CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-873

MEDICAL REVIEW(S)

DIVISION OF REPRODUCTIVE AND UROLOGIC PRODUCTS (DRUP)
DIVISION DIRECTOR MEMORANDUM

NDA	NDA 21-873
Type of Application	Complete Response to Approvable Action
Applicant	Berlex, Inc. Montville, NJ 07045
Proprietary Drug Name	YAZ
Established Drug Name	(Drospirenone and Ethinyl Estradiol) Tablets
Drug Class	Combination Oral Contraceptive
Indication	Treatment of symptoms of premenstrual dysphoric disorder (PMDD) in women who choose to use an oral contraceptive as their method of contraception
Route of administration	Oral
Dosage Form	Tablet
Dosage Strength	Drospirenone (DRSP) 3 mg/ethinyl estradiol (EE) 0.02 mg per tablet
Dosing Regimen	One DRSP/EE tablet daily for 24-consecutive days followed by 4 placebo tablets (a 28-day dosing cycle that is repeated)
CDER Receipt Date	March 2, 2006
PDUFA Goal Date	December 2, 2006 (3-month extension)
Date of Memorandum	September 4, 2006
Reviewer	Scott E. Monroe, MD Acting Division Director, DRUP

1. RECOMMENDATIONS

1.1 Recommendation regarding Approvability

I concur with the recommendations of the Medical Reviewer (Gerry Willett, MD) and the clinical Team Leader (Lisa Soule, MD) that NDA 21-873 (drospirenone/ethinyl estradiol tablets [YAZ]) be approved for the secondary indication of "treatment of symptoms of premenstrual dysphoric disorder (PMDD) in women who choose to use an oral contraceptive as their method of contraception."

1.2 Basis for Recommendation regarding Approvability

Data contained in the original submission of December 2004 (safety and efficacy data) and the present submission of March 2006 (safety data and risk management program) support a determination that (drospirenone [DRSP-3 mg]/ethinyl estradiol [EE-0.02 mg]) tablets (hereafter

referred to as DRSP/EE) are safe and effective for the treatment of symptoms of PMDD in women who choose to use an oral contraceptive as their method of contraception.

The Applicant has provided adequate statistical evidence from 2 adequate and well controlled clinical trials that DRSP/EE, relative to placebo, is effective for the treatment of symptoms of PMDD. The magnitude of the treatment effect appears to be comparable to that attributable to treatment with selective serotonin reuptake inhibitors (SSRIs) previously approved for the treatment of PMDD. The data for DRSP/EE provided in both the original and present submissions from more than 40,000 28-day treatment cycles in women using the product primarily for prevention of pregnancy indicated that the safety profile is acceptable for a highly effective hormonal contraceptive. The safety data provided from the PMDD clinical trials do not indicate that the safety profile for DRSP/EE in women with PMDD will differ from that observed in the prevention of pregnancy trials. The safety profile for DRSP/EE for the treatment of PMDD is therefore acceptable for women "who choose to use an oral contraceptive as their method of contraception" as stated in the indication section of approved labeling.

In summary, considering the risk/benefit profiles of DRSP/EE and the approved SSRI treatments, approval of DRSP/EE for the treatment of symptoms of PMDD will offer women with PMDD who desire to use an oral contraceptive for prevention of pregnancy a safe and effective alternative treatment.

1.3 Recommendation on Risk Management Steps and/or Post Approval Studies

1.3.1 Risk Management Steps

The Applicant has proposed (1) an Educational Outreach Program specific to the PMDD indication for DRSP/EE and (2) a risk management plan similar to that used for Yasmin (an oral contraceptive approved for marketing in 2001 that also contains DRSP) regarding the potential risk of hyperkalemia.

Based on the Applicant's original Complete Response and discussions conducted during the review process, the Educational Outreach Program will include the following features:

- The program will provide clear statements that YAZ is first and foremost an oral contraceptive that should be used for PMDD only in women choosing to use an oral contraceptive for the purpose of birth control.
- The educational outreach for patients and of health care providers (HCPs) will establish a clear understanding of what PMDD is. HCPs will be educated on the DSM-IV criteria, including the use of a prospective diary. Patients will be encouraged to complete a prospective daily diary to use in discussions with their HCPs.
- Materials provided to HCPs will include information about how to diagnose PMDD, such as the DSM-IV criteria for diagnosis of PMDD.
- Presently in development, the print and TV campaigns intended for consumers will clearly identify that YAZ is an oral contraceptive with unique risks and benefits and will provide clear statements that YAZ should be used for PMDD only in women choosing to use an oral contraceptive for the purpose of birth control. The campaign seeks to educate women on the differences between premenstrual syndrome (PMS) and PMDD through education on PMDD

and encouragement to complete a prospective daily diary. The HCP will make the differential diagnosis between PMS and PMDD.

Division Director's Comments

- *I concur with the Medical Reviewer (Dr. Willett) and the clinical Team Leader (Dr. Soule) that the proposed Educational Outreach Program is adequate and acceptable.*
- *Additional risk management will be handled through labeling of the product, which clearly specifies that YAZ should be used to treat PMDD only in women who have already decided to use an oral contraceptive for birth control. The importance of differentiating PMDD from PMS is also emphasized.*
- *Risk management for hyperkalemia will include (1) educating HCPs regarding the potential pharmacologic effects of DRSP on renal-handling of potassium and (2) retention in physician and patient labeling of the warnings regarding hyperkalemia.*

1.3.2 Post Approval Studies

As discussed in the March 16, 2006 review of NDA 21-676 (DRSP/EE for prevention of pregnancy), the Applicant has committed to conducting a large prospective Phase 4 postmarketing safety study with DRSP/EE, similar to the recently completed European Active Surveillance Study (EURAS) assessing risk of arterial and venous thrombotic events in users of Yasmin, as compared to users of other oral contraceptives. The study for DRSP/EE (which also will include women using Yasmin) will include both U.S. and European sites, and plans to recruit 50,000 women who will be followed semi-annually for 3 years.

Division Director's Comments

- *The large Phase 4 post marketing study will provide important safety information (primarily related to venous and arterial thrombotic events) associated with the use of DRSP/EE (YAZ) compared to other oral contraceptive products.*
- *I concur with the other Medical Reviewers that no Phase 4 clinical studies directed specifically to the PMDD indication are required.*

2. BACKGROUND

2.1 Description of Drug Product

Drospirenone is a 17-α spironolactone derivative with progestational, anti-mineralocorticoid, and anti-androgenic properties. The active estrogen moiety in this product is ethinyl estradiol, which is complexed with β-cyclodextrin clathrate to protect against degradation.

Drospirenone 3 mg/EE 0.02 mg tablets (YAZ) contain less EE than the Applicant's currently marketed product Yasmin tablets (DRSP 3 mg/EE 0.03 mg tablets, NDA 21-098). Yasmin was approved in the U.S. in 2001 for prevention of pregnancy and is currently available in over 40 countries worldwide. Yasmin and YAZ are the only contraceptive products marketed in the U.S. that contain the progestin DRSP.

2.2 Regulatory History and Prior Approvability Issues

DRSP/EE (YAZ) for prevention of pregnancy was approved in March 2006. The regulatory history of the development of this product for the secondary indication of treatment of symptoms of PMDD is detailed in the Team Leader Memorandum (dated January 23, 2006) from the first cycle review. The initial application for the PMDD indication received an approvable action on January 23, 2006, pending:

- Review of safety data submitted on December 2, 6, and 9, 2005 and January 10, 2006, which were not reviewed in the initial review cycle because of the lateness of the submission
- Submission of acceptable labeling for both the Package Insert and the Patient Package Insert
- Additional education and training activities related to ensuring the appropriate use of YAZ in the target population

A Complete Response was submitted to the Division on March 1, 2006, containing proposed labeling, a proposal for training and educational activities to ensure the use of YAZ in the appropriate target population for PMDD, and a safety update.

The Applicant submitted final reports for the European contraceptive studies 308020 and 308021 on August 8, 2006. A notice of NDA review extension was submitted to the Applicant on August 25, 2006 to allow for a safety review of these large final study reports.

3. EFFICACY OF DRSP/EE FOR TREATMENT OF PMDD

3.1 Overview of Clinical Program

Two Phase 3, randomized, double-blind, placebo-controlled, multicenter trials were conducted in the U.S. to evaluate the clinical efficacy and safety of DRSP/EE as compared to placebo in treating symptoms of PMDD. The population studied in each trial comprised women diagnosed with PMDD by DSM-IV criteria.

Study 304049 was a parallel group trial, in which 450 subjects participated in a 2-cycle run-in phase followed by a treatment phase lasting 3 menstrual cycles. Subjects were randomized to DRSP/EE or placebo in a 1:1 ratio, with 232 subjects randomized to DRSP/EE and 218 to placebo. The study was conducted at 64 sites in the U.S.

Study 305141 was a crossover study conducted over a total of 7 menstrual cycles after the baseline assessment. Following a 2-cycle run-in phase, subjects were randomized to one of 2 treatment sequences. Each treatment sequence consisted of (a) randomized treatment with DRSP/EE or placebo over 3 menstrual cycles (Treatment Period 1 [TP1]), (b) a one-cycle wash-out period, and (c) a second treatment period with the alternate study drug over 3 menstrual cycles (Treatment Period 2 [TP2]). Subjects were randomized to sequence DRSP/EE→placebo or placebo→DRSP/EE in a 1:1 ratio. It was originally intended that the study would enroll 126 subjects; however, following early termination of the protocol due to recruitment difficulties,

actual enrollment was only 64 subjects. Of these, 34 were randomized to the sequence DRSP/EE→placebo and 30 were randomized to the sequence placebo→DRSP/EE. The study was conducted at 17 sites.

3.2 Efficacy Findings

The Daily Rating of Severity of Problems Scale (DRSPS) was used to assess the effect of treatment. Subjects completed this questionnaire daily, beginning on the first day of menses in run-in Cycle 1. The primary efficacy endpoint was the change from baseline in the average over 3 treatment cycles of the first 21 items of the DRSPS instrument. Each of the first 21 items was averaged over the 5 days preceding menses for each menstrual cycle, and the averages were then summed. The primary efficacy variable was the difference between treatment arms in the change in the average of the non-missing treatment cycle scores from the average of the baseline scores. The baseline score was the average over the 2 run-in (pretreatment) cycles for Study 304049 and for the first Treatment Period for Study 305141. The baseline score for the second Treatment Period in Study 305141 was based on the single wash-out cycle between Treatment Period 1 and Treatment Period 2. Data were analyzed using an analysis of covariance (ANCOVA).

In both studies, the primary efficacy analysis of the Full Analysis Set demonstrated a statistically significant difference between DRSP/EE and placebo groups. The improvement in the DRSP/EE group in Study 304049 was 7.5 points greater (95% confidence limits 3.8 to 11.2) than that experienced by placebo subjects (p=0.0001). In the cross-over trial, Study 305141, where results were calculated by an ANCOVA model that collapsed treatment assignment over treatment period (with treatment sequence as a fixed factor), the improvement in the DRSP/EE group was 12.5 points greater (95% confidence limits 6.7 to 18.3) than that experienced by placebo subjects (p=0.0001).

Statistically significant differences between DRSP/EE and placebo groups were demonstrated for a number of secondary endpoints, typically those which tended to assess symptoms and function over the week preceding menses, rather than over a longer time period. The most consistently positive secondary endpoints were the 3 functional impairment items on the DRSPS. These 3 items of the DRSPS questionnaire relate to (1) reduction in productivity, (2) interference with social activities, and (3) interference with relationships.

Division Director's Comments

- *In my original review of the efficacy of DRSP/EE in the treatment of symptoms of PMDD (Team Leader Memorandum, dated January 23, 2006), I concluded that "(1) treatment with DRSP/EE reduces symptoms of PMDD to a greater extent than treatment with placebo and (2) and the benefit of treatment is comparable to that of at least one SSRI (i.e., fluoxetine) approved by the Division of Neuropharmacologic Drug Products for treatment of PMDD." My assessment has not changed.*
- *It also should be noted that the indication for treatment of PMDD with SSRIs is a primary indication while that for treatment with DRSP/EE is a secondary indication for women who have chosen to use an oral contraceptive for prevention of pregnancy.*

- *The finding of a benefit from DRSP/EE treatment on the 3 functional items of the DRSPS is particularly relevant because of their utility in assessing the effects of treatment on social and professional functioning.*
- *Because of concerns that some aspects of study design or study analyses might have had an impact on the findings, the Applicant was asked to conduct several additional analyses to support the original findings. In all instances, the FDA-requested analyses supported the Applicant's original findings.*

4. SAFETY PROFILE

Safety data from a number of sources were reviewed: the 2 PMDD trials, other trials for contraception and acne indications, final reports from postmarketing pharmacoepidemiologic surveillance studies of Yasmin, and postmarketing safety reports. Reviews of these data are provided in the primary Medical Reviews for DRSP/EE for prevention of pregnancy (NDA 21-676, dated November 16, 2004 and March 16, 2006) and the primary Medical Reviews for PMDD (dated January 20, 2006 and September 28, 2006).

4.1 PMDD Clinical Trials

The original review for NDA 21-873 (PMDD indication), dated January 20, 2006, contains a detailed discussion of the safety data from the 2 clinical trials submitted in support of the PMDD indication. The Medical Reviewer's conclusion in the Safety Summary of that review is:

> *"There were no signals of concern in regard to the occurrence of SAEs [serious adverse events] or changes in vital signs or laboratory evaluations associated with DRSP/EE. Selected adverse events of particular relevance to this product are: intermenstrual bleeding and menorrhagia, nausea, breast pain, decreased libido, emotional lability, and migraine, all of which occurred with at least twice the frequency in the subjects exposed to DRSP/EE as compared to placebo and were considered to be drug-related. As noted previously, most of these events are known to be associated with oral contraceptive use, and are labeled in the Yasmin label."*

Division Director's Comment

- *I concur with Dr. Soule's assessment of the safety findings from the 2 clinical trials conducted in women with PMDD.*

4.2 Safety Issues of Particular Importance or Interest across All Clinical Trials for All Indications

4.2.1 Deaths

Among the clinical trials conducted with DRSP/EE (24-day active dosing regimen [YAZ] or 21-day active dosing regimen) that included more than 40,000 treatment cycles, there were 4 reported deaths. Two of these deaths occurred in Protocol 303740 (24-day regimen) at the single US study site. Neither of these deaths was related to study drug. 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 Protocol 308021, an open label European study of the

24-day regimen for 13 cycles in 1,010 volunteers. One of these deaths was secondary to Goodpasture's Syndrome, and the other death was secondary to murder. Neither of these deaths was attributed to DRSP/EE.

There were no deaths in the PMDD trials.

4.2.2 Thrombotic Adverse Events and Other Serious Adverse Events

There were no reports of thromboembolic events in clinical trial subjects receiving the 24-day active dosing regimen of DRSP/EE. There were 2 confirmed venous thromboembolic (VTE) adverse events (both pulmonary emboli) in subjects receiving the 21-day active dosing regimen of DRSP/EE (Study 303860).

Division Director's Comments

- *According to the primary Medical Reviewer, this represents an overall VTE rate of approximately 6.1 per 10,000 women-years for the DRSP/EE product (clinical trial data combined for the 24- and 21-day active dosing regimens) based on an exposure of 42,366 28-day treatment cycles or 3,259 women-years of exposure. The rate of 6.1 thromboembolic events per 10,000 women-years is less than that reported in the postmarketing surveillance studies of Yasmin, which ranged from 13.7 to 15 cases per 10,000 women-years.*
- *The rate of 6.1 thromboembolic events per 10,000 women-years is similar to or less than that reported for other combination hormonal products.*

4.3 Overall Assessment of Safety

Division Director's Comments

- *The safety profile for DRSP/EE in the PMDD clinical trials was acceptable for a hormonal contraceptive product. There were no safety signals of concern in regard to the occurrence of SAEs [serious adverse events] or changes in vital signs or laboratory evaluations (e.g., serum potassium concentrations) associated with DRSP/EE.*
- *The total subject exposure to DRSP/EE in the PMDD trials, in terms of months of treatment, was relatively small compared to the total subject exposure to DRSP/EE in the clinical trials for prevention of pregnancy. The safety profile of DRSP/EE, based on the data from the prevention of pregnancy clinical trials, is acceptable for a combination oral contraceptive. The acceptability of the safety profile of DRSP/EE (YAZ) also is supported by the reassuring safety data from 2 large post marketing studies with Yasmin, which contains the same daily dose of DRSP (3 mg) but a higher daily dose of EE (0.03 mg vs. 0.02 mg).*

5. LABELING

All labeling issues have been satisfactorily resolved. Labeling agreed to by the Applicant on September 15, 2006 and submitted on October 3, 2006 is acceptable. Of note is the indication for PMDD that states that "YAZ is also indicated for the treatment of symptoms of premenstrual dysphoric disorder (PMDD) in women who choose to use an oral contraceptive as their method of contraception. The effectiveness of YAZ for PMDD when used for more than three menstrual cycles has not been evaluated."

Patient labeling specially related to the PMDD indication includes the following statements:

> *YAZ may also be taken to treat premenstrual dysphoric disorder (PMDD) if you choose to use the Pill for birth control. Unless you have already decided to use the Pill for birth control, you should not start YAZ to treat your PMDD because there are other medical therapies for PMDD that do not have the same risks as the Pill.*
>
> *You should only use YAZ for treatment of PMDD if you:*
> - *Have already decided to use oral contraceptives for birth control, and*
> - *Have been diagnosed with PMDD by your healthcare provider*
>
> *YAZ has not been shown to be effective for the treatment of premenstrual syndrome (PMS), a less serious cluster of symptoms occurring before menstruation. If you or your healthcare provider believes you have PMS, you should only take YAZ if you want to prevent pregnancy and not for the treatment of PMS.*

6. PRIMARY MEDICAL REVIEWER'S AND TEAM LEADER'S RECOMMENDATIONS FOR APPROVABILITY

In his complete response review, dated September 20, 2006, the primary Medical Reviewer, Dr. Gerald Willett, stated the following:

> *I recommend that NDA 21-873, drospirenone (DRSP) (3 mg) /ethinyl estradiol (EE) (0.02 mg) oral tablets (YAZ), be approved for the secondary indication of "treatment of symptoms of premenstrual dysphoric disorder (PMDD) in women who choose to use an oral contraceptive as their method of contraception."*
>
> *This recommendation is based on the following:*
>
> - *The submissions referenced in the approvable letter (December 2, 6, 9, 2005 and January 10, 2006) that were not reviewed prior to the January 23, 2006 approvable letter for NDA 21-873 have now been reviewed. These submissions included safety data from the Applicant's finalized acne studies (306820 & 306996) and unfinalized European contraceptive studies (308020 & 308021). There are no safety concerns in those submissions that would impact approval of YAZ for the secondary indication of PMDD.*
> - *Final study reports from European contraceptive trial protocols 308020 & 308021 submitted on August 8, 2006 show no safety concerns. No new safety concerns were identified on the last safety update which was also submitted on August 8, 2006. This safety update is current up through August 7, 2006.*
> - *YAZ was approved for the primary indication of contraception on March 16, 2006, thus allowing for approval of secondary indications.*
> - *Acceptable labeling has been received from the Applicant.*
> - *I concur with the primary reviewer (Lisa Soule, MD) and secondary reviewer (Scott Monroe, MD) of the initial submission that the clinical studies (304049 & 305141) under NDA 21-873, which focused specifically on the secondary indication of PMDD, showed that YAZ was both safe and effective.*

Division Director's Comment

- *Dr. Willett's last bullet above does not accurately capture the overall conclusion of the initial review of this Application. Although the clinical studies for PMDD demonstrated effectiveness, additional information was necessary to establish safety. This additional information to establish safety was reviewed during the current review cycle and found to be acceptable.*

In her review of the Complete Response, dated September 27, 2006, the clinical Team Leader, Dr. Lisa Soule, stated the following:

> *I concur with the recommendation of the primary medical reviewer that the application be approved. Acceptable labeling has been negotiated in this review cycle.*

Division Director's Comment

- *I fully concur with the recommendations of Drs. Willett and Soule that this Application be approved.*

APPEARS THIS WAY
ON ORIGINAL

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

/s/

Scott Monroe
10/4/2006 06:13:59 PM
MEDICAL OFFICER

DIVISION OF REPRODUCTIVE AND UROLOGIC PRODUCTS
CLINICAL TEAM LEADER MEMORANDUM

NDA	NDA 21-873
Type of Application	Complete Response
Applicant	Berlex
Proprietary Drug Name	YAZ
Established Drug Name	Drospirenone/Ethinyl Estradiol
Drug Class	Combined Oral Contraceptive
Indications	Treatment of symptoms of premenstrual dysphoric disorder (PMDD)
Route of Administration	Oral
Dosage Form	Tablet
Dosage Strength	Drospirenone 3 mg/Ethinyl Estradiol 0.02 mg
Dosing Regimen	Drospirenone 3 mg/Ethinyl Estradiol 0.02 mg daily for 24 days followed by placebo for 4 days
CDER Receipt Date	March 2, 2006
PDUFA Goal Date	September 2, 2006 (clock extended to December 2, 2006)
Date of Memorandum	September 27, 2006
Reviewer	Lisa M. Soule, M.D.

1 RECOMMENDATIONS

1.1 RECOMMENDATION REGARDING APPROVABILITY

I recommended that NDA 21-873, drospirenone (3 mg) / ethinyl estradiol (0.02 mg) oral tablets (YAZ), be approved for the indication of "treatment of symptoms of premenstrual dysphoric disorder (PMDD) in women who choose to use an oral contraceptive as their method of contraception."

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

The Applicant has provided adequate statistical evidence of efficacy relative to placebo for drospirenone/ethinyl estradiol (DRSP/EE) in treatment of PMDD symptoms. The magnitude of the treatment effect appears to be consistent with that attributable to treatment with the three selective serotonin reuptake inhibitors (SSRIs) approved for treatment of PMDD. In addition, the safety data do not raise concern for a safety profile discrepant from that of the approved product, Yasmin, and, in fact, the lower total exposure to EE afforded by use of YAZ as compared to Yasmin may offer a safety advantage. Considering the risk/benefit profiles of DRSP/EE and the

approved SSRI treatments, approval of this product would offer women with PMDD who desire oral contraception a useful treatment alternative.

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

1.3.1 Risk Management Steps

In the Complete Response, the Applicant submitted a brief outline of its "Educational Outreach Protocol for Providers and Patients." The stated objectives of the program are to:

- Educate healthcare providers on the diagnostic criteria and the various existing tools to differentiate and identify the various premenstrual disorders
- Educate healthcare providers on the interpretation of one of the tools (the Daily Record of Severity of Problems [DRSPS, the instrument used for the primary endpoint in the PMDD trials]) used to assess the severity of a patient's premenstrual disorder
- Educate healthcare providers on the treatment options
- Educate women on the advantages of using diaries to better understand their symptomatology, and foster better discussion with their healthcare provider
- Provide women with opportunities to increase their understanding and awareness of PMDD and the treatment options available to them

Several teleconferences were held between the Division and the Applicant to refine the features of the Outreach program. In a submission dated September 14, 2006, the Applicant noted the following revised features of the program:

- The program will provide clear statements that YAZ is first and foremost an oral contraceptive that should be used for PMDD only in women choosing to use an oral contraceptive for the purpose of birth control.
- The educational outreach for patients and health care providers (HCPs) will establish a clear understanding of what PMDD is. HCPs will be educated on the DSM-IV criteria, including the use of a prospective diary. Patients will be encouraged to complete a prospective daily diary to use in discussions with their HCPs.
- Materials provided to HCPs will include information about how to diagnose PMDD, such as the DSM-IV criteria for diagnosis of PMDD.
- The print and TV campaigns intended for consumers, in development, will clearly identify that YAZ is an OC with unique risks and benefits and will provide clear statements that YAZ should be used for PMDD only in women choosing to use an oral contraceptive for the purpose of birth control. The campaign seeks to educate women on the differences between PMS and PMDD through education on PMDD and encouragement to complete a prospective daily diary. The HCP will make the differential diagnosis between PMS and PMDD.

Team Leader Comment

- **The proposed Educational Outreach Program, as revised, is acceptable. The advertising campaign and internet sites intended for patients will benefit from further review by the Division of Advertising, Marketing and Communication (DDMAC) post approval.**

Additional risk management will be handled through labeling of the product, which clearly specifies that YAZ should be used to treat PMDD only in women who have already decided to use an oral contraceptive for birth control. The importance of differentiating PMDD from premenstrual syndrome (PMS) is also emphasized.

1.3.2 Phase 4 Studies

As discussed in the March 16, 2006 review of NDA 21-676, the Applicant has committed to conducting a large prospective phase 4 postmarketing safety study with YAZ, similar to the recently completed European Active Surveillance Study (EURAS) assessing risk of arterial and venous thromboembolic events in users of Yasmin, as compared to users of other oral contraceptives. The study for YAZ (which also will include women using Yasmin) will include both U.S. and European sites, and plans to recruit 50,000 women who will be followed semi-annually for three years. Recruitment into the non-YAZ treatment arms of this study began in August 2005. As of late July 2006, more than 10,000 women have been enrolled into the study, including approximately 1,000 YAZ initiators. Extension of the study into Europe will depend on the international registration and launch status of YAZ.

No phase 4 clinical studies directed to the PMDD indication are recommended.

2 BACKGROUND

2.1 DESCRIPTION OF PRODUCT

Drospirenone is a 17-alpha-spironolactone derivative with progestational, antimineralocorticoid, and antiandrogenic properties. The active estrogen moiety in this product is ethinyl estradiol, which is complexed with β-cyclodextrin clathrate to protect against degradation.

2.2 REGULATORY HISTORY

The regulatory history of the development of the product for a PMDD indication is detailed in the first cycle review of January 20, 2006. The initial application for this secondary indication received an approvable action on January 23, 2006, pending:

- Review of safety data submitted on December 2, 6, and 9, 2005 and January 10, 2006, which were not reviewed in the initial review cycle
- Submission of acceptable labeling for both the Package Insert and the Patient Package Insert
- Additional education and training activities related to ensuring the appropriate use of YAZ in the target population

A Type A meeting was held with the Applicant on February 27, 2006, to discuss the extent of requisite data submission to support a decision on approvability.

A Complete Response was submitted to the Division on March 1, 2006, containing proposed labeling, a proposal for training and educational activities to ensure the use of YAZ in the appropriate target population, and a safety update. The final reports of two large European

contraceptive studies were submitted for review on August 8, 2006; due to the magnitude of the safety data submitted, a three-month extension of the action date was made.

2.3 PRIMARY MEDICAL REVIEWER'S RECOMMENDATION FOR APPROVABILITY

In his complete response review, dated September 20, 2006, the primary medical reviewer, Dr. Gerald Willett, recommended:

> *I recommend that NDA 21-873, drospirenone (DRSP) (3 mg) /ethinyl estradiol (EE) (0.02 mg) oral tablets (YAZ), be approved for the secondary indication of "treatment of symptoms of premenstrual dysphoric disorder (PMDD) in women who choose to use an oral contraceptive as their method of contraception."*
>
> *This recommendation is based on the following:*
>
> - *The submissions referenced in the approvable letter (December 2, 6, 9, 2005 and January 10, 2006) that were not reviewed prior to the January 23, 2006 approvable letter for NDA 21-873 have now been reviewed. These submissions included safety data from the Applicant's finalized acne studies (306820 & 306996) and unfinalized European contraceptive studies (308020 & 308021). There are no safety concerns in those submissions that would impact approval of YAZ for the secondary indication of PMDD.*
> - *Final study reports from European contraceptive trial protocols 308020 & 308021 submitted on August 8, 2006 show no safety concerns. No new safety concerns were identified on the last safety update which was also submitted on August 8, 2006. This safety update is current up through August 7, 2006.*
> - *YAZ was approved for the primary indication of contraception on March 16, 2006, thus allowing for approval of secondary indications.*
> - *Acceptable labeling has been received from the Applicant.*
> - *I concur with the primary reviewer (Lisa Soule, MD) and secondary reviewer (Scott Monroe, MD) of the initial submission that the clinical studies (304049 & 305141) under NDA 21-873, which focused specifically on the secondary indication of PMDD, showed that YAZ was both safe and effective.*

Team Leader Comment

- **I concur with the recommendation of the primary medical reviewer that the application be approved. Acceptable labeling has been negotiated in this review cycle.**

3 INDICATION OF PREMENSTRUAL DYSPHORIC DISORDER

3.1 OVERVIEW OF CLINICAL PROGRAM

Two phase 3, randomized, double-blind, placebo-controlled, multicenter trials were conducted in the U.S. to evaluate the clinical efficacy and safety of DRSP/EE as compared to placebo in treating symptoms of PMDD. The population studied in each trial comprised women diagnosed with PMDD by DSM-IV criteria.

Study 304049 was a parallel group trial, in which 450 subjects participated in a two-cycle run-in phase followed by a treatment phase lasting three menstrual cycles. Subjects were randomized to DRSP/EE or placebo in a 1:1 ratio, with 232 subjects randomized to DRSP/EE and 218 to placebo. The study was conducted at 64 sites in the U.S.

Study 305141 was a crossover study conducted over a total of seven menstrual cycles. Following a two cycle run-in phase, subjects were enrolled in a treatment phase consisting of three menstrual cycles of randomized treatment with DRSP/EE or placebo (Treatment Period 1 [TP1]), a one-cycle wash-out period, then three cycles of treatment with the alternate test article (Treatment Period 2 [TP2]). Subjects were randomized to DRSP/EE or placebo in a 1:1 ratio. The study was planned to enroll 126 subjects; however, following early termination of the protocol due to recruitment difficulties, actual enrollment was only 64 subjects. Of these, 34 were randomized to the sequence DRSP/EE→placebo, while 30 were randomized to the placebo→DRSP/EE sequence. The study was conducted at 17 sites in the U.S.

3.2 EFFICACY FINDINGS

The Daily Rating of Severity of Problems Scale (DRSPS) was used to assess the effect of treatment. Subjects completed this questionnaire daily, beginning on the first day of menses in run-in Cycle 1. The primary efficacy endpoint was the change from baseline in the average over three treatment cycles of the first 21 items of the DRSPS. For each cycle, each of the first 21 items was averaged over the five days preceding menses, and the averages were then summed. The primary efficacy variable was the difference between treatment arms in change in the average of the non-missing treatment cycle scores (from 1-3 cycle scores averaged per subject) from the baseline score, which was averaged over the two run-in cycles.

In both studies, the primary efficacy analysis of the Full Analysis Set demonstrated a statistically significant difference between DRSP/EE and placebo groups. The improvement in the DRSP/EE group in Study 304049 was 7.5 points greater (95% confidence limits 3.8 to 11.2) than that experienced by placebo subjects (p=0.0001). In the cross-over trial, Study 305141, where results were calculated by an ANCOVA model that collapsed treatment assignment over treatment period (with treatment sequence as a fixed factor), the improvement in the DRSP/EE group was 12.5 points greater (95% confidence limits 6.7 to 18.3) than that experienced by placebo subjects (p=0.0001). Results were very similar, and remained statistically significant, when analyzed using the per protocol population.

Statistically significant differences between DRSP/EE and placebo groups were demonstrated for a number of secondary endpoints; typically those which tended to assess symptoms and function over the week preceding menses, rather than over a longer time period. The most consistently positive secondary endpoints were the three items on the DRSPS relating to a woman's ability to function in the spheres of work/school, hobbies/social activities and relationships (these items differed from the 21 items assessing symptomatology). The finding of a benefit from DRSP/EE treatment on these items is particularly relevant due to their utility in assessing the effects of treatment on social and professional functioning.

3.3 SAFETY FINDINGS

Safety data from a number of sources were reviewed: the two PMDD trials, other trials for contraception and acne indications, final reports from postmarketing pharmacoepidemiologic surveillance studies of Yasmin, and postmarketing safety reports. The following submissions are the specific focus of the Complete Response safety review:

<u>The submissions referenced in the approvable letter of January 23, 2006</u>

- December 2, 2005 (containing Tables for YAZ-Mercilon comparative study 308020; clinical study reports and datasets for two acne studies, 306996 & 306820)
- December 6, 2005 (containing appendices, except appendix #3, for the two acne studies, 306996 & 306820; tables from a preliminary analysis of a large safety and efficacy European contraceptive study 308021)

- December 9, 2005 (containing appendix #3 for the two acne studies, 306996 & 306820)
- January 10, 2006 (containing updated safety information on Yasmin)
- March 1, 2006 (containing a safety update covering the period from February 22, 2005 through January 23, 2006)

Subsequent submission

- August 8, 2006 (containing final study reports on the YAZ-Mercilon comparative study [308020] and a large European safety and efficacy contraceptive study [Study 308021]; and a safety update covering the period from January 23, 2006 through August 7, 2006)

The complete review of safety in the PMDD trials (304049 & 305141) was addressed in the January 20, 2006 medical review of the initial submission. Major results of the PMDD, contraception and acne clinical trials are summarized below; postmarketing data are discussed in Section 3.3.5.

3.3.1 Deaths and Serious Adverse Events

There were four deaths reported in all of the clinical studies of the DRSP/EE product. 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 drug. One of the deaths, secondary to pesticide poisoning, occurred one month following discontinuation of YAZ. The other death, occurring three months after starting YAZ, was secondary to smoke inhalation in a fire. The other two deaths occurred in study 308021, an open label European 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 YAZ. There were no deaths in the PMDD trials.

Of 96 nonfatal SAEs in 11 clinical studies (including both the 21 and 24 day regimens), 15 were considered to be related to DRSP/EE. These SAEs include:

- migraine (2)
- depression (3)
- cholelithiasis/cholecystitis (2)
- pulmonary embolism (2)
- fibrocystic breast symptoms (2)
- ovarian cyst (2)
- breast fibroadenoma (1)
- cervical dysplasia (1)

Team Leader Comment

- **All of these events have been reported with the use of combination oral contraceptives. There is no safety signal indicating that DRSP/EE produces more of any of these SAEs than other oral contraceptives.**

3.3.2 Venous Thromboembolic Events

There were no reports of thromboembolic events in clinical trial subjects receiving the 24-day active dosing regimen of DRSP/EE. There were two confirmed venous thromboembolic (VTE) adverse events (both pulmonary emboli) in subjects receiving the 21-day active dosing regimen of DRSP/EE (Study 303860). This represents an overall VTE rate of approximately 6.1 per 10,000 women-years for the DRSP/EE product (clinical trial data combined for the 24 and 21-day

active dosing regimens) based on an exposure of 42,366 total 28-day treatment cycles or 3,259 women-years of exposure.

Team Leader Comment

- **As might be expected from the lower dose of estrogen in YAZ as compared to Yasmin, the VTE rate is lower than that calculated in postmarketing surveillance studies of Yasmin, which ranged from 13.7 to 15 cases per 10,000 women-years.**

3.3.3 Events Possibly Related to Hyperkalemia

A total of 12 subjects over the two PMDD trials experienced cardiovascular events (arrhythmia, bradycardia, syncope, tachycardia, dizziness and palpitations) identified as possibly resulting from hyperkalemia (2.8% of DRSP/EE subjects and 1.5% of placebo subjects); however, none of these subjects had a potassium level above the normal range at any measurement. A single YAZ subject in a contraceptive trial experienced dizziness and an elevated potassium level. In the two acne trials, dizziness and palpitations occurred in five subjects in each treatment arm; all ten subjects had potassium levels in the normal range.

Evaluation of laboratory assessments in the PMDD trials showed that a small but increased percent of DRSP/EE subjects as compared to placebo subjects had increases in potassium level to 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. There did not appear to be an increased risk of renal impairment with DRSP/EE use; however, it appears that subjects with mild renal impairment at baseline who take DRSP/EE may experience greater mean change in potassium than do placebo subjects, or subjects with normal renal function.

Potassium levels were assessed in only one of the contraception trials. A single YAZ subject had hyperkalemia on treatment; however, the sample was hemolyzed. Four YAZ and four placebo subjects had elevated potassium levels 10-17 days after last dose; one YAZ case was associated with dizziness. None of the other selected cardiovascular events potentially related to elevated potassium were reported. Similarly, in the acne studies, the frequency of elevated potassium post-baseline was similar in both treatment arms, and none of the subjects experiencing elevated levels reported any of the selected cardiovascular events.

3.3.4 Other Adverse Events

Adverse events that occurred in >5% of subjects and at a higher rate in the DRSP/EE group than the placebo group, over all trials, included:

- Breast pain
- Headache
- Metrorrhagia
- Nasopharyngitis
- Nausea
- Suspicious Pap smear
- Upper respiratory infection
- Vaginal infection

Over the eight studies using the 24-day dosing regimen, the rate of premature discontinuation due to adverse events was 6.3%. The adverse events most often leading to discontinuation included headache, bleeding irregularities (metrorrhagia, intermenstrual bleeding and amenorrhea), nausea, depression, decreased libido, dysmenorrhea, emotional lability, vomiting, breast pain and weight gain.

Team Leader Comment

- **All of the adverse events resulting in premature discontinuation are known to be associated with combination oral contraceptives and are listed in class labeling for combination hormonal contraceptive products.**

In the PMDD trials, review of physical examination findings and vital signs did not reveal any clinically significant abnormal findings. ECGs conducted at screening and end of the study were all normal.

3.3.5 Postmarketing Safety Assessments

The final study reports for the Ingenix and EURAS postmarketing pharmacoepidemiologic surveillance studies on Yasmin were submitted to NDA 21-098 in February and June, 2006, respectively, and reviewed by Dr. Lesley Furlong in the Division of Reproductive and Urologic Products. In her review of the Ingenix study, she concluded that:

- While inappropriate prescribing to patients with underlying renal, hepatic or adrenal impairment occurs, this did not occur differentially with Yasmin as compared to other oral contraceptives
- There were modest trends toward increased compliance with potassium monitoring in patient staking Yasmin, and fewer dispensings of Yasmin to women receiving concurrent therapy that might predispose to hyperkalemia
- Increased risk of hyperkalemia, electrolyte disturbances or possible sequelae of hyperkalemia or of thromboembolic events in Yasmin users was not detected
- A teratogenic effect was not detected in the offspring of women exposed to Yasmin during pregnancy
- Overall, the Ingenix study did not detect any safety concerns that differentiate Yasmin from other oral contraceptives

Dr. Furlong's review of the EURAS study concluded that:

- *The European Active Surveillance Study (EURAS) compared the incidence of certain adverse events among Yasmin users, users of levonorgestrel-containing oral contraceptives, and users of oral contraceptives containing other progestins. EURAS did not detect an increased incidence of adverse events among Yasmin users for any of the outcomes studied. In particular, Yasmin users did not have an increased risk for death or cardiovascular events compared with users of other oral contraceptives.*

3.3.6 Postmarketing Experience and Safety Update

YAZ has not yet been marketed outside the U.S., where it was launched in April, 2006.

The reporting interval for the Safety Updates submitted in the Complete Response is January 23, 2006 through August 7, 2006. These dates correspond to the cut-off date for inclusion of data into the previous Safety Update for this NDA. There were no US or foreign clinical studies ongoing with YAZ tablets during the reporting period and therefore no new safety information to report from clinical studies. In addition, the Applicant identified no new safety information in the

literature that might reasonably affect the statement of contraindications, warnings, precautions and adverse reactions in the YAZ labeling.

The first Periodic Adverse Drug Experience Report for YAZ NDA 21-676, approved on March 16, 2006, for the indication of oral contraception, was submitted on July 14, 2006 (reporting period March 16, 2006 – June 15, 2006). Three initial non-serious reports were included: blue stools, pain and burning in left forearm and thigh, and severe acne.

Team Leader Comment

- **The Safety Updates and Periodic Adverse Drug Experience Report for YAZ do not reveal any safety information that would affect approvability or labeling.**

3.3.7 Overall Assessment of Safety Findings

Overall, there were no signals of concern in regard to the occurrence of SAEs or changes in vital signs or laboratory evaluations associated with DRSP/EE. Selected adverse events of particular relevance to this product are: intermenstrual bleeding and menorrhagia, nausea, breast pain, decreased libido, emotional lability, and migraine, all of which occurred with at least twice the frequency in the subjects exposed to DRSP/EE as compared to placebo and were considered to be drug-related. As noted previously, most of these events are known to be associated with oral contraceptive use, and are labeled in the Yasmin and YAZ labels.

4 LABELING ISSUES

Negotiations on the Package Insert and Patient Package Insert have concluded successfully. All submitted labeling and packaging is now acceptable.

5 RECOMMENDATIONS OF OTHER DISCIPLINES AND DIVISIONS

5.1 TOXICOLOGY AND PRECLINICAL PHARMACOLOGY

The Pharmacology/Toxicology reviewer, Dr. Krishan Raheja, recommended approval of NDA 21-873 in the first cycle, based on the similarity in composition and intended treatment populations to the Applicant's previously approved product, Yasmin. In his review of the Complete Response, dated May 17, 2006, he states:

> *Based on review and approval of NDA 21-098 for Yasmin, Pharmacology recommends approval of NDA 21-873 for YAZ.*

5.2 CMC AND PRODUCT MICROBIOLOGY

In the first cycle review, the DMFs referenced by the Applicant for DRSP, EE and β-cyclodextrin clathrate were found to be adequate by the Chemistry Reviewer, Dr. Donna Christner. She recommended approval at that time, pending submission of acceptable labeling. In her review of the Complete Response, dated August 4, 2006, she states:

> *Acceptable labeling has been submitted and NDA 21-873 can be approved from a CMC standpoint.*

5.3 CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS

The Clinical Pharmacology and Biopharmaceutics Team Leader, Dr. Ameeta Parekh, stated the following in her review dated August 7, 2006:

> *NDA 21-873 was originally submitted on 12-22-04 for PMDD. The same drug product was also reviewed under NDA [21-676], submitted on 10/16/03. Both NDAs were acceptable from clinical pharmacology and biopharmaceutics perspective... Labeling for*

YAZ is acceptable and no further action is indicated from Clinical Pharmacology perspective.

5.4 STATISTICS

No new clinical data were submitted in the Complete Response. The Statistical Reviewer, Shahla Farr stated the following in her review dated September 14, 2006:

NDA 21-873 was originally submitted on 12-22-04 for the indication of premenstrual dysphoric disorder (PMDD). Moreover, the Sponsor had presented the same drug product under NDA 21-676 for indication of contraception on October 16, 2003. Both NDAs were deemed acceptable from a statistical perspective. The purpose of the March 1, 2006 submission of NDA 21-873 for the indication of PMDD was, solely, for safety issues and concerns of the Medical Division. No new statistical evaluation was requested for this submission. Hence, from a statistical standpoint, no further action is indicated.

5.5 DIVISION OF SCIENTIFIC INVESTIGATION

The Division of Scientific Investigation (DSI) inspected two sites for NDA 21-873 during the first cycle review (Site #27 – Robert Moreines, MD and Site #8 – Steven Drosman, MD). Roy Blay, Ph.D. from DSI stated in his review dated August 8, 2005:

The data submitted in support of this application by Dr. Moreines appear adequate in support of the relevant submission. The submitted in support of this application by Dr. Drosman appear adequate in support of the relevant submission despite a lack of timely assessment and reporting of adverse events.

5.6 DIVISION OF MEDICATION ERRORS AND TECHNICAL SUPPORT

Laura Pincock, Pharm.D., of the Division of Medication Errors and Technical Support (DMETS) made recommendations in her first cycle review (August 18, 2005) concerning container, carton and package insert labeling. Specific recommendations were conveyed to the Applicant and satisfactory resolution was reached. DMETS recommended against the proprietary name "YAZ" on the basis of possible name confusion with Yasmin. The Division did not believe that such a possible dispensing error would pose either a safety risk to patients nor increase the risk of an unplanned pregnancy.

5.7 DIVISION OF DRUG MARKETING, ADVERTISING AND COMMUNICATIONS AND DIVISION OF SURVEILLANCE, RESEARCH AND COMMUNICATION SUPPORT

Michelle Safarik, PA-C of the Division of Drug Marketing, Advertising and Communications (DDMAC) noted in her first cycle review, dated May 20, 2005:

DDMAC has reviewed the proposed carton labeling submitted in a consult requested by DRUDP on April 7, 2005, for YAZ tablets and we have no comments at this time.

Jeanine Best, M.S.N., R.N., P.N.P of the Division of Surveillance, Research and Communication Support (DSRCS) made several recommendations in her first cycle review, dated April 14, 2005, which were conveyed to the Applicant. Satisfactory resolution was reached.

Neither Division was consulted again for the Complete Response submission, as there were no new issues of relevance.

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/s/

Lisa Soule
10/2/2006 12:17:54 PM
MEDICAL OFFICER

Scott Monroe
10/3/2006 06:26:44 AM
MEDICAL OFFICER
I concur with the recommendation of Dr. Soule that NDA 21-873 (YAZ) be approved for the indication of "treatment of symptoms of premenstrual dysphoric disorder (PMDD) in women who choose to use an oral contraceptive as their method of contraception."

DIVISION OF REPRODUCTIVE AND UROLOGIC PRODUCTS
CLINICAL TEAM LEADER MEMORANDUM

NDA	NDA 21-873
Type of Application	Original NDA
Applicant	Berlex, Inc. Montville, NJ 07045
Proprietary Drug Name	YAZ (proposed)
Established Drug Name	Drospirenone 3 mg /Ethinyl Estradiol 0.02 mg Tablets
Drug Class	Progestin and estrogen combination
Indications	(1) Prevention of pregnancy in women (primary) (2) Treatment of symptoms of premenstrual dysphoric disorder (PMDD) in women who have no known contraindications to oral contraceptives and who desire contraception (secondary)
Route of Administration	Oral
Dosage Form	Tablet
Dosage Strength	Drospirenone 3 mg/ethinyl estradiol 0.02 mg per tablet
Dosing Regimen	One daily DRSP/EE tablet for 24-consecutive days followed by 4 placebo tablets (a 28-day dosing cycle that is repeated)
CDER Receipt Date	December 23, 2004
PDUFA Goal Date	January 23, 2006 (Based on 3-month extension)
Date of Memorandum	January 23, 2006
Reviewer	Scott E. Monroe, MD Clinical Team Leader/Deputy Director, DRUP

1. RECOMMENDATIONS

1.1 RECOMMENDATION REGARDING APPROVABILITY

I recommend that drospirenone (DRSP) 3 mg/ethinyl estradiol (EE) 0.02 mg tablets with a dosing regimen consisting of 24 days of active tablets followed by 4 placebo tablets (hereafter referred to as DRSP/EE) receive *approvable actions* for both the primary indication of "*prevention of pregnancy in women*" and the secondary indication of "*treatment of symptoms of premenstrual dysphoric disorder (PMDD) in women who choose to use an oral contraceptive for prevention of pregnancy.*"

1.1.1 Indication of Prevention of Pregnancy in Women

Approval of DRSP/EE for "prevention of pregnancy" is contingent upon (1) the Division not identifying any new safety issues as a result of its ongoing review of new supportive safety data submitted within 90 days of the PDUFA goal date that could not be reviewed during the present review cycle, (2) the Division's determination that (a) the Applicant has provided evidence that the dosing regimen consisting of 24 days of active dosing provides a benefit over that provided by the 21-day dosing regimen or (b) the 24-day regimen is safe and effective for the secondary indication of PMDD (see Section 2.2.1), and (3) the Applicant submitting acceptable product labeling.

1.1.2 Secondary Indication of Treatment of Symptoms of PMDD

Approval of DRSP/EE for "treatment of symptoms of premenstrual dysphoric disorder (PMDD) in women who choose to use an oral contraceptive for prevention of pregnancy" is contingent upon (1) the Division's approval of DRSP/EE for prevention of pregnancy and (2) the Applicant submitting acceptable product labeling.

1.2 Basis for Recommendation Regarding Approvability (Risk/Benefit Analysis)

1.2.1 Indication of Prevention of Pregnancy in Women

For this indication, the Applicant has (1) cross-referenced NDA 21-676 (original submission of October 2003 for the indication of prevention of pregnancy with DRSP/EE) and/or (2) concurrently submitted to this NDA (NDA 21-873) all information that has been submitted to NDA 21-676 as part of the Complete Response to the Approvable Action of November 17, 2004 for NDA 21-676 (see Section 2.2.2 for further background information). Based on the Pearl Index of 1.41 (95% confidence interval (CI): 0.73-2.47) in primary Phase 3 Study 303740, the Applicant has demonstrated that DRSP/EE is effective for prevention of pregnancy. However, a final decision on the overall risk/benefit assessment for DRSP/EE for prevention of pregnancy cannot be made until the safety data that could not be reviewed during the present cycle (i.e., data submitted within 90 days of the PDUFA goal date) has been reviewed and found to be acceptable.

1.2.2 Secondary Indication of Treatment of Symptoms of PMDD

The Applicant has demonstrated in 2 adequate and well controlled clinical trials that treatment with DRSP/EE is statistically superior to treatment with placebo in reducing the symptoms of PMDD. The limited safety data obtained from women with PMDD and reported in NDA 21-873 do not raise any safety concerns beyond those associated with all combination oral contraceptive products. Assuming that DRSP/EE tablets are approved for prevention of pregnancy, the risk/benefit ratio for DRSP/EE tablets is acceptable for the indication of "*treatment of symptoms of premenstrual dysphoric disorder (PMDD) in women who choose to use an oral contraceptive for prevention of pregnancy.*"

1.3 Recommendation on Risk Management Steps and/or Phase 4 Studies

1.3.1 Risk Management Steps

1.3.1.1 Indication of Prevention of Pregnancy in Women

The Applicant should conduct an educational program for healthcare providers, similar to that conducted for the presently marketed DRSP-containing contraceptive product (Yasmin). This

program should stress (1) the potential risks associated with the use of DRSP because of its anti-mineralocorticoid activity (i.e., potential for producing clinically significant hyperkalemia) and (2) the contraindications to the use of DRSP/EE for prevention of pregnancy. The Applicant has committed to conducting such a program.

1.3.1.2 Secondary Indication of Treatment of Symptoms of PMDD

In addition to the risk management steps listed above in Section 1.3.1.1, the Applicant will need to conduct an educational program for healthcare providers that (1) stresses the importance of distinguishing PMDD from Premenstrual Syndrome (PMS) and (2) provides guidance on how to accurately identify women who have PMDD. The program must also stress that if a woman is not currently using a hormonal contraceptive product or was not intending to use a hormonal contraceptive product for prevention of pregnancy, she should not use DRSP/EE for treatment of the symptoms of PMDD.

1.3.2 Phase 4 Studies

1.3.2.1 Indication of Prevention of Pregnancy in Women

The Applicant should conduct a large, adequately powered postmarketing surveillance study to compare the incidence of serious thrombotic and thromboembolic events in DRSP/EE users to the incidence of these events in users of other combination oral contraceptives that do not contain DRSP. The Applicant has committed to conducting such a study

1.3.2.2 Secondary Indication of Treatment of Symptoms of PMDD

No Phase 4 studies specifically directed to the PMDD indication are recommended.

2. BACKGROUND

2.1 DESCRIPTION OF PRODUCT

Drospirenone 3 mg/EE 0.02 mg tablets contain less ethinyl estradiol than the Applicant's currently marketed product YASMIN™ tablets (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 marketed in the U.S. that contains the progestin DRSP. Drospirenone differs from other progestins in combination oral contraceptives in that it (1) is a derivative of 17α-spironolactone and not of 19-nortestosterone and (2) 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) is developing 2 dosing regimens for DRSP 3 mg/EE 0.02 mg tablets. One dosing regimen (the subject of this NDA) consists of a daily active tablet for 24 days followed by a daily placebo tablet for 4 days. [redacted]. In addition to seeking approval for the indications of prevention of pregnancy and treatment of symptoms of PMDD, the Applicant also plans to obtain market approval for another secondary indication – treatment of acne. [redacted] other than NDA 21-873 (this application) and NDA 21-676 for prevention of pregnancy (see below).

The second dosing regimen (for which Schering AG, but not Berlex, plans to obtain marketing approval in selected countries) consists of 21 days of active dosing followed by either 7 placebo tablets or no tablets for 7 days. According to the Applicant, marketing approval for the 21-day active dosing regimen has been obtained in the Netherlands.

2.2 REGULATORY HISTORY

2.2.1 Indication of Prevention of Pregnancy in Women (NDA 21-676)

The Applicant first sought approval for DRSP/EE for the indication of prevention of pregnancy under NDA 21-676. Although NDA 21-676 contained clinical trial data for both 21 and 24 days of active dosing, the Applicant sought approval only for the 24-day active dosing regimen. On November 17, 2004, the Division issued an approvable letter for DRSP/EE which 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.*

2.2.2 Prevention of Pregnancy and Secondary Indication of Treatment of Symptoms of PMDD (NDA 21-873)

Following the approvable action for DRSP/EE tablets for the indication of prevention of pregnancy, the Applicant submitted NDA 21-783 (the present Application) that includes 2 indications: (1) the primary indication of prevention of pregnancy (with cross-reference to NDA 21-676) and (2) the secondary indication of treatment of symptoms of PMDD. This Memorandum focuses on the efficacy and safety of DRSP/EE tablets for the secondary indication of PMDD and includes only a limited review of the new information submitted in support of the prevention of pregnancy indication. A detailed review of the Complete Response to the Approvable Letter of November 17, 2004 for the indication of prevention of pregnancy will be provided separately in the clinical review of the Applicant's June 15, 2005 submission to NDA 21-676. The extended goal date for NDA 21-676 (prevention of pregnancy) is March 16, 2006.

2.3 PRIMARY MEDICAL REVIEWERS' RECOMMENDATIONS FOR APPROVABILITY (NDA 21-873)

The primary clinical review of the safety and efficacy of DRSP/EE tablets for the prevention of pregnancy in women under NDA 21-873 was conducted by Gerald Willett MD, who also conducted the primary review of the Applicant's original submission for this indication under NDA 21-676. The primary clinical review of the safety and efficacy of DRSP/EE tablets for the treatment of the symptoms of PMDD was conducted by Lisa Soule MD.

2.3.1 Prevention of Pregnancy

The following is Dr. Willett's recommendation for the approvability of DRSP/EE tablets for prevention of pregnancy in women:

> *An approvable action is recommended by this reviewer for the contraceptive indication of YAZ (24-day active dosing regimen of drospirenone 3 mg/ethinyl estradiol betadex 0.02 mg tablets) under NDA 21-873. Approval is contingent on (1) a determination that the overall safety profile is acceptable (which will require review of supportive safety data submitted within 90 days of the PDUFA goal date and not reviewed during this cycle) and (2) acceptable labeling.*

2.3.2 Secondary Indication of Treatment of Symptoms of PMDD

The following is Dr. Soule's recommendation for approvability of DRSP/EE tablets for the secondary indication of treatment of symptoms of PMDD:

> *It is recommended that NDA 21-873, DRSP (3 mg)/EE (0.02 mg) oral tablets (YAZ), be approved for the indication of "treatment of symptoms of premenstrual dysphoric disorder (PMDD) in women who choose to use an oral contraceptive as their method of contraception," contingent upon submission of acceptable labeling by the Applicant and approval of NDA 21-676 for the indication of prevention of pregnancy.*
>
> *The reviewer finds that:*
>
> - *Adequate statistical evidence of efficacy relative to placebo has been demonstrated for DRSP/EE in treatment of PMDD symptoms.*
> - *The clinical benefit of treatment with DRSP/EE has been satisfactorily indicated by statistically significant improvement on several secondary endpoints that assess social and professional functioning and global improvement.*
> - *The magnitude of the treatment effect appears to be consistent with that attributable to treatment with the three SSRIs approved for treatment of PMDD.*
> - *The safety data do not raise concern for a safety profile discrepant from that of the approved product, Yasmin, and, in fact, the lower total exposure to EE afforded by use of YAZ as compared to Yasmin may offer a safety advantage.*
> - *Considering the risk/benefit profiles of DRSP/EE and the approved SSRI treatments, approval of this product would offer women with PMDD who desire oral contraception a useful treatment alternative.*

Team Leader Comment

- *For the indication of "prevention of pregnancy," I concur with the primary Medical Reviewer that the Application is approvable.*

- *For the secondary indication of "treatment of symptoms of premenstrual dysphoric disorder (PMDD) in women who choose to use an oral contraceptive as their method of contraception," I concur with the primary Medical Reviewer that the Application is approvable contingent upon satisfactory resolution of all outstanding issues (see Section 3.2.2 and Section 3.4).*

3. INDICATION OF PREVENTION OF PREGNANCY IN WOMEN

3.1 OVERVIEW OF CLINICAL PROGRAM

Detailed descriptions of the Applicant's clinical program 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 January 19, 2006) of NDA 21-873 and (2) the Team Leader Memorandum (dated November 17, 2004) for original NDA 21-676.

In the present Application, the Applicant submitted (1) a Final Report from a new Phase 2 descriptive pharmacodynamic study (Study 308382) that compared the effectiveness of the 24-day dosing regimen to that of 21-day dosing regimens in terms of suppression of ovarian activity, (2) a draft Final Report of a Phase 3 trial (Study 308020) that compared the safety and effectiveness of DRSP/EE to that of Mercilon (a combination oral contraceptive containing 150 mg desogestrel/0.02 mg EE) over 7 cycles, and (3) supportive safety data from (a) an ongoing non-comparative prevention of pregnancy trial (Study 308021), (b) two Phase 3 clinical trials that compared the safety and effectiveness of DRSP/EE to that of placebo for the treatment of acne, (c) two Phase 3 clinical trials that compared the safety and effectiveness of DRSP/EE to that of placebo for the treatment of PMDD, and (d) updated postmarketing safety data for Yasmin. Findings from Studies 303740, 308020, and 308382 and updated supportive postmarketing safety data for Yasmin are discussed in this Memorandum.

3.2 EFFICACY FINDINGS

3.2.1 Phase 3 Efficacy Studies

3.2.1.1 Principal Efficacy Study

The Applicant's protocol for establishing contraceptive efficacy was similar to other product submissions in this class. The primary study (Study 303740) that supported the safety and efficacy of DRSP/EE (24-day dosing regimen) included data from over 10,000 (28)-day treatment cycles and more than 200 women who completed 13 cycles of use. The primary efficacy endpoint was the number of "on-treatment" pregnancies. The primary efficacy analysis was based on the Pearl Index, which is the number of "on-treatment" pregnancies per 100 women-years of use. The value for the Pearl Index in Table 1 is based on the FDA Medical Officer's determination of the number of "on-treatment" pregnancies and exclude (1) cycles where backup contraception was used, (2) cycles for women over age 35 at entry, and (3) cycles for women listed as sexually inactive.

Table 1 Efficacy of DRSP/EE Tablets (24-day active dosing regimen) (Study 303740)

24-day Dosing Regimen (Study 303740)					
Total Days of Exposure	Total 28-day Cycles of Exposure	Total Number of 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.
Source: Table A, pg 7, Primary Medical Review by Dr. Willett for NDA 21-873 (January 19, 2006).

Team Leader Comment

- *A Pearl Index of 1.41 is acceptable for a combination oral contraceptive.*

3.2.1.2 Supportive Efficacy Study

Study 308020 was a comparative Study of DRSP/EE versus Mercilon over 7 28-day cycles. In the DRSP/EE group, 201 of 220 subjects completed treatment. There were no pregnancies in the DRSP/EE group which resulted in a Pearl Index of 0.0 with the upper bound of a 2-sided 95% CI of 3.41. The Pearl Index for the Mercilon group based on 1 pregnancy detected during the Study was 0.93 with the upper bound of a 2 sided 95% CI of 5.16.

3.2.2 Phase 2 Supportive Efficacy Study

To address the Division's request that approval of the 24-day active dosing regimen of DRSP/EE 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 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-ß-estradiol (E2) concentrations. Ovarian activity was classified according to the Hoogland scoring system that is described in Table 2.

Table 2 Hoogland Scoring System

Score	Ovarian Activity	Diameter of FLS (mm)	P (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;
* To Convert from nmol/L to ng/mL , multiply by 0.3145
Source: Table 4, pg 23, Primary Medical Review by Dr. Willett for NDA 21-873 (January 19, 2006).

The treatment phase consisted of three 28-day cycles, during which subjects received either 24 or 21 days of DRSP/EE. 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 3 and Table 4, respectively

Table 3 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 26, Primary Medical Review by Dr. Willett for NDA 21-873 (January 19, 2006).

Table 4 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 6, pg 26, Primary Medical Review by Dr. Willett for NDA 21-873 (January 19, 2006).

Medical Officer's Comment

- *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 5). 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 5: 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 27, Primary Medical Review by Dr. Willett for NDA 21-873 (January 19, 2006).

Team Leader Comment

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

3.2.3 Overall Assessment of Effectiveness

Drospirenone (3 mg)/EE (0.02 mg) tablets (24-day dosing regimen) are highly effective for prevention of pregnancy. The Pearl Index of 1.41 (95% CI: 0.73-2.47) is acceptable for a combination oral contraceptive.

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

3.3 SAFETY FINDINGS

This Memorandum focuses only on serious adverse events that are known to occur in users of combination oral contraceptives or serious events that occurred in clinical trials with DRSP 3 mg/EE 0.02 mg tablets (both the 24- and 21-day dosing regimens). The primary Medical Reviewer (Dr. G. Willett) has reviewed in detail the safety profile of DRSP/EE in his primary Medical Reviews of November 16, 2004 (NDA 21-676) and January 19, 2006 (the present Application). Dr. Willett's review of safety data for the supportive acne studies (Study 306820 and Study 306996 and the on-going supportive prevention of pregnancy study (Study 308021) is ongoing. Therefore, comments about the safety profile of DRSP 3 mg/EE 0.02 mg tablets in this Memorandum must be considered as preliminary until the review of safety data from these latter studies has been completed. Based on the clinical trial information provided by the Applicant in this NDA, data previously submitted data to NDA 21-676, and postmarketing 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) is acceptable for a highly effective combination oral contraceptive.

3.3.1 Clinical Trials with DRSP 3 mg/EE 0.02 mg

The following safety information concerning serious adverse events is based on information provided by the Applicant with a cut-off date of October 2005 for on-going clinical trials (unless otherwise stated).

3.3.1.1 Deaths

Four deaths have been reported in clinical studies of DRSP/EE. 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 ongoing non-U.S. Study 308021, which is an open label study of the 24-day regimen for 13 cycles in approximately 1000 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.*

3.3.1.2 Serious Thrombotic and 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, 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/EE is approximately 6.3 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 41,155 total treatment cycles or 3,165 women years of exposure, which includes both completed and ongoing trials for all indications under study with DRSP 3 mg/EE 0.02 mg tablets.*

- *According to the primary Medical Reviewer, the rate of 6.3 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 3.3.2). 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 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.*

3.3.1.3 Hyperkalemia

Because DRSP possesses anti-mineralocorticoid activity, DRSP/EE 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."

Team Leader Comment

- *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. 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.*

3.3.2 Supportive Safety Data (Postmarketing Safety Data for Yasmin)

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

3.3.2.1 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 on-going study were last 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 6.

Table 6 EURAS Study – Confirmed Thromboembolic Adverse Events

Event Category	Yasmin (34,310 WY)			LNG-containing OCs (32,415 WY)			Other OCs (50,428 WY			Total
	N	Events Per 10^4 WY	95% CI	N	Events Per 10^4 WY	95% CI	N	Events Per 10^4 WY	95% CI	N
All VTE & ATE	28	8.2	5.4 –11.8	25	7.7	5.0-11.4	48	9.5	7.0-12.6	101
All VTE	25	7.3	4.7 - 10.8	20	6.2	3.8-9.5	42	8.3	6.0-11.3	87
PE	7	2.0	0.8 – 4.2	5	1.5	0.5-3.6	8	1.6	0.7-3.1	20
All ATE	3	0.9	0.2 – 2.6	5	1.5	0.5-3.6	6	1.2	0.4-2.6	14
AMI	0	0.0	0.0 – 1.1	2	0.6	0.1-2.2	4	0.8	0.2-2.0	6
CVA	3	0.9	0.2 – 2.6	3	0.9	0.2-2.7	2	0.4	0.0-1.4	8
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	2

VTE = venous thromboembolic event, ATE = arterial thromboembolic event, AMI = acute myocardial infarction, CVA = cerebrovascular accident, WY = women-years.
Source: Table B, pg 10, Primary Medical Review by Dr. Willett for NDA 21-873 (January 19, 2006).

Team Leader Comment

- *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.*
- *Since these are interim results and EURAS has not yet achieved its intended power, it is still possible that small statistically significant differences will be detected in the final analysis.*

3.3.2.2 Ingenix Study

The U.S. postmarketing surveillance study (Ingenix Study based on the claims database of United Health Care) was initially designed to monitor adverse events related to hyperkalemia. There have been no signals indicating that hyperkalemia has been a clinical problem in users of Yasmin. The Ingenix Study was subsequently modified to monitor thrombotic and thromboembolic adverse events. The most recent interim analysis for thrombotic/thromboembolic adverse events in the Ingenix Study is presented in Table 7.

Table 7. Ingenix Study: Confirmed Cases of Thrombotic and Thromboembolic Events

	Yasmin Cohorts (N=15,767)				Other OC Cohorts (N=31,534)					
	N	PY	IR (1)	95% CI	N	PY	IR	95% CI	RR	95% CI
Pulmonary embolism	5	13,160	0.4	0.1-0.8	7	25,361	0.3	0.1-0.5	1.4	0.3-5.0
Venous thrombosis	12	13,160	0.9	0.5-1.5	22	25,361	0.9	0.6-1.3	1.1	0.5-2.2
Venous thrombosis + pulmonary embolism	1	13,160	0.1	0.0-0.4	4	25,361	0.2	0.1-0.4	0.5	0.0-4.9
Stroke (2)	1	13,160	0.1	0.0-0.4	4	25,361	0.2	0.1-0.4	0.5	0.0-4.9

PY = Person-years; IR= Incidence rate; RR= Rate ratio
1 Incidence rates expressed as events per 1,000 person-years
2 TIA outcomes also counted in stroke.
Source: Table C, pg 10, Primary Medical Review by Dr. Willet for NDA 21-873 (January 19, 2006).

Team Leader Comment

- *This interim analysis 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.*
- *Because this is an interim analysis and the power of the study is not yet adequate to show small differences in event rates, it is possible that small but statistically significant differences may be observed in the analysis of the final data.*

3.3.3 Summary of Safety Assessment

The number of subjects exposed to DRSP 3 mg/EE 0.02 mg (24-day dosing regimen) and number of subjects taking the drug for one year is acceptable. The primary Medical Reviewer's preliminary estimate of the number of 28-day treatment cycles completed to date (including acne studies and ongoing Study 308021) is 41,155 28-day treatment cycles based on both the 21- and 24-day dosing regimens. His preliminary estimate of the number of subjects completing one year (13 cycles) of therapy is 2,045.

Based on safety data reviewed to date, the safety profile for DRSP 3 mg/EE 0.02 tablets appears to be acceptable for a highly effective contraceptive product. However, review of the safety data submitted within 90 days of the PDUFA goal date (and not reviewed during this review cycle) is required before a final determination of the acceptability of the safety profile of DRSP 3 mg/EE 0.02 mg for prevention of pregnancy can be made.

3.4 Risk/Benefit Assessment of DRSP/EE (24-Day Dosing Regimen) for Prevention of Pregnancy

Based on the data provided in NDA 21-873 and cross-referenced in NDA 21-676, the efficacy of DRSP 3 mg/EE 0.02 mg tablets is acceptable for a combination oral contraceptive. In the principal efficacy study, the Pearl Index was 1.41. Based on safety data reviewed to date, the safety profile for DRSP 3 mg/EE 0.02 tablets appears to be acceptable for a highly effective contraceptive product. However, review of the safety data submitted within 90 days of the PDUFA goal date (and not reviewed during this review cycle) is required before a final determination of the risk/benefit profile of DRSP 3 mg/EE 0.02 (24-day dosing regimen) for prevention of pregnancy can be made.

4. TREATMENT OF SYMPTOMS OF PMDD

The primary Medical Reviewer, Dr. Lisa Soule, has reviewed the Applicant's two Phase 3 clinical trials submitted in NDA 21-873 in support of the secondary indication for the treatment of symptoms of PMDD. Based on her review, she has recommended that "NDA 21-873, DRSP (3 mg)/EE (0.02 mg) oral tablets (YAZ), be approved for the indication of 'treatment of symptoms of premenstrual dysphoric disorder (PMDD) in women who choose to use an oral contraceptive as their method of contraception,' contingent upon submission of acceptable labeling by the Applicant and approval of NDA 21-676 for the indication of prevention of pregnancy." No safety findings were identified in her review of the two Phase 3 PMDD studies that would have a negative impact on the approvability of DRSP/EE for this indication. Therefore, the focus of the Team Leader review (described in this Memorandum) was on the quality and strength of the efficacy data supporting the PMDD indication.

4.1 OVERVIEW OF CLINICAL PROGRAM

Two Phase 3, randomized, double-blind, placebo-controlled, multicenter trials were conducted in the U.S. to evaluate the efficacy and safety of DRSP/EE, compared to that of placebo, in treating symptoms of PMDD. The population studied in each trial was comprised of women diagnosed with PMDD by DSM-IV criteria.

Study 304049 was a parallel group trial in which 450 subjects participated in a 2-cycle run-in phase followed by a treatment phase conducted over a total of 3 menstrual cycles. Subjects were randomized to DRSP/EE or placebo in a 1:1 ratio, with 232 subjects randomized to DRSP/EE and 218 to placebo. The study was conducted at 64 sites.

Study 305141 was a crossover study conducted over a total of 7 menstrual cycles. Following a 2 cycle run-in phase, subjects were randomized to one of 2 treatment sequences. Each treatment sequence consisted of (a) randomized treatment with DRSP/EE or placebo over 3 menstrual cycles (Treatment Period 1 [TP1]), (b) a one-cycle wash-out period, and (c) a second treatment period with the alternate study drug over 3 menstrual cycles (Treatment Period 2 [TP2]). Subjects were randomized to sequence DRSP/EE→placebo or placebo→DRSP/EE in a 1:1 ratio. It was originally intended that the study would enroll 126 subjects; however, following early termination of the protocol due to recruitment difficulties, actual enrollment was only 64 subjects. Of these, 34 were randomized to the sequence DRSP/EE→placebo and 30 were randomized to the sequence placebo→DRSP/EE. The study was conducted at 17 sites.

An overview of each of the 2 clinical trials, including information regarding study design, number of patients enrolled and trial duration is provided in Table 8.

Table 8 Summary of Phase 3 Studies Providing Efficacy and Safety Data for PMDD Indication

Report/Protocol Number	Study Type Phase	Study Design	Study Medication	Duration of Treatment (regimen)	Number of Subjects Treated	Age Range in Years (Mean)
A21566/304049	Efficacy/Safety Phase 3	Multicenter, randomized, double blind, placebo-controlled, parallel	DRSP/EE	3 cycles (24-day regimen)	231	18-40 (31.0)
			Placebo		218	18-42 (32.0)
A07545/305141	Efficacy/Safety Phase 3	Multicenter, randomized, double blind, placebo-controlled, crossover	DRSP/EE; Placebo[a]	6 cycles (24-day regimen)	34	19-39 (31.0)
			Placebo; DRSP/EE[b]		30	20-40 (33.0)

DRSP = drospirenone; EE = ethinyl estradiol; DRSP/EE = drospirenone 3 mg/ethinyl estradiol 0.02 mg.

[a] Treatment group first received DRSP/EE for 3 treatment cycles, then no study medication for 1 cycle, and then placebo for 3 treatment cycles.

[b] Treatment group first received placebo for 3 treatment cycles, then no study medication for 1 cycle, and then DRSP/EE for 3 treatment cycles.

Source: Text Table 1, ISE, p 13, submission of December 22, 2004.

4.2 DEMOGRAPHICS

The characteristics of the subjects who participated in the 2 clinical trials (combined across the trials) are listed by treatment assignment in Table 9.

Table 9 Demographics by Treatment Group (Studies 304049 and 305141 Combined)

Variable	YAZ (24 days) (N=285)	Placebo (N=267)
Age (years)		
n	285	267
Mean ± SD	31.2 ± 5.59	32.0 ± 5.57
Median	32.0	32.0
Min – Max	18 – 40	18 – 42
Race (n [%])		
Caucasian	216 (75.8)	207 (77.5)
Black	31 (10.9)	24 (9.0)
Hispanic	26 (9.1)	25 (9.4)
Asian	3 (1.1)	4 (1.5)
Other	9 (3.2)	7 (2.6)
Height (cm)		
n	284	265
Mean ± SD	165.49 ± 6.399	166.05 ± 7.021
Median	166.00	166.37
Min – Max	144.8 – 184.6	144.8 – 194.9
Weight (kg)		
n	285	264
Mean ± SD	70.48 ± 13.676	69.10 ± 13.361
Median	68.49	66.23
Min – Max	44.5 – 108.9	45.7 – 112.0
BMI (kg/m^2)		
n	284	264
Mean ± SD	26.083 ± 4.682	25.377 ± 4.508
Median	25.510	24.370
Min – Max	17.20 – 37.58	14.00 – 36.46

BMI = body mass index; Max = maximum; Min = minimum; N = total number of subjects treated; n =number of subjects; SD = standard deviation.

Source: Text Table 5 ISS, pg 24 of 95, submission of December 22, 2004.

Team Leader Comment

- *There were no noticeable differences between the DRSP/EE and placebo groups. Approximately 75 % of subjects were Caucasian. Black and Hispanic subjects each comprised about 10% of the total population.*

4.3 DISPOSITION OF SUBJECTS

The disposition of subjects combined across the 2 studies by treatment group is presented in Table 10.

Table 10 Disposition of Subjects (Studies 304049 and 305141 Combined)

Subject Disposition	DRSP/EE		Placebo	
	n	%	n	%
Subjects Enrolled and Treated	285	100.0	267	100.0
Completed treatment	198	69.5	203	76.0
Prematurely discontinued treatment	87	30.5	64	24.0
Adverse event	40	14.0	11	4.1
Lost to follow-up	20	7.0	18	6.7
Withdrawal of consent	16	5.6	21	7.9
Protocol deviation	5	1.8	10	3.7
Other	4	1.4	2	0.7
Pregnancy	1	0.4	1	0.4
Lack of efficacy	1	0.4	0	0

Source: Modified from Text Table 4 of ISS, pg. 23 of 95, submission of December 22, 2004.

Team Leader Comment

- *A higher percentage of subjects discontinued treatment prematurely in the DRSP/EE group (30.5%) than in the placebo group (24.0%). The most noticeable difference in the reported reasons for premature discontinuation across the treatment groups was in the category of adverse event, reported for 14.0% and 4.1% of the DRSP/EE and placebo subjects, respectively.*

4.4 EFFICACY FINDINGS

4.4.1 Assessment of Efficacy (Studies 304049 and 305141)

In each of the clinical trials, the 21 symptom assessment items of the Daily Rating of Severity of Problems (DRSP) questionnaire were used to assess the primary effect of treatment. Subjects completed this questionnaire daily, beginning on the first day of menses in run-in Cycle 1. Items were rated on a scale from 1 (not at all) to 6 (extreme); thus a maximum daily score of 126 was possible. The questions comprising the DRSP are shown in Table 11. The 3 functional impairment items of the DRSP, along with the outcomes from several other instruments, were used for secondary assessments of efficacy.

Table 11 Daily Rating of Severity of Problems (DRSP) Questionnaire

Item No.	Description of Item [A]
1a	Felt depressed, sad, "down," or "blue"
1b	Felt hopeless
1c	Felt worthless or guilty
2	Felt anxious, tense, "keyed up," or "on edge"
3a	Had mood swings (e.g., suddenly felt tearful or sad)
3b	Was more sensitive to rejection or my feelings were easily hurt
4a	Felt angry, irritable
4b	Had conflicts or problems with people
5	Had less interest in usual activities (e.g., work, school, friends, hobbies)
6	Had difficulty concentrating
*7	Felt lethargic, tired, fatigued or had a lack of energy
8a	Had increased appetite or overate
8b	Had cravings for specific foods
*9a	Slept more, took naps, found it hard to get up when intended
*9b	Had trouble getting to sleep or staying asleep
10a	Felt overwhelmed or that I could not cope
10b	Felt out of control
*11a	Had breast tenderness
*11b	Had breast swelling, felt "bloated" or had weight gain
*11c	Had headache
*11d	Had joint or muscle pain
Functional impairment items: • At work, at school, at home, or in daily routine, at least one of the problems noted above caused reduction of productivity or inefficiency • At least one of the problems noted above interfered with hobbies or social activities (e.g., avoid or do less) • At least one of the problems noted above interfered with relationships with others	

[A] Items were rated on a scale from 1 (not at all) to 6 (extreme).
* physical symptom

Team Leader Comment

- *The 2 clinical trials in support of the indication of treatment of symptoms of PMDD were conducted under IND 61,304. The 2 Phase 3 trials submitted in support of the PMDD indication in NDA 21-873 were initiated while IND 61,304 was under the purview of the Division of Neuropharmacologic Drug Products (DNDP). As described in detail in the primary Medical Review, DNDP agreed with the design of these trials and with the use of the first 21 items of the DRSP questionnaire for assessment of the primary efficacy endpoint.*
- *The DRSP questionnaire has been used previously to assess the effectiveness of medical therapies (i.e., fluoxetine and sertraline) that have been approved by DNDP for the treatment of symptoms of PMDD.*

The primary efficacy endpoint was the change from baseline in the average over 3 treatment cycles of the first 21 items of the DRSP instrument. Each of the first 21 items was averaged over the five days preceding menses for each menstrual cycle, and the averages were then summed. The primary efficacy variable was the difference between treatment arms in the change in the average of the non-missing treatment cycle scores from the average of the baseline scores. The

baseline score was the average over the two run-in (pretreatment) cycles for Study 304049 and for the first Treatment Period for Study 305141. The baseline score for the second Treatment Period in Study 305141 was based on the single wash-out cycle between Treatment Period 1 and Treatment Period 2. Data were analyzed using an analysis of covariance (ANCOVA).

4.4.2 Study 304049 – Efficacy Findings

4.4.2.1 Primary Efficacy Analysis

Two hundred thirty one (231) and 218 subjects each received one or more doses of DRSP/EE or placebo, respectively. Sufficient efficacy data (i.e., 3 or more days of luteal phase data) were available from 190 subjects (DRSP/EE group) and 194 subjects (placebo group) to be included in the Applicant's primary efficacy analysis. The mean baseline DRSP-21 scores, the mean scores for the change from baseline in each treatment cycle, and the overall mean change from baseline across the 3 treatment cycles for each treatment arm are listed in Table 12. In both the DRSP/EE and placebo groups, the mean on-treatment DRSP-21 score was significantly lower than the baseline value (a decrease in score represents an improvement in symptoms). The mean on-treatments changes in DRSP-21 score from baseline were -36.2 and -30.0 in the DRSP/EE and placebo groups, respectively.

Table 12 Mean (SD) DRSP-21 Baseline Scores and Changes from Baseline (Study 304049)

Treatment	Statistic	Baseline average	Change from Baseline			
			Cycle 1	Cycle 2	Cycle 3	Cycle 1-3 (average)
DRSP/EE	N	190	190	165	138	190
	Mean (SD)	**77.4 (16.7)**	**-34.5 (22.2)**	**-37.1 (21.4)**	**-38.5 (22.2)**	**-36.2 (20.3)**
Placebo	N	194	194	170	130	194
	Mean (SD)	**78.1 (17.8)**	**-26.7 (26.0)**	**-31.6 (26.2)**	**-32.0 (26.4)**	**-30.0 (23.2)**

Source: Table 16, Final Report for Study 304049, submission of December 22, 2004.

The adjusted mean difference from baseline between the 2 treatment groups was 7.5 points better in the DRSP/EE treated subjects (DRSP/EE score minus placebo score = -7.5; 95% CI: -11.2 to -3.8), p = 0.0001 (see Table 13).

Table 13 Comparison Between Treatments of Mean Changes from Baseline in DRSP-21 Scores (Study 304049)

Efficacy Variable	Mean Change from Baseline by Treatment		Difference Between Treatments	P- Value of Difference
	DRSP/EE (n=190)	Placebo (n=194)	(95% CI)	
Change from Baseline	**-37.49**	**-29.99**	**-7.5** (-11.2 to -3.8)	**0.0001**

n = total number of subjects with sufficient data to be included in Applicant's efficacy analysis.
Mean change from baseline is the average of adjusted means of all 3 treatment cycles derived from ANCOVA.
Difference is the difference of the adjusted treatment means (DRSP/EE minus placebo).
P-value is derived from ANCOVA with terms for treatment and center and baseline as covariate.
Source: Table 17, Final Report for Study 304049, submission of December 22, 2004.

Team Leader Comment

- *The absolute difference between treatment groups (-7.5) is relatively small when compared to the magnitude of the change from baseline in both the DRSP/EE (-37.49) and placebo (-29.99) treatment groups. The difference between groups, however, is statistically significant (p=0.0001).*
- *The difference between treatments is comparable to that observed in clinical trials for fluoxetine and sertraline that supported approval of these drugs by DNDP for the treatment of PMDD (see primary Medical Review).*

Effect of treatment on symptoms of PMDD during the first treatment (menstrual) cycle. Because of concern that treatment with DRSP/EE, in contrast to placebo, might alter the length of a subject's menstrual cycle, the Applicant was asked to assess the effect of treatment during the first of the 3 treatment cycles. Such an analysis would minimize the potential of a change in cycle length affecting a subject's DRSP-21 values since the days of primary interest would be scored before the subject had knowledge of when her menstrual cycle would begin. The results of this analysis are summarized in Table 14. The adjusted mean changes from baseline in the DRSP-21 score were -34.69 and -26.44 in the DRSP/EE and placebo treatment groups, respectively. The adjusted mean difference between the 2 treatment groups from baseline was 8.249 points better in the DRSP/EE treated subjects compared to the change in the placebo subjects (DRSP/EE score minus placebo score = -8.249; p=0.0002).

Table 14 Comparison Between Treatments of Mean Changes from Baseline in DRSP-21 Scores (Treatment Cycle 1 only) (Study 304049)

Instrument	Change from Baseline[a] (n)		Difference[b]	p-value
	DRSP/EE N = 231	Placebo N = 218		Primary[c]
DRSP scale first 21 Items	-34.69 (190)	-26.44 (194)	-8.249	0.0002

ANCOVA = analysis of covariance; DRSP = Daily Record of Severity of Problems scale; DRSP/EE = drospirenone 3 mg/ethinyl estradiol 0.02 mg; N = total number of subjects in treatment group; n = total number of subjects with available data.

[a] Adjusted mean change from baseline for Treatment Cycle 1.

[b] The difference in adjusted treatment means (DRSP/EE minus placebo).

[c] P-value from ANCOVA with terms for treatment and center, baseline as covariate.

Source: Text Table 11, pg. 42 of ISE, submission of December 22, 2004.

Team Leader Comment

- *The point estimate of the differences between mean treatment responses based on the first treatment cycle (-8.249) was similar to that based on the 3 treatment cycles (-7.5). This finding indicates that the demonstrated treatment effect was not likely to have been affected by a potential loss of blinding.*

4.4.2.2 Secondary Efficacy Endpoints

The Applicant conducted several secondary efficacy analyses using the 3 functional impairment items in the DRSP questionnaire and other instruments. The 3 functional impairment items of the DRSP questionnaire relate to (1) reduction in productivity, (2) interference with social activities, and (3) interference with relationships (see Table 11). Mean changes from baseline for

each of these functional impairment items are listed in Table 15. For each of the items, the decrease from baseline was statistically significantly greater in the DRSP/EE group.

Table 15 Comparisons of Mean Changes from Baseline in Average Functional Impairment Items from DRSP Questionnaire (Study 304049)

		DRSP/EE (N =231)	Placebo (N =218)	
Item 22 Reduction of Productivity	n	189	194	
	Adjusted Mean	-1.976	-1.643	
	Difference [1]			-0.334
	P-Value [2]			0.0022
	95% Confidence Limits			-0.546,-0.121
	P-Value [3]			0.0030
Item 23 Interference with Social Activities	n	189	194	
	Adjusted Mean	-1.941	-1.606	
	Difference [1]			-0.335
	P-Value [2]			0.0020
	95% Confidence Limits			-0.546,-0.124
	P-Value [3]			0.0030
Item 24 Interference with Relationships	n	189	194	
	Adjusted Mean	-2.102	-1.682	
	Difference [1]			-0.419
	P-Value [2]			0.0002
	95% Confidence Limits			-0.641,-0.198
	P-Value [3]			0.0003

[1] The difference in adjusted treatment means (i.e. DRSP/EE minus placebo).
[2] P-value from ANCOVA with terms for treatment and center, baseline as covariate.
[3] P-value from rank ANCOVA with terms for treatment, center, baseline as covariate, done if test for normality sig. at .05 .

Source: Table 27, Final Report for Study 304049, submission of December 22, 2004.

Team Leader Comment

- *Although the Applicant conducted several secondary efficacy analyses, the analysis that I believe to be the most useful is that based on the 3 functional impairment items in the DRSP questionnaire. Subjects in the DRSP/EE group showed a greater improvement in each of the 3 functional impairment items than subjects in the placebo group, providing further support for the effectiveness of DRSP/EE therapy.*

4.4.3 Study 305141 – Efficacy Findings

4.4.3.1 Primary Efficacy Analysis

Thirty-four (34) subjects were randomized to the sequence DRSP/EE→placebo and 30 subjects were randomized to the sequence placebo→DRSP/EE sequence. The number of subjects who took 1 or more doses of study drug in each treatment period and the number of subjects in each treatment period for whom sufficient data were available to include in the efficacy analyses are listed in Table 16. Across both treatment periods, 42 of the 54 subjects who received one or more doses of DRSP/EE and 41 of the 49 subjects who received one or more doses of placebo were include in the primary efficacy analysis. For Treatment Period 1 only, 26 of 34 subjects who received DRSP/EE and 23 of 30 subjects who received placebo were include in the primary efficacy analysis.

Table 16 Number of Subjects In Efficacy Analysis by Treatment Assignment and Treatment Period (Study 305141)

	DRSP/EE→Placebo (N=34)	Placebo→DRSP/EE (N=30)
Period 1 Treatment	DRSP	Placebo
No. Subjects receiving ≥ 1 dose of drug	34	30
No. Subjects in efficacy analysis	26	23
Period 2 Treatment	Placebo	DRSP
No. Subjects receiving ≥ 1 dose of drug	19	20
No. Subjects in efficacy analysis	18	16

The mean baseline DRSP-21 scores, the mean scores for the change from baseline in each treatment cycle, and the overall mean change from baseline across the 3 treatment cycles for each treatment arm in Treatment Period 1 are listed in the top panel of Table 17. In both the DRSP/EE and placebo groups, the mean on-treatment DRSP-21 score was statistically significantly lower than the baseline value (a decrease in score represents an improvement in symptoms). The mean on-treatment changes in DRSP-21 score from baseline were -34.0 and -19.9 in the DRSP/EE and placebo groups, respectively.

The mean washout period DRSP-21 scores, the mean scores for the change from the washout period in each treatment cycle, and the overall mean change from the washout period across the 3 treatment cycles for each treatment arm in Treatment Period 2 are listed in the lower panel of Table 17. The mean on-treatment changes in DRSP-21 score from the washout period were -17.0 and +7.5 in the DRSP/EE and placebo treatment groups, respectively.

Table 17 Mean (SD) DRSP Baseline/Washout Scores and Changes from Baseline/Washout (Study 305141)

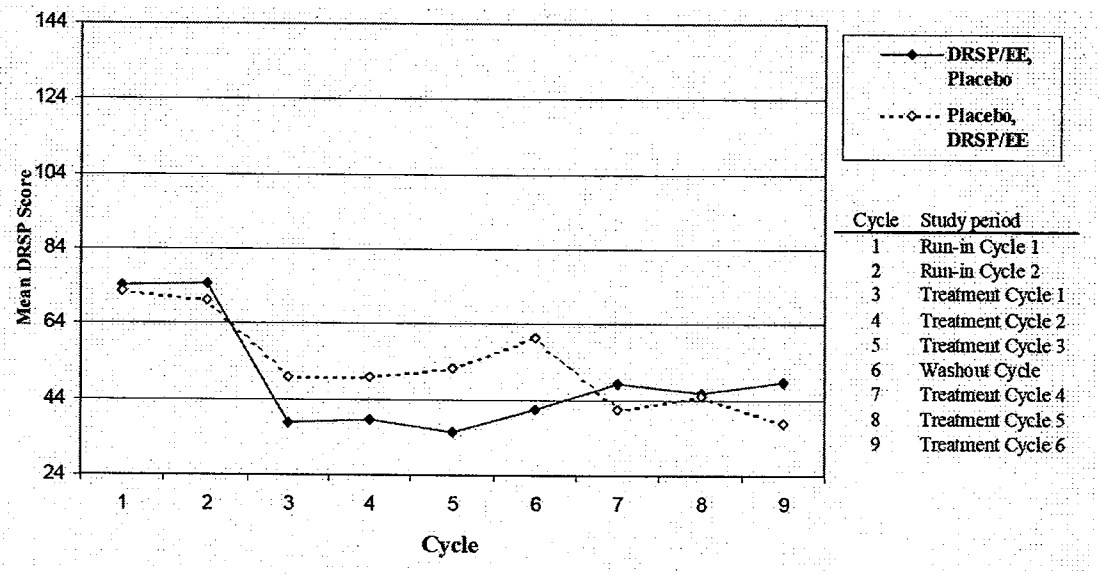
Treatment Period 1						
Treatment	Statistic	Baseline average	Change from Baseline			
			Cycle 1	Cycle 2	Cycle 3	Cycle 1-3 (average)
DRSP/EE	N	26	26	26	25	26
	Mean (SD)	**71.3 (17.7)**	**-33.5 (23.6)**	**-32.8 (20.1)**	**-36.3 (20.6)**	**-34.0 (18.3)**
Placebo	N	23	23	20	18	23
	Mean (SD)	**69.8 (13.5)**	**-19.7 (26.0)**	**-21.4 (26.6)**	**-19.3 (18.6)**	**-19.9 (20.8)**

Treatment Period 2						
Treatment	Statistic	Washout average	Change from Baseline			
			Cycle 4	Cycle 4	Cycle 6	Cycle 4-6 (average)
DRSP/EE	N	16	16	12	9	16
	Mean (SD)	**57.5 (23.3)**	**-16.1 (13.0)**	**-10.1 (23.3)**	**-25.8 (22.9)**	**-17.0 (15.4)**
Placebo	N	18	18	15	14	18
	Mean (SD)	**40.0 (14.3)**	**+8.2 (16.5)**	**+4.5 (19.9)**	**+8.9 (24.7)**	**+7.5 (16.2)**

Source: Modified from Table 14, pp 155-156, Final Report for Study 305141, Submission of December 22, 2004.

Mean DRSP-21 scores by treatment sequences and treatment cycle (also referred to as Study Period) are presented in Figure 1.

Figure 1 Mean DRSP Scores by Treatment Sequence and Cycle (Study Period) (Study 305141)



Source: Text Figure 2, pg. 57 of 81, ISS, submission of December 22, 2004.

Mean changes in DRSP-21 scores (ANCOVA adjusted values) from Baseline or Washout across both treatment periods are shown in Table 18. The adjusted mean difference from baseline (Treatment Period 1) or the washout period (Treatment Period 2) between the DRSP/EE and placebo treatments was 12.47 points better during treatment with DRSP/EE than during treatment with placebo (DRSP/EE score minus placebo score = -12.47; 95% CI: -18.28 to -6.66), p = 0.0001.

Table 18 Comparison Between Treatments of Mean Changes in DRSP-21 Scores (ANCOVA adjusted values) from Baseline or Washout (Study 305141)

	Treatment		
	DRSP/EE N = 54	Placebo N = 49	
n	42	41	
Adjusted mean	-22.94	-10.46	
Difference [a]			-12.47
P-value [b]			0.0001
95% confidence limits			-18.28,-6.660
P-value [c]			0.0001

[a] The difference in adjusted treatment means (ie, DRSP/EE minus placebo).
[b] P-value from ANCOVA model with terms for sequence, period, treatment, center, baseline as a covariate, subjects as random.
[c] P-value from Wilcoxon statistic, computed if Shapiro-Wilk normality test was significant at 0.05 level.
DRSP/EE = drospirenone 3 mg/ethinyl estradiol 20 µg.

Source: Text Table 11, Final Report for Study 305141, submission of December 22, 2004.

Team Leader Comment

- *The point estimate of the treatment effect in Study 305141 (-12.47) was numerically greater than that of Study 304049 (-7.5) but there was overlap of the 95% CIs for the point estimates, indicating no statistical difference. The results of Study 305141 (a smaller crossover study) appear to support fully those of Study 304049 (a much larger parallel group trial).*
- *The failure of DRSP scores to return to baseline values during the washout period, however, complicates interpretation of the treatment effects in Treatment Period 2 of Study 305141. In this study, the mean DRSP-21 score in the DRSP/EE treatment group decreased by -17.0 points from the washout period value while the mean DRSP-21 score in the placebo group increased by 7.5 points.*
- *Because of the failure of DRSP-21 values to return to baseline values during the washout period, the Applicant was asked to analyze the difference in DRSP-21 values from baseline, based only on the on-treatment DRSP-21 values during Treatment Period 1. Results of this analysis are shown in Table 19.*

Table 19 Comparison Between Treatments of Mean Changes in DRSP-21 Scores from Baseline for Treatment Period 1 (Study 305141)

Instrument	Change from Baseline[a] (n)		Difference[b]	p-value[c]
	DRSP/EE N = 34	Placebo N = 30		
DRSP scale first 21 Items	-33.25 (26)	-19.80 (23)	-13.45	0.0040

ANCOVA = analysis of covariance; DRSP = Daily Record of Severity of Problems scale; DRSP/EE = drospirenone 3 mg/ethinyl estradiol 0.02 mg; N = total number of subjects in treatment group; n = total number of subjects with available data.

[a] Adjusted mean change from baseline in the average of adjusted means for Treatment Period 1.

[b] The difference in adjusted treatment means (DRSP/EE minus placebo).

[c] P-value from ANCOVA with terms for treatment and center, baseline as covariate, using Treatment Period 1 data only.

Source: Text Table 23, Final Report for Study 305141, submission of December 22, 2004.

Team Leader Comment

- *Using only data from Treatment Period 1, the adjusted mean difference in the response to treatment was 13.45 points better in the DRSP/EE treatment group (DRSP/EE score minus placebo score = -13.45), p = 0.004. The outcome of this analysis, which eliminates potential confounding factors due to the crossover design, was virtually the same as that from the analysis of the full population.*

Effect of treatment on symptoms of PMDD during the first treatment (menstrual) cycle. The Applicant also was asked to assess the effect of treatment during the first treatment cycle of Treatment Period 1 of Study 305141 for the reasons previously described in Section 4.4.2.1. The results of this analysis are summarized in Table 20. The adjusted mean changes from baseline in the DRSP-21 score were -33.11 and -20.74 in the DRSP/EE and placebo treatment groups, respectively. The adjusted mean difference between the 2 treatment groups, based on the mean changes (i.e., improvement) from baseline within each treatment group, was 12.37 points better in the DRSP/EE treated subjects compared to the change in the placebo treated subjects (DRSP/EE score minus placebo score = -12.37; p = 0.0213).

Table 20 Comparison Between Treatments of Mean Changes from Baseline in DRSP-21 Scores (Treatment Cycle 1 only) (Study 305141)

Instrument	Change from Baseline[a] (n)		Difference[b]	p-value
	DRSP/EE N = 34	Placebo N = 30		Primary[c]
DRSP scale first 21 Items	-33.11 (26)	-20.74 (23)	-12.37	0.0213

ANCOVA = analysis of covariance; DRSP = Daily Record of Severity of Problems scale; DRSP/EE = drospirenone 3 mg/ethinyl estradiol 0.02 mg; N = total number of subjects in treatment group; n = total number of subjects with available data.

[a] Adjusted mean change from baseline for Treatment Cycle 1.

[b] The difference in adjusted treatment means (DRSP/EE minus placebo).

[c] P-value from ANCOVA with terms for treatment and center, baseline as covariate.

Source: Text Table 25, Final Report for Study 305141, submission of December 22, 2004.

Team Leader Comment

- *The point estimate of the differences between mean treatment responses based on the first treatment cycle of Treatment Period 1 (-12.37) was similar to that based on the 3 treatment cycles of Treatment Period 1 (-13.45). This finding, as with that for Study 304049, indicates that the demonstrated treatment effect was not likely to have been affected by a potential loss of blinding.*

4.4.3.2 Secondary Efficacy Endpoints

The Applicant also conducted several secondary efficacy analyses using the same analyses as those previously described for Study 304049. The results of one of these analyses, based on the 3 functional impairment items of the DRSP questionnaire, are listed in Table 21. Mean changes from baseline for each of the functional impairment items and the model estimate of the difference between treatment groups are listed in the Table.

Table 21 Comparisons of Mean Changes from Baseline in Average Functional Impairment Items from DRSP Questionnaire (Study 305141)

		DRSP/EE (N = 54)	Placebo (N = 49)	
Item 22 Reduction of Productivity	n	42	41	
	Adjusted Mean	-1.205	-0.185	
	Difference [1]			-1.019
	P-Value [2]			0.0004
	95% Confidence Limits			-1.548,-0.491
Item 23 Interference with Social Activities	n	42	41	
	Adjusted Mean	-1.333	-0.333	
	Difference [1]			-1.000
	P-Value [2]			0.0002
	95% Confidence Limits			-1.491,-0.509
Item 24 Interference with Relationships	n	42	41	
	Adjusted Mean	-1.628	-0.561	
	Difference [1]			-1.067
	P-Value [2]			0.0002
	95% Confidence Limits			-1.577,-0.558

Source: Table 25 of Final Report for Study 305141, pg. 181, submission of December 22, 2004.

Team Leader Comment

- *Subjects in the DRSP/EE group showed a statistically greater improvement in each of the 3 functional impairment items than subjects in the placebo group, providing further support for the effectiveness of DRSP/EE therapy.*

4.4.4 Additional Exploratory Efficacy Analyses Requested by FDA

Sensitivity analyses for premature terminations. The Applicant's primary efficacy analysis was done on the "Full Analysis" set, defined by the Applicant as all randomized subjects who received at least one dose of study medication. However, subjects who took at least one dose of study drug but withdrew before recording at least 3 days of luteal phase data for Treatment Cycle 1 were not included in the efficacy analyses. Thus, the "Full Analysis" set was actually a modified Intent to Treat (mITT) population. In Study 304049, 41 DRSP/EE subjects and 24 placebo subjects were excluded from the primary efficacy analysis on this basis. In Study 305141, 12 and 8 subjects who receive one or more doses of DRSP/EE or placebo, respectively, were excluded from the primary efficacy analysis.

Team Leader Comment

- *To explore the possible impact of excluding subjects who received study drug from the primary efficacy analyses, the Applicant was asked to conduct a sensitivity analysis for each of the clinical trials. In these analyses, subjects in the DRSP/EE treatment groups who provided no efficacy data were assigned the mean response for subjects in the respective placebo group. The results of these sensitivity analyses for Study 304049 and Study 305141 are listed in Table 22, Table 23, and Table 24.*

Table 22 Comparison Between Treatments of Mean Changes from Baseline in DRSP-21 Scores (Sensitivity Analysis for Study 304049)

Efficacy Variable	Mean Change from Baseline by Treatment		Difference Between Treatments	P- Value of Difference
	DRSP/EE (n=231)	Placebo (n=194)	(95% CI)	
Change from Baseline	**-36.72**	**-30.08**	**-6.638** (-10.102 to -3.175)	**0.0002**

Source: Table 17 for Study 304049, e-mail submission of January 19, 2006.

Table 23 Comparison Between Treatments of Mean Changes from Baseline/Washout in DRSP-21 Scores Across Treatment Period 1 and 2 (Sensitivity Analysis for Study 305141)

Efficacy Variable	Mean Change from Baseline or Washout by Treatment		Difference Between Treatments	P- Value of Difference
	DRSP/EE (n=53)	Placebo (n=41)	(95% CI)	
Change from Baseline	**-22.78**	**-10.39**	**-12.39** (-18.27 to -6.501)	**0.0002**

Source: Table 15 for Study 305141, e-mail submission of January 19, 2006.

Table 24 Comparison Between Treatments of Mean Changes from Baseline in DRSP-21 Scores in Treatment Period 1 (Sensitivity Analysis for Study 305141)

Efficacy Variable	Mean Change from Baseline or Washout by Treatment		Difference Between Treatments	P- Value of Difference
	DRSP/EE (n=34)	Placebo (n=23)	(95% CI)	
Change from Baseline	**-32.19**	**-20.96**	**-11.23 (-19.718 to -2.744)**	**0.0105**

Source: Table 15, e-mail submission of January 20, 2006.

- *The results of these additional sensitivity analyses were very similar to the Applicant's original primary efficacy analyses. For both Study 304049 and Study 305141, treatment with DRSP/EE resulted in a statistically greater reduction in the symptoms of PMDD as assessed by the first 21 items of the DRSP Questionnaire.*

4.4.5 Overall Assessment of Efficacy

The Applicant has shown in 2 Phase 3 clinical trials that treatment with DRSP/EE resulted in a statistically greater reduction in the symptoms of PMDD than treatment with placebo. Efficacy was assessed by the subject's response to the first 21-items of the DRSP questionnaire averaged over the 5 days preceding menses. In Study 304049, the improvement in the DRSP/EE treatment group was 7.5 points greater (95% CI: 3.8 to 11.2) than that experienced by placebo subjects ($p = 0.0001$). In Study 305141 (a crossover study) the improvement during treatment with DRSP/EE was 12.5 points greater (95% CI: 6.7 to 18.3) than that experienced during treatment with placebo($p = 0.0001$). Because of concerns that some aspects of study design or study analyses might have had an impact on the findings, the Applicant was asked to conducted several additional analyses to support the original findings. In all instances, the FDA-requested analyses supported the Applicant's original findings.

Because the benefit of treatment with DRSP/EE above that of treatment with placebo was modest, the primary Medical Reviewer compared the efficacy findings for DRSP/EE to those for 3 SSRIs approved for the treatment of PMDD. In her review, Dr. Soule stated the following:

> *In the most relevant comparison, to that of the fluoxetine luteal phase dosing trial, which used the identical outcome measure over the same treatment period, the changes from baseline in DRSPS score with treatment by the active study drug were -28 to -31 depending on fluoxetine dose, compared to -37.5 for DRSP/EE in Study 304049 and -17 to -34 for DRSP/EE in Study 305141, depending on treatment sequence. The magnitude of the difference between active study drug and placebo in change from baseline in DRSPS 21 scores was similar (5 to 8 for fluoxetine, 7.5 for DRSP/EE in Study 304049, and 9.5 to 14 for DRSP/EE in Study 305141).*

Team Leader Comment

- *Based on the data provided by the Applicant in NDA 21-873 and the comparisons to treatment effects of approved SSRIs for PMDD provided by Dr. Soule in her review, I believe that (1) treatment with DRSP/EE reduces symptoms of PMDD to a greater extent than treatment with placebo and (2) and the benefit of treatment is comparable to of at least one SSRI (i.e., fluoxetine) approved by the Division of Neuropharmacologic Drug Products for treatment of PMDD.*

- *It also should be noted that the indication for treatment with SSRIs is a primary indication while that for treatment with DRSP/EE (if approved) will be a secondary indication (see Section 5, Labeling Issues).*

4.5 SAFETY FINDINGS (STUDIES 304049 AND 305141)

4.5.1 Deaths and Serious Adverse Events

There were no deaths in either of the trials. There were a total of 5 serious adverse events (SAEs). Three occurred in subjects exposed to DRSP/EE (1.1% of subjects) and 2 occurred in subjects during placebo exposure (0.7% of subjects). Only one of the 3 SAEs in a DRSP/EE subject was considered possibly drug-related (severe dysplasia on a Pap smear).

Team Leader Comment

- *Treatment with DRSP/EE for 3 months or less is unlikely to be related to this single case of severe dysplasia.*

4.5.2 Other Adverse Events

Across the 2 studies, adverse events occurred in 79% of DRSP/EE subjects and 64% of placebo subjects. A greater proportion of subjects taking DRSP/EE terminated treatment prematurely (30.5% of DRSP/EE subjects vs. 24% of placebo subjects). A higher percentage of subjects using DRSP/EE withdrew due to adverse events (14.0% of DRSP/EE subjects compared to 4.1% of placebo subjects). Adverse events judged to be treatment-related that were reported for ≥ 2% of DRSP/EE subjects are listed in Table 25.

Table 25 Most Common Drug-Related Adverse Events (≥ 2%) – Pooled Data

Preferred Term	DRSP/EE N=285		Placebo N=267	
	N	%	N	%
Intermenstrual bleeding	65	22.8	10	3.7
Headache	38	13.3	26	9.7
Nausea	48	16.8	12	4.5
Breast pain	31	10.9	10	3.7
Asthenia	14	4.9	7	2.6
Abdominal pain	6	2.1	3	1.1
Libido decreased	13	4.6	3	1.1
Emotional lability	10	3.5	3	1.1
Menorrhagia	10	3.5	3	1.1
Menstrual disorder	9	3.2	5	1.9
Nervousness	8	2.8	4	1.5
Depression	8	2.8	0	0
Weight gain	7	2.5	5	1.9

Number of individual events exceeds total, because some subjects experienced multiple events.
Source: Modified from Text Table 14, pp 42, ISS, submission of December 22, 2004.

Team Leader Comment

- *These events are known to be associated with oral contraceptive use and are to be expected. Based on the relatively high percentage of subjects who withdrew due to an adverse in the*

risk/benefit ratio for DRSP/EE for the treatment of symptoms of PMDD would be acceptable if a woman was not already using or planning to use a combination oral contraceptive as her method of contraception.

Labeling will also need to clearly state the importance of distinguishing PMDD from Premenstrual Syndrome (PMS) and will need to provide guidance on how to accurately identify women who have PMDD in contrast to women with PMS. Labeling will also need to indicate that the benefit of treatment beyond 3 months has not been demonstrated.

Labeling (both that for healthcare providers and consumers) also will need to stress that if a woman is not currently using a hormonal contraceptive product or was not intending to use a hormonal contraceptive product for prevention of pregnancy, she should not use DRSP/EE for treatment of symptoms of PMDD.

6. RECOMMENDATIONS OF NON-MEDICAL DISCIPLINES AND DIVISIONS

6.1 TOXICOLOGY AND PRECLINICAL PHARMACOLOGY

The primary Toxicology Reviewer (Krishan Raheja, PhD.) made the following recommendations in his review (2/24/2005) :

Recommendation on approvability: *This NDA is similar in composition and indication to the sponsor's NDA 21-676 (YAZ containing drospirenone 3 mg/ethinyl estradiol 0.02 mg tablets) and NDA 21-098 (Yasmin containing 0.3 mg drospirenone/0.03 mg ethinyl estradiol tablets), both approved for oral contraception. Under NDA 21-873 the sponsor has evaluated YAZ for the treatment of premenopausal dysphoric disorder (PMDD). Based on the similarity in composition and intended treatment populations with the sponsor's previously approved products, Pharmacology recommends approval of NDA 21-873.*

Recommendations for nonclinical studies: *None*

Recommendations on labeling: *Labeling will be similar to that for NDAs 21-098 and 21-676.*

6.2 CMC AND PRODUCT MICROBIOLOGY

The primary Chemistry Reviewer (Donna Christner, Ph.D.) made the following recommendation in her review (dated 9/30/2005):

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

6.3 CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS

The primary Clinical Pharmacology and Biopharmaceutics Reviewer (Julie M. Bullock, Pharm.D.) stated the following in her review (dated 12/05/2005):

NDA 21-873, YAZ for PMDD is acceptable from a Clinical Pharmacology and Biopharmaceutics perspective.

6.4 STATISTICS

The Statistical Reviewer (Shahla Farr, M.S.) stated the following in the "Conclusions" of her review(dated 1/17/2006) for the PMDD component of NDA 21-873:

Study A21566, the placebo controlled, parallel group trial, for the indication of Premenstrual Dysphoric Disorder (PMDD) showed statistically significant superiority, ($p < 0.001$) based on the results submitted by the sponsor. Based on the analysis of the reviewer, using electronic data submitted to the Agency, the results were consistent with those of the sponsor.

Study A07545, the cross-over study, although discontinued prematurely, showed statistically significant results in period one for both sponsor and reviewer ($p \leq 0.05$). The results for period two should be interpreted with caution since problems existed due to drop-outs, possible carry over effect and inability to maintain the randomization (due to drop-outs). Nonetheless, strong results still held for the second period as well ($p=0.001$). Also, when statistical comparison between treatments for mean change from baseline in DRSP scores was estimated with the period effect included in the model, both outcomes from the sponsor and the reviewer were comparable ($p=0.0001$).

The Statistical Reviewer (Shahla Farr, M.S.) stated the following in the "Conclusions" of her review (dated 1/18/2006) for the contraceptive efficacy component of NDA 21-873 (which is cross referenced from NDA 21-676:

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 seems 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.

6.5 DIVISION OF SCIENTIFIC INVESTIGATION

The Division of Scientific Investigation (DSI) inspected two sites for NDA 21-873 (Site #27-Robert Moreines, MD and Site # 8-Steven Drosman, MD)

Roy Blay, PhD from DSI made the following overall assessment and general recommendations in his review dated 8/8/2005:

The data submitted in support of this application by Dr. Moreines appear adequate in support of the relevant submission. The data submitted in support of this application by Dr. Drosman appear adequate in support of the relevant submission despite a lack of timely assessment and reporting of adverse events. The review division medical officer should determine whether the data from subject 840069 who was on a daily antibiotic regimen should be excluded from study analysis.

6.6 Office of Drug Safety/Division of Medication Errors and Technical Support

Laura Pincock, Pharm.D of the Division of Medication Errors and Technical Support (DMETS) made the following recommendations in her review (dated 8/18/2005):

DMETS continues to not recommend the use of the proprietary name, "YAZ™".

DMETS recommends implementation of the label and labeling revisions outlined in the Section III of this review in order to minimize potential errors with the use of this product.

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/EE under NDA 21-676. DMETS expressed concern that the proposed name could be misinterpreted as an abbreviation for the medication Yasmin. The Division discussed the concerns expressed by DMETS but not concur with their assessment of the risks associated with the use of the name "YAZ." It was felt by the Division, that should a dispensing error occur, this would not pose a safety risk nor would it increase the risk that a woman would experience an unplanned pregnancy.

6.7 Division of Drug Marketing, Advertising, and Communications

The Division of Drug Marketing, Advertising, and Communications (DDMAC) recommended many changes to the proposed label during their review of NDA 21-676. All recommendations will be considered in final labeling if DRSP/EE is eventually approved for marketing.

6.8 Division of Surveillance, Research, and Communication Support (DSRCS)

Jeanine Best of The Division of Drug Marketing, Advertising, and Communications (DDMAC) had the following comments and recommendations in its review (dated 4/14/2005):

1. Revise the patient labeling for Yaz following the March 2004, Draft Guidance; Guidance for Industry: Labeling for Combined Oral Contraceptives.

2. Avoid the use of UPPER CASE lettering to emphasize important information. Upper case lettering is difficult to read. Bold or underline for word or statement emphasis. The trade name is the exception to this recommendation and may be in upper case letters.

All recommendations will be considered in final labeling if DRSP/EE is eventually approved for marketing.

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

/s/

Scott Monroe
1/23/2006 03:26:40 PM
MEDICAL OFFICER

Daniel A. Shames
1/23/2006 04:28:00 PM
MEDICAL OFFICER

CLINICAL REVIEW

Application Type	NDA
Submission Number	21-873
Submission Code	AZ-000
Letter Date	March 1, 2006
Stamp Date	March 2, 2006
PDUFA Goal Date	December 1, 2006 (extension date)
Reviewer Name	Gerald Willett, M.D.
Review Completion Date	September 28, 2006
Established Name	Drospirenone/Ethinyl Estradiol
Trade Name	YAZ
Therapeutic Class	Combined Oral Contraceptive
Applicant	Berlex
Priority Designation	S
Formulation	Tablet
Dosing Regimen	Drospirenone 3 mg/Ethinyl Estradiol 0.02 mg daily for 24 days followed by placebo for 4 days
Secondary Indication	Treatment of symptoms of premenstrual dysphoric disorder (PMDD)
Intended Population (Sponsor's Proposal)	Women who desire oral contraceptives and have no contraindications to their use

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1 EXECUTIVE SUMMARY

1.1 RECOMMENDATION ON REGULATORY ACTION

I recommend that NDA 21-873, drospirenone (DRSP) (3 mg) /ethinyl estradiol (EE) (0.02 mg) oral tablets (YAZ), be approved for the secondary indication of "treatment of symptoms of premenstrual dysphoric disorder (PMDD) in women who choose to use an oral contraceptive as their method of contraception."

This recommendation is based on the following:

- The submissions referenced in the approvable letter (December 2, 6, 9, 2005 and January 10, 2006) that were not reviewed prior to the January 23, 2006 approvable letter for NDA 21-873 have now been reviewed. These submissions included safety data from the Applicant's finalized acne studies (306820 & 306996) and unfinalized European contraceptive studies (308020 & 308021). There are no safety concerns in those submissions that would impact approval of YAZ for the secondary indication of PMDD.

- Final study reports from European contraceptive trial protocols 308020 & 308021 submitted on August 8, 2006 show no safety concerns. No new safety concerns were identified on the last safety update which was also submitted on August 8, 2006. This safety update is current up through August 7, 2006.

- YAZ was approved for the primary indication of contraception on March 16, 2006, thus allowing for approval of secondary indications.

- Acceptable labeling has been received from the Applicant.

- I concur with the primary reviewer (Lisa Soule, MD) and secondary reviewer (Scott Monroe, MD) of the initial submission that the clinical studies (304049 & 305141) under NDA 21-873, which focused specifically on the secondary indication of PMDD, showed that YAZ was both safe and effective.

1.2 RECOMMENDATION ON POSTMARKETING ACTIONS

Postmarketing actions that are already in place for YAZ (via the contraceptive NDA 21-676) include a Phase 4 Commitment surveillance study for arterial and venous thromboembolic events and a risk management plan similar to Yasmin in regard for the potential for hyperkalemia. Specific risk management in regard to correct prescribing for PMDD is summarized in the subsequent section.

1.2.1 Risk Management Activity

The principal risk management activity for this secondary indication of PMDD is addressed through labeling. Labeling for this product stresses that women should initially decide to use this product primarily for birth control and that PMDD is a secondary indication. The label cautions women not to use YAZ primarily for treatment of PMDD since there are other medical alternatives. The label also addresses the fact that PMDD is a specific mood disorder and should be diagnosed by clinicians according to strict criteria.

1.3.2 Efficacy in the PMDD Trials

The Daily Rating of Severity of Problems Scale (DRSPS) was used to assess the effect of treatment. Subjects completed this questionnaire daily, beginning on the first day of menses in run-in Cycle 1. The primary efficacy endpoint was the change from baseline in the average over three treatment cycles of the first 21 items of the DRSPS.

In both studies, the primary efficacy analysis of the full analysis set demonstrated a statistically significant difference between DRSP/EE and placebo groups. The improvement in the DRSP/EE group in Study 304049 was 7.5 points greater (95% confidence limits 3.8 to 11.2) than that experienced by placebo subjects (p=0.0001). In the cross-over trial, Study 305141, the improvement in the DRSP/EE group was 12.5 points greater (95% confidence limits 6.7 to 18.3) than that experienced by placebo subjects (p=0.0001). These results were calculated by an ANCOVA model that collapsed treatment assignment over treatment period (with treatment sequence as a fixed factor). Results were very similar, and remained statistically significant, when analyzed using the per protocol population.

1.3.3 Safety

Safety in the PMDD Trials (derived from Executive Summary, Medical Review of NDA 21-873, January 20, 2006)

The complete review of safety in the PMDD trials (304049 & 305141) was addressed in the January 20, 2006 medical officer review by Dr. Soule.

There were no deaths in either of the PMDD trials. The only SAE out of three occurring in a YAZ subject that was considered possibly drug-related by the Applicant (severe dysplasia on Pap smear) was not judged by the reviewer to be drug-related. Adverse events occurred in 79% of YAZ subjects and 64% of placebo subjects. A greater proportion of subjects taking YAZ withdrew prematurely (30.5% vs. 24% of placebo subjects), with most of the discrepancy attributable to the number who withdrew due to adverse events (14.0%, compared to 4.1% of placebo subjects). Events that were judged to be treatment-related and differentially distributed across treatment groups included: intermenstrual bleeding, nausea, breast pain, decreased libido, emotional lability, menorrhagia and migraine, all of which occurred with at least twice the frequency in the subjects exposed to DRSP/EE as compared to placebo. These events are known to be associated with oral contraceptive use, and are listed in class labeling for combination hormonal contraceptive products.

Special attention was paid to adverse events of particular concern, including cardiovascular events possibly related to venous thromboembolic events (VTEs) and hyperkalemia.

There were no VTEs in either PMDD trial.

A total of 12 subjects over the two trials experienced cardiovascular events identified as possibly resulting from hyperkalemia (2.8% of DRSP/EE subjects and 1.5% of placebo subjects); however, none of these subjects had a potassium (K+) level above the normal range at any measurement. Evaluation of laboratory assessments showed that a small but increased percent of YAZ subjects as compared to placebo subjects had increases in potassium level to 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.

Safety in Other Trials Including Contraception and Acne Indications (derived from Executive Summary and body of the report of NDA 21-676, March 14, 2006)

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.

The following safety section includes data from both the 24-day regimen (24 active, 4 placebo) studies of YAZ and the 21-day regimen (21 active, 7 placebo) studies of Yasminelle. Both regimens employ a combination drug product that contains 3mg of drospirenone and 0.02 mg of ethinyl estradiol (3 mg DRSP / 0.02 mg EE).

There were four deaths reported in all of the clinical studies of the 3 mg DRSP / 0.02 mg EE product. 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 drug. One of the deaths, secondary to pesticide poisoning, occurred one month following discontinuation of YAZ. The other death, occurring three months after starting YAZ, was secondary to smoke inhalation in a fire. The other two deaths occurred in study 308021, which is an open label European 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 YAZ.

Of 96 nonfatal SAEs in 11 clinical studies (including both the 21 and 24 day regimens), 15 were considered to be related to 3 mg DRSP / 0.02 mg EE tablets. These SAEs include migraine (2), depression (3), cholelithiasis/cholecystitis (2), pulmonary embolism (2), fibrocystic breast symptoms (2), ovarian cyst (2) breast fibroadenoma (1) and cervical dysplasia (1). All of these events have been reported with the use of combination oral contraceptives. There is no safety signal indicating that the 3 mg DRSP / 0.02 mg EE tablets produce more of any of these SAEs than other oral contraceptives.

There were no reports of 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 3 mg DRSP / 0.02 mg EE product (clinical trial data combined for the 24 and 21-day active dosing regimens) based on an exposure of 42,366[A] total 28-day treatment cycles or 3,259 women-years of exposure.

{ A = Treatment cycles derived from either treatment days provided in the study results or calculated using mean days of exposure for eleven clinical studies 303740, 301888, 303860, 14523, 14588, 305466, 308382, 308020, 308021, 306996, and 306820}

Medical Officer's Comment

- ***This rate of 6.1 per 10,000 women years is lower than the VTE rate of the approved combination oral contraceptive Yasmin (0.03 mg ethinyl estradiol/ 3mg drospirenone) in the first year of the European Active Surveillance 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 have been no safety concerns to date in regard to drospirenone's potential for hyperkalemia in all of the clinical studies and in the postmarketing analysis for Yasmin. Many of the cases of hyperkalemia in the clinical studies were documented as false elevations due to hemolysis. The symptoms of subjects that might be secondary to hyperkalemia were not associated with elevated blood levels of potassium.

The discontinuation rate due to adverse events in the 24-day regimen studies of YAZ (studies 303740, 301888, 304049, 305141, 306820, 306996, 308020 and 308021) was 6.3% (187 out of 2,941 subjects). This discontinuation rate is comparable to the findings in other clinical studies of combination oral contraceptives.

In the YAZ 24-day regimen pivotal contraceptive 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.

In Study 308021 (large European contraceptive trial, final report August 8, 2006), the adverse events contributing to the greatest number of drug-related discontinuations were metrorrhagia (11 incidents, 1.0% of subjects) headache (10 incidents, 0.9% of subjects) followed by nausea (0.3%), weight increase (0.3%) and amenorrhea (0.4%). All of these events are known side effects of combination oral contraceptives.

1.3.4 Dosing Regimen and Administration

The dosing regimen proposed is DRSP 3 mg/EE 20 μg, administered once daily in tablet form for 24 days, followed by 4 days of inert tablets.

1.3.5 Drug-Drug Interactions

Drug-drug interaction studies were discussed in the first cycle review of NDA 21-873, dated January 20, 2006. There was no evidence of interaction between DRSP 3 mg/EE 20 μg and omeprazole, used as a marker substrate for the CYP2C19 enzymes. Two studies investigating potential interaction with CYP3A4 marker surrogates reached differing conclusions; one (using simvastatin) was unable to rule out a potential interaction and one (using midazolam) found no evidence of interaction.

1.3.6 Special Populations

Race
The population in the combined PMDD studies was over 75% Caucasian; no efficacy or safety analyses of racial subgroups were conducted.

Gender & Pediatrics
The proposed indication is for postmenarchal females; as such, it is not anticipated that the drug will be used in prepubertal females or in men.

Renal and Hepatic Impairment
Subjects were generally healthy; in fact, women with diabetes, liver disease or cardiovascular disease were specifically excluded. In addition, women with laboratory values that would suggest hepatic or renal dysfunction were excluded; therefore the effect of DRSP/EE on patients with such concomitant conditions cannot be assessed from the population studied. The proposed labeling would contraindicate DRSP/EE in women with hepatic dysfunction and renal impairment, as does the current Yasmin label.

2 INTRODUCTION AND BACKGROUND

2.1 PRODUCT INFORMATION

Drospirenone (DRSP) is a 17-alpha-spironolactone derivative with progestational, antimineralocorticoid and antiandrogenic properties. The active estrogen moiety in this product is ethinyl estradiol (EE), which is complexed with β-Cyclodextrin clathrate to protect against degradation.

2.2 CURRENTLY AVAILABLE TREATMENT FOR INDICATIONS

Three drugs, all selective serotonin-reuptake inhibitors (SSRIs), (fluoxetine [Sarafem®], paroxetine [Paxil®] and sertraline [Zoloft®]) are marketed in the US for the treatment of PMDD. Recommended dose regimens include either daily dosing throughout the menstrual cycle or dosing limited to the luteal phase of the cycle. The Cochrane Database of Systematic Reviews[1] concluded that there is "very good evidence to support" the use of SSRIs in treatment of PMDD.

Oral contraceptives are also used off-label for treatment of PMDD. However, the American College of Obstetrics and Gynecology (ACOG) recommended in 2000[2] that management strategies proceed in a stepwise manner, beginning with supportive therapy, including diet, exercise and nutritional supplements, then moving on to SSRIs as needed, with hormonal ovulation suppression, using oral contraceptives or gonadotropin releasing hormone (GnRH) agonists as third line agents.

2.3 AVAILABILITY OF PROPOSED ACTIVE INGREDIENT IN THE UNITED STATES

YAZ was approved for the primary indication, prevention of pregnancy, on March 16, 2006. Yasmin (also known as Yasmin 30), a combined oral contraceptive approved for marketing in the U.S. on May 11, 2001, contains the same two ingredients, although the EE dose is higher, 30 μg, and the product is administered as 21 days of active tablets followed by 7 days of placebo tablets.

2.4 IMPORTANT ISSUES WITH PHARMACOLOGICALLY RELATED PRODUCTS

YAZ shares all of the risks and benefits noted in the drug class of combination oral contraceptives. The most significant risks for oral contraceptives are the rare thromboembolic events that may occur. In addition, the drospirenone-containing oral contraceptives have a potential for development of hyperkalemia. However, this has not proven to be a significant safety issue either in the clinical trials or postmarketing analyses to date.

2.5 REGULATORY ACTIVITY

The regulatory history of the development of the product for a PMDD indication is detailed in the first cycle review of January 20, 2006. The initial application for this secondary indication received an approvable action on January 23, 2006, pending:

- Review of safety data submitted on December 2, 6, and 9, 2005 and January 10, 2006, which were not reviewed in the initial review cycle
- Submission of acceptable labeling for both the Package Insert and the Patient Package Insert
- Additional education and training activities related to ensuring the appropriate use of YAZ in the target population

A Type "A" meeting was held with the Applicant on February 27, 2006, to discuss the extent of requisite data submission to support a decision on approvability.

A Complete Response was submitted to the Division on March 1, 2006, containing proposed labeling, a proposal for training and educational activities to ensure the use of YAZ in the appropriate target population, and a safety update.

The Applicant submitted final reports for the European contraceptive studies 308020 and 308021 on August 8, 2006. A notice of NDA review extension was submitted to the Applicant on August 25, 2006 to allow for a safety review of these large final study reports.

2.6 OTHER RELEVANT BACKGROUND INFORMATION

As noted, YAZ was approved for the primary indication, prevention of pregnancy, on March 16, 2006.

3 SIGNIFICANT FINDINGS FROM OTHER REVIEW DISCIPLINES

3.1 CMC (AND PRODUCT MICROBIOLOGY, IF APPLICABLE)

In the first cycle review, the DMFs referenced by the Applicant for DRSP, EE and β-cyclodextrin clathrate were found to be adequate by the Chemistry Reviewer, Dr. Donna Christner. She recommended approval at that time, pending submission of acceptable labeling. In her review of the Complete Response, dated August 4, 2006, she states:

> *Acceptable labeling has been submitted and NDA 21-873 can be approved from a CMC standpoint.*

3.2 ANIMAL PHARMACOLOGY/TOXICOLOGY

The Pharmacology/Toxicology reviewer, Dr. Krishan Raheja, recommended approval of NDA 21-873 in the first cycle, based on the similarity in composition and intended treatment populations to the Applicant's previously approved product, Yasmin. In his review of the Complete Response, dated May 17, 2006, he states:

> *Based on review and approval of NDA 21-098 for Yasmin, Pharmacology recommends approval of NDA 21-873 for YAZ.*

4 DATA SOURCES, REVIEW STRATEGY, AND DATA INTEGRITY

This section was fully discussed in the first cycle review, dated January 20, 2006.

5 CLINICAL PHARMACOLOGY

The Human Pharmacokinetics and Bioavailability section of NDA 21-873 was cross-referenced to NDA 21-676. The initial submission of NDA 21-676 for the oral contraceptive indication was found acceptable by the Clinical Pharmacology reviewer in 2004. No new pharmacokinetic or pharmacodynamic studies were submitted in NDA 21-873; studies from NDA 21-676 were cross-referenced. In her review of the Complete Response, dated August 7, 2006, Dr. Ameeta Parekh, Clinical Pharmacology Team Leader states:

> *Labeling for YAZ is acceptable and no further action is indicated from Clinical Pharmacology perspective.*

6 REVIEW OF EFFICACY

No new efficacy data were submitted in the Complete Response. Efficacy is discussed in detail in the first cycle review dated January 20, 2006. The Medical Reviewer's conclusion at that time was:

> *The reviewer concurs that the results of Studies 304049 and 305141 provide evidence of the efficacy of DRSP/EE in treating symptoms of PMDD.*

7 REVIEW OF SAFETY

The current safety review is focused on the following submissions listed by date:

The submissions referenced in the approvable letter of January 23, 2006

- December 2, 2005 (containing Tables for YAZ-Mercilon comparative study 308020; clinical study reports and datasets for two acne studies, 306996 & 306820)
- December 6, 2005 (containing appendices, except appendix #3 for the two acne studies, 306996 & 306820; tables from a preliminary analysis of a large safety and efficacy European contraceptive study 308021)
- December 9, 2005 (containing appendix #3 for the two acne studies, 306996 & 306820)
- January 10, 2006 (containing updated safety information on Yasmin)
- March 1, 2006 (containing a safety update covering the period from February 22, 2005 through January 23, 2006)

Subsequent submission

- August 8, 2006 (containing final study reports on the YAZ-Mercilon comparative study 308020 and Study 308021; and a safety update covering the period from January 23, 2006 through August 7, 2006)

The key safety data submitted up through early March of 2006 was reviewed and discussed in the March 16, 2006 review of NDA 21-676. This included the safety data from the draft report of study 308020 and preliminary data from study 308021. The final study reports for these two studies are reviewed for this present submission.

The original review, dated January 20, 2006, contains a detailed discussion of the safety data from the two clinical trials submitted in support of the PMDD indication. The Medical Reviewer's conclusion in the Safety Summary in the first cycle review of NDA 21-873 was:

There were no signals of concern in regard to the occurrence of SAEs [serious adverse events] or changes in vital signs or laboratory evaluations associated with DRSP/EE. Selected adverse events of particular relevance to this product are: intermenstrual bleeding and menorrhagia, nausea, breast pain, decreased libido, emotional lability, and migraine, all of which occurred with at least twice the frequency in the subjects exposed to DRSP/EE as compared to placebo and were considered to be drug-related. As noted previously, most of these events are known to be associated with oral contraceptive use, and are labeled in the Yasmin label.

Postmarketing pharmacoepidemiologic surveillance data for Yasmin were discussed in the first and second cycle reviews of NDA 21-676, dated November 16, 2004 and March 16, 2006, respectively. The final reports of the two pharmacoepidemiologic studies are summarized in Section 7.1.17 of the current review.

7.1 METHODS AND FINDINGS

Data presented from these various studies are not integrated, but are presented individually by safety category and indication.

7.1.1 Deaths

Two deaths in subjects using Yaz occurred in Study 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 on [redacted]. 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 [redacted]. 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. In the final study report for Protocol 308021 there are no additional deaths and no new information on either of these deaths to suggest any relationship to study drug. The total number of deaths in all of the YAZ studies is 4. The other two deaths occurred in the pivotal contraceptive study 303740 which was reported in the NDA 21-676 reviews. Neither of these deaths was drug related. One was secondary to pesticide poisoning and the other was secondary to smoke inhalation in an apartment fire.***

7.1.2 Other Serious Adverse Events

Contraception Trials

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).

Medical Officer's Comment:

- ***There were no changes to the serious adverse events in the final study report.***

Protocol 308021 - In the data submitted by the Applicant on August 8, 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 1.

Table 1: 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 x 2	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/ Laparoscopy	No	Resolved
2737	Multiple sclerosis/ Paresthesia	No	Not Resolved
2868	Breast fibroadenoma	Unlikely	Resolved
3250	Murder	No	Fatal
3295	Unilateral blindness	No	Residual effects
3308	Salmonellosis	No	Residual effects

Source: Final study report for Protocol 308021 in study report A30713, page 70

Medical Officer's Comment:

- ***The deaths listed above 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 (Phase 3 acne study), 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 (Phase 3 acne study), there was one serious adverse event (depression) in the YAZ regimen arm and one serious adverse event in the placebo arm (appendicitis). The serious adverse event of depression in the YAZ arm was considered by the Applicant to be unrelated to drug. It occurred at Day 10 in the study.

Medical Officer's Comment:

- ***This depression event may have been related to treatment with YAZ***

7.1.3 Dropouts and Other Significant Adverse Events

Contraception Trials

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 irregular bleeding (4 of 229 or 1.7%); headache (3 of 229 or 1.3%); mood changes (3 of 229 or 1.3%).

Medical Officer's Comment:

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

Protocol 308021. There were 69 volunteers (6.3%) with 92 AEs (8.8%) which led to withdrawal of study medication and premature discontinuation from the study. The most common adverse events leading to discontinuation in Study 308021 are listed in Table 2.

Table 2: Adverse Events Leading to Subject Discontinuation in Study 308021 (for 3 or more subjects)

MedDRA TERM	Total N= 1101	
	Subjects (n)	(%)
Metrorrhagia	11	1.0
Headache	10	0.9
Nausea	5	0.5
Weight increased	5	0.5
Amenorrhea	4	0.4
Breast discomfort	3	0.3
Breast pain	3	0.3
Vaginal bleeding	3	0.3
Hypertension	3	0.3

Source: Applicant's March 3, 2006 submission and study report A30713 page 71 of 1058.

Medical Officer's Comment:

- ***The level of metrorrhagia for this product is similar to or less than that of other oral contraceptives. Only 1% of subjects discontinued for metrorrhagia.***

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).

Medical Officer's Comment:

- ***The adverse events leading to discontinuation in the acne studies are no different than those found in all oral contraceptives.***

7.1.5 Common Adverse Events

Contraception Trials

Protocol 308020 - In protocol 308020 (comparative Study with Mercilon), the most common AEs (≥ 5% of all volunteers) are listed in Table 3.

Table 3: 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	21	9.2	16	7.3
Influenza	14	5.2	15	5.9
Cystitis	7	3.1	14	5.0

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

Protocol 308021 – A listing of frequently occurring common adverse events is found in Table 4.

Table 4: Study 308021 – Most Frequently Reported Adverse Events (> 1% of subjects; total N = 1101)

Most Frequent AEs MedDRA Term	N	%
Metrorrhagia	95	8.6
Vaginal infection	56	5.1
Amenorrhea	54	4.9
Vulvovaginal mycotic infection	48	4.4
Headache	47	4.3
Vomiting	37	3.4
Diarrhea	32	2.9
Cystitis	26	2.3
Vaginal candidiasis	24	2.2
Breast pain	19	1.7
Nasopharyngitis	16	1.6
Nausea	18	1.6
Cervical dysplasia	16	1.4
Cervical smear abnormal	15	1.4
Influenza	13	1.2

Source: Finalized study report for Protocol 308021, page 65 from Report A30713 submitted August 8, 2006

Medical Officer's Comment:

- ***The level of metrorrhagia for this product is similar to the findings for other oral contraceptives. Only 1% of subjects discontinued for metrorrhagia. The most common adverse reaction is actually vaginitis (when the individual terms are added). Vaginitis, especially yeast infections, has been associated with oral contraceptive use in some patients.***

Acne Studies

Protocol 306996 - In Study 306996, common adverse events were defined as those occurring in ≥2% of the subjects. The four most frequently reported AEs in the YAZ group were upper respiratory infection (25 [9.3%] subjects), metrorrhagia (25 [9.3%] subjects), suspicious Pap smear (15 [5.6%) subjects), and headache (14 [5.2%] subjects). The four 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 306820, common AEs were defined as those occurring in ≥2% of subjects. The four 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 five most common AEs in the placebo group were upper respiratory infection (25 [9.3%] subjects), vaginal moniliasis (12 [4.5%] subjects), suspicious Pap smear (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.***

7.1.7 Laboratory Findings

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.

Contraception Studies

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 five of 229 (2.2%) women in the YAZ group and in five of 220 (2.3%) subjects in the Mercilon group. Of the 10 subjects with elevated potassium, only two had elevated values on treatment (one each in the YAZ and Mercilon treatment groups, respectively). In the YAZ group, the on-treatment serum K+ 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 308021 – Potassium levels were not assessed in this study.

Acne Studies

In the combined data from the two Phase 3 acne studies (YAZ vs. placebo in both), 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 six cardiovascular events identified by the Applicant as possibly related to hyperkalemia. There were no reported cases of four of the six potassium related cardiovascular events (arrhythmia, bradycardia, syncope or tachycardia) in either treatment group. The remaining two events (dizziness and palpitations) occurred in five 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 one post-baseline sodium value below the lower reference range, two each in the YAZ group and the placebo group.

7.1.17 Postmarketing Experience

The final study reports for the Ingenix and EURAS postmarketing pharmacoepidemiologic surveillance studies on Yasmin were submitted to NDA 21-098 in February and June, 2006, respectively, and reviewed by Dr. Lesley Furlong in the Division of Reproductive and Urologic Products. The principal summary comments are as follows:

Ingenix Study

One goal of the Ingenix study was to evaluate the extent of prescription to patients with underlying renal, hepatic or adrenal impairment. Dr. Furlong concluded:

The data show that inappropriate prescribing occurs, but the study did not detect a difference in inappropriate prescribing of Yasmin compared to other OCs.

Regarding compliance with potassium monitoring in subjects concomitantly using a drug that predisposes to hyperkalemia, Dr. Furlong concluded:

The study detected very modest trends toward

- *Fewer Yasmin dispensings among women receiving concurrent therapy with drugs that predispose to hyperkalemia*
- *Increased compliance with potassium monitoring in subjects taking Yasmin [as compared to other OCs, although monitoring was conducted in only 40% of such patients]*

This study also used a database to evaluate all patients prescribed Yasmin for subsequent outcomes including death, hospitalization, hyperkalemia, electrolyte disturbances and other possible sequelae of hyperkalemia, and thromboembolic events. Nine deaths occurred, none involving hyperkalemia or thrombotic events. Dr. Furlong concluded:

The study did not detect an increased risk for users of Yasmin compared to users of other OCs for any of the outcomes evaluated.

Finally, the Ingenix study evaluated pregnancy outcomes in infants of women exposed to Yasmin. Dr. Furlong concluded:

The prevalence of congenital anomalies is consistent with historical data for the general population, and the study did not identify a particular organ system or pattern of congenital defects. The study did not detect a teratogenic effect of oral contraceptives.

Overall, Dr. Furlong concluded that:

The Ingenix study did not detect any safety concerns that differentiate **Yasmin** *from other oral contraceptives.*

EURAS Study

Dr. Furlong's summary of the final report of the EURAS was:

The European Active Surveillance Study (EURAS) compared the incidence of certain adverse events among Yasmin users, users of levonorgestrel-containing oral contraceptives, and users of oral contraceptives containing other progestins. EURAS did not detect an increased incidence of adverse events among Yasmin users for any of the outcomes studied. In particular, Yasmin users did not have an increased risk for death or cardiovascular events compared with users of other oral contraceptives (OCs).

7.2.2 Description of Secondary Clinical Data Sources Used to Evaluate Safety

7.2.2.1 Other studies

Studies 306820 and 306996 were conducted to support a secondary indication of treatment of acne. Studies 308020 and 308021 were additional studies of 24-day oral contraception regimens.

7.2.2.2 Postmarketing experience

YAZ has not yet been marketed outside the U.S., where it was launched in April, 2006. The postmarketing surveillance study specific for YAZ is discussed in Section 7.2.9 and 9.3.2. Results of the first periodic adverse events report for YAZ are discussed in Section 7.2.9. Postmarketing experience with the related product, Yasmin, is discussed in Section 7.1.17.

7.2.2.3 Literature

No additional clinical literature reports were submitted in this cycle.

7.2.9 Safety Update

Clinical Studies

The reporting interval for this Safety Update is January 23, 2006 through August 7, 2006. These dates correspond to the cut-off date for inclusion of data into the previous Safety Update for this NDA.

There were no US or foreign clinical studies ongoing with YAZ Tablets during the reporting period and therefore no new safety information to report from clinical studies.

Literature

The Applicant identified no new safety information in the literature that may reasonably affect the statement of contraindications, warnings, precautions and adverse reactions in the YAZ labeling.

Approvals and Marketing

DRSP 3 mg and EE 0.02 mg Tablets have only been marketed in the USA to date. A cumulative table of the approvals granted to date is provided below (see Table 5). During the reporting interval, new approvals for the 21-day dosing regimen were granted in Argentina, Austria, Czech Republic, Denmark, Estonia, Finland, France, Germany, Hungary, Iceland, Ireland, Latvia, Lithuania, Malta, Norway, Portugal, Slovakia, Sweden, Switzerland, and the USA. Note: The Netherlands is the only country that obtained approval prior to the reporting period of this Safety Update.

Table 5: Listing of Approvals for YAZ

Country	24+4 Tablets Approval Date	21 Tablets Approval Date	21+7 Tablets Approval Date
Argentina		29 Mar 2006	
Austria		26 May 2006	
Czech Republic		07 Jun 2006	
Denmark		27 Jun 2006	
Estonia		18 May 2006	
Finland		19 Jun 2006	
France		10 Jul 2006	
Germany		04 Jul 2006	
Hungary		17 May 2006	
Iceland		14 Jun 2006	
Ireland		24 Jul 2006	
Latvia		05 Jul 2006	
Lithuania		10 Jul 2006	
Malta		04 Aug 2006	
The Netherlands		04 Aug 2005	17 Nov 2005
Norway		27 Jun 2006	27 Jun 2006
Portugal		04 Jul 2006	
Slovakia		30 June 2006	
Sweden		21 Jul 2006	21 Jul 2006
Switzerland		22 Feb 2006	
USA	16 Mar 2006		

Source: Safety Update, August 8,2006 submission, pages 4-5