation with exclusion of progesterone levels not higher than 1.57 ng/mL in baseline cycle	4 from 24-day regimen 4 from 21-day regimen	2	7.56	[2.88; 22.68]
		3	2.68	[1.24; 5.92]
Recalculation with exclusion of progesterone levels not higher than 4.0 ng/mL in baseline cycle	9 from 24-day regimen 9 from 21-day regimen	2	8.47	[3.14; 25.96]
		3	2.65	[1.17; 6.12]

Source: November 1, 2005 Applicant submission (NDA 21-676)

**Medical Officer's Comment**

- *In the above table, the odds ratio always exceeds one and the 95% CI does not include one.*

*6.1.4.2.11 Secondary Efficacy Results*

Of the secondary endpoints examined, the changes in follicle size, LH and cervical mucus appeared supportive of the comparative findings reflected by the Hoogland scoring evidence of greater ovarian suppression with the 24-day regimen compared to the 21-day regimen.

6.1.5 Review of Efficacy by Biostatistics

The conclusion of the ovarian suppression Study by biostatistician Shahla Farr in her review is presented below:

“This study lacked a prospective statistical analysis plan and can only be considered to be descriptive. There is an apparent trend that the 24-day regimen might have some benefit over the 21-day regimen. The statistical methods that the sponsor has used seem to be reasonable. This reviewer assessed and re-evaluated the sponsors’ results. The findings were similar to that of the Sponsor’s.

Comparing the results of three different recalculations of the primary efficacy endpoints with the original evaluation, better follicular suppression is indicated with the 24 day regimen compared to the 21 day regimen.”

### 6.1.6 Efficacy Conclusions

The efficacy conclusions for the 24-Day regimen of YAZ are the following:

- The total 28-day cycles of exposure used to calculate the Pearl Index in the principal efficacy study (303740) was adequate (11,050 cycles) for the efficacy determination. The division has requested that Applicants have at least 10,000 cycles.
- The Pearl Index of 1.41 is acceptable for approval for contraceptive efficacy.
- Preliminary results from 2 additional Phase 3 contraceptive studies with YAZ also indicate the efficacy of YAZ is acceptable for a combination hormonal contraceptive. The Pearl Index values for YAZ in these 2 studies were 0 (Study 308020 – no pregnancies) and 0.5 (Study 308021).
- The comparative Study (protocol 308382) shows better follicular suppression with the 24-day regimen compared to the 21-day regimen.

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## 7 INTEGRATED REVIEW OF SAFETY

### 7.1 Methods and Findings

#### 7.1.1 Deaths

There were four deaths reported in the clinical studies of YAZ. Two of these deaths occurred in protocol 303740 (YAZ, 24-day regimen) at the single US Study site. Neither of these deaths was related to Study medication. One death, secondary to pesticide poisoning, occurred one month following discontinuation of Study drug. The other death, occurring three months after starting Study medication, was secondary to smoke inhalation in a fire.

The clinical summaries for the two deaths reported for subjects participating in Protocol 303740 are as follows:

- **PID #40.** Approximately 1 month after discontinuation of the Study treatment, the volunteer suddenly died. She had received her first dose of Study medication on 22 Feb 2001. She returned to the clinic on 12 Mar 2001 and reported a self-diagnosed upper respiratory infection beginning on 8 Mar 2001, which she treated with Tylenol Cold Capsules from 9 Mar to 10 Mar 2001. The volunteer missed Study visit 4 on 3 May 2001. She was contacted by the site on 4 May 2001 and reported experiencing nausea and vaginal spotting and elected not to continue in the Study. She informed the site that she had discontinued Study medication 2 weeks prior on 20 Apr 2001. In an attempt to reschedule a termination visit, the Study site contacted the volunteer's workplace and was notified that the volunteer had expired on \_\_\_\_\_ while on vacation in Jamaica. The deceased had died almost a sudden death. Based on autopsy findings, observations from toxicological analyses of stomach contents and blood sample (dated \_\_\_\_\_) and histopathological examination of tissues from various internal organs, the opinion as to the cause of death is acute hemorrhagic pancreatitis and pulmonary edema, secondary to toxic effects of Endosulfan (an organochlorine pesticide) and caffeine. The vaginal spotting which had started on 1 May 2001 was considered a non-serious adverse event of mild intensity, continuous, and had required no drug treatment. It was classified as being probably related to the Study medication by the Study investigator. The nausea which had started on 1 May 2001 was also considered a non-serious adverse event of mild intensity, intermittent, and had required no drug treatment; it was classified as being possibly related to the Study medication by the Study investigator. Both events had reportedly resolved on 22 Apr 2001.

*Source: Clinical Study Report No. A12007, page 2207 of 3206*

- **PID # 61.** Approximately 3 months after start of the Study treatment, the volunteer suddenly died. The cause of death as listed on the certificate of death was carbon

monoxide toxicity sustained from inhalation of fumes caused by a fire in her apartment building or \_\_\_\_\_

*Source: Clinical Study Report No. A12007, page 2208 of 3206*

The other two deaths in subjects using Yaz occurred in recently completed Study protocol 308021, which is an open label non-US Study of the 24-day regimen for 13 cycles in 1010 volunteers. One of the deaths was secondary to Goodpasture's syndrome, and the other death was secondary to murder. Neither of these deaths is attributable to Study drug. The clinical summaries for these two deaths are as follows:

- **Subject 3250/Volunteer 1056 had** received 3 mg DRSP/0.02 mg EE tablets (24 day regimen) for 161 days when she was murdered by shooting or \_\_\_\_\_. In agreement with the reporting investigator, the event is considered by the company as unrelated to the Study drug (none).
- **Subject 2466/Volunteer 533** died of Goodpasture's syndrome. She had started intake of 3 mg DRSP/0.02 mg EE (24 day regimen) on 03 Mar 2004 and died suddenly on \_\_\_\_\_. Patient's family history was unremarkable, except for type II diabetes in her father. The patient's own medical history included the fact that she was a non- smoker and that she had suffered from renal colic on 05 Jan 2005 which had been treated with cotrimoxazol 1.5 g daily. It was reported that the patient had no further relevant medical history.

The autopsy revealed lung hemorrhage due to Goodpasture's syndrome (pulmorenal syndrome) as the cause of death in this patient.

**Medical Officer's Comment:**

- *There is no indication from the scientific literature of any relationship of Goodpasture's disease with oral contraceptives. Research has focused on this disease as having an autoimmune basis related to the basement membranes found in numerous tissues.*

The following table (Table 10) lists the aforementioned deaths, SAEs and premature discontinuations due to AE in the 3 mg DRSP / 0.02 mg EE clinical studies.

**Table 10: Deaths, SAEs and Premature Discontinuations due to AEs in the Clinical Studies of 3 mg DRSP / 0.02 mg EE Tablets**

Study	Regimen <sup>A</sup>	Phase	Deaths/ Drug Related (yes,no)	SAEs No Subjects	Possibly Drug Related SAEs & (Comment)	No. Adverse Event Related Premature Discontinuations (All/Drug Related)	No. of YAZ Subjects in Study
301780	N/A	1	0	0	0	0	18
300080	N/A	1	0	0	0	0	18
304326	N/A	1	0	0	0	0	18
305103	21	1	0	0	0	1/0	48
303741	N/A	1	0	0	0	0	24
305466	21	2	0	1	0	1/1	23
14588	21	2	0	0	0	0	30
303740	24	3	2 (no)	27	4 (migraine x1, depression x2, cholelithiasis x1)	77/65	1027
301888	24	3	0	0	0	3/3	29
304049	24	3	0	4	1 (cervical dysplasia)	0	231
305141	24	3	0	1	0	4/4	54
14523	21	3	0	3	0	15/13 <sup>B</sup>	220
303860	21	3	0	30	6 (pulm embol x2, fibrocystic breast x2, cholecystitis, x1, migraine x1)	38/33	516
306946	N/A	1	0	0	0	0	24
308382	24 v. 21	3	0	2	1 (ovarian cyst)	1/1	104
306820	24	3	0	2	1 (depression)	14/12	266
306996	24	3	0	1	0	16/16	270
308020 <sup>C</sup>	24 v. Mercilon	3	0	3	0	18/18	229
308021 <sup>D</sup>	24	3	2 (no)	22	Possibly related: ovarian cyst x1 Breast fibroadenoma x1	69/56	1101
<b>Totals</b>			<b>2</b>	<b>96</b>	<b>16</b>	<b>257/222</b>	<b>4250</b>

A = Regimen (whether 24-day, 21-day or comparative)

B = The two cases not felt to be related were depression events which may be related

C = Information derived from draft report

D = Information from March 3, 2006 submission

Sources = Individual study reports

## 7.1.2 Serious Adverse Events

### 7.1.2.1 Thrombotic and Thromboembolic Adverse Events

#### **Clinical trials with 3 mg DRSP / 0.02 mg EE**

Two cases of pulmonary embolus were reported to have occurred in women using the 21-day regimen of 3 mg DRSP / 0.02 mg EE in protocol 303860. The Applicant's clinical summaries of these two cases of pulmonary embolism are reported verbatim below:

“Volunteer number 110 (PID 163) felt pain in the area poplitea of the left leg about two years after start of treatment. At first the complaints had been interpreted as contusion or possible muscle fiber tear and was treated with diclofenac from 5 Aug to 9 Aug 2002. The 22 year-old patient had been sent to establish the diagnosis because of additional breathing problems. She discontinued the Study medication on 26 Aug 2002 and was hospitalized on \_\_\_\_\_ existing or previous thromboembolic diseases or risk factors of herself or mother and grandmother were known, she was a smoker of 6 cigarettes per day. Thrombosis of Vena femoralis superficialis until adductors-channel and embolization of the right lung were diagnosed. She was treated with diclofenac, Novalgin, heparin, and after hospitalization she started with Marcumar. The relationship to treatment of this SAE was assessed by the investigator as 'probable' and sponsor as being 'possible' as a causal relationship cannot be excluded. The patient discontinued the Study drug, and fully recovered.”

“Volunteer number 472 (PID 371), 24 year-old, non smoker with no history or family history of thrombosis and no factor V Leiden mutation, suffered from abdominal pain about four months after treatment start. The patient felt pain in the abdomen and back for two days like already a week before. The tentative diagnosis was an acute appendicitis. The appendectomy on \_\_\_\_\_ revealed a subacute appendicitis. Postoperatively, the patient developed increasing discomfort in the right leg. Phlebography was performed on \_\_\_\_\_ and revealed deep leg and right pelvic vein thrombosis. CT angiography of Vena pulmonalis showed a pulmonary embolism with thromboembolism of the left inferior pulmonary lobe artery of the apical inferior right pulmonary lobe. Pelvic CT showed thrombosis of the right Vena iliaca reaching about 5 cm in the Vena cava inferior. On \_\_\_\_\_ venous thrombectomy of leg and pelvic vein was performed. Histologic examination showed parts of 'fresh and not so fresh thrombosis' (3 weeks and ~1 week old) with focal mild signs of parietal organization. Laboratory investigations while taking coagulants on 5 Apr 2001 showed 37% decreased protein C, APC resistance ratio: 0.66 APC ratio, Protein S, phospholipid antibodies (IgG), cardiolipin, and phosphatidylserine were not increased. A ventilation perfusion scintigraphy on \_\_\_\_\_ confirmed the pulmonary embolism. She was treated with Marcumar, Ultiva, Succinyl, Novalgin, Tramundin, Fragmin, Ambroxol, Unazid, heparin, Orgaran, Valoron, DHB, Dolantin, and ferro-Folgamma, and recovered after having mild fever of 38.5°C on 11 Apr 2001. The patient was advised to wear pressure stockings for one year. Both, investigator and sponsor assessed the treatment relationship as 'possible'. The patient discontinued the Study drug, and fully recovered from the SAE.”

### **Medical Officer's Comment**

- *The finding of two confirmed venous thromboembolic adverse events (2 cases of pulmonary emboli in the 21-day regimen Study 303860) would result in an approximate VTE rate of 6.1 per 10,000 women-years for the 3 mg DRSP / 0.02 mg EE products based on combined safety data for 24 and 21-day regimens using clinical trial exposure data of 42,338 28-day cycles or 3,257 women years of treatment. (The total exposure data is a close approximation of the true value since data from recently completed Study 308021 have not undergone full validation.) This rate is lower than the VTE rate of the approved product Yasmin in the first year of the EURAS Study (approximately 15 cases per 10,000 women-years of use). This rate is also lower than the VTE rate in the Prescription-Event Monitoring (PEM) Study for Yasmin carried out in the UK. The VTE incidence rate in the PEM Study was 13.7 cases per 10,000 women-years.*
- *There were no other cases of thrombotic or thromboembolic adverse events in subjects receiving 3 mg DRSP / 0.02 mg EE tablets as of the March 3, 2006 safety update.*
- *The VTE rate of approximately 6.3 per 10,000 women-years is also comparable to the findings in the three arms of the EURAS Study (Yasmin, levonorgestrel based oral contraceptives and other contraceptives) which ranged from 7.4 to 10.1 VTEs per 10,000 women years. Some of the highest rates for VTE in women occur in the postpartum period. A VTE rate of 51.1 per 10,000 women-years was found in the Olmstead County Minnesota 30-year population Study for women in the postpartum period (Heit et al. Trends in the Incidence of Venous Thromboembolism during Pregnancy or Postpartum: A 30-Year Population-Based Study. Annals of Internal Medicine; Volume 143, pages 697-706; Nov 15, 2005.)*

#### 7.1.2.2 Serious Adverse Events in the 24-Day Regimen Studies

##### **Contraceptive Studies**

**Protocol 303740** - In protocol 303740 (principle safety and efficacy Study for the 24-day regimen) there were 37 serious adverse events in 30 subjects (see Table 11). The relationship to Study drug was characterized by the investigator as possible for three events (epistaxis, vascular disorder and abnormal Pap smear). The drug relationship was characterized by the investigator as probable in two events (migraine and depression)

**Table 11: Serious Adverse Events in Study 303740 (Primary Efficacy and Safety Study)**

PID	Country	HARTS Term	Drug Relationship	Discontinuation Due to AE
14	Austria	Migraine	Probable	Yes
		Epistaxis	Possible	Yes
		Depression	Probable	Yes
40	USA	Death, pesticide poisoning	None	-
61	USA	Death, accidental injury	None	-
193	Austria	Surgery (arthroscopy of knee)	None	No
243	Austria	Accidental injury (ruptured tendon)	None	No
244	Austria	Accidental injury (dog bite)	None	No
277	Austria	Ovarian cyst	None	No
		Surgery (chronic tonsillitis)	None	No
337	Austria	Surgery (conization)	None	No
363	Austria	Abdominal pain (pelvic inflammatory disease)	None	No
420	Austria	Surgery (appendicitis)	None	No
422	Austria	Upper respiratory infection (acute tonsillitis)	None	No
424	Austria	Surgery (appendicitis)	None	No
512	Austria	Hernia	None	No
545	Argentina	Vascular disorder	Possible	Yes
589	Argentina	Abortion	Unlikely	Yes
604	Argentina	Abortion	Unlikely	Yes
643	Argentina	Accidental injury (burns)	None	No
668	Argentina	Suicide attempt other than overdose	Unlikely	Yes
743	Argentina	Papanicolaou smear suspicious (HSIL)	Possible	No
745	Argentina	Bone fracture (not spontaneous)	None	Yes
844	Poland	Eye disorder	Unlikely	Yes
		Headache	Unlikely	Yes
		Dizziness	Unlikely	Yes
		Myasthenia	Unlikely	Yes
		Neuropathy	Unlikely	Yes
973	Austria	Surgery (chronic tonsillitis)	None	No
974	Austria	Cholelithiasis	None	No
1019	Austria	Laboratory test abnormal (creatinine increase)	Unlikely	No
1033	Austria	Laboratory test abnormal (creatinine increase)	Unlikely	No
1093	Brazil	Psychotic depression	Unlikely	Yes
1133	Brazil	Accidental injury	None	Patient lost
1143	Brazil	Allergic reaction (bronchitis)	None	No
1160	Brazil	Pyelonephritis	None	No
1196	Brazil	Pharyngitis	Unlikely	No

PID – Patient Identification number

Source: Protocol 303740, Study report page 121 of 3785 (NDA 21-676)

**Medical Officer's Comment**

- *Of the serious adverse events characterized by the investigators as having no relationship or an unlikely relationship to Study drug, this reviewer feels that four events including an ovarian cyst, headache, cholelithiasis and depression are possibly related. The two events of migraine and depression listed in the probable category in the preceding paragraph*

*occurred in the same subject. The vascular disorder mentioned above led to meningeal symptoms and was found to be congenital and not related to Study drug.*

**Protocol 308020** - In protocol 308020 (comparative Study with Mercilon), there were 4 serious adverse events in 3 subjects in the YAZ, 24-day regimen arm (broken finger, abnormal Pap smear, tonsillitis and peritonsillar abscess). Five serious adverse events occurred in five Mercilon subjects (abscess, enteritis, gastroenteritis, optic neuritis and abnormal Pap smear). None of these events were considered to be related to Study drug (Medical officer concurs).

**Protocol 308021** - In the data provided by the Applicant on March 3, 2006 for protocol 308021 (safety and efficacy for 24-day regimen, study completed January 30, 2006) there are 22 subjects with serious adverse events. These events are listed in Table 12.

**Table 12: Serious Adverse Events in Study 308021**

Subject number	Serious adverse event	Study drug relation	Outcome
2046	Multiple fractures (crash)	No	Resolved
2322	Urethral stricture	No	Resolved
2331	Anaphylactic shock	No	Resolved
2391	Epidermal nevus	No	Resolved
2412	Ovarian cyst	No	Resolved
2425	Forearm fracture	No	Resolved
2466	Goodpasture's syndrome	No	Fatal
2472	Asthma	No	Resolved
2482	Cervical Conization	No	Resolved
2528	Corneal transplant	No	Resolved
2548	Appendicitis	No	Resolved
2584	Lipoma	No	Resolved
2603	Enthesopathy	No	Resolved
2634	Appendectomy	No	Resolved
2682	Tonsillitis	No	Resolved
2684	Pneumonitis	No	Resolved
2700	Appendectomy	No	Resolved
2737	Multiple sclerosis	No	Not Resolved
2868	Breast fibroadenoma	Unlikely	Resolved
3250	Murder	No	Fatal
3295	Unilateral blindness	No	Residual effects
3308	Salmonellosis	No	Residual effects

Source: Applicant's March 3, 2006 submission

**Medical Officer's Comment:**

- *The deaths listed above were commented upon previously and are not felt to be related to study drug. The ovarian cyst and breast fibroadenoma cases are considered by this medical reviewer to be possibly related. The case of unilateral blindness was related to chorioretinitis (felt to be secondary to toxoplasmosis) and not to thrombosis.*

### **Acne Trials**

**Protocol 306996** - In protocol 306996 (one of 2 Phase 3 acne studies), there was one serious adverse event (pneumonia) in the YAZ regimen arm and five serious adverse events in the placebo arm (drug abuse, pelvic pain, convulsion, ectopic pregnancy/abdominal pain, and accidental injury). The serious event of pneumonia was not considered to be related to YAZ by the investigator.

### **Medical Officer's Comment**

- *This medical officer concurs with the Applicant's assessment.*

**Protocol 306820** - In protocol 306820 (one of 2 Phase 3 acne studies), there was one serious adverse event (depression) in the YAZ regimen arm and one serious adverse event in the placebo arm (appendicitis). The serious event of depression in the YAZ arm was considered by the applicant to be unlikely related to drug. It occurred at Day 10 in the study.

### **Medical Officer's Comment**

- *The serious adverse of depression may have been related to treatment with YAZ.*

### **PMDD Trials**

**Studies 304049 and 305141.** There were a total of five serious adverse events (SAEs) in the two trials (see Table 13 ). Three occurred in subjects randomized to DRSP /EE in Study 304049: incarcerated incisional hernia, abnormal Pap and spinal bone spurs. Two occurred in subjects taking placebo (one in each trial): appendicitis and miscarriage following a pregnancy diagnosed during the placebo exposure period. The overall rates of SAEs in the two exposure groups were therefore 1.1% in the DRSP/EE-exposed subjects and 0.7% in the placebo-exposed subjects. For the individual trials, the SAE rate was 1.3% in the DRSP /EE group and 0.5% in the placebo group of Study 304049, and 0% during DRSP/EE exposure and 2.0% during placebo exposure in Study 305141.

**Table 13: Serious Adverse Events during Treatment**

SAE (Subject #)	Treatment	Causality	Timing	Intensity	Resolution
Lower abdominal pain (Incarcerated incisional hernia) (510008)	DRSP /EE	Unrelated	5 weeks after first dose	Moderate	Recovered following surgery
Lower back bone spurs (190004)	DRSP /EE	Unrelated	5 weeks after first dose	Severe	Recovered following surgery
Severe dysplasia on Pap (HSIL) (560002)	DRSP /EE	Possibly related	12 weeks after first dose (Visit 7)	Severe	Unknown – colposcopic dx and LEEP pathology unknown
Appendicitis (380066)	Placebo	Unrelated	8 weeks after first dose	Severe	Recovered following surgery
Miscarriage (231002)	Placebo	Unrelated	59 days after starting placebo	Severe	Recovered

Source: Table 91, a21566.pdf, Section 16, p 219 and Table 90, a07545.pdf, Section 14, p 306 (NDA 21-676)

#### 7.1.2.3 Serious Adverse Events in the 21-Day Regimen Studies

**Protocol 303860** - In protocol 303860 (principal safety and efficacy Study for the 21-day active dosing regimen) there were 34 serious adverse events in 30 subjects (see Table 14). The drug relationship was characterized by the investigator as possible in three events (ovarian cyst/back pain; pain in extremity and pulmonary embolus/pelvic vein thrombosis). The drug relationship was characterized by the investigator as probable in four events (fibrocystic breast; pulmonary embolus/left leg; abnormal vision and migraine).

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**Table 14: Listing of Serious Adverse Events in 21-Day Regimen Protocol 303860**

PID	HARTS Code/ Diagnosis	Drug Relation	Discontinued
10	Surgery / appendectomy	None	No
6	Fibrocystic breast / fibroadenoma left breast Skin hypertrophy / keloid scar	Probable None	Yes
118	Surgery / right knee	None	No
156	Surgery / appendectomy	None	No
149	Surgery / tonsillectomy	None	No
163	Pulmonary embolus / + thrombosis left leg	Probable	Yes
215	Fibrocystic breast / fibroadenoma right breast	Unlikely	No
194	Pain in extremity	Possible	Yes
268	Gastroenteritis	Unlikely	No
262	Surgery / gnathoplasty (deviated maxilla)	None	No
306	Constipation	None	No
329	Accidental injury / smoke intoxication	None	No
189	Surgery plastic surgery (nasal septum)	None	No
317	Ovarian cyst / pain in back and abdomen	Possible	No
313	Surgery / appendectomy	None	Yes (wt. gain)
60	Bone fracture / left leg	None	No
671	Abnormal vision / sudden visual disturbance Migraine	Probable Probable	Yes
655	Tooth disorder / teeth correction Tooth disorder / teeth correction	None None	No No
96	Surgery / appendectomy	None	No
115	Cholecystitis	None	No
94	Encephalitis	None	No
75	Surgery / plastic surgery (nasal septum)	None	No
70	Surgery / breast reduction	None	No
371	Pulmonary embolus / + pelvic vein thrombosis Surgery / appendectomy	Possible None	Yes
355	Surgery / appendectomy	None	No
399	Infection / erysipelas	None	No
450	Surgery / appendectomy	None	No
462	Skin melanoma / superficial spreading melanoma (abdominal skin right, level III, 0.7cm depth)	Unlikely	Yes
486	Abdominal pain	None	No
512	Cervix carcinoma in situ / (cervix uteri)	None	Yes

Source: Study Report for Protocol 303860, page 94 of 1143 (NDA 21-676)

**Medical Officer's Comment**

- *Of the serious adverse events characterized by the investigator as having no relationship to Study drug, this reviewer feels that a case of cholecystitis is possibly related. The cases of pulmonary emboli were fully described in section 7.1.2.1.*
- *The case of the painful extremity had imaging studies performed to rule out deep vein thrombosis (DVT). The studies were negative for DVT. The abnormal vision and migraine events occurred in a single subject and can be related solely to migraine.*

**Protocol 14523** - In protocol 14523 (21-day regimen compared to Mercilon) there were three serious adverse events in the 21-day regimen arm (accidental injury and two surgeries). There was one serious adverse event in the Mercilon arm (gastroenteritis). None of these events was considered to be related to drug use.

### 7.1.3 Dropouts and Other Significant Adverse Events

#### 7.1.3.1 Adverse Events Associated With Dropouts in the 24-Day Regimen

##### Contraceptive Trials

**Protocol 303740** - In Study protocol 303740 (principle safety and efficacy Study for the 24-day regimen) a total of 125 AEs in 77 of 1027 volunteers (7.5%) led to discontinuation of the Study medication. The most common reasons for discontinuation of the Study medication due to AEs were headache in 14 volunteers (1.4%), intermenstrual bleeding and nausea in 7 volunteers (0.7%) each, and decreased libido and depression in 6 volunteers (0.6%) each. A total of 65 volunteers prematurely discontinued the Study medication due to treatment-related AEs. A more complete description is found in Table 15 that follows.

**Table 15: Most Common Reasons for Discontinuation of Study Medication Due to AEs in Study Protocol 303740**

HARTS TERM	N = 1027	
	AEs	(%)
Headache	14	1.4
Intermenstrual bleeding	7	0.7
Nausea	7	0.7
Libido decreased	6	0.6
Depression	6	0.6
Emotional lability	5	0.5
Vomiting	5	0.5
Dysmenorrhea	5	0.5
Breast pain	4	0.4
Weight gain	4	0.4
Abdominal pain	4	0.4
Rash	3	0.3
Acne	3	0.3
Migraine	3	0.3
Back pain	2	0.2
Asthenia	2	0.2
Abnormal laboratory test	2	0.2
Edema	2	0.2
Sweating increased	2	0.2
Dizziness	2	0.2
Somnolence	2	0.2
Menorrhagia	2	0.2

Source: Study Report A12007, page 116 of 3785 (NDA 21-676)

**Protocol 308020** - In protocol 308020 (comparative Study with Mercilon), a total of 18 volunteers prematurely discontinued the Study because of AEs in the YAZ-24 day regimen. All AEs that led to discontinuation were considered related to the Study medication. The most common reasons were headache (3 of 229 or 1.3%); mood changes (3 of 229 or 1.3%) and irregular bleeding (3 of 229 or 1.3%)

**Medical Officer's Comment**

- *The adverse events reported in Study 303740 and Study 308020 are commonly seen with all combination oral contraceptives and may lead to drug discontinuation. The percentages reported for Study 303740 and Study 308020 are not increased above expected rates.*

**Protocol 308021.** The most common adverse events leading to discontinuation in Study 308021 are listed in Table 16.

**Table 16: Number of Subjects Discontinuing for Adverse Events in Study 308021 ( $\geq 0.5\%$ )**

Medra TERM	N = 1101	
	AEs	(%)
Any Event	92	100
Metrorrhagia	11	1.0
Headache	10	0.9
Nausea	5	0.5
Weight increased	5	0.5

Source: Applicant's March 3, 2006 submission

**Acne Trials**

In **protocol 309996** (Phase 3 acne study), there were 18 (6.7%) subjects in the DRSP/EE group and 9 (3.4%) subjects in the placebo group that took study medication who prematurely discontinued the study due to an AE. The most frequently reported AEs in the DRSP/EE group that resulted in premature discontinuation from the study were menorrhagia (3 [1.1%] subjects), headache, acne, and menstrual disorder (2 [0.7%] subjects each). The most frequently reported AEs in the placebo group that resulted in discontinuation from the study were migraine and thrombocythemia (2 [0.7%] subjects each).

In **protocol 306820** (Phase 3 acne study) there were 26 (4.9%) subjects (14 [5.3%] subjects in the DRSP/EE group and 12 [4.5%] subjects in the placebo group) who took study medication and prematurely discontinued the study due to an AE. The most frequently reported AEs in the DRSP/EE group that resulted in premature discontinuation from the study were dysmenorrhea (4 [1.5%] subjects), metrorrhagia (3 [1.1%] subjects), and nausea (3 [1.1%] subjects). The most frequently reported AEs in the placebo group that resulted in discontinuation from the study were depression (4 [1.5%] subjects) and emotional lability (3 [1.1%] subjects).

**PMDD Trials**

**Studies 304049 and 305141.** Forty (40) subjects terminated prematurely across the two clinical trials because of one or more adverse events that occurred during DRSP /EE exposure (14.0 %), as did 11 subjects during their exposure to placebo (4.1%). For the individual trials, the rate of

withdrawal due to adverse events was 15.5% in the DRSP /EE group and 4.1% in the placebo group of Study 304049, and 7.4% during DRSP /EE exposure and 4.1% during placebo exposure in Study 305141. Adverse events leading to withdrawal (>1%) are listed in Table 17.

**Table 17: Adverse Events (>1%) Leading to Withdrawal in the PMDD trials**

Preferred Term	DRSP /EE N=285		Placebo N=267	
	N	%	N	%
Nausea	13	4.6	3	1.1
Intermenstrual bleeding	8	2.8	0	0
Asthenia	7	2.5	1	0.4
Breast pain/tenderness	5	1.7	0	0
Depression	4	1.4	0	0
Nervousness	4	1.4	2	0.7
Headache	3	1.1	2	0.7
Emotional lability	3	1.1	0	0
Increased appetite	3	1.1	0	0
Menorrhagia	3	1.1	0	0
Vomiting	3	1.1	0	0

Source: Text Table 35, a21566.pdf, p 119 and Table 91, Section 14, a07545.pdf, p 307 (NDA 21-676)

**Medical Officer's Comment**

- *The adverse events in the acne and PMDD studies are no different than those found in all oral contraceptives*

7.1.3.2 Adverse Events Associated With Dropouts in the 21-Day Regimen

**Protocol 303860** - Of a total of 38 volunteers in protocol 303860 (21-day regimen safety and efficacy) that had AEs leading to discontinuation of the Study medication, 33 volunteers prematurely discontinued the Study medication due to treatment related AEs. The most common reasons for discontinuation of the Study medication due to AEs were decreased libido and depression each in 5 volunteers (1.0%), headache and emotional lability each in 4 volunteers (0.8%) and acne and weight gain each in 3 volunteers (0.6%).

**Protocol 14523** -Twenty-four (5.4%) volunteers discontinued Study protocol 14523 (21-day regimen compared to Mercilon) due to AEs, i.e., 15 (6.8%) from the 21-day group (including one SAE, subject No. 649, accidental injury) and 9 (4.0%) from the Mercilon group. The most frequent AE leading to a discontinuation of the Study medication was weight gain (four volunteers in the 21-day group and two in the Mercilon group). Other events, which occurred more than once overall, were headache (one in the 21-day group and one in the Mercilon group), depression (one in the 21-day group and one in the Mercilon group), menorrhagia (one in the 21-day group and one in the Mercilon group), skin disorder/acne (one in the 21-day group and one in the Mercilon group) and emotional lability (one in the 21-day group and one in the Mercilon group).

## 7.1.5 Common Adverse Events

### 7.1.5.1 Common Adverse Events in the 24-Day Regimen Studies

#### Contraceptive Studies

**Protocol 303740** - In protocol 303740 (principle safety and efficacy Study for the 24-day regimen) signs and symptoms most frequently reported as AEs were headache for 137 volunteers (13.3%) assessed as treatment related for 67 volunteers (6.5%), upper respiratory tract infections for 137 volunteers (13.3%) all of which were assessed to be without treatment relationship, and breast pain for 71 volunteers (6.9%) assessed as treatment related for 65 volunteers (6.3%). A more complete listing is presented in Table 18 derived from the medical officer's review during the first review cycle.

**Table 18: Adverse Events (>2% of subjects) in Protocol 303740 (Total N = 1027)**

HARTS term	Related and Not Related		Treatment Related	
	N	%	N	%
Headache	137	13.3	67	6.5
Upper respiratory infection	137	13.3	0	0
Breast pain	71	6.9	65	6.3
Vaginal moniliasis	67	6.5	12	1.2
Leukorrhea	58	5.6	5	0.5
Diarrhea	52	5.1	2	0.2
Nausea/ Vomiting	47	4.6	38	3.7
Vaginitis	45	4.4	2	0.2
Abdominal pain	42	4.1	10	1.0
Flu syndrome	39	3.8	0	0
Dysmenorrhea	38	3.7	9	0.9
Allergic reaction	33	3.2	0	0
Accidental injury	32	3.1	2	0.2
Urinary tract infection	32	3.1	0	0
Cystitis	31	3.0	0	0
Tooth disorder	29	2.8	0	0
Sore Throat	28	2.7	0	0
Infection	26	2.5	0	0
Fever	24	2.3	0	0
Surgery	23	2.2	0	0
Sinusitis	23	2.2	0	0
Back pain	21	2.0	3	0.3

Source: Clinical Study Report No. A12007, pages 1470-1476 of 3206 (NDA 21-676)

#### Medical Officer's Comment

- *These adverse events are commonly seen in combination oral contraceptive trials. There are no safety signals in the percentages found for these events.*

**Protocol 308020** - In protocol 308020 (comparative Study with Mercilon), the most common AEs ( $\geq 5\%$  of all volunteers) are listed in Table 19.

**Table 19: Comparative Study 308020 – Frequent Adverse Events ≥ 5%**

Adverse Event	YAZ 24-Day Regimen		Mercilon	
	N (229)	%	N (220)	%
Headache	29	12.7	23	10.5
Nasopharyngitis	16	7.3	16	7.3
Influenza	14	5.2	15	5.9
Cystitis	7	3.1	8	3.6

Source: Study Report A29551 submitted to NDA 21-676 on November 22, 2005

**Protocol 308021** – A formal analysis of common adverse events from this recently completed clinical trial was not available at the time of this review.

**Medical Officer’s Comment**

- *The absence of an analysis of commonly reported AEs in this Study does not affect the ability of this reviewer to assessment the overall safety profile of YAZ. The more important categories of serious adverse events and adverse events leading to discontinuation have been reviewed described previously.*

**Acne Studies**

**Protocol 306996** - In study protocol 306996 (acne) common adverse events were defined as those occurring in ≥2% of the subjects. The 4 most frequently reported AEs in the YAZ group were upper respiratory infection (25 [9.3%] subjects), metrorrhagia (25 [9.3%] subjects), Pap smear suspicious (15 [5.6%] subjects), and headache (14 [5.2%] subjects). The 4 most frequently reported AEs in the placebo group were upper respiratory infection (31 [11.6%] subjects), headache (14 [5.2%] subjects), flu syndrome (12 [4.5%] subjects), and Pap smear suspicious (8 [3.0%] subjects).

**Protocol 306820** - In study protocol 306820 (acne) common AEs were defined as those occurring in ≥2% of subjects. The 4 most common AEs in the DRSP/EE group were upper respiratory infection (35 [13.2%] subjects), metrorrhagia (28 [10.5%] subjects), headache (23 [8.6%] subjects), and nausea (17 [6.4%] subjects). The 5 most common AEs in the placebo group were upper respiratory infection (25 [9.3%] subjects), vaginal moniliasis (12 [4.5%] subjects), Pap smear suspicious (12 [4.5%]), headache (10 [3.7%] subjects), and pharyngitis (10 [3.7%] subjects).

**Medical Officer’s Comment**

- *The common adverse event profile is similar to that found for combination oral contraceptives in general.*

**PMDD Studies**

The most common adverse events in the pooled PMDD studies are listed in Table 20.

**Table 20: Most Common Adverse Events (≥2%) Pooled Data from PMDD studies**

Preferred Term	DRSP/EE	Placebo	Preferred Term	DRSP/EE
	N=285	N=267		N=285
	N	%	N	%
Intermenstrual bleeding	69	24.2	11	4.1
Headache	53	18.6	51	19.1
Nausea	53	18.6	16	6.0
Breast pain	37	13.0	7	2.5
Upper respiratory infection	32	11.2	27	10.1
Asthenia	23	8.1	12	4.5
Abdominal pain	13	4.6	8	3.0
Libido decreased	13	4.6	3	1.1
Emotional lability	11	3.9	5	1.9
Suspicious pap smear	11	3.9	7	2.6
Menorrhagia	10	3.5	4	1.5
Nervousness	10	3.5	4	1.5
Pain in extremity	10	3.5	1	0.4
Depression	9	3.2	2	0.7
Menstrual disorder	9	3.2	5	1.9
Migraine	9	3.2	4	1.5
Sinusitis	9	3.2	14	5.2
Weight gain	9	3.2	8	3.0
Vaginal moniliasis	8	2.8	7	2.6
Vaginitis	8	2.8	8	3.0
Hyperlipemia	7	2.5	1	0.4
Back pain	7	2.5	4	1.5
Diarrhea	7	2.5	5	1.9
Increased appetite	7	2.5	0	0
Abdomen enlarged	6	2.1	6	2.2
Accidental injury	6	2.1	9	3.4
Acne	6	2.1	7	2.6
Dysmenorrhea	6	2.1	10	3.7
Urinary tract infection	5	1.8	9	3.4
Flu syndrome	2	0.7	6	2.2
Tooth disorder	2	0.7	6	2.2
Bronchitis	1	0.4	6	2.2

Source: NDA 21-873 Text Table 11, ISS pp 35-7

**Medical Officer's Comment:**

- *The type and percentage of these adverse events is consistent with other studies of combination oral contraceptives and other studies of YAZ presented in this review. The percentage of intermenstrual bleeding is comparable to the cycle control data presented in 7.1.6 for study protocol 303740. In the PMDD studies the subjects characterized this as a common adverse event more often but the data is similar.*

7.1.5.2 Common Adverse Events in the 21-Day Regimen Contraceptive Studies

**Protocol 303860** - The most common adverse events listed in a comparative fashion between the pivotal Phase 3 studies for the 24-day and 21-day regimens of 3 mg DRSP / 0.02 mg EE, respectively are shown in Table 21.

**Table 21: Comparison of most frequent AEs (≥ 5% of subjects) 24 versus 21 – Day Regimen**

Adverse Event	24-Day Regimen Protocol 303740		21-Day Regimen Protocol 303860	
	N (1027)	%	N (516)	%
Headache	137	13.3	70	13.6
Upper respiratory infection	137	13.3	77	14.9
Breast pain	71	6.9	32	6.2
Vaginal moniliasis	67	6.5	89	17.2
Leukorrhea	58	5.6	5	1.0
Diarrhea	52	5.1	59	11.4
Abdominal pain	42	4.1	42	8.1
Flu syndrome	39	3.8	29	5.6
Vaginitis	45	4.4	34	6.6

Source: Clinical Study Report No. A12007, pages 1470-1476 of 3206 and Clinical Study Report No. A15129, page 89 of 1143 (NDA 21-676)

**Medical Officer’s Comment**

- *The common adverse event profile is similar in these two regimens except for moniliasis and leukorrhea. This may just be a recording discrepancy. There is no theoretic reason that a 21-day regimen should be associated with more yeast infections.*

**Protocol 14523** - In protocol 14523 (21-day YAZ regimen compared to Mircilon) the most common treatment related adverse events in the 21-day regimen were metrorrhagia (n = 9, 4.1%); headache and weight gain (each n=7, 3.2%) and alopecia & emotional lability (n = 3, 1.4% for each). The most common treatment related adverse events in the Mircilon arm were headache (n =21, 4.8%); metrorrhagia (n =20, 4.5%) and weight gain (n =8, 1.8%).

7.1.6 Cycle Control

**Intracyclic Bleeding**

The numbers (%) of subjects with intracyclic bleeding during each cycle in Study protocols 303740 (24-day regimen) and 303860 (21-day regimen) are shown respectively in Table 22 and Table 23.

**Table 22: Intracyclic Bleeding Analysis for Protocol 303740 (24-day regimen)**

Cycle	Intracyclic Bleeding			
	No		Yes	
	N	%	N	%
1	704	75	231	25
2	768	86	123	14
3	753	86	121	14
4	757	86	115	14
5	766	90	87	10
6	727	86	116	14
7	748	91	73	9
8	713	89	84	11
9	687	90	76	10
10	678	90	72	10
11	674	92	59	8
12	645	90	68	10
13	442	85	81	15

Source: Clinical Study Report No. A12007, pages 1448 of 3206 (NDA 21-676)

**Table 23: Intracyclic Bleeding Analysis for Protocol 303860 (21-day regimen)**

Cycle	Intracyclic Bleeding			
	No		Yes	
	N	%	N	%
1	287	78.6	78	21.4
2	325	91.8	29	8.2
3	319	89.6	37	10.4
4	327	90.8	33	9.2
5	348	94.8	19	5.2
6	334	90.0	37	10.0
7	344	93.2	25	6.8
8	339	93.6	23	6.4
9	336	93.8	22	6.2
10	333	92.7	26	7.2
11	340	93.4	24	6.6
12	331	92.2	28	7.8
13	341	94.2	21	5.8
20	314	95.1	16	4.9
26	258	93.4	18	6.5

Source: Clinical Study Report No. A15129, pages 552-553 of 1143 (NDA 21-676)

The numbers (%) of subjects with intracyclic bleeding in each treatment cycle are directly compared by treatment cycle for the 21- and 24-day dosing regimens (see Table 24).

**Table 24 Number (%) of Subjects with Intracyclic Bleeding in Studies 303740 and 303860**

Cycle	Number (%) with No Intracyclic Bleeding			
	24-day regimen		21-day regimen	
	N	%	N	%
1	704	25	287	21
2	768	14	325	8
3	753	14	319	10
4	757	14	327	9
5	766	10	348	5
6	727	14	334	10
7	748	9	344	7
8	713	11	339	6
9	687	10	336	6
10	678	10	333	7
11	674	8	340	7
12	645	10	331	8
13	442	15	341	6

Source: Modified from Table 22 and Table 23 of this review (NDA 21-676)

**Medical Officer's Comment**

- *After the first cycle of use, the percentage of days with intracyclic bleeding remains generally in the 10-15% range, which is acceptable. Intracyclic or "mid-cycle bleeding" is a common side effect of many combination oral contraceptives. Intracyclic bleeding may increase slightly when the estrogenic component of the pill is lessened. There were 7 (0.6%) incidents of intermenstrual bleeding leading to discontinuation of YAZ in protocol 303740 (24-day regimen). There were 2 (0.4%) incidents of intermenstrual bleeding leading to discontinuation in the 21-day regimen. The pattern of intracyclic bleeding appears slightly better in the 21-day protocol, but both products overall have a very acceptable bleeding profile.*
- *In comparative Study 308020, intracyclic bleeding percentages for Mercilon were 12.5%, 9.4% and 11.1% for cycles 2, 4 and 6, respectively. Intracyclic bleeding percentages for YAZ in this comparative Study were 15.3%, 16.5% and 8.8% for cycles 2, 4 and 6, respectively.*

**Withdrawal Bleeding in Protocol 303740 (24-day regimen)**

A majority (89.6%) of the volunteers in the full analysis set (FAS) experienced withdrawal bleeding in treatment cycle 1. The number of volunteers with withdrawal bleeding increased slightly afterwards and ranged between 91.7% and 94.4% at cycles 2 to 13. In the FAS, the mean length of withdrawal bleeding was 5.2 days (SD 3.2) at cycle 1, ranged between 4.6 days (SD 2.1) and 4.9 days (SD 2.2) at cycles 2 to 12, and was 2.6 days (SD 1.7) at cycle 13.

**Medical Officer's Comment**

- *The absence of a withdrawal bleeding episode may disturb some patients and make them think that they have become pregnant.*

In the FAS, the maximum intensity at cycles 1 to 12 was normal in 51.2% to 59.4% of the volunteers, light in 23.4% to 28.5% of the volunteers, spotting in 6.8% to 11.3% of the volunteers, and heavy in 8.1% to 11.9% of the volunteers. At cycle 13, the maximum intensity was normal in 39.4% of the volunteers, light in 33.4% of the volunteers, spotting in 21.2% of the volunteers, and heavy in 6.0% of the volunteers. In the FAS, the mean onset of withdrawal bleeding was 3.1 days (SD 4.1) at cycle 1, ranged between 3.2 days (SD 3.5) and 3.6 days (SD 4.4) at cycles 2 to 12, and was 2.2 days (SD 2.7) at cycle 13.

Source: Clinical Study Report No. A12007, pages 100-101 of 3206

**Medical Officer's Comment:**

- *Withdrawal bleeding approaches 94%. Therefore, the number of amenorrheic episodes on this product is small. The mean length of withdrawal bleeding is acceptable as well as the percentage of subjects who reported somewhat heavier withdrawal bleeding (8-12%)*
- *In Study 308020 the overall cycle control pattern appeared similar to Mercilon. There was no evidence of significant irregular bleeding with either product.*

7.1.7 Laboratory Findings

7.1.7.1 Potassium Monitoring

Because of a potential for drospirenone products to cause retention of potassium, potassium measurements and assessment for hyperkalemic symptoms have been undertaken, first for Yasmin and also for YAZ.

**Contraceptive Trials (24-Day Active Dosing Regimen)**

**Protocol 303740** - The section on potassium monitoring in protocol 303740 (pivotal Study for 24-day regimen for contraception) in the Medical Reviewer's first cycle clinical review is reproduced below:

*"Mean potassium levels varied only slightly throughout the Study. Potassium values were within the reference range for the majority of volunteers at all time points."*

Source: Clinical Study Report No. A12007, page 141 of 3206

*The reference range for potassium in the central lab for this Study was 3.6-5.0 mEq/L. The mean and median values along with the mean changes from baseline are listed in Table 25.*

**Table 25: Mean Potassium Levels During Protocol 303740**

Visit	Mean/median absolute value (mEq/L)				Mean change from baseline (mEq/L)		
	N	Mean	SD	Median	N	Mean	SD
Screening	1020	4.25	0.34	4.20			
Cycle 1	980	4.29	0.37	4.30	978	0.05	0.42
Cycle 6	872	4.20	0.41	4.20	870	-0.05	0.46
Cycle 13	714	4.25	0.43	4.20	713	0.01	0.46
Final	915	4.18	0.58	4.10	913	-0.07	0.63

Source: Clinical Study Report No. A12007, page 141 of 3206 (NDA 21-676)

Single potassium values above 5 mEq/L were reported for 65 volunteers. In most of these cases, values were only slightly increased and did not exceed the Applicant's alert range (>5.75 mEq/L). For 14 volunteers potassium values above the alert range were recorded after the screening visit. In volunteers (PIDs 949, 320, 854, 325, 943, 945), potassium values reached levels not compatible with life. For none of the volunteers with potassium values above the alert range, were any AEs reported that were likely to be related to hyperkalemia. In all cases, potassium values were normal at the next visit and /or were verified as within the normal range by repeated tests at the same or a subsequent time point. In 1 volunteer, the unphysiologically high potassium value was caused by a hemolytic blood sample as shown by high serum hemoglobin concentration (PID 1310 / vol. no. 689 at cycle 13). In several other cases, preanalytical problems are suspected because the occurrences of unphysiologically high potassium values were clustered in 3 centers.

Source: Clinical Study Report No. A12007, pages 151-152 of 3206

**Medical Officer's Comments:**

- *The Applicant was asked to verify that there were no adverse events at the time of these spuriously elevated potassium values. The data from their response (May 21, 2004) indicated that there were no adverse events recorded at the time of these potassium elevations. Retesting and other potassium determinations during treatment did not indicate any true hyperkalemia. Practically all the cases of increased potassium determinations (levels above 5.5 mEq/L) were reported from 3 Study sites, which strongly suggest either a collection or transport problem. These sites were:*

- Study site 9 (Austria) 3 instances*
- Study site 71 (Poland) 4 instances*
- Study site 72 (Poland) 8 instances*

A listing of the subjects with potassium values > 5.5 mEq/L is provided in Table 26.

**Table 26: Subject Listing for Serum Potassium Values >5.5 mEq/L (Study 303740)**

PID	Site #	Study Day	Potassium mEq/L	Re-Test Potassium mEq/L	Comment	Clinical Adverse event at time of potassium elevation?
74	90	375	5.7			No
242	9	419	7.7	3.8	Latent hemolysis	No
320	72	160	10.8	4.4 in cycle 13 4.1 at final	Latent hemolysis	No
321	72	161	7.9	4.6 in cycle 13 4.1 at final	Increased transport time	No
325	72	429	10.7	4.5	Latent hemolysis	No
333	6	353	5.6			No
447	5	373	5.5			No
799	74	12	5.5			No
824	71	310	5.7		Latent hemolysis	No
854	71	361	9.1	4.4 at final	Latent hemolysis	No
866	71	357	6.6	4.0 at final	Latent hemolysis	No
914	71	355	6.3	3.7 at final	Long tourniquet time	No
943	72	399	15.4	3.8	Latent hemolysis	No
944	72	395	6.6		Latent hemolysis	No
944	72	401	6.9	4.0	Latent hemolysis	No
945	72	395	11.5	3.9	Latent hemolysis	No
949	72	13	9.7	4.3	Increased transport time	No
1001	9	25	6.2	4.0	Latent hemolysis	No
1033	11	163	5.6		Increased transport time	No
1050	9	378	5.5		Increased transport time	No
1310	58	319	6.7	4.1 at final	Increased free hemoglobin	No

Source: Lab dataset for Study 303740 (NDA 21-676)

**Medical Officer's Comment**

- Although there is a theoretical risk of hyperkalemia with drospirenone based on its mechanism of action, there is no evidence in this pivotal trial of true hyperkalemia with accompanying symptomatology. The outlier potassium elevations in this trial are felt to be spurious levels related to collection and transport issues and not reflective of true hyperkalemia. This assessment is based on normal levels of potassium at retesting and no adverse events recorded at the time of the elevated levels. Additionally, the segregation of most of these events to three Study sites further suggests collection and/or transport problems. Two subjects in protocol 303740 took ACE inhibitors (PIDs 844 and 1277). Neither of these subjects had elevated potassium values during the Study, nor adverse events related to hyperkalemia. Subject 844 had Study medication withdrawn due to an SAE not related to Study drug (retrobulbar neuritis). Only 1 subject taking NSAIDs in the protocol 303740 had a significantly elevated potassium determination. Subject 949 took ibuprofen for endometriosis. Her potassium of 9.7 mEq/L was repeated and found to be normal. Her Study site had 7 other instances of apparent "pseudohyperkalemia". No subject in this Study used spironolactone or potassium-sparing diuretics.*

- ***In Study protocol 14523 which compared 3 mg DRSP/0.02 mg EE tablets (21 day dosing regimen) versus Mercilon, spurious elevations of potassium without associated adverse events also occurred. Three of the elevations occurred in the Mercilon treatment arm, which has no theoretical mechanism for elevating potassium.***

**Protocol 308020** - In European Study 308020 (YAZ vs Mercilon), hyperkalemia (serum potassium above the normal range of 5.3 mEq/L) occurred at least once in post baseline samples in 5 of 229 (2.2%) women in the YAZ group and in 5 of 220 (2.3%) subjects in the Mercilon group. Of the 10 subjects with elevated potassium, only 2 had elevated values on treatment (one each in the YAZ and Mercilon treatment groups, respectively). In the YAZ group, the on-treatment serum K<sup>+</sup> value was > 6.0 mEq/L (subject 500249). However, the blood sample was assessed as hemolytic. The remaining 8 values were measured in the YAZ (n=4) and Mercilon (n=4) groups during follow up 10 to 17 days after last tablet intake. There was one case of dizziness among the subjects in the YAZ group with post-baseline serum potassium values >5.5 mEq/L which was not an SAE. None of the other selected cardiovascular events potentially related to elevated potassium (arrhythmia, bradycardia, syncope, tachycardia, and palpitations) were reported. Hyponatremia was not seen in any of the subjects during the treatment phase of the Study,

**Protocol 308382** - In the Applicant's complete response to NDA 21-676 (15 June 2005), there was only one subject (PID# 307) in the ovarian suppression Study (protocol 308382) with a potassium value of 5.6 mEq/L which is slightly above the upper limit of the reference range (upper limit of the reference range in this Study was: 5.3 mEq/L).

### **Acne Studies**

In the US Phase 3 Acne Studies (YAZ vs placebo): The number of subjects who had at least 1 post-baseline serum potassium value > 5.5 mEq/L was comparable between the YAZ group and placebo group (7 [1.3%] versus 8 [1.5%], respectively). None of the subjects with post-baseline serum potassium values >5.5 mEq/L experienced any of the 6 cardiovascular events identified by the Applicant as possibly related to hyperkalemia. There were no reported cases of 4 of the 6 potassium related cardiovascular events (arrhythmia, bradycardia, syncope or tachycardia) in either treatment group. The remaining 2 events (dizziness and palpitations) occurred in 5 subjects in each group. None of these cases were SAEs. All subjects with selected cardiovascular treatment-emergent AEs had serum potassium levels that were within the normal range (3.5 to 5.3 mEq/L) throughout the study. Four subjects had at least 1 post-baseline sodium value below the lower reference range, 2 were in the YAZ group and 2 in the placebo group.

**Protocol 306996** - In study protocol 306996 (acne), 2 subjects in the YAZ group had an elevated potassium value. Subject 11007 had one elevated potassium at visit 5 of 6 (6.5 mEq/L) that was not associated with any adverse symptoms of arrhythmia, bradycardia, dizziness, palpitations, syncope or tachycardia. Likewise subject 11041 had one elevated potassium at the follow up visit (5.7 mEq/L) with no adverse symptoms. Five subjects on placebo had elevated potassium levels in this study. The mean serum potassium value at baseline (4.12 mEq/L) was the same for both treatment groups. The mean changes from baseline in post-baseline maximum serum

potassium value were 0.15 mEq/L and 0.16 mEq/L in the DRSP/EE and placebo groups, respectively.

**Protocol 306820** - In study protocol 306820 (acne), 5 subjects in the YAZ arm and 3 subjects in the placebo arm had elevated potassium levels. None of these subjects had any adverse symptoms of arrhythmia, bradycardia, dizziness, palpitations, syncope or tachycardia. The subjects are listed in the following table (Table 27). At endpoint, the mean change from baseline was similar between treatment groups (0.040 mEq/L versus 0.030 mEq/L in the DRSP/EE and placebo groups, respectively). There was no statistically significant difference between the treatment groups.

**Table 27: Elevated Potassium Levels in Study Protocol 306820**

Subject #	Subject Age	Treatment cycle	Elevated potassium level (mEq/L)	Related symptoms
<i>YAZ arm</i>				
9011	35	6	5.7	No
11113	14	1	5.6	No
		6	5.7	No
17015	27	1	6.5*	No
19036	22	1	5.6	No
23051	23	1	5.6	No
<i>Placebo arm</i>				
11063	16	Screening	5.8	No
		1	5.5	No
19028	24	Screening	5.5	No
		Follow-up	5.5	No
23062	25	1	5.8	No

\* The specimen was left out overnight  
 Source: Clinical Study Report A25083 page 483 of 659

**Medical Officer's Comment**

- *The slight increases in potassium appear relatively similar in both the treated and placebo groups. No clinically related symptoms are reported for any of these values..*

**PMDD Studies**

The major focus of the analysis of chemistry laboratory values was to assess the potential effect of DRSP /EE on potassium concentrations. The subjects with potassium levels above 5.4 mEq/L are shown in Table 28 . Across the 2 studies, the proportions of subjects in each treatment group with a serum potassium above 5.4 mEq/L were similar (1.4% of DRSP /EE subjects, 1.1% of placebo subjects). None of these subjects experienced any of the cardiovascular adverse events potentially associated with hyperkalemia; only one subject in each treatment arm was taking a concomitant medication (NSAID) thought to possibly affect potassium levels. All except 2 of the placebo subjects normalized their values while remaining on treatment. Only one elevated value (subject #380112 in Study 304049, assigned to DRSP /EE, who increased from a baseline

level of 4.4 mEq/L to 6.0 at Cycle 2, and then returned to normal, by the end of treatment) was considered by the investigator to be clinically relevant.

**Table 28: Subjects with Elevated Post-treatment Potassium Values – Pooled Data**

Protocol	Treatment	Subject	Visit	PBSP ≥5.5 mEq/L	Serum Creatinine mg/dL	Creatinine Clearance mL/min	Creatinine Clearance Category (a)
304049	YAZ	200056	Treatment Cycle 2 (31 days)	5.5	1.0	69.1	Mild
	YAZ	380122	Treatment Cycle 2 (26 days)	6.0	0.9	81.6	Normal
	YAZ	510008	Treatment Cycle 2 (30 days)	5.7	0.6	129.9	Normal
	Placebo	840058	End of Treatment Cycle (127 days)	5.6	0.6	145.2	Normal
305141	YAZ	80001	End of Treatment Cycle (87 days)	5.6	1.0	67.2	Mild
	Placebo	80021	Treatment Cycle 2 (140 days)	5.7	0.7	116.0	Normal
	Placebo	80039	End of Treatment Cycle (246 days)	6.2	4.2	27.6	Severe

PBSP = Postbaseline Serum Potassium

(a) = Creatinine clearance categories: >80 mL/min = normal; 50 to ≤80 mL/min = mild; 30 to ≤50 mL/min = moderate; ≤30 mL/min = severe.

Source: Text Table 21, iss.pdf, p 61 (NDA 21-873)

Change from baseline in potassium level was minimal, and similar between treatment arms, as shown in Table 29.

**Table 29 Change from Baseline in Potassium Level – Pooled Data (Studies 304049 and 305141)**

Treatment	Number of Subjects (a)	Baseline Mean ± SD	Change from Baseline in	
			Postbaseline Maximum (b) Mean ± DS	Postbaseline Average (b) Mean ± SD
YAZ	255	4.27 ± 0.374	0.17 ± .431	0.04 ± 0.394
Placebo	245	4.23 ± 0.359	0.18 ± 0.393	0.04 ± 0.360

SD = Standard Deviation

Note: Normal ranges of serum potassium are 3.4 – 5.4 mEq/L for Protocol 304049 and 3.6 - 5.2 mEq/L for Protocol 305141

(a) = Number of subjects who had a baseline and at least 1 postbaseline serum potassium value.

(b) = All serum potassium values, including results from unscheduled and repeat visits, were used in the calculation of average and maximum serum potassium values.

Source: Text Table 22, iss.pdf, p 65 (NDA 21-873)

The percent of subjects with transitions in potassium values from normal findings at baseline to values outside the normal range over all treatment visits was greater in the DRSP /EE group (2.8%) than the placebo group (1.6%) (See Table 30).

**Table 30 Transitions\* in Serum Potassium Values (Baseline vs. End of Treatment) – Pooled Data**

Treatment Group	Baseline Potassium Value (%)	Any Treatment Potassium Value			
		Low (%)	Normal (%)	High (%)	Total (%)
DRSP /EE	Low	0	1 (0.4)	0	1 (0.4)
	Normal	1 (0.4)	245 (96.1)	7 (2.8)	253 (99.2)
	High	0	1 (0.4)	0	1 (0.4)
	Total	1 (0.4)	247 (96.9)	7 (2.8)	255 (100)
Placebo	Low	0	2 (0.8)	0	2 (0.8)
	Normal	2 (0.8)	237 (96.7)	4 (1.6)	243 (99.2)
	High	0	0	0	0
	Total	2 (0.8)	239 (97.6)	4 (1.6)	245 (100)

\* Normal range varied slightly over the two studies, with an upper limit of normal of 5.4 mEq/L in study 304049 and of 5.2 mEq/L in Study 305141 (NDA 21-873)

Source: Table 38, ise.pdf, pp 472 NDA 21-873

**Medical Reviewer’s Comment**

- *A small but increased percent of DRSP /EE subjects as compared to placebo subjects had increases in potassium level outside of the normal range over the course of treatment. However, these elevated potassium levels were not associated with cardiovascular sequelae in any case, and tended to resolve without discontinuation of DRSP /EE. The overall mean change in potassium level with treatment was minimal and similar to that experienced in the placebo group.*

In addition, creatinine clearance was assessed as a measure of renal function that may affect potassium balance (see Table 31). In the DRSP /EE group, 2.3% of subjects experienced a shift from normal function to mild renal impairment (as estimated by serum creatinine levels), compared to 3.3% of placebo subjects.

**Table 31 Transitions in Creatinine Clearance (Baseline vs. End of Treatment) – Pooled Data**

Treatment Group (N)	Baseline Renal Function	End of Treatment Renal Function			
		Normal (%)	Mild (%)	Moderate (%)	Severe (%)
DRSP /EE (256)	Normal	243 (94.9)	6 (2.3)	0	0
	Mild	6 (2.3)	1 (0.4)	0	0
	Moderate	0	0	0	0
	Severe	0	0	0	0
Placebo (242)	Normal	226 (93.4)	8 (3.3)	0	1* (0.4)
	Mild	3 (1.2)	4 (1.7)	0	0
	Moderate	0	0	0	0
	Severe	0	0	0	0

\* This subject, #80039 in the placebo group, had elevations in creatinine clearance, creatinine and potassium that were determined to be spurious

Source: Table 41, ise.pdf, pp 481 (NDA 21-873)

**Medical Reviewer's Comment:**

- *There does not appear to be an increased risk of renal impairment with DRSP /EE use.*

7.1.7.2 Postmarketing Potassium Monitoring of Yasmin

**Ingenix Study**

A postmarketing safety surveillance of Yasmin was undertaken for the theoretical possibility of hyperkalemia developing with drospirenone. Initiators were identified from June 11, 2001 to June 30, 2004 and followed from June 11, 2001 through the earlier of the patient's end of enrollment or June 30, 2004 or 180 days following the last dispensing of their oral contraceptive (OC). Within the matched cohorts of Yasmin and Other OC initiators there was no difference in risk of hyperkalemia by oral contraceptive exposure status (rate ratio (RR) for Yasmin versus Other OC: 0.5, 95% confidence interval (CI): 0.0-4.9) (see Table 32). The rate ratio for hyperkalemia was not meaningfully different from the rate ratios for any of the individual surrogate measures of that condition (arrhythmia, syncope, electrolyte disturbance and myocardial infarction)..

**Table 32 Intent-to-Treat Incidence Rates of Chart-Confirmed Outcomes for Hyperkalemia and Possibly Related Symptoms (Ingenix Postmarketing Study)**

Outcome	Yasmin Initiators N=22,429 Person Years = 14540.5			Other OC Initiators N=44,858 Person Years =28,169.2			Rate Ratio	95% CI
	N	IR	95% CI	N	IR	95% CI		
Hyperkalemia	1	0.1	0.0-0.4	4	0.1	0.0-0.4	0.5	0.0-4.9
Hospitalization with Hyper/Hypokalemia	0	0.0	0.0-0.2	7	0.2	0.1-0.5	0.0	0.0-1.3
Other Electrolyte Disturbance	24	1.7	1.1-2.5	52	1.8	1.4-2.4	0.9	0.5-1.5
Other Findings								
Syncope	59	4.1	3.1-5.2	151	5.4	4.5-6.3	0.8	0.6-1.0
Arrhythmia	39	2.7	1.9-3.7	57	2.0	1.6-2.6	1.3	0.9-2.0
Dialysis	0	0.0	0.0-0.2	4	0.1	0.0-0.4	0.0	0.0-2.9
Myocardial Infarction	0	0.0	0.0-0.2	3	0.1	0.0-0.3	0.0	0.0-4.7
Death	3	0.2	0.0-0.6	7	0.2	0.1-0.5	0.8	0.1-3.6

IR = Incidence rate, CI = Confidence interval

Source: Applicant's 22 Feb 2006 submission of final study report for Ingenix Study

**Medical Officer's Comment**

- *Although the rate ratio for arrhythmia is slightly increased in the Yasmin initiators (1.3, 95% CI: 0.9 to 2.0) there is no evidence from analysis of the individual cases that this is due to hyperkalemia. Most of these cases represent pre-existing conditions and in the new events of arrhythmia the level of potassium identified in the chart was within normal*

*limits. In addition, there was no specific EKG finding of hyperkalemia in any of these cases of arrhythmia (peaked T waves, widened QRS or flattened p waves). The safety advisory board also evaluated the arrhythmia cases and identified the preponderance as having a preexisting diagnosis. There is no evidence that Yasmin contributed to the deaths in the Yasmin initiator cohort. The deaths were related to an auto accident and oral malignancy in two of the three cases. The cause of death was undetermined in the third but felt to not be related to Yasmin by a reviewing physician.*

**Spontaneous Postmarketing Safety Reports**

The Applicant submitted an updated report on hyperkalemia found through spontaneous postmarketing safety reporting. These cases are listed in Table 33.

**APPEARS THIS WAY  
ON ORIGINAL**

Clinical Review  
 Gerald Willett MD  
 NDA 21-676  
 YAZ (Drospirenone 3 mg / Ethinyl estradiol 0.02 mg)

**Table 33: Postmarketing Reports of Hyperkalemia in Women Using Yasmin**

Case number	Potassium level	EKG changes	Symptoms	Comment
01/00187-GBD	Mild (value unknown)	None reported	None reported	Treatment duration unknown. Laboratory error suspected by physician
US-2005-009728	Elevated (value unknown)	None reported	None reported	Value measured after 3 days of use
FR-2004-031662	5.0	None reported	weight increase, increased triglycerides and aldosterone	Hyperaldosteronism suspected (not in line with hyperkalemia), adrenal adenoma ruled out by US, positive de-challenge
US-SHR-04-022934	5.9 (nl range unknown)	None reported	None reported	Blood glucose 56 mg/dl. No concurrent drugs mentioned. No info on Yasmin discontinuation, physician refused to provide additional information
US-SHR-03-015436	K 5.6 and 5.9 (normal range 3.5-5.3)	None reported	None listed	K values during the 1st month of use Serum Creatinine 1.3 (baseline unknown) No concurrent drugs, Renal insufficiency since age of 1 year
US-SHR-03-008562	"over 5.5"(nl range and baseline unk)	None reported	None reported	Treatment duration unknown
US-SHR-03-004094 (consumer)	"high end of normal"(baseline and normal range unknown)	None reported	None reported	Treatment duration approx. 8 months. Indication: HT and ovarian cyst suppression. Fluid retention for which triamterene-HCTZ was described. Thereafter weakness and dizzy spells. Diuretic changed to HCTZ alone. In addition, ovarian cyst rupture was reported. Symptoms abated, Yasmin continues.
USA-2002-007308	"elevated K level"(not specified)	None reported	None reported	Treatment duration unknown. No case details available
02/05035-USE	"hyper-kalemia" (value unk)	None reported	None reported	Treatment duration 2 weeks. H/o aldosterone disorder. No case details available
02/04297-USE	"slight elevation", (no values prior to or during use)	None reported	Breast enlargement, 8-10 lb weight gain	Finding during the month of initiation. H/o slightly elevated K prior to Yasmin due to chronic ibuprofen use (800 mg tid).
02/02398-USE	"elevated"	None reported	None reported	Treatment duration unknown. Test performed more than once with different results (unspecified). No case details available.
02/01905-USE	"high"	None reported	None reported	Treatment duration unknown. No case details available.
02/01883-USE	"high"	None reported	None reported	Treatment duration unknown. No case details available.
02/00406-USE	5.5-5.6 (normal range not provided)	None reported	Fatigue, near syncope	Value measured during the first month of use. Conc.drugs:Zoloft, Cafegot, Vicodin, OTC NSAIDS.
01/07332-USE	5.6 mEq/l (3.6-5.0)	None reported	None reported	Treatment duration 3 weeks. Until 2 wks prior to Yasmin start spironolactone had been used for <b>acne</b> (K 4.8)
01/06273-USE	5.0 mEq/l, "increased" (nl: 3.6-5.0)	Ventricular ectopics in EKG	Palpitation	Treatment duration approx. 1 month. No treatment initiated, symptoms continued 1.5 months after Yasmin was stopped.
01/05736-USE	5.6 mEq/l (nl: 3.6-5.3)	None reported	None reported	Treatment duration 2 months

Source: The 10 Jan 06 submission to both NDA 21-873 and NDA 21-676

**Medical Officer's Comment**

- *Most of the listed cases lack evidence of any symptomatic sequelae. Only one case (01/06273-USE) had EKG alterations and this case had symptoms continue past discontinuation of Yasmin. In most of the cases, the potassium elevation appears to be mild, but the normal range for the determination is missing. It appears that other medical conditions and concurrent drugs may be also playing a role. The evidence to date does not suggest any alteration to our present labeling and safety monitoring for Yasmin. This reporting information does not preclude an approval recommendation for YAZ.*

7.1.7.3 Other Laboratory Findings

**Medical Officer's Comment:**

- *In Study 303740 standard hematological and chemistry safety labs showed either normal findings or laboratory changes consistent with class effects known for combination oral contraceptives.*

7.1.8 Vital Signs

In the pivotal contraceptive Study 303740, there were no significant mean changes in heart rate or blood pressure. Rare subjects had slight elevations in blood pressure which is a known side effect of combination oral contraceptives.

7.1.17 Postmarketing Experience with Yasmin

The Applicant has provided data from two large ongoing postmarketing safety surveillance trials supporting the safety of the presently marketed DRSP product Yasmin.

7.1.17.1 EURAS Study

The European Active Surveillance Study (EURAS) was initiated for Yasmin in March 2001. This surveillance Study is part of a European effort to perform postmarketing safety on contraceptive formulations with new progestins and/or estrogen. This Study completed on December 31, 2006. The final numbers of venous and arterial thromboembolic events were provided by the applicant in the submission of February 28, 2006. The Applicant has provided close estimates, but not the final figures for the exposure as these are not yet available. The thrombotic/thromboembolic adverse event rates for Yasmin, levonorgestrel-based oral contraceptives and "other" oral contraceptives based on the submission of February 28, 2005 are shown in Table 34. The results demonstrate that in thrombotic/thromboembolic adverse events rates for Yasmin are similar to those of other combination oral contraceptives.

**Table 34 EURAS Study: Confirmed Thromboembolic AEs (Number of Events, Incidence, 95% CI)**

Event Category	Yasmin (40,193 WY)			LNG-containing OCs (37,891 WY)			Other OCs (58,575 WY)			Total
	N	Per 10 <sup>4</sup> WY	95% CI	N	Per 10 <sup>4</sup> WY	95% CI	N	Per 10 <sup>4</sup> WY	95% CI	N
All VTE & ATE	33	8.2	5.7-11.5	38	10.0	7.1-13.1	71	12.1	9.5-15.3	142
All VTE	30	7.5	5.0-10.6	28	7.4	4.9-10.7	59	10.1	7.7-13.0	117
Of which PE	7	1.7	0.7-3.6	7	1.8	0.7-3.8	11	1.9	0.9-3.4	25
All ATE	3	0.7	0.2-2.2	10	2.6	1.3-4.8	12	2.0	1.1-3.6	25
Of which AMI	0	0.0	0.0-0.9	6	1.6	0.6-3.4	5	0.9	0.3-2.0	11
Of which CVA	3	0.7	0.2-2.2	3	0.8	0.2-2.3	7	1.2	0.5-2.5	13
All Fatal VTE/ATE	0	0.0	0.0-0.9	3	0.8	0.2-2.3	0	0.0	0.0-0.6	3

VTE = venous thromboembolic event; ATE = arterial thromboembolic event; AMI = acute myocardial infarction; CVA = cerebrovascular accident; WY = women-years

Based on ITT analysis

Exposure data are "close" to final values per the Applicant as final data analysis is ongoing.

Source: Applicant's 28 Feb 2006 submission (NDA 21-676)

#### 7.1.17.2 Ingenix Study

The US postmarketing surveillance study (Ingenix Study of United Health Care Patients) was initially designed to evaluate the use of Yasmin among women with contraindications or warnings related to its use, to assess compliance of healthcare providers with the recommendation to measure serum potassium in the first cycle of Yasmin among women receiving long-term therapy with drugs that predispose to increased serum potassium, and to assess the occurrence of electrolyte disturbances (particularly hyperkalemia) and related clinical outcomes among women taking Yasmin. A total of 22,429 Yasmin initiators and 44,858 other OC initiators contributed 14,540 and 28,169 person years, respectively, to the outcome analysis.

The Ingenix Study was modified after its inception to also monitor thrombotic and thromboembolic adverse events. The final report of the Ingenix Study (see Table 35) shows a similar risk for Yasmin, compared to other oral contraceptives, for thrombotic and thromboembolic adverse events.

**Table 35 Ingenix Study Results (Intent-to Treat Incidence Rates of Chart-Confirmed VTE/ATE Outcomes by Subgroup and Rate Ratios for Yasmin vs. Other OC Cohorts)**

Outcome/Subgroup	Yasmin Cohorts (N=22,429) (PY = 14,540.5)			Other OC Cohorts (N=44,858) (PY = 28,169.2)			RR	95% CI
	N	IR (1)	95% CI	N	IR	95% CI		
All VTE	18	1.2	0.8-1.9	39	1.4	1.0-1.9	0.9	0.5-1.6
Pulmonary embolism	5	0.3	0.1-0.8	12	0.4	0.2-0.7	0.8	0.2-2.5
Venous thrombosis	12	0.8	0.5-1.4	25	0.9	0.6-1.3	1.1	0.5-2.2
Venous thrombosis & pulmonary embolism	1	0.1	0.0-0.3	2	0.1	0.0-0.2	1.0	0.2-18.6
Strokes (2)	1	0.0	0.0-0.2	1	0.0	0.0-0.2	1.9	0.2-152.0

PY = Person-years; IR= Incidence rate; RR= Rate ratio  
 (1) = Incidence rates expressed as events per 1,000 person-years  
 (2) = Of ATEs there were also 3 myocardial infarctions reported in the other OC cohort but none in the Yasmin cohort  
 Source: Applicant's 22 Feb 2006 submission of final study report for Ingenix Study

7.1.17.3 AERS Database

The Office of Drug Safety periodically provides DRUP with updates on reports of thromboembolic adverse events in the FDA's AERS database for selected contraceptive products. The estimated reporting rates for Yasmin based on the AERS database and utilization data are shown in Table 36:

**Table 36 Vascular Adverse Events and Deaths for Yasmin in AERS Reporting Data Since U.S. Product Launch.**

	Yasmin (May 2001-May 2004)		Yasmin (May 2001-Aug 2005)	
	N	Reporting Rate (per 100,000)	N	Reporting Rate (per 100,000)
Estimated Total Prescriptions	13,033,000		24,857,000	
Person-Years of Exposure	749,844		1,906,838	
All Embolism & Thrombosis	89	11.9	123	6.5
Pulmonary Embolism	43	5.7	53	2.7
Cerebrovascular Events	16	2.1	23	1.2
Myocardial Infarction	Not assessed		2	0.1
All Deaths	6	0.8	6	0.3

Source: ODS reports of August 31, 2004 and November 1, 2005

**Medical Officer's Comment:**

- *Post marketing reporting rates can only provide limited data regarding the true incidence of adverse events compared to similar products due to marketing influences and increased reporting after media attention. It is noteworthy that the reporting rates for all embolism and thrombosis have dropped since the analysis in 2004. The rates listed for Yasmin are less than some other marketed products. It is anticipated that spontaneous reporting for YAZ will show lower numbers since the product contains one third less ethinyl estradiol per tablet.*

### 7.1.9 Congenital Anomalies

In the January 10, 2006 letter from the Applicant they provided a listing of congenital anomalies found in infants of women taking “Yasmin” type products. These are listed in the following table (Table 37).

**Table 37: Reports of Congenital Anomalies**

Initial Report Date	Mother's Age	Congenital Anomaly and comment
<b>Occurring in association with clinical trials</b>		
19-Nov-1996	26	Esophageal atresia (Yasmin drug exposure max. 4 weeks)
23 Jun-2004	23	Spina bifida (abortion performed after 22 weeks of pregnancy, conception occurred 6 months after Yasmin use)
<b>Identified in postmarketing safety reports for Yasmin</b>		
09-Jun-2004	27	Bilateral metatarsus varus (Yasmin for first two weeks after conception)
03-Oct-2005	Not listed	Pyloric stenosis (duration not listed)
<b>Identified in the Ingenix study</b>		
Not listed	Not listed	Cleft lip
Not listed	Not listed	Ventricular septal defect

Source: Applicant's Jan 10, 2006 submission

**Medical Officer's Comment:**

- *There is no apparent signal for any congenital anomaly related to Yasmin use early in pregnancy.*

### 7.2 Adequacy of Patient Exposure and Safety Assessments

Table 38 lists the completed phase 2/3 studies comprising the safety exposure database for 3 mg DRSP/ 002 mg EE. There were another 101 subjects in phase 1 and phase 2 studies with limited treatment duration.

**Table 38: Subject Exposure Completed studies of 3 mg DRSP / 0.02 mg EE (24 and 21 day regimens)**

Study No. (Regimen)	Purpose of Study	No. Subjects on DRSP /EE	Treatment Duration (cycles)	No. Treatment Cycles	No. Subjects treated for ≥ 1 yr
<b>24 day active dosing regimen</b>					
303740	Contraception (24-day)	1027	13	11,480	746
301888	Lipid, hemostatic and CHO	29	7	182	0
304049	PMDD	231	3	579	0
305141	PMDD	54	3	140	0
308020	Cycle control comparative	227	7	1354	0
306996	Acne	270	6	~1407*	0
306820	Acne	266	6	~1346*	0
308021	Contraception	1,101	13	~12,493**	961
Subtotal		2,442	NA	28,981	1,707
<b>21 or 24 day active dosing regimens</b>					
308382	Ovarian suppression 24-day vs 21-day	104	3	311	0
<b>21 day active dosing regimen</b>					
303860	Contraception (21-day)	516	26	11,510	438
14523	Cycle control	220	7	1,435	0
305466	Ovarian suppression (21-day)	23	2	43	0
14588	Ovarian suppression (21-day)	30	2	58	0
Subtotal		789	NA	13,046	438
<b>All completed 24 and 21 day active dosing regimens</b>					
<b>Total of all</b>		<b>3335</b>	<b>NA</b>	<b>42,338</b>	<b>2145</b>

\* = Derived from multiplying #subjects x mean days on drug/ 28 days

\*\*= Based on 961 subjects completing, does not include the cycles from those prematurely discontinuing

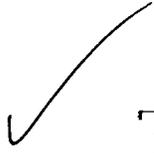
Source: Tables of studies and individual Study reports (NDA 21-676 and NDA 21-873)

**Medical Officer's Comment**

- *The overall exposure in terms of numbers of subjects and duration of exposure is acceptable.*

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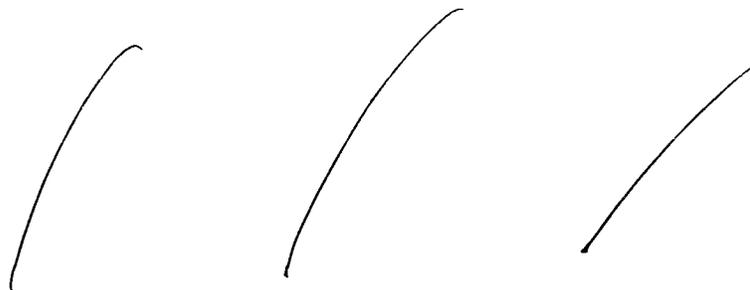
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## 9 OVERALL ASSESSMENT

### 9.1 Conclusions

The efficacy conclusions for the 24-Day regimen of YAZ are the following:

- The total 28-day cycles of exposure used to calculate the Pearl Index in the principal efficacy study (303740) was adequate (11,050 cycles) for the efficacy determination. The division has requested that Applicants have at least 10,000 cycles.
- The Pearl Index of 1.41 is acceptable for approval for contraceptive efficacy.
- Preliminary results from 2 additional Phase 3 contraceptive studies with YAZ also indicate the efficacy of YAZ is acceptable for a combination hormonal contraceptive. The Pearl Index values for YAZ in these 2 studies were 0 (Study 308020 – no pregnancies) and 0.5 (Study 308021).
- The comparative Study (protocol 308382) shows better follicular suppression with the 24-day regimen compared to the 21-day regimen.

Safety data reviewed to date indicate that the safety exposure was adequate and that the safety profile of YAZ is satisfactory for a highly effective hormonal contraceptive product.

### 9.2 Recommendation on Regulatory Action

Approval is recommended for YAZ (24-day active dosing regimen of drospirenone 3 mg/ethinyl estradiol betadex 0.02 mg tablets) based on the contraceptive efficacy, comparative ovarian suppression data, and safety data submitted to NDA 21-676 through all review cycles. Additionally the data submitted in the applicant's complete response (June 15, 2005) supports that a 24-day active dosing regimen of this product shows more ovarian follicular suppression than a comparable 21-day active dosing regimen of this product. Acceptable labeling was submitted on April 9, 2006.

### 9.3 Recommendation on Postmarketing Actions

The proposed risk management activity and postmarketing safety Study are acceptable

### 9.3.1 Risk Management Activity

Product labeling will include, in addition to the standard class warnings for combination oral contraceptives, a Bolded Warning (similar to that for Yasmin) that informs healthcare providers and consumers about the risk of hyperkalemia associated with the use of drospirenone.

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### 9.3.2 Required Phase 4 Commitments

In addition to the risk management activities described above, the Applicant has committed to (and has initiated) a large prospective Phase 4 postmarketing safety Study of drospirenone containing OCs called the International Active Surveillance Study of Women taking Oral Contraceptives (INAS OC). The Study has commenced already with patients taking Yasmin. The amended protocol for this surveillance study is found in the Applicant's 18-Aug-2005 submission. This Study is designed in a similar manner to the ongoing European Active Surveillance (EURAS) Study that is assessing vascular adverse events for Yasmin users compared to users of other combination oral contraceptives. These vascular adverse events include deep vein thrombosis, pulmonary embolism, myocardial infarction and cerebrovascular accident. The INAZ Study has a U.S. component in addition to a European component (prescribing physicians in the US and approximately \_\_\_\_\_ in Europe). It will compare drospirenone combination oral contraceptives (Yasmin and YAZ) to those which contain other progestagens. The Study will recruit \_\_\_\_\_

### 9.4 Labeling Review

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## 10 APPENDICES

10.1 *Ovarian Suppression Study (Protocol 308382)* “Single center, double-blind, randomized Study to compare the effect of SH T 00186 D ( 3 mg DRSP / 0.02 mg EE ) on follicular development in a 24-day regimen versus a 21-day regimen in 100 healthy female volunteers in cycle 2 and after intentional dosing errors in cycle 3”

### 10.1.1 Entry Criteria for Study Protocol 308382

#### 10.1.1.1 Inclusion Criteria

1. Signed informed consent
2. Age: 18 - 35 years (inclusive), smokers aged 30 years (inclusive) at visit 1
3. Willingness to use non-hormonal methods of contraception (e.g., condoms, diaphragms, spermicidal vaginal suppositories, or abstinence) during pretreatment, treatment, and follow-up cycles
4. Laboratory test results without clinically relevant abnormalities
5. Non-suspicious Papanicolaou (Pap) smear taken at screening (visit 1) or within the last six months before Study entry and written result available
6. Follicular diameter  $\geq$  15 mm at visit 6 (admission to treatment) or observed ovulation during pretreatment cycle

#### 10.1.1.2 Exclusion Criteria:

1. Pregnancy or lactation (less than 3 cycles following delivery, abortion, or lactation before start of pretreatment cycle)
2. Substantial overweight, i.e., body mass index (BMI)  $>$  30, where BMI = body weight in kilograms / (body height in meters squared)
3. Known hypersensitivity to any of the Study drug ingredients
4. Any known 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

5. Any disease that may worsen under hormonal treatment or might interfere with the conduct of the Study, or the interpretation of the results (e.g., herpes gestationis or idiopathic icterus during a previous pregnancy; middle-ear deafness [otosclerosis]; Sydenham chorea, porphyria, disturbances in the bile flow (presence or history of cholestasis, gallstones, systemic lupus erythematosus)
6. Diagnosed or suspected malignant or pre-malignant disease
7. Liver diseases: presence and / or history of severe hepatic diseases including benign or malignant tumors. There should be an interval of at least 3 months between the start of Study medication intake, and the return of liver function values to normal
8. Vascular diseases: presence and / or history of venous thromboembolic diseases (deep vein thrombosis, pulmonary embolism), presence of history of arterial thromboembolic diseases (myocardial infarction, stroke), and / or any condition which could increase the risk to suffer from any of the above mentioned disorders, e.g., a positive family history (an event that occurred in a sibling or a parent at an early age) or a suspected hereditary predisposition
9. Other diseases: chronic inflammatory bowel disease (Crohn's disease or ulcerative colitis), hemolytic uremic syndrome, migraine with focal neurologic symptoms (complicated migraine)
10. Undiagnosed vaginal bleeding
11. Uncontrolled thyroid disorder
12. Severe dyslipoproteinemia
13. Pancreatitis or a history thereof, if associated with severe hypertriglyceridaemia
14. Uncontrolled arterial hypertension: confirmed systolic blood pressure > 140 mm Hg or confirmed diastolic blood pressure > 90 mm Hg
15. Diabetes mellitus with vascular involvement
16. Sickle-cell anemia
17. Current or history of clinically significant depression
18. Current or history of alcohol or drug abuse
19. Prohibited concomitant medication: use of additional steroid hormones; anticoagulants (e.g., heparin, coumarin), antiepileptics / hydantoin derivatives (e.g., phenytoin), carboxamid derivatives, (e.g., carbamazepin, oxcarbamazepin), other anti-epileptics (e.g., felbamate, topiramate), hypnotica and sedativa / barbiturate derivatives (e.g., primidone), tuberculostatics, (e.g., rifampicin), oral antimycotics (e.g., griseofulvin, ketoconazole), virostatic agents (e.g.,

ritonavir), products containing the herbal remedy St. John's Wort, and continuous systemic use of antibiotics over a period of more than 10 days

20. Subject is a dependent person, (e.g., a relative, family member and/or is a member of the investigator's staff)

21. Intake of an experimental drug within 1 month before inclusion in the Study.

### 10.1.2 Treatment Protocol for Study 308382

**Table 39: Treatment Dosages in Protocol 308382**

Regimen	Investigational products	
	24-day regimen	21-day regimen
Package	Blister pack containing 28 tablets	
Dosage form	Film coated tablets	
Dosage in Cycle 1,2	24 tablets of SH T 00186 D each with 3 mg DRSP / 0.02 mg EE , and 4 placebo tablets of SH T 00186 PB	21 tablets of SH T 00186 D each with 3 mg DRSP / 0.02 mg EE , and 7 placebo tablets of SH T 00186 PB
Dosage in Cycle 3	21 tablets of SH T 00186 D each with 3 mg DRSP / 0.02 mg EE , and 7 placebo tablets of SH T 00186 PB	18 tablets of SH T 00186 D each with 3 mg DRSP / 0.02 mg EE, and 10 placebo tablets of SH T 00186 PB

Source: Page 31 of 5895, Study report A25848 (NDA 21-676)

Missed tablet management was based on the following 2 basic rules:

1. Tablet intake was not to be discontinued at any time in cycles 1 to 3.
2. Seven days of uninterrupted hormone-containing tablet intake were necessary to attain adequate suppression of the hypothalamic-pituitary-ovarian axis.

Therefore, the following advice was given in daily practice:

- If the subject was more than 12 hours late in taking the table, the general recommendation was to take the last missed tablet as soon as remembered, even if this meant taking 2 tablets at the same time. After this, tablet intake was to be continued as usual.
- Not more than 2 tablets were to be taken on a given day.
- If the subject vomited within 4 hours after tablet intake, absorption may have been incomplete. In such an event, another hormone tablet was to be taken from the reserve blister. The same procedure applied for diarrhea.

If the woman missed tablets and subsequently had no withdrawal bleeding, the possibility of a pregnancy was to be considered and ruled out immediately by a human chorionic gonadotropin (HCG)-urine test.

Non-hormonal back-up contraception was to be used during the whole Study period, from pretreatment until the end of the follow-up cycle.

### 10.1.3 Study Flowcharts for Study 308382

Table 40, Table 41 and Table 42 list the flowcharts for screening, and the pretreatment Cycle, Cycles 2 and 3 (treatment) and the follow-up Cycle, respectively.

**Table 40: Screening and Pretreatment Cycle Flowchart**

Assessment	Screen	Pretreatment Cycle						
		1	2	3	4	5	6 Adm (1)	7 (2)
Visit	1	2	3	4	5	6 Adm (1)	7 (2)	8 (2)
Day	1-6	7	11	15	19	23	27	31
Subject information	X							
Informed consent	X							
Demographics, smoking, alcohol	X					Update		
Entry criteria	X							
Medical history	X							
Vitals, weight	X					X		
Physical exam	X							
Gyn exam	X							
Cervical smear	X	Check						
Transvaginal ultrasound	X	X	X	X	X	X	X	X
Hormones	X	X	X	X	X	X	X	X
Safety lab	X	Check						
Update medical history		X	X	X	X	X	X	X
Randomization						X		
Medication dispensed						X		
Diary cards dispensed						X		
Condoms dispensed	X	X	X	X	X	X	X	X
HCG urine test dispensed						X		

- (1) Admission to treatment only after follicular diameter  $\geq 15$  mm or ovulation was observed  
 (2) Visits 7 and 8 were to be skipped if menstruation started earlier, if no menstruation occurred until day 31, additional visits may have been scheduled  
 (3) Cycle started with first bleeding day  
 (4) If necessary  
 (5) Cervical smear could be waived if a normal result from the last 6 months before visit 1 was available  
 (6) Boxes for first and second cycle treatment and reserve blister  
 (7) Human chorionic gonadotropin (HCG)-urine test was to be performed by the subject before first tablet intake  
 Source: Page 23 of 5895, Study report A25848 (NDA 21-676)

Clinical Review  
 Gerald Willett MD  
 NDA 21-676  
 YAZ (Drospirenone 3 mg / Ethinyl estradiol 0.02 mg)

**Table 41: Flowchart for Cycles 2 and 3**

Assessment	Treatment cycle 2				Treatment cycle 3		
	9	10-16	17	18	19-24	25	26
Visit	3	5,8,11,14,17,20,23	26	2	5,8,11,14,17,20	23	26
Day	X	X	X	X	X	X	X
Transvaginal sonogram	X	X	X	X	X	X	X
Hormonal evaluation	X	X	X	X	X	X	X
Safety Lab						X	Check (1)
Adverse events (7)	X	X	X	X	X	X	X
Medication dispensed			X (3)				
Blister collection	X			X			
Diary collected (2,6)	X	X	X	X	X	X	X
Condoms dispensed (5)	X	X	X	X	X	X	X
HCG urine test (4)	X						If required

- (1) If result not yet available, checked during follow-up cycle, at the latest on visit 35  
 (2) Diary cards for cycle 2 were to be filled in until the last tablet intake in cycle 2  
 (3) Boxes for third treatment cycle and reserve blister  
 (4) In the absence of monthly bleeding a HCG-urine pregnancy test was to be performed (including cycle 1)  
 (5) If required  
 (6) As soon as a calendar month was complete, the diary card was to be collected  
 (7) Also for cycle 1  
 Source: Page 24 of 5895, Study report A25848 (NDA 21-676)

**Table 42: Study Flowchart of Follow-up Cycle**

Assessment	Follow-up cycle								
	27	28	29	30	31	32	33	34	35
Visit	3	7	11	15	19	23	27	31	**
Day									
Vitals, weight									X
Physical exam, Gyn exam, Cervical smear (3)									X
TVU	X(6)	X(6)	X(6)	X(6)	X(6)	X(6)	X(6)	X(6)	X
Hormonal testing	X(7)	X(7)	X(7)	X(7)	X(7)	X(7)	X(7)	X(7)	X
Safety lab									X (9)
AEs	X	X	X	X	X	X	X	X	X
Blister collection	X								
Diary card collection	X (3,8)								X (3,8)
Condoms dispensed	X	X	X	X	X	X	X	X	X
End of Study evaluation									X (1,4)

- \*\* = Day of first scheduled visit after ovulation has been observed  
 1. To be performed also in the event of premature discontinuation of Study medication / Study course  
 2. Visit(s) may have been skipped if menstruation had already started earlier  
 3. Diary cards were to be filled in until last tablet intake in cycle 3  
 4. End of Study documentation on subject's last visit  
 5. If required  
 6. Until ovulation was observed  
 7. Until the visit after ovulation was observed  
 8. Diary cards of cycle 3 to be collected; check whether all diary cards were collected  
 9. In the event of premature discontinuation before visit 25  
 Source: Page 25 of 5895, Study report A25848 (NDA 21-676)

## 10.2 Associated INDs and NDAs

**Table 43: Associated INDs and NDAs**

INDs	
60,738	Submitted to Division of Reproductive and Urologic Drug Products on August 22, 2000 for drospirenone 3 mg/ ethinyl estradiol betadex 0.020 mg tablets; indication is for prevention of pregnancy (Principal IND related to this NDA submission)
61,304	Submitted to the Division of Neuropharmacological Drug Products on November 20, 2000 for drospirenone 3 mg/ ethinyl estradiol betadex 0.020 mg tablets; indication is for prevention of premenstrual dysphoric disorder
65,370	Submitted to the Division of Dermatological and Dental Drug Products on October 28, 2002 for drospirenone 3 mg/ethinyl estradiol betadex 0.020 mg tablets; indication is for treatment of acne
51,693	Submitted to Division of Reproductive and Urologic Drug Products on October 7, 1996 for drospirenone 3 mg/ ethinyl estradiol 0.030 mg tablets; indication is for prevention of pregnancy
NDAs	
21-098	Yasmin - drospirenone 3 mg/ ethinyl estradiol 0.030 mg, developed from IND 51,693, submitted to DRUDP on May 14, 1999 and approved on May 11, 2001 for contraception
21-355	Angeliq - drospirenone 3 mg /estradiol 1 mg, developed from IND 53,842, submitted to DRUDP on December 14, 2001 and approved on September 28, 2005.
21-873	YAZ - drospirenone 3 mg/ ethinyl estradiol 0.020 mg (Contraceptive and PMDD indications)

## **10.3 Executive Summary - Medical Officer's Review of NDA 21-676 (First Review Cycle)**

### **RECOMMENDATIONS**

#### **1 Recommendation on Approvability**

Approval is recommended for both the 24-day active dosing regimen and the 21-day active dosing regimens of drospirenone 3 mg/ethinyl estradiol betadex 0.020 mg tablets based on the contraceptive efficacy and safety data submitted to NDA (21-676). This approval recommendation is contingent on acceptable labeling for each dosing regimen.

Approval of the 21-day active dosing regimen is preferable from a safety perspective because it provides the same efficacy with less hormonal exposure than the 24-day active dosing regimen. Based on presently submitted data, there is no proven added clinical benefit associated with the use of the 24-day regimen.

#### **1.2 Recommendation on Phase 4 Studies and/or Risk Management Steps**

The general outlines of the applicant's proposed Phase 4 safety surveillance study for the 24-day regimen are acceptable. The final protocol should be submitted to the Division for review and agreement within 90 days of the approval of this application. It is recommended that

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No Phase 4 safety surveillance study is required for the 21-day dosing regimen.

### **2 SUMMARY OF CLINICAL FINDINGS**

#### **2.1 Brief Overview of Clinical Program**

Berlex seeks approval of a second drospirenone based combination oral contraceptive, hereafter referred to as Yasmin 20 (24-day). This contraceptive contains two-thirds the daily level of ethinyl estradiol (EE) that is found in the applicant's approved product Yasmin (0.02 mg compared to 0.03 mg per tablet) and the same amount of drospirenone (3 mg DRSP) per tablet. The product also differs from Yasmin in that the dosing regimen consists of 24 days of active tablets followed by 4 days of placebo tablets compared to 21 days of active tablets followed by 7 days of placebo tablets for Yasmin

In the present NDA, the applicant also has submitted safety and efficacy data from a second combination oral contraceptive that contains 0.02 mg EE and 3 mg DRSP (hereafter referred to as Yasmin 20 (21-day). The dosing regimen for this product consists of one active tablet daily for 21 consecutive days followed by 7 tablet-free days. The Applicant has not requested approval of this product.

## 2.2 Efficacy

The applicant's protocol for establishing contraceptive efficacy is similar to other product submissions in this class. Over ten thousand 28-day cycles were studied in both the 24-day

regimen (protocol 303740) and the 21-day regimen (protocol 303860). More than 200 women completed 13 cycles of use in both protocols.

The primary efficacy endpoint was the number of "during treatment" pregnancies defined as all pregnancies with an estimated date of conception after the onset of treatment with study drug and through 4 days (applicant's definition) or 14 days (DRUDP's definition) after the last dose of study drug. The primary efficacy analysis was the Pearl Index, which is the number of "during treatment" pregnancies per 100 women-years of use. The efficacy for both the 24-day and 21-day dosing regimens, expressed in terms of the Pearl Index is listed in Table A. The values for the Pearl Index in Table A are based on the Medical Officer's determination of the number of "during treatment" pregnancies and exclude cycles where backup contraception was used, cycles for women over age 35, and cycles for women listed as sexually inactive

**Table A. Efficacy of the 24 and 21-day Regimens of DRSP 3 mg/ EE 0.02 mg\***

24-day regimen (protocol 303740)					
Total days of exposure	Total 28-day cycles of exposure	Total Number Pregnancies		Pearl Index **	2-sided 95% confidence interval
		Applicant's Determination	FDA's Determination		
309,386	11,050 *	11	12	1.42	0.73-2.47
21-day regimen (protocol 303860)					
Total days of exposure)	Total 28-day cycles of exposure	Total Number Pregnancies		Pearl Index *	2-sided 95% confidence interval
		Applicant's Determination	FDA's Determination		
309,136	11,040	2	3	0.35	0.07-1.04

\* Calculated by dividing number of days of exposure by "28".

\*\* Pearl Index based on using 12 "during treatment" pregnancies in protocol 303740 and 3 "during treatment" pregnancies in protocol 303860).

## 2.3 Safety

The overall exposure in terms of numbers of subjects and duration of exposure is acceptable. The three large studies for both the Yasmin 20 product (protocols 303740, 303860 and 14523) provide exposure of a total of 1763 separate subjects. These studies account for 24,425 28-day cycles of safety data or 1,878 women-years.

There were two deaths reported in the clinical studies of Yasmin 20. These deaths both occurred in protocol 303740 (Yasmin 20, 24-day regimen) at the single US study site. Neither of these deaths was related to study medication. One death, secondary to pesticide poisoning, occurred one month following discontinuation of study drug. The other death, occurring three months after starting study medication, was secondary to smoke inhalation in a fire.

The serious adverse events attributable to study drug in the pivotal trial for the 24-day regimen (303740) included one case of migraine, one case of depression and one case of cholelithiasis. The serious adverse events attributable to study drug in the pivotal trial for the 21-day regimen (303860) included two cases of pulmonary emboli, one case of migraine, one case of ovarian cyst and one case of cholecystitis. All of these adverse events have been previously associated with combination oral contraceptive use. There were no SAEs attributable to study drug in any of the other submitted studies

With caveats regarding rate estimations of rare events derived from typical Phase 3 registry studies for oral contraceptives, the finding of two confirmed venous thromboembolic adverse events (2 cases of pulmonary emboli in study 303860) translates to a rate of 10.6 per 10,000 women-years for the Yasmin 20 products. This rate is similar to the findings of the approved product Yasmin in the first year of the EURAS study (approximately 15 per 10,000) which is described in greater detail later in this summary.

In Yasmin 20, 24-day regimen (303740) the adverse event contributing to the greatest number of drug discontinuations was headache (14 incidents, 1.3%). Headache was also the most common adverse event at 13.3%. The most common reasons for study discontinuation in the Yasmin 20, 21-day regimen (303860) were decreased libido and depression (5 subjects each, 1.0%). Vaginal moniliasis (17.2%) constituted the highest number of adverse events in the 21-day regimen with headache (13.6%) showing similar numbers as in the 24-day regimen.

Safety labs were performed only in the 24-day regimen protocol. The laboratory analysis from the 24-day regimen study is sufficient for safety evaluation of the Yasmin 20 product overall. Increased mean levels of lipids were seen in women who used Yasmin 20 (24-day regimen). These findings are comparable to the well-characterized effects on lipids by combination oral contraceptives (COCs). Careful potassium monitoring was performed due to the potential potassium sparing effects of drospirenone. All of the elevated potassium levels identified in the 24-day regimen protocol appeared to represent "pseudohyperkalemia" resulting from hemolysis or transport problems. There was no evidence of true hyperkalemia or any hyperkalemic type symptomatology found at the time of these elevated values. Repeat testing in each case revealed normal values. Neither regimen showed any significant mean changes in vital signs or body weight.

Both the Yasmin 20, 24-day regimen and the Yasmin 20, 21-day regimen had acceptable menstrual cycle control data. The levels of pill-associated amenorrhea and intracyclic bleeding were low for both regimens.

The applicant, has provided data from two large ongoing postmarketing safety surveillance trials supporting the safety of the presently marketed DRSP product Yasmin:

The European Active Surveillance study (EURAS) was initiated for Yasmin in March 2001. This surveillance study is part of a European effort to perform postmarketing safety on contraceptive formulations with new progestins and/or estrogen. This study was last updated on 9 June 2004. At that time 50,000 women were enrolled representing 64,000 women-years of observation. The

comparative table (see Table B) shows the thrombotic/thromboembolic adverse event rates for Yasmin, levonorgestrel-based oral contraceptives and “other” oral contraceptives. The results demonstrate that Yasmin does not have a thrombotic/thromboembolic rate higher than other COCs that do not contain DRSP.

**Table B: EURAS Study: Confirmed Thromboembolic AEs – Number of Events, Incidence, 95% CI**

Event Category	Yasmin (19,530 WY)			LNG-containing OCs (18,476 WY)			Other OCs (26,097 WY)			Total
	N	Per 104 WY	95% CI	N	Per 104 WY	95% CI	N	Per 104 WY	95% CI	N
All VTE & ATE	13	6.7	3.5 - 11.4	14	7.6	4.1 - 12.7	23	8.8	5.6 - 13.2	50
All VTE	12	6.1	3.2 - 10.7	11	6.0	3.0 - 10.7	19	7.3	4.4 - 11.4	42
PE	3	1.5	0.3 - 4.5	2	1.1	0.1 - 3.9	2	0.8	0.1 - 2.8	7
All ATE	1	0.5	0.0 - 2.9	3	1.6	0.3 - 4.8	4	1.5	0.4 - 3.9	8
AMI	0	0.0	0.0 - 1.9	1	0.5	0.0 - 3.0	2	0.8	0.1 - 2.8	3
CVA	1	0.5	0.0 - 2.9	2	1.1	0.1 - 3.9	2	0.8	0.1 - 2.8	5
All Fatal VTE/ATE	0	0.0	0.0 - 1.9	2	1.1	0.1 - 3.9	0	0.0	0.0 - 1.4	2

VTE = venous thromboembolic event, ATE = arterial thromboembolic event, AMI = acute myocardial infarction, CVA = cerebrovascular accident, WY = women-years

Source: Applicant's 17 Aug 2004 submission, page 10 of 37

The US postmarketing surveillance study (Ingenix Study of United Health Care Patients) was initially designed to monitor adverse events related to hyperkalemia. There has been no signal to suggest that hyperkalemia has been a clinical problem with Yasmin since its approval. The Ingenix Study was later modified to monitor thrombotic and thromboembolic adverse events. The most recent interim analysis of the Ingenix Study (see Table C) does not show a higher risk for Yasmin, compared to other oral contraceptives, for thrombotic and thromboembolic adverse events.

**Table C: Ingenix Study Results (Confirmed Cases of Thrombotic and Thromboembolic Events)**

Outcome (a)	Yasmin Initiators (n=14,295)			Other OC Initiators (n=28,590)		
	Claims-Based	Chart Confirmed	Chart Not Found	Claims-Based	Chart Confirmed	Chart Not Found
Number of Charts Requested	20			58		
Pulmonary embolism	4	1	0	11	9	1
Venous thrombosis	12	8	1	27	20	3
Arterial embolism	1	1	0	8	0	1
Stroke	2	0	0	7	3	1
TIA	0	0	0	0	0	0

(a) A woman can have multiple events in multiple categories

(b) Women with claims for procedures or anticoagulant therapy only

Source: Applicant submission 7 Oct 2004

## 2.4 Dosing

The daily dosing of both the 24-day and 21-day regimens incorporates 0.02 mg of ethinyl estradiol compared to 0.03 mg ethinyl estradiol in the approved product Yasmin. Most combination oral contraceptives utilize 21 days of active drug that are followed by 7 placebo tablets. Seasonale is an oral contraceptive that is taken for 84 days and followed by 7 placebo

tablets. Mircette utilizes 21 active combination tablets followed by 2 placebo tablets and then 5 tablets containing 0.01 mg of ethinyl estradiol.

If the applicant receives marketing approval for the 24-day regimen, it will be the first 24-day regimen available. Although the medical literature (provided by the applicant) suggests that expanding the active phase of oral contraceptives may have potential benefits, adequate and controlled clinical trials have not performed comparing the 24-day to the 21-day regimen. It has been suggested that follicular development appears to be suppressed more with longer duration of active tablets by sonogram analysis. This could translate into some contraceptive benefit for low dose pills where missing just a few pills leads to unintended pregnancies. Proving this potential benefit however would require an extremely large clinical study.

The applicant also is developing the 24-day regimen for the added indications of prevention of PMDD and treatment of acne in women desiring contraception and who elect to use oral contraception.

Table D provides the annual hormonal exposure of the presently marketed drospirenone product (Yasmin) and the two Yasmin 20 products described in this review:

**Table D: Annual Exposure to Ethinyl estradiol and DRSP with Yasmin and the Yasmin 20 Products**

Product	Ethinyl Estradiol	DRSP
Yasmin	8.19 mg	819 mg
Yasmin 20, 24-day regimen	6.24 mg	936 mg
Yasmin 20, 21-day regimen	5.46 mg	819 mg

Although both of the Yasmin 20 regimens are deemed safe and effective based on the data presented in this NDA, this reviewer prefers the 21-day regimen since it provides the same contraceptive efficacy with less hormonal exposure. It is acknowledged that the applicant has ongoing programs for the 24-day regimen that seek the additional secondary indications of PMDD and acne. Approval of either of these supplemental indications would impact this reviewer's assessment of the risk/benefit ratio for the 24-day regimen and would further support approval of the 24-day dosing regimen.

## 2.5 Special Populations

**Gender.** Combination oral contraceptives are intended for the population of women at risk for pregnancy.

**Race.** A small pharmacokinetic study was performed by the applicant comparing Japanese and Caucasian women. This study showed no differences in these two ethnic populations.

The racial distribution for the 24 and 21-day regimens in the pivotal trials for the 21-day and 24-day regimens are listed in Table E.

**Table E: Racial Distribution in the Pivotal 24 and 21-Day Studies**

Dosing Regimen	Caucasian (%)	Hispanic (%)	Black (%)	Asian (%)	Other (%)
24-day (303740)	87.8	4.6	4.3	1.2	2.1
21-day (303860)	98.1	0.5	0.2	0.5	0.5

Although there are very few non-Caucasians in these studies, there is no evidence from previous combination oral contraceptive NDAs or from the literature to suspect that the safety or efficacy of estrogen/progestin combination orals differ based on the race of the user.

**Renal and Hepatic Impairment.** No studies with Yasmin 20 (both regimens) were conducted in subjects with renal or hepatic impairment. Because of anti-mineralocorticoid activity and potential risk for producing hyperkalemia, Yasmin 20 (both regimens), are contraindicated in women with renal insufficiency, hepatic dysfunction, or insufficiency.

**Pediatric Studies.** No additional pediatric studies are required. It is generally accepted that the safety and efficacy profiles of combination oral contraceptives are similar in all post-menarchal, reproductively competent adolescents and women

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/s/

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Gerald Willett  
3/14/2006 01:41:47 PM  
MEDICAL OFFICER

Scott Monroe  
3/15/2006 05:26:00 PM  
MEDICAL OFFICER

I concur with Dr. Willett that the safety and efficacy data support approval of DRSP 3 mg/EE 0.02 mg tablets (YAZ) for prevention of pregnancy in women.

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this page is the manifestation of the electronic signature.**  
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/s/

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Scott Monroe  
11/17/04 04:59:00 PM  
MEDICAL OFFICER

Donna Griebel  
11/17/04 05:05:48 PM  
MEDICAL OFFICER  
I have read Dr. Monroe's review and concur with  
his conclusions and recommendations.

**Division of Reproductive and Urologic Drug Products**

**Clinical Review**

**NDA 21-676**

**YAZ**

drospirenone 3 mg/ethinyl estradiol betadex 0.02 mg,  
(24-day active dosing regimen)

drospirenone 3 mg/ethinyl estradiol betadex 0.02 mg,  
(21-day active dosing regimen)

**Berlex Laboratories**

Gerald Willett M.D. (Medical Reviewer)

November 16, 2004

## CLINICAL REVIEW

NDA 21-676

**Date Submitted:**

October 16, 2003

**Review Completed:**

November 16, 2004

**Reviewer:**

Gerald D. Willett MD

Division of Reproductive and Urologic Drug Products

**Applicant:**

Berlex Laboratories, Inc.

340 Changebridge Road

P.O. Box 1000

Montville, NJ 07045-1000

(973) 487-2305

**Proposed Trade Name:**

YAZ: 24-day active dosing regimen

**Established Name:**

YAZ: drospirenone 3 mg/ethinyl estradiol betadex 0.02 mg (tablets)

**Chemical Names for Components of Active Tablets (IUPAC):**

Drospirenone: 6 $\beta$ , 7 $\beta$ ; 15 $\beta$ , 16-Dimethylene-3-oxo-17 $\alpha$ -pregn-4-ene-21, 17-carbolactone

Ethinyl estradiol betadex: 19-Nor-17 $\alpha$ -pregna-1,3,5(10)-trien-20-yne-3,17-diol, ( $\beta$ -cyclodextrin clathrate)

**Dosage and Dosing Regimen:**

YAZ: One active tablet (drospirenone 3 mg/ethinyl estradiol betadex 0.020 mg) daily for 24 consecutive days followed by one placebo tablets for 4 consecutive days)

**Route of Administration:**

Oral

**Proposed Indication:**

YAZ Tablets are indicated for prevention of pregnancy in women who elect to use an oral contraceptive.

## CLINICAL REVIEW

NDA 21-676

### Related INDs:

IND 60,738 submitted to Division of Reproductive and Urologic Drug Products on August 22, 2000 for drospirenone 3 mg/ ethinyl estradiol betadex 0.020 mg tablets; indication is for prevention of pregnancy (Principal IND related to this NDA submission)

IND 61,304 submitted to the Division of Neuropharmacological Drug Products on November 20, 2000 for drospirenone 3 mg/ ethinyl estradiol betadex 0.020 mg tablets; indication is for prevention of premenstrual dysphoric disorder IND

IND 65,370 submitted to the Division of Dermatological and Dental Drug Products on October 28, 2002 for drospirenone 3 mg/ethinyl estradiol betadex 0.020 mg tablets; indication is for treatment of acne

IND 51,693 submitted to Division of Reproductive and Urologic Drug Products on October 7, 1996 for drospirenone 3 mg/ ethinyl estradiol 0.030 mg tablets; indication is for prevention of pregnancy

### Related NDAs:

NDA 21-098 (Yasmin) drospirenone 3 mg/ ethinyl estradiol 0.030 mg, developed from IND 51,693, submitted to DRUDP on May 14, 1999 and approved on May 11, 2001

NDA 21-355 (Angeliq) drospirenone 3 mg /estradiol 1 mg, developed from IND 53,842, submitted to DRUDP on December 14, 2001 (approvable status)

# CLINICAL REVIEW

NDA 21-676

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## EXECUTIVE SUMMARY

### 1. RECOMMENDATIONS

#### 1.1 RECOMMENDATION ON APPROVABILITY

Approval is recommended for both the 24-day active dosing regimen and the 21-day active dosing regimens of drospirenone 3 mg/ethinyl estradiol betadex 0.020 mg tablets based on the contraceptive efficacy and safety data submitted to NDA (21-676). This approval recommendation is contingent on acceptable labeling for each dosing regimen.

Approval of the 21-day active dosing regimen is preferable from a safety perspective because it provides the same efficacy with less hormonal exposure than the 24-day active dosing regimen. Based on presently submitted data, there is no proven added clinical benefit associated with the use of the 24-day regimen.

#### 1.2 RECOMMENDATION ON PHASE 4 STUDIES AND/OR RISK MANAGEMENT STEPS

The general outlines of the applicant's proposed Phase 4 safety surveillance study for the 24-day regimen are acceptable. The final protocol should be submitted to the Division for review and agreement within 90 days of the approval of this application. It is recommended that

No Phase 4 safety surveillance study is required for the 21-day dosing regimen.

### 2. SUMMARY OF CLINICAL FINDINGS

#### 2.1 BRIEF OVERVIEW OF CLINICAL PROGRAM

Berlex seeks approval of a second drospirenone based combination oral contraceptive, hereafter referred to as Yasmin 20 (24-day). This contraceptive contains two-thirds the daily level of ethinyl estradiol (EE) that is found in the applicant's approved product Yasmin (0.02 mg compared to 0.03 mg per tablet) and the same amount of drospirenone (3 mg DRSP) per tablet. The product also differs from Yasmin in that the dosing regimen consists of 24 days of active tablets followed by 4 days of placebo tablets compared to 21 days of active tablets followed by 7 days of placebo tablets for Yasmin

In the present NDA, the applicant also has submitted safety and efficacy data from a second combination oral contraceptive that contains 0.02 mg EE and 3 mg DRSP (hereafter referred to as Yasmin 20 (21-day)). The dosing regimen for this product consists of one active tablet daily for 21 consecutive days followed by 7 tablet-free days. The Applicant has not requested approval of this product,

#### 2.2 EFFICACY

The applicant's protocol for establishing contraceptive efficacy is similar to other product submissions in this class. Over ten thousand 28-day cycles were studied in both the 24-day

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regimen (protocol 303740) and the 21-day regimen (protocol 303860). More than 200 women completed 13 cycles of use in both protocols.

The primary efficacy endpoint was the number of “during treatment” pregnancies defined as all pregnancies with an estimated date of conception after the onset of treatment with study drug and through 4 days (applicant’s definition) or 14 days (DRUDP’s definition) after the last dose of study drug. The primary efficacy analysis was the Pearl Index, which is the number of “during treatment” pregnancies per 100 women-years of use. The efficacy for both the 24-day and 21-day dosing regimens, expressed in terms of the Pearl Index is listed in Table A. The values for the Pearl Index in Table A are based on the Medical Officer’s determination of the number of “during treatment” pregnancies and exclude cycles where backup contraception was used, cycles for women over age 35, and cycles for women listed as sexually inactive

**Table A. Efficacy of the 24 and 21-day Regimens of DRSP 3 mg/ EE 0.02 mg\***

<b>24-day regimen (protocol 303740)</b>					
Total days of exposure	Total 28-day cycles of exposure	Total Number Pregnancies		Pearl Index **	2-sided 95% confidence interval
		Applicant's Determination	FDA's Determination		
309,386	11,050 *	11	12	1.42	0.73-2.47
<b>21-day regimen (protocol 303860)</b>					
Total days of exposure)	Total 28-day cycles of exposure	Total Number Pregnancies		Pearl Index *	2-sided 95% confidence interval
		Applicant's Determination	FDA's Determination		
309,136	11,040	2	3	0.35	0.07-1.04

\* Calculated by dividing number of days of exposure by “28”.

\*\* Pearl Index based on using 12 “during treatment” pregnancies in protocol 303740 and 3 “during treatment” pregnancies in protocol 303860).

### 2.3 SAFETY

The overall exposure in terms of numbers of subjects and duration of exposure is acceptable. The three large studies for both the Yasmin 20 product (protocols 303740, 303860 and 14523) provide exposure of a total of 1763 separate subjects. These studies account for 24,425 28-day cycles of safety data or 1,878 women-years.

There were two deaths reported in the clinical studies of Yasmin 20. These deaths both occurred in protocol 303740 (Yasmin 20, 24-day regimen) at the single US study site. Neither of these deaths was related to study medication. One death, secondary to pesticide poisoning, occurred one month following discontinuation of study drug. The other death, occurring three months after starting study medication, was secondary to smoke inhalation in a fire.

The serious adverse events attributable to study drug in the pivotal trial for the 24-day regimen (303740) included one case of migraine, one case of depression and one case of cholelithiasis. The serious adverse events attributable to study drug in the pivotal trial for the 21-day regimen (303860) included two cases of pulmonary emboli, one case of migraine, one case of ovarian

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cyst and one case of cholecystitis. All of these adverse events have been previously associated with combination oral contraceptive use. There were no SAEs attributable to study drug in any of the other submitted studies

With caveats regarding rate estimations of rare events derived from typical Phase 3 registry studies for oral contraceptives, the finding of two confirmed venous thromboembolic adverse events (2 cases of pulmonary emboli in study 303860) translates to a rate of 10.6 per 10,000 women-years for the Yasmin 20 products. This rate is similar to the findings of the approved product Yasmin in the first year of the EURAS study (approximately 15 per 10,000) which is described in greater detail later in this summary.

In Yasmin 20, 24-day regimen (303740) the adverse event contributing to the greatest number of drug discontinuations was headache (14 incidents, 1.3%). Headache was also the most common adverse event at 13.3%. The most common reasons for study discontinuation in the Yasmin 20, 21-day regimen (303860) were decreased libido and depression (5 subjects each, 1.0%). Vaginal moniliasis (17.2%) constituted the highest number of adverse events in the 21-day regimen with headache (13.6%) showing similar numbers as in the 24-day regimen.

Safety labs were performed only in the 24-day regimen protocol. The laboratory analysis from the 24-day regimen study is sufficient for safety evaluation of the Yasmin 20 product overall. Increased mean levels of lipids were seen in women who used Yasmin 20 (24-day regimen). These findings are comparable to the well-characterized effects on lipids by combination oral contraceptives (COCs). Careful potassium monitoring was performed due to the potential potassium sparing effects of drospirenone. All of the elevated potassium levels identified in the 24-day regimen protocol appeared to represent "pseudohyperkalemia" resulting from hemolysis or transport problems. There was no evidence of true hyperkalemia or any hyperkalemic type symptomatology found at the time of these elevated values. Repeat testing in each case revealed normal values. Neither regimen showed any significant mean changes in vital signs or body weight.

Both the Yasmin 20, 24-day regimen and the Yasmin 20, 21-day regimen had acceptable menstrual cycle control data. The levels of pill-associated amenorrhea and intracyclic bleeding were low for both regimens.

The applicant, has provided data from two large ongoing postmarketing safety surveillance trials supporting the safety of the presently marketed DRSP product Yasmin:

The European Active Surveillance study (EURAS) was initiated for Yasmin in March 2001. This surveillance study is part of a European effort to perform postmarketing safety on contraceptive formulations with new progestins and/or estrogen. This study was last updated on 9 June 2004. At that time 50,000 women were enrolled representing 64,000 women-years of observation. The comparative table (see Table B) shows the thrombotic/thromboembolic adverse event rates for Yasmin, levonorgestrel-based oral contraceptives and "other" oral contraceptives. The results demonstrate that Yasmin does not have a thrombotic/thromboembolic rate higher than other COCs that do not contain DRSP.