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APPLICATION NUMBER:

22-045

MEDICAL REVIEW

CLINICAL REVIEW

Application Type: NDA
Submission Number: 22-045
Submission Code: 0000

Letter Date: March 24, 2006
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Reviewer Name: David Kettl, MD
Review Completion Date: December 12, 2006

Established Name: Drospirenone 3 mg/ethinyl estradiol 0.02 mg tablets
(Proposed) Trade Name: Yaz
Therapeutic Class: Oral contraceptive
Applicant: Berlex Inc.

Priority Designation: S

Formulation: Tablets
Dosing Regimen: One tablet daily (24 days of active followed by 4 days of non-active tablets)
Indication: Moderate Acne Vulgaris
Intended Population: Women ≥ 14 years of age, who have achieved menarche, who have no known contraindications to oral contraceptives, desire contraception,

Table of Contents

1. EXECUTIVE SUMMARY

1.1 Recommendation on Regulatory Action

This reviewer recommends that YAZ (drospirenone 3 mg/ethinyl estradiol 0.02 mg) be approved for the indication of moderate acne vulgaris in women seeking oral contraception

YAZ has been reviewed for the indications of contraception, PMDD (premenstrual dysphoric disorder), both under the Division of Reproductive and Urologic Products, and now for acne vulgaris. No safety concerns have been identified in any of these submissions that would preclude the approval of YAZ for the indication of moderate acne vulgaris in women ≥ 14 years of age, who have no known contraindications to oral contraceptive therapy, desire oral contraception, have achieved menarche, and are [redacted] There is adequate evidence of efficacy for this additional moderate acne vulgaris indication as well.

YAZ was approved for the primary indication of contraception on March 16, 2006, and the indication of PMDD on October 4, 2006.

1.2 Recommendation on Postmarketing Actions

Risk management for the acne vulgaris indication will be addressed through labeling, which will reinforce the contraception indication as primary and women should not consider YAZ as a primary acne treatment. Instructions specifically recommend that acne may respond to other treatments, and YAZ should used for the treatment of acne only if the patient desires an oral contraceptive for birth control [redacted]

1.2.1 Risk Management Activity

No additional risk management programs and post-marketing safety studies are recommended by this reviewer for YAZ beyond the current post-marketing surveillance already in place under the original NDA 21-676 for contraception in the Division of Reproductive and Urology Products (DRUP).

A large, prospective phase 4 post-marketing safety study is underway in the United States and Europe. The International Active Surveillance Study (INAS) will assess the risk of arterial and venous thromboembolic events in approximately 50,000 women over three years. Recruitment began in the U.S. following its market introduction in late April 2006. At the end of July 2006, more than 10,000 women have been enrolled into the study, including approximately 1,000 patients on YAZ.

1.2.2 Required Phase 4 Commitments

No additional phase 4 commitments are recommended by this reviewer.

1.2.3 Other Phase 4 Requests

No additional phase 4 requests are made.

1.3 Summary of Clinical Findings

Complete details of the prior submissions for contraception can be found in the reviews for NDA 21-676, and complete details for the indication of PMDD can be found in the reviews for NDA 21-873.

Two multicenter phase 3, randomized, double blind, placebo controlled, multicenter trials were conducted to evaluate the efficacy and safety of the DRSP/EE as compared to placebo in the treatment of acne vulgaris. This review will focus on the two acne studies, 306820, and 306996, submitted under this efficacy supplement submitted March 24, 2006.

1.3.1 Brief Overview of Clinical Program

The product, YAZ, was approved for the indication of oral contraception on March 16, 2006 under NDA 21-676. This submission seeks to propose an additional indication of moderate acne vulgaris in women seeking oral contraception.

Two phase 3 studies were performed to establish efficacy and safety in the acne population. In total, 1891 women were screened to enroll 1072 patients who were dispensed medication for six 28 day cycles. The 451 women who were exposed to YAZ comprise the primary efficacy population.

The safety database includes not only the 1072 patients in the YAZ studies for acne vulgaris, but also the safety data from the studies for the indication of oral contraception (NDA 21-676), and pre-menstrual dysphoric disorder (PMDD) (NDA 21-873).

1.3.2 Efficacy

The primary efficacy variables were percent change in inflammatory lesion counts, percent change in non-inflammatory lesion counts, percent change in total lesion counts, and percentage of subjects classified as clear or almost clear on a 6 point investigator global assessment scale.

In both studies, the results of all four efficacy variables demonstrated that YAZ was statistically significantly more effective than placebo in the treatment of acne vulgaris. At day 15 of Treatment Cycle 6, 15.4% of YAZ subjects reached success status based on the Investigator Static Global Assessment (ISGA) score versus 4.3% of placebo subjects in Study 306820 and in Study 306996, 21.1% of YAZ subjects reached success versus 8.9% of the placebo subjects.

YAZ subjects had a mean percent change at day 15 of Treatment Cycle 6 from baseline in inflammatory lesions of 47.6% while placebo subjects had a 32.2% change in Study 306820. In Study 306996, the percent change in inflammatory lesions of YAZ subjects was 50.6% versus 34.5% in placebo subjects. For non-inflammatory lesion counts, Study 306820 YAZ subjects had a 38.0% reduction while placebo subjects had an 18.2% reduction and in Study 306996, YAZ subjects had a 42.3% reduction versus 26.0% for placebo subjects.

All co-primary endpoints were statistically significant in both studies, with p-values less than 0.0003.

1.3.3 Safety

The safety assessment of YAZ based on all submitted data indicates that YAZ has an acceptable safety profile, and most adverse events seen in the acne studies are known to be associated with oral contraceptives and are labeled as such. There were no signals of concern in regards to the occurrence of adverse events or laboratory abnormalities associated with YAZ.

No deaths occurred in either acne study. There were no reports of thrombotic or thromboembolic adverse events in either study in the YAZ groups. One subject in each study reported a serious adverse event, (depression requiring hospitalization; pneumonia), but this reviewer concurs with the applicant assessment that the relationship of the study drug with the serious adverse events is unlikely.

Slightly more subjects (5.6% in the YAZ group compared to 3.9% in the placebo group) discontinued the study due to adverse events in the YAZ group compared to placebo, but the complaints of dysmenorrhea, metrorrhagia, and nausea are not unexpected with combination oral contraceptive use.

Specific attention was directed to cardiovascular events given the possible risk of hyperkalemia associated with the use of drospirenone, which is an analog of spironolactone and possesses antimineralocorticoid activity. No patient discontinued from the study due to cardiovascular adverse events. 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). There was no evidence that YAZ was associated with an increased risk of hyperkalemia in these two trials.

No subject with post-baseline serum potassium levels > 5.5 experienced any cardiovascular adverse events. There is no evidence in either study of significant adverse cardiovascular events being related to study medication.

In the acne trials, 59.5% of the YAZ treated subjects had at least one treatment emergent adverse event compared to 47.0% in the placebo group. The greatest difference between the YAZ and placebo groups was observed in metrorrhagia (9.9% versus 1.7%, respectively) and menorrhagia (3.0% versus 0.9%, respectively). Metrorrhagia and menorrhagia are known to be estrogen-dependent and frequently occur in women taking oral contraceptives. There were no treatment-emergent adverse events of severe intensity reported by $\geq 1\%$ of the subjects in either the YAZ or placebo group.

No significant hematology findings were attributable to the drug product. Both studies showed a small, but statistically significant difference in creatinine clearance at endpoint

when compared to baseline. The original NDA does not report any increased risk of renal impairment with DRSP/EE use. In fact, the changes in creatinine clearance for the DRSP/EE groups in those studies were less than the placebo arm. There were no clinically relevant changes in serum creatinine in either study. No changes to current labeling are suggested for these small changes in creatinine clearance demonstrated in these acne trials.

1.3.4 Dosing Regimen and Administration

The dosing regimen is DRSP 3 mg/EE 0.02 mg administered once daily in tablet form for 24 days, followed by 4 days of inert tablets, packaged in blister packs.

Dose ranging studies were not performed.

1.3.5 Drug-Drug Interactions

No new drug-drug interaction studies were performed for this submission.

No literature reports were found regarding interactions between YAZ and these acne products. In a study to evaluate the effect of oral minocycline on low dose oral contraceptives, minocycline-related changes in estradiol, progesterone, FSH and LH plasma levels, of breakthrough bleeding, or of contraceptive failure, could not be ruled out. Labeling should include a precaution that states that patients are advised to use a second form of contraception when treated with minocycline to avoid contraceptive failure.

1.3.6 Special Populations

The applicant's efforts to evaluate the effects of age, race and ethnicity were adequate in the two studies. There was no evidence of clinically significant effect for any of these parameters on safety or efficacy.

The findings for ISGA (pooled data and individual study findings) indicated that the highest percentage of women who had a rating of 'clear' or 'almost clear' on the ISGA assessment scale at endpoint were Caucasians in the YAZ subgroup compared with the respective placebo subgroup. In the subgroups of Blacks and Hispanics, the difference

between the YAZ and placebo groups in the percentage of women with a rating of 'clear' or 'almost clear' was smaller. The number of women in the Asian and Other subgroups was too small to make any meaningful conclusions.

The proposed indication is for post-menarchal females. This drug should not be used in prepubertal females or in men.

2. INTRODUCTION AND BACKGROUND

2.1 Product Information

The product, YAZ, was approved for the indication of oral contraception on March 16, 2006 under NDA 21-676. An indication for premenstrual dysphoric disorder (PMDD) was approved on October 4, 2006 under NDA 21-873. YAZ is an orally administered tablet for oral contraception, and this submission seeks to propose an additional indication of moderate acne vulgaris in women seeking oral contraception.

Each film coated tablet contains the estrogen ethinyl estradiol (EE) at a dose of 0.02 mg and the progestin drospirenone, (DRSP) at a dose of 3 mg. One YAZ tablet is administered daily for 24 days followed by one inert tablet daily for four days.

The combination of the drug substances DRSP and EE has previously been approved for the use in Yasmin film-coated tablets (3 mg DRSP and 0.03 mg EE). The first marketing authorization for Yasmin was granted in the Netherlands on March, 7, 2000 and the first launch was in Germany in November, 2000. By May, 2005, Yasmin had been approved in 90 countries, including all EU countries and the US, and the product has been launched in 74 countries worldwide.

Yasmin was approved in the United States on May 5, 2001, under NDA 21-098.

YAZ is a lower-dose formulation of Yasmin in which the reduced amount of EE is complexed with β-cyclodextrin [redacted] as the EE betadex clathrate to ensure shelf stability at low concentrations. The active estrogen moiety of this EE betadex clathrate is EE which rapidly dissociates from the β-cyclodextrin in aqueous media with a calculated dissociation half-life of 2.6 minutes. EE betadex clathrate is referred to as EE in this document. To date, YAZ has only been marketed in the United States.

2.2 Currently Available Treatment for Indications

Currently, two oral contraceptive products share an additional indication for acne vulgaris. Ortho Tri-Cyclen® [ethinyl estradiol 35 mcg in fixed combination with norgestimate 0.18, 0.215, or 0.25 mg], or Estrostep® [ethinyl estradiol 20, 30, or 35 mcg in fixed combination with norethindrone acetate 1 mg]) can be used for the treatment of moderate acne vulgaris in females 15 years of age or older who have no known contraindications to oral contraceptive therapy, desire contraception, have achieved menarche, and are unresponsive to topical anti-acne medication. The manufacturer of Estrostep® states that the drug should be used for the treatment of acne vulgaris only in women who desire oral contraception and plan to take the drug for at least 6 months.

2.3 Availability of Proposed Active Ingredient in the United States

YAZ is currently marketed for oral contraception in the United States and was approved on March 16, 2006.

Yasmin was approved in the United States on May 5, 2001, and contains 3 mg DRSP and 0.03 mg EE. Yasmin 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 in any of the clinical trials or post-marketing analyses to date.

2.5 Presubmission Regulatory Activity

In the first review cycle for prevention of pregnancy with YAZ (NDA 21-676), the applicant received an Approvable Action. The applicant was asked to demonstrate that

there was added clinical benefit for the 24-day active dosing regimen compared to a 21-day active dosing regimen.

The 17 November 2004 Approvable letter stated: "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.

In the applicant's complete response of June 15, 2005 for NDA 21-676, they chose to provide additional evidence of benefit for the 24-day regimen by providing a final study report for protocol 308382 that indicates more ovarian suppression with the 24-day regimen compared to the 21-day regimen. Although this study was not powered or designed to show more escape ovulations than in the 21-day dosing regimen, DRUP accepted the design of protocol 308382 as providing potential supportive evidence for the justification of the 24 day dosing regimen.

The applicant also provided a safety update and commitments in the June 15, 2005 submission to (a) apply a risk management program for YAZ similar to Yasmin and (b) conduct a large, adequately powered post-marketing surveillance study to compare the incidence of serious thrombotic and thromboembolic events in users of this product to that in users of other combination oral contraceptives that do not contain drospirenone.

Based on the review of the complete response of June 15, 2005, the product was approved on March 16, 2006 for the indication of oral contraception.

An End of Phase 2 meeting was held with the applicant and the Division of Dermatologic and Dental Products on September 4, 2002. Endpoint success for the acne indication was reviewed, and the studies were conducted with success in both primary variables: a static investigator global assessment (IGA), as well as change in at least two of three lesion counts (total, inflammatory, and non-inflammatory). The applicant was informed that acne would not be a stand-alone indication, and this efficacy supplement could not be submitted prior to approval from the DRUP.

A pre-NDA meeting was scheduled for November 10, 2005, with DDDP, but was cancelled by the applicant November 9, 2005 upon receipt of the draft reviewer comments.

2.6 Other Relevant Background Information

The 21-day regimen of 3 mg DRSP / 0.02 mg EE (marketed under the name Yasminelle) has been marketed in Europe, in Austria, Czech Republic, Finland, France, Germany, Ireland and Switzerland. To date, YAZ, the 24 day product, has only been marketed in the United States.

3. SIGNIFICANT FINDINGS FROM OTHER REVIEW DISCIPLINES

The Pharm/Tox review states: "The nonclinical database associated with the approved NDA 21-676 adequately addresses the nonclinical issues associated with NDA 22-045. There are no unresolved non-clinical issues."

4. DATA SOURCES, REVIEW STRATEGY, AND DATA INTEGRITY

4.1 Sources of Clinical Data

The sources of clinical data include:

- Original submission for NDA 22-045, for the acne vulgaris indication, was the primary source of clinical data used in this review
- Original submission for NDA 21-676, and the DRUP review of March 14, 2006 for the oral contraception indication
- Original submission for NDA 21-873, and the DRUP review of September 28, 2006, for the premenstrual dysphoric disorder indication
- Additional efficacy and safety information submitted at the request of the Division during the review process.

4.2 Tables of Clinical Studies

Overview of Phase 3 clinical studies to evaluate the efficacy of YAZ in the treatment of moderate acne vulgaris, with each cycle equaling 28 days of therapy:

Clinical Review Table 1
Overview of phase 3 clinical studies for acne vulgaris indication

Study	Study Period	Enrollment (Modified Population)			Enrollment (Amended ITT)		
		YAZ	Placebo	Total	YAZ	Placebo	Total
306820	1/13/03 – 7/15/04	228	230	458	229	227	456
306996	1/23/03 – 6/22/04	218	213	431	222	215	437

Efficacy was demonstrated at Day 15 of the sixth treatment cycle (approximately after 155 days of treatment).

4.3 Review Strategy

Both phase 3 acne trials were reviewed with regard to efficacy and safety.

4.4 Data Quality and Integrity

In study 306820, pooled site 6 [redacted] showed a large treatment effect. Data was reanalyzed with this center excluded, and was still found to statistically significant.

No study site investigations by the Division of Scientific Integrity were performed.

4.5 Compliance with Good Clinical Practices

The applicant affirmed that the conduct of clinical studies met all local legal and regulatory requirements. The studies were conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki and the International Conference on Harmonization (ICH) guideline E6: Good Clinical Practice (GCP).

4.6 Financial Disclosures

The applicant certified in form 3454 that they had not entered into any financial arrangements any of the clinical investigators.

5. CLINICAL PHARMACOLOGY

The Human Pharmacokinetics and Bioavailability section 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 22-045.

6. INTEGRATED REVIEW OF EFFICACY

6.1 Indication

The proposed indication for YAZ is for the treatment of moderate acne vulgaris in females ≥ 14 years of age, who have achieved menarche, who have no known contraindications to oral contraceptives, desire contraception

6.1.1 Methods

The clinical efficacy of YAZ in the treatment of moderate acne vulgaris is based on the data of two independent, randomized, placebo controlled multicenter clinical phase 3 studies. Endpoint and study design agreements were made in response to a Special Protocol Assessment by the Agency dated December 12, 2002.

6.1.2 General Discussion of Endpoints

The primary efficacy variables were the percent change from baseline to endpoint [i.e. day 15 of cycle 6 data with missing values replaced in accordance with the last observation carried forward (LOCF) procedure] in inflammatory lesion counts (including papules, pustules, and nodules), non-inflammatory lesion counts (including open and closed comedones) and total lesion counts, as well as the percent of subjects classified as '0' (clear skin) or '1'(almost clear skin) on the 6-point Investigator Static Global Assessment (ISGA) scale.

The secondary efficacy variables were the change from baseline in the count of papules, pustules, nodules, open comedones, and closed comedones, and the percentage of subjects showing improvement according to the Investigator's Overall Improvement Rating, and classifying themselves as improved on the Subject's Overall Self-assessment Rating. Further variables were the change from baseline to cycle 6 in the Ferriman-Gallwey hirsutism scale score for upper lip and chin. In study A25083, the change from baseline to cycle 6 in total testosterone, free testosterone, dehydroepiandrosterone sulfate (DHEAS), androstenedione and SHBG was also assessed for a subgroup of women.

The secondary endpoints for hirsutism and hormonal changes were not reviewed since the proposed indication was for acne vulgaris.

In discussions with the Agency (FDA response to Special Protocol Assessment; December 12, 2002), it was clarified by the Agency that 'success' for YAZ would be, if the percent change from baseline to treatment endpoint (i.e. cycle 6 data with missing values replaced in accordance with the LOCF procedure) was statistically significantly greater in at least 2 of the 3 lesion counts (inflammatory, non-inflammatory or total lesion counts), and that the percent of subjects classified as 'clear' or 'almost clear' on the ISGA at treatment endpoint was statistically significantly greater in the YAZ group.

At a follow-up guidance meeting on February 4, 2003, the Agency requested that oral contraceptives should not be indicated for —— acne vulgaris and the proposed indication should be "moderate acne vulgaris". The applicant amended the inclusion criteria early in the study course to change the inclusion lesion counts from 10-100 non-inflammatory (comedones), 10-50 inflammatory lesions (papules or pustules) and not more than 5 nodules with an ISGA score of 2 and above. The revised inclusion criteria were a minimum of 40 lesions with at least 20 inflammatory and 20 non-inflammatory lesions with not more than 3 nodules on the face with an ISGA score of 3 or above. The ISGA score was also amended from a 5 point scale to a 6 grade scale.

Due to these changes in inclusion criteria to study "moderate" acne, as opposed to "mild to

moderate acne", the Agency analysis was modified to include only those subjects which met the "moderate" criteria. Thus the efficacy data presented by the applicant will differ slightly from this modified population as analyzed by the Biostatistics reviewer, Dr. Kim.

There were 4 subjects in Study 306820 and 6 subjects in Study 306996 that were included in the applicant's efficacy analyses with an ISGA score of 2 measured using the 5-point ISGA scale prior to the Agency's request. The applicant's efficacy analysis of Study 306820 also excluded 6 subjects who had baseline inflammatory lesion counts of 20 or 21. In this review, only the population with "moderate acne criteria" will be reported and recommended for labeling.

6.1.3 Study Design

Both studies utilized a multicenter, double-blind, randomized, placebo controlled design to evaluate the safety and efficacy of DRSP/EE as an acne therapy in female subjects with moderate acne vulgaris. A total of 451 YAZ patients and 442 placebo subjects comprised the amended full analysis set. Each group was treated for 6 treatment cycles. In each treatment cycle, the participants took 1 tablet containing active substance daily for 24 days followed by a 4-day inert tablet, or 28 placebo tablets (in identical-appearing blister packs containing color-matched, inert tablets).

Studies 306820 and 306996 had the same inclusion, exclusion and withdrawal criteria:

Women who met all of the following criteria were included in the study:

- Age 14 to 45 years (inclusive), $\geq$ 1 year post-menarche. If a subject is a heavy smoker (>10 cigarettes per day) inclusion was possible if she was not older than 30 years; subjects that smoked less than 10 cigarettes per day could have been included up to the age of 35 years
- Subjects with a minimum of 40 lesions with at least 20 inflammatory lesions (papules or pustules), 20 non-inflammatory lesions (comedones), not more than 3 small inactive nodules and who would not be classified as Grade 0, 1, or 2 on the ISGA scale
- Normal Pap smear within the last 6 months. For an "atypical squamous cells of undetermined significance" (ASCUS) Pap, Human Papilloma Virus (HPV) testing was performed. Either a negative HPV test or a benign subtype was required for inclusion in the study. Subjects with Pap smear results worse than low grade squamous intraepithelial lesions (LGSIL) were excluded from the study.
- At least 1 menstruation during the last 3 months before screening
- Negative pregnancy test at screening and randomization

- Able to use nonhormonal methods of contraception during the study period
- Agree to avoid any topical or systemic acne treatment
- Cosmetics, moisturizer, and facial cleanser could have been used if they were noncomedogenic
- Signed informed consent prior to screening procedures

A subject presenting with any of the following were excluded from the study:

- Pregnancy, lactation
- Not less than 3 months after delivery, abortion, or lactation prior to the start of treatment
- Washout periods before initial acne lesion count not observed:
  To guarantee stable baseline conditions, the following washout periods have to be observed before the initial acne lesion count:
  - Three months free of contraceptive implants (e.g., Norplant) or hormonal contraceptive intrauterine devices/systems (e.g., Mirena)
  - Two months free of oral contraceptives
  - Six months free of systemic isotretinoin (e.g., Accutane) or injectable contraception (e.g., Depo-Provera)
  - Eight weeks free of other systemic ethical anti-acne agents (e.g., antibiotics)
  - Four weeks free of topical retinoids
  - Two weeks free of other topical anti-acne agents (e.g., topical antibiotics, benzoyl peroxide)
- Vascular or metabolic disease including existing or previous arterial thromboembolic diseases (myocardial infarction, stroke), existing or previous venous thromboembolic diseases (deep vein thrombosis, pulmonary embolism), and any condition which could increase the risk to suffer any of the above mentioned disorders
- Any disease or condition that could compromise the function of the body systems and could result in altered absorption, excessive accumulation, impaired metabolism, or altered excretion of the study medication
- Any disease that may worsen under hormonal treatment or might interfere with the conduct of the study or the interpretation of the results (e.g., herpes gestationis or idiopathic icterus during a previous pregnancy; middle-ear deafness (otosclerosis); Sydenham's chorea, porphyria, disturbances in the bile flow (presence or history of cholestasis, gallstones, systemic lupus erythematosis)
- Liver diseases: Presence or history of severe hepatic diseases including benign or malignant tumors and/or clinically significant abnormal liver function tests
- Other diseases: Chronic inflammatory bowel disease (Crohn's disease or ulcerative colitis), hemolytic uremic syndrome, migraine with focal neurologic symptoms (complicated migraine), epilepsy, asthma with chronic use of oral corticosteroids, multiple sclerosis, chorea minor, tetany, leiomyomatous uterus confirmed by ultrasound, endometriosis, mastopathy, current or history of clinically significant premenstrual dysphoric disorder (PMDD)

- Uncontrolled thyroid disorders
- Dyslipoproteinemia
- Pancreatitis or a history thereof if associated with severe hypertriglyceridemia
- Uncontrolled arterial hypertension (confirmed systolic blood pressure ≥140 mmHg or confirmed diastolic blood pressure ≥90 mmHg
- Diabetes mellitus with vascular involvement
- Sickle-cell anemia
- Current or history of clinically significant depression
- Use of additional steroid hormones, heparin, coumarin, hydantoins, barbiturates, phenytoin, primidone, carbamazepine, rifampicin, griseofulvin, topiramate, felbamate, ritonavir and products containing St. John's wort, spironolactone, and continuous use of antibiotics
- Undiagnosed vaginal bleeding
- Known or suspected malignant or pre-malignant disease
- History of steroid hormone dependent malignancy
- Abnormal clinically significant findings during gynecological examination that could have, in the opinion of the principal investigator, worsened with oral contraceptives
- History of alcohol or drug abuse within the last 2 years
- Participation in another clinical study within 1 month or use/intake of an investigational drug within the last 3 months prior to study entry
- Abnormal baseline laboratory values that were considered to be clinically significant by the principal investigator
- Hypersensitivity to any of the drug ingredients
- Substantially overweight (body mass index [BMI] > 35 kg/m^2)
- Subjects on daily, long-term treatment of angiotensin-converting enzyme (ACE) inhibitors, angiotensin II receptor antagonists, potassium-sparing diuretics, aldosterone antagonists, and non-steroidal anti-inflammatory drugs (NSAIDs) for chronic conditions or diseases

Specific dermatologic exclusion criteria:

- Subjects with acne and atopy, comedonal acne or acne conglobata, sandpaper acne or acne with multiple large nodes, cysts, fistular comedones, or abscessing fistular ducts
- Use of comedogenic covering cream, comedogenic sunscreens, other sex hormone preparations or any other anti-acne therapy (e.g., light therapy, oleic acids, chemical peelings, mechanical extraction of comedones)
- Preparations that have had an acne-inducing effect, e.g., iodinated or bromated drugs, tuberculostatics, lithium, Vitamin B1 (>1.5 mg daily), B6 (>2 mg daily), B12 (>6 g daily), corticoids, andrenocorticotropic hormone (ACTH), anabolics, quinine, disulfiram, methoxypsoralene, phenobarbital, phenytoin, trimethadione, thyroid depressants, and certain oily cosmetics

Withdrawal Criteria:

- First signs of venous inflammation or blood clots (thrombosis, embolism), i.e., unusual pain or swelling in the legs, stabbing pain on breathing or cough of unknown origin, pain or the sensation of chest constriction, before scheduled operations (6 weeks beforehand), and prolonged immobility (i.e., after accidents)
- Headache occurring for the first time in the form of migraine or more frequently with unusual severity
- Sudden sensory disturbances (visual, auditory, etc.)
- Motor disturbances (particularly paralysis)

  In the above-mentioned cases, an increased risk of blood clot formation could have existed
- Pregnancy
- Repeated, excessive, persistent intracyclic bleeding
- Clinically significant increase in blood pressure
- Clinically significant increase in serum potassium
- Occurrence of liver inflammation, jaundice, itching over the entire body, disturbances of bile drainage (cholestasis), and unusual liver function values
- Occurrence of epileptic seizures while on the medication
- Withdrawal of consent

Blinding:

Neither the subject nor the investigator knew the identity of the study medication assigned. Each subject kit containing the study medication had a 2-part, tear-off label affixed to the box. The tear-off part, which contains a blinded area, was affixed to the appropriate page in the CRF. The label was blinded with a laminate overlay that could be scratched off to reveal treatment group information to which the subject had been assigned. The blinded area was not to be revealed unless required in a medical emergency when knowledge of the respective treatment may have influenced medical care. Breaking the code automatically disqualified the subject from further study participation. The medical monitor was informed immediately if the code was broken for a medical emergency. In this case, each scratched off blind label bore the date, and reason as well as the name and signature of the person who had opened it.

The study remained blinded until database lock and authorization of data release by the study manager according to standard operation procedures (SOPs).

Both studies used a similar schedule of evaluations, shown on the following page:

Clinical Review Table 2
Study Schedule of Evaluation Visits

	Screening & Baseline/Randomization		Treatment (count cycle days from start of medication)			Follow-up
	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5[a]	Visit 6[a]
	Screening	Baseline/ Randomization	Cycle 1 Day 15±3	Cycle 3 Day 15±3	Cycle 6 Day 15±3	Day 8-15 after last tablet
Informed consent, medical & medication history	X					
Inclusion, exclusion criteria	X	Check				
Physical & gynecological exam (with Pap smear)[b]	X					X
Dispense diary card		X	X	X		
Urine pregnancy test		X	If required[c]			
Dispense home pregnancy test[d]		X				
Dispense study medication		X	X	X		
Review and/or collect diary cards			X	X	X	X
Review and/or collect study medication			X	X	X	X
Vital signs: Blood pressure, heart rate, & weight	X	X	X	X	X	X
Adverse events and concomitant medication		X	X	X	X	X
Facial acne lesion count	X[e]		X	X	X	
Investigator Static Global Assessment (ISGA)	X		X	X	X	
Investigator's Overall Improvement Rating & Subject's Overall Self-Assessment Rating					X	
Facial hair assessment	X				X	
Safety laboratory tests[f]	X		X		X	X
Photographs (subgroup)		X		X	X	
Hormones (subgroup)		X			X	

[a] The procedures for Visits 5 and 6 should have been completed if the subject prematurely discontinued.
[b] If a negative Pap smear and pelvic exam were reported as normal 6 months prior to the screening visit (provided documentation was available) it was not necessary to repeat.
[c] Performed in the absence of monthly bleeding. In case of a pregnancy, the pregnancy report form was completed.
[d] Performed at home before the 1st tablet intake (on first day of menstrual bleeding), and the result was documented by the investigator at Visit 3.
[e] Baseline was performed on cycle Day 15±3 days.
[f] Included serum chemistry, hematology, urinalysis, and serum pregnancy tests (Serum pregnancy was only performed at Screening and Visit 6).

Papules, pustules, and nodules were summarized as "inflammatory lesion count." Open and closed comedones were summarized as "non-inflammatory lesion count." Open and closed comedones, papules, pustules, and nodules were summarized as "total lesion count."

The following six-point ISGA was obtained at screening, and each scheduled treatment visit:

Clinical Review Table 3
Investigator's Static Global Assessment

0	Normal, clear skin with no evidence of acne vulgaris
1	Skin is almost clear: few non-inflammatory lesions present, with rare noninflamed papules (papules must be resolving and may be hyperpigmented, though not pink-red), no nodular lesions
2	Few inflammatory lesions (papules or pustules), little inflammation, some comedones, no nodular lesions
3	Many comedones (non-inflammatory lesions predominate), several inflammatory lesions (papules or pustules), one small nodular lesion may or may not be present
4	Many inflammatory lesions (papules and pustules), up to many comedones, there may or may not be a few nodular lesions
5	Numerous highly inflammatory lesions predominate. Variable number of comedones, many papules and pustules or nodular lesions

Efficacy Variables:

The primary efficacy variables were:

- Percent change from baseline in inflammatory lesion count (papules, pustules, and nodules)
- Percent change from baseline in non-inflammatory lesion count (open and closed comedones)
- Percent change from baseline in total lesion count (comedones, papules, pustules, and nodules)
- Percentage of subjects classified as "clear" (score 0) or "almost clear" (score 1) on the 6-point ISGA scale

The secondary efficacy variables were:

- Change from baseline in count of papules
- Change from baseline in count of pustules
- Change from baseline in count of nodules
- Change from baseline in count of open comedones
- Change from baseline in count of closed comedones
- Percentage of subjects classified as "improved" according to the Investigator's Overall Improvement Rating
- Percentage of subjects classifying themselves as "improved" on the Subject's Overall Self-Assessment Rating

Reviewer comment: The Agency previously conveyed comments to the applicant that the Investigator's Overall Improvement Rating and the Subject's Overall Self-Assessment Rating have little regulatory utility. Also, multiplicity adjustment would be needed for labeling claims. The other secondary endpoints, changes from baseline in individual lesion counts are not relevant to labeling claims. Detailed analysis and comments regarding the secondary endpoints are thus not included in this review.

6.1.4 Efficacy Findings

Disposition of Subjects:

Study 306820:

Out of 1107 women screened, 534 (266 YAZ and 268 placebo) were dispensed medication. 229 YAZ patients and 227 placebo subjects were eligible for the "amended" full analysis (FA) set, satisfying the amended inclusion criteria for lesion numbers. (Minimum lesion counts were increased from 10 to 20 in both inflammatory and non-inflammatory categories early in the study to comply with the Agency request to study "moderate", rather than "mild-to-moderate acne"). The per-protocol set included 150 YAZ patients and 143 placebo subjects. The modified efficacy analysis population using the revised inclusion criteria as recommended by the Agency for moderate acne includes 228 YAZ patients and 230 placebo subjects.

Clinical Review Table 4
Subject Disposition—Study 306820

Disposition/Reason	DRSP/EE	Placebo	Total
Screened			1,107
Randomized	266	268	534
Safety Analysis Set[a]	266 (100.0%)	268 (100.0%)	534 (100.0%)
FA Set Who Met Amended Inclusion Criteria[b]	229 (86.1%)	227 (84.7%)	456 (85.4%)
PP Analysis Set[c]	150 (56.4%)	143 (53.4%)	293 (54.9%)
Completed the Study	191 (71.8%)	188 (70.1%)	379 (71.0%)
Prematurely Discontinued From the Study[d]	75 (28.2%)	80 (29.9%)	155 (29.0%)
Reasons for Premature Discontinuation from the Study			
Withdrawal of Consent	17 (6.4%)	15 (5.6%)	32 (6.0%)
Protocol Deviation	5 (1.9%)	4 (1.5%)	9 (1.7%)
Adverse Event	17 (6.4%)	13 (4.9%)	30 (5.6%)
Death	0 (0.0%)	0 (0.0%)	0 (0.0%)
Subject Lost, No Further Information Available	16 (6.0%)	22 (8.2%)	38 (7.1%)
Pregnancy	4 (1.5%)	3 (1.1%)	7 (1.3%)
Lack of Efficacy	0 (0.0%)	3 (1.1%)	3 (0.6%)
Other	16 (6.0%)	20 (7.5%)	36 (6.7%)
Completed the Study Medication	192 (72.2%)	188 (70.1%)	380 (71.2%)
Prematurely Discontinued the Study Medication	74 (27.8%)	80 (29.9%)	154 (28.8%)
Reasons for Premature Discontinuation from Study Medication			
Withdrawal of Consent	17 (6.4%)	15 (5.6%)	32 (6.0%)
Protocol Deviation	5 (1.9%)	4 (1.5%)	9 (1.7%)
Adverse Event	17 (6.4%)	13 (4.9%)	30 (5.6%)
Death	0 (0.0%)	0 (0.0%)	0 (0.0%)
Subject Lost, No Further Information Available	16 (6.0%)	22 (8.2%)	38 (7.1%)
Pregnancy	4 (1.5%)	3 (1.1%)	7 (1.3%)
Lack of Efficacy	0 (0.0%)	3 (1.1%)	3 (0.6%)
Other	15 (5.6%)	20 (7.5%)	35 (6.6%)

DRSP = drospirenone 3 mg; EE = ethinyl estradiol 0.02 mg; FA = Full Analysis; PP = Per Protocol.

Note: All percentages are based on the number of randomized subjects.

[a] The Safety Analysis Set is the FA set and includes all randomized subjects who were dispensed medication.

[b] The amended criterion is a minimum of 40 total lesions, including 20 inflammatory and 20 non-inflammatory lesions in order to include only women with moderate acne vulgaris.

[c] Defined as a FA set subject who met the amended inclusion/exclusion criteria, took no prohibited medications, had 80% or greater overall study medication compliance, had no major protocol deviations, and who completed a minimum of 5 treatment cycles.

[d] A subject who discontinued from study for more than 1 reason is counted once when determining overall number of discontinuations.

Disposition of Subjects:
Study 306996:

Out of 784 women screened, 538 (270 YAZ and 227 placebo subjects) were dispensed medication. 229 YAZ patients and 227 placebo subjects were eligible for "amended" full analysis (FA) set efficacy review. The per-protocol group included 147 women in the YAZ group and 139 placebo subjects. The modified efficacy analysis population using the

revised inclusion criteria for moderate acne includes 218 YAZ patients and 213 placebo subjects.

Clinical Review Table 5
Subject Disposition—Study 306996

Disposition/Reason	DRSP/EE	Placebo	Total
Screened			784
Randomized	270	268	538
Safety Analysis Set[a]	270 (100.0)	268 (100.0)	538 (100.0)
Full Analysis Set Who Meet Amended Inclusion Criteria[b]	222 (82.2)	215 (80.2)	437 (81.2)
Per Protocol Analysis Set[c]	147 (54.4)	139 (51.9)	286 (53.2)
Completed the Study	211 (78.1)	192 (71.6)	403 (74.9)
Prematurely Discontinued From the Study[d]	59 (21.9)	76 (28.4)	135 (25.1)
Reasons for Premature Discontinuation from the Study			
Withdrawal of Consent	15 (5.6)	18 (6.7)	33 (6.1)
Protocol Deviation	0 (0.0)	5 (1.9)	5 (0.9)
Adverse Event	18 (6.7)	9 (3.4)	27 (5.0)
Death	0 (0.0)	0 (0.0)	0 (0.0)
Subject Lost, No Further Information Available	18 (6.7)	23 (8.6)	41 (7.6)
Pregnancy	4 (1.5)	8 (3.0)	12 (2.2)
Lack of Efficacy	0 (0.0)	2 (0.7)	2 (0.4)
Other	4 (1.5)	11 (4.1)	15 (2.8)
Completed the Study Medication	211 (78.1)	192 (71.6)	403 (74.9)
Prematurely Discontinued the Study Medication	59 (21.9)	76 (28.4)	135 (25.1)
Reason for Premature Discontinuation from Study Medication			
Withdrawal of Consent	15 (5.6)	18 (6.7)	33 (6.1)
Protocol Deviation	0 (0.0)	5 (1.9)	5 (0.9)
Adverse Event	18 (6.7)	9 (3.4)	27 (5.0)
Death	0 (0.0)	0 (0.0)	0 (0.0)
Subject Lost, No Further Information Available	18 (6.7)	23 (8.6)	41 (7.6)
Pregnancy	4 (1.5)	8 (3.0)	12 (2.2)
Lack of Efficacy	0 (0.0)	2 (0.7)	2 (0.4)
Other	4 (1.5)	11 (4.1)	15 (2.8)

FA = Full Analysis; PP = Per Protocol

Note: All percentages are based on the number of randomized subjects.

[a] The Safety Analysis Set is the Full Analysis Set and includes all randomized subjects who were dispensed medication.

[b] The amended criterion is a minimum of 40 total lesions, including 20 inflammatory and 20 non-inflammatory lesions in order to include women with moderate acne vulgaris.

[c] Defined as a FA Set subject who met the amended inclusion/exclusion criteria, took no prohibited medications, had 80% or greater overall study medication compliance, had no major protocol deviations, and who completed a minimum of 5 treatment cycles.

[d] A subject who discontinued from study for more than 1 reason is counted once when determining overall number of discontinuations.

Reviewer comment: The number of subjects who discontinued from the study was slightly higher in the placebo arm than the YAZ arm in both studies.

Demographics and Baseline Characteristics:

Study 306820:

Demographic and baseline characteristics with regard to age, race, and smoking history were comparable between treatment groups, showing no statistically significant differences. All 534 subjects were female, ranging in age from 14 to 45 years (mean age: 25.2 years and 25.4 years in the DRSP/EE and placebo groups, respectively). The largest percentage of subjects in both the DRSP/EE and placebo groups were Caucasian (69.5% and 65.3%, respectively), and nonsmokers (73.7% and 70.9%, respectively). The mean weight, height, and BMI were statistically significantly lower in the DRSP/EE group compared with the placebo group; however, these differences were not expected to have any clinical impact on the outcome of the study.

Clinical Review Table 6
Study 306820--Summary of Demographic and Baseline Characteristics By Treatment Group (safety analysis set)

	DRSP/EE (N = 266)	Placebo (N = 268)	Total (N = 534)	P-value
Mean age (years [range])	25.2 (14 - 44)	25.4 (14 - 45)	25.3 (14 - 45)	0.6874[a]
Race (n [%])				
Caucasian	185 (69.5%)	175 (65.3%)	360 (67.4%)	0.4989[b]
Black	35 (13.2%)	46 (17.2%)	81 (15.2%)	
Hispanic	32 (12.0%)	28 (10.4%)	60 (11.2%)	
Asian	5 (1.9%)	8 (3.0%)	13 (2.4%)	
Other	9 (3.4%)	11 (4.1%)	20 (3.7%)	
Mean weight (kg)	64.53	68.74	66.64	0.0003[a]
Mean height (cm)	163.41	164.81	164.11	0.0161[a]
Body Mass Index (kg/m^2)	24.0	25.1	24.6	0.0039[a]
History of smoking (n [%])				
No	196 (73.7%)	190 (70.9%)	386 (72.3%)	0.4712[b]
Yes	70 (26.3%)	78 (29.1%)	148 (27.7%)	
If yes, currently smoking (n [%])				
No	23 (8.6%)	33 (12.3%)	56 (10.5%)	0.3159[b]
Yes	47 (17.7%)	45 (16.8%)	92 (17.2%)	
If yes, average cigarettes per day	6.46	6.63	6.54	0.8639[c]

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

[a] P-value computed from a linear model with terms for treatment and pooled center.

[b] P-value computed from generalized Cochran Mantel Haenszel test for general association, stratified by pooled center.

[c] P-value computed from a linear model with term for treatment.

Study 306996:

Demographic and baseline characteristics with regard to age, race, and smoking history were comparable between treatment groups, showing no statistically significant

differences. All 538 subjects were female, ranging in age from 14 to 44 years (mean age: 25.2 years and 25.1 years in the DRSP/EE and placebo groups, respectively). The largest percentage of subjects in both the DRSP/EE and placebo groups were Caucasian (70.7% and 66.4%, respectively), and nonsmokers (80.0% and 84.0%, respectively). There was no statistically significant difference in mean weight, height, and BMI between treatment groups.

Clinical Review Table 7
Study 306996—Summary of Demographic and Baseline Characteristics By Treatment Groups (safety analysis set)

	DRSP/EE (N = 270)	Placebo (N = 268)	Total (N = 538)	P-value
Mean age (years [range])	25.2 (14-44)	25.1 (14-44)	25.1 (14-44)	0.8883[a]
Race (n [%])				
Caucasian	191 (70.7%)	178 (66.4%)	369 (68.6%)	0.5164[b]
Black	39 (14.4%)	36 (13.4%)	75 (13.9%)	
Hispanic	29 (10.7%)	36 (13.4%)	65 (12.1%)	
Asian	7 (2.6%)	10 (3.7%)	17 (3.2%)	
Other	4 (1.5%)	8 (3.0%)	12 (2.2%)	
Mean weight (kg)	65.71	65.52	65.61	0.8697[a]
Mean height (cm)	165.14	164.49	164.82	0.2750[a]
Body Mass Index (kg/m^2)	23.8	23.8	23.8	0.9611[a]
History of smoking (n [%])				
No	216 (80.0%)	225 (84.0%)	441 (82.0%)	0.2404[b]
Yes	54 (20.0%)	43 (16.0%)	97 (18.0%)	
If yes, currently smoking (n [%])				
No	23 (8.5%)	14 (5.2%)	37 (6.9%)	0.3354[b]
Yes	31 (11.5%)	29 (10.8%)	60 (11.2%)	
If yes, average cigarettes per day	4.46	4.86	4.66	0.6658[c]

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

[a] P-value computed from a linear model with terms for treatment and pooled center.

[b] P-value computed from generalized Cochran Mantel Haenszel test for general association, stratified by pooled center.

[c] P-value computed from a linear model with term for treatment.

Reviewer comment: Age and race appear to be comparably distributed across the study arms. For both studies, the YAZ arm had slightly more Caucasians enrolled than the placebo arms. Racial enrollment approximates that of the US population. The differences in mean weight, height, and BMI in study 306820 are not felt to significantly affect efficacy results.

Baseline Severity:

Baseline ISGA scores were fairly balanced between the two arms in both studies. The proportions of ISGA scores of 3 were slightly larger in the YAZ arms than the placebo arms, whereas the proportions of ISGA scores of 4 were marginally larger in the placebo arms compared to the YAZ arms in both studies. The mean baseline inflammatory and non-inflammatory lesion counts of the YAZ and placebo arms are very close in both studies.

These are presented in Clinical Review Table 8:

Clinical Review Table 8
Baseline Severity by Treatment Arm

	Study 306820		Study 306996	
	YAZ N=228	Placebo N=230	YAZ N=218	Placebo N=213
ISGA				
3	134 (59%)	128 (56%)	134 (61%)	125 (59%)
4	81 (36%)	91 (40%)	74 (34%)	76 (36%)
5	14 (6%)	8 (3%)	14 (6%)	14 (7%)
Inflammatory lesion counts				
mean (std)	32.6 (16.1)	32.8 (14.6)	31.7 (12.4)	31.8 (13.7)
median	27	26.5	28	27
min,max	(20,152)	(20,100)	(20,98)	(20,104)
Non-inflammatory lesion counts				
mean (std)	47.3 (31.4)	47.0 (30.8)	43.9 (22.9)	43.8 (25.9)
median	36	36	37	36
min,max	(20,256)	(20,194)	(20,143)	(20,133)

Efficacy Endpoint Outcomes

Tables are provided for the analyses of endpoints by the applicant, followed by Agency analyses using the modified moderate acne populations.

The Agency Biostatistical reviewer, Dr. Clara Kim, commented that the applicant's analysis was based on data sets that included all subjects enrolled with both mild and moderate acne. Her analysis is based on data sets that used the modified population which excludes all subjects with Baseline ISGA score of 2 and includes all subjects with Baseline inflammatory/non-inflammatory lesion counts greater or equal to 20. These were inclusion criteria amendments as specified by the Agency at the February 4, 2003 guidance meeting. However, the differences in the results based on the applicant's data and the Agency data set are minor. All co-primary endpoints were statistically significant in both studies with p-values less than 0.0003. The results were relatively consistent across subgroups and investigative sites.

Clinical Review Table 9
ISGA efficacy results (Applicant analysis)

	Study 306820		Study 306996	
	YAZ N=229	Placebo N=227	YAZ N=222	Placebo N=215
Number (Proportion) of Successes	37 (16.2%)	10 (4.4%)	47 (21.2%)	20 (9.3%)
p-value*		<0.0001‡		0.0004‡

† P-value computed from logistic regression model with terms for treatment and pooled center.

‡ P-value computed from Cochran Mantel-Haenszel statistic stratified by pooled center, since the logistic regression model did not converge.

Source: Clinical Study Report No. A25083, p. 71 and Clinical Study Report No. A25152, p. 71

The Agency review of the ISGA results showed robust, statistically significant results across the study sites.

Clinical Review Table 10
ISGA efficacy results (FDA Analysis)

	Study 306820		Study 306996	
	YAZ N=228	Placebo N=230	YAZ N=218	Placebo N=213
Number (Proportion) of Successes	35 (15.4%)	10 (4.3%)	46 (21.1%)	19 (8.9%)
p-value*		0.0001		0.0003

* p-values are calculated using a logistic model with treatment and pooled centers as factors

Analysis by lesion counts also show robust efficacy results in both the applicant's analysis and Agency analysis.

Clinical Review Table 11
Mean (SD) Baseline and Percent Change in Lesion Counts from Baseline to Cycle 6 (Applicant Analysis)

	Study 306820		Study 306996	
	YAZ N=229	Placebo N=227	YAZ N=222	Placebo N=215
Inflammatory				
Baseline count	32.6 (16.1)	33.1 (14.6)	31.7 (12.3)	31.8 (13.6)
% reduction	47.8% (35.3%)	32.7% (36.4%)	50.9% (38.1%)	34.7 (49.6%)
p-value†		<0.0001		<0.0001
Non-inflammatory				
Baseline count	47.1 (31.4)	47.0 (30.8)	43.9 (22.8)	43.8 (25.8)
% reduction	38.4% (39.1%)	18.2% (48.7%)	42.8% (38.3%)	26.3% (48.1%)
p-value†		<0.0001		<0.0001
Total				
Baseline count	79.6 (42.3)	80.0 (37.4)	75.6 (30.5)	75.6 (33.7)
% reduction	42.6% (32.6%)	25.4% (36.7%)	46.5% (33.5%)	30.9% (41.8%)
p-value†		<0.0001		<0.0001

† p-values are calculated using ANCOVA model: Baseline lesion count as covariate, and treatment, center as factors.

Source: Clinical Study Reports No. A25083 and No. A25152, pages 60, 61, 65, 68 and Tables 22, 30, 38.

Agency review of changes in lesion counts also showed a statistically significant reduction in both inflammatory and non-inflammatory lesion counts.

Clinical Review Table 12
Mean (SD) Baseline and Percent Change in Lesion Counts from Baseline to Cycle 6 (FDA Analysis)

	Study 306820		Study 306996	
	YAZ N=228	Placebo N=230	YAZ N=218	Placebo N=213
Inflammatory				
Baseline count	32.61 (16.1)	32.84 (14.6)	31.73 (12.4)	31.81 (13.7)
% reduction	47.60% (35.4%)	32.34% (37.3%)	50.60% (38.3%)	34.46 (49.7%)
p-value†		<0.0001		<0.0001
Non-inflammatory				
Baseline count	47.27 (31.4)	46.99 (30.6)	43.85 (22.9)	43.85 (25.9)
% reduction	38.08% (39.0%)	18.22% (47.9%)	42.35% (38.5%)	26.02% (48.2%)
p-value†		<0.0001		<0.0001
Total				
Baseline count	79.88 (42.3)	79.83 (37.2)	75.60 (30.7)	75.67 (33.9)
% reduction	42.33% (32.7%)	25.29% (36.4%)	46.13% (33.7%)	30.64% (41.9%)
p-value†		<0.0001		<0.0001

† p-values are calculated using ANCOVA model: Baseline lesion count as covariate, and treatment, center, and treatment by center interaction (if statistically significant) as factors.

Source: Reviewer analysis based on modified population which excludes all subjects with Baseline ISGA score of 2 and includes all subjects with Baseline inflammatory/non-inflammatory lesion counts greater or equal to 20.

Reviewer comment: By both the applicant's analysis and the FDA analysis, YAZ was superior in all primary efficacy variables for the population with moderate acne with robust statistical significance. From a clinical perspective, YAZ would not be considered a primary therapy for acne, nor would it be likely utilized as the only acne therapy for women who choose oral contraception. In this population of women who had not used any concomitant acne therapy for at least two weeks prior to entering the study, as well as the six month duration of the study, efficacy was adequately demonstrated. YAZ should prove a useful adjunctive therapy for women who desire oral contraception.

6.1.5 Clinical Microbiology

The applicant did not perform any clinical microbiologic studies. No changes in labeling regarding microbiology are requested by the applicant.

6.1.6 Efficacy Conclusions

The overall efficacy assessment from both the applicant-submitted data and the Agency review of YAZ as a treatment for moderate acne vulgaris in post-menarchal women desiring oral contraception demonstrates statistically and clinically significant responses to treatment with YAZ as compared to placebo in all primary efficacy variables.

7. INTEGRATED REVIEW OF SAFETY

7.1 Methods and Findings

Safety data are presented from each study individually.

7.1.1 Deaths

There were no deaths in either acne study with YAZ.

7.1.2 Other Serious Adverse Events

One subject in the DRSP/EE group in study 306820 reported a serious adverse event. Subject 20037 reported depression, requiring hospitalization, starting on study day 10, and was listed as severe. The patient had not yet recovered by the end of the study. The relationship to study medication was judged by the investigator and the applicant to be

unlikely.

Reviewer comment: While oral contraceptive drugs may cause mood changes and depression, this subject had a history of depression for several years prior to study entry and this was not disclosed at the screening visit. The relationship to the study drug is unlikely.

There were no reports of thrombotic or thromboembolic adverse events in either study in the DRSP/EE groups. One subject (10079), in study 306820's placebo group, developed "superficial phlebitis" of severe intensity which resolved 9 days after the end of the study.

7.1.3 Dropouts and Other Significant Adverse Events

In the YAZ treated subjects, 7.8% discontinued therapy due to an adverse event compared to 5.0% for the placebo treated subjects. The following table outlines all reasons for dropouts pooled for both acne studies:

Clinical Review Table 13
Reason for Prematurely Discontinuation of Study Medication, pooled

	YAZ, N=451	Placebo, N=442
Completed study medication	342 (75.8%)	315 (71.3%)
Prematurely discontinued from study medication [1]	109 (24.2%)	127 (28.7%)
Reason for premature discontinuation of study medication		
withdrawal of consent	32 (7.1%)	33 (7.5%)
protocol deviation	5 (1.1%)	9 (2.0%)
adverse event	35 (7.8%)	22 (5.0%)
death	0 (0%)	0 (0%)
patient lost, no further information available	34 (7.5%)	45 (10.2%)
pregnancy	8 (1.8%), [3]	11 (2.5%)
lack of efficacy	0 (0%)	5 (1.1%)
other [2]	19 (4.2%)	31 (7.0%)

[1] Note: a woman who discontinued from study medication for more than one reason is counted once when determining overall number of discontinuations.
[2] In both treatment groups, the most frequently reported reason for study medication discontinuation included in this category was non-compliance.

One significant adverse event was reported in Study 306820. Subject 21010 was diagnosed with pneumonia that did not require hospitalization. This occurred on day 32 and was listed as moderate in intensity. The patient recovered by day 48 and both the investigator and the applicant assessed the relationship to study drug as unlikely.

Reviewer comment: This reviewer concurs with the assessment that the relationship of the study drug with the adverse event of pneumonia is unlikely.

In study 306820, 26 subjects prematurely discontinued the study due to a treatment emergent AE including 14 [5.3%] subjects in the YAZ group and 12 [4.5%] subjects in the placebo group. 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).

In study 306996, 51 subjects prematurely discontinued the study due to a treatment-emergent AE including 30 (5.6%) subjects in the YAZ group and 21 (3.9%) subjects in the placebo group. Frequently reported AEs leading to premature discontinuations in the YAZ group included menorrhagia (0.9% of the subjects), dysmenorrhea (0.7% of the subjects), and metrorrhagia (0.7% of the subjects). Depression was the most common AE leading to premature discontinuation in the placebo group (0.7% of the subjects).

The treatment-emergent AEs that led to premature discontinuation of participation in the study are listed in the following table. All AEs which led to premature discontinuation of participation in the study were reported in <0.9% of the subjects in either treatment group.

Clinical Review Table 14
Treatment Emergent Adverse Events Leading to Premature Discontinuation By Preferred Term and Treatment Group

	Number (%) of Subjects		
Preferred Term[a]	YAZ (N=536) n (%)	Placebo (N=536) n (%)	Total (N=1072) n (%)
Subjects with at least 1 treatment-emergent AE leading to premature termination	30 (5.6)[b]	21 (3.9)[c]	51 (4.8)
Menorrhagia	5 (0.9)	0	5 (0.5)
Dysmenorrhea	4 (0.7)	0	4 (0.4)
Metrorrhagia[d]	4 (0.7)	0	4 (0.4)
Depression	3 (0.6)	4 (0.7)	7 (0.7)
Nausea	3 (0.6)	2 (0.4)	5 (0.5)
Weight gain	3 (0.6)	2 (0.4)	5 (0.5)
Menstrual disorder	3 (0.6)	0	3 (0.3)
Headache	2 (0.4)	1 (0.2)	3 (0.3)
Abdominal pain	2 (0.4)	0	2 (0.2)
Acne	2 (0.4)	0	2 (0.2)
Emotional lability	1 (0.2)	3 (0.6)	4 (0.4)
Thrombocythemia	1 (0.2)	2 (0.4)	3 (0.3)
Hyperlipemia	1 (0.2)	1 (0.2)	2 (0.2)
Hypertension	1 (0.2)	1 (0.2)	2 (0.2)
Rash	1 (0.2)	1 (0.2)	2 (0.2)
Vomiting	1 (0.2)	1 (0.2)	2 (0.2)
Asthenia	1 (0.2)	0	1 (0.1)
Breast pain	1 (0.2)	0	1 (0.1)
Hematuria	1 (0.2)	0	1 (0.1)
Malaise	1 (0.2)	0	1 (0.1)
Peripheral edema	1 (0.2)	0	1 (0.1)
Migraine	0	2 (0.4)	2 (0.2)
Alopecia	0	1 (0.2)	1 (0.1)
Convulsion	0	1 (0.2)	1 (0.1)
Drug abuse	0	1 (0.2)	1 (0.1)
Flatulence	0	1 (0.2)	1 (0.1)
Lymphocytosis	0	1 (0.2)	1 (0.1)

Footnotes for Clinical Review Table 14 follow on the next page:

CNS = central nervous system; N = total number of subjects treated; n = number of subjects with AEs.
[a] Preferred terms are listed in the order of descending frequency of subjects in the YAZ group.
[b] Does not include the following: Subject 5018 (Report A25083; menorrhagia) and Subject 6027 (Report A25083; nausea) who discontinued due to AEs that were not treatment-emergent; Subject 20051 (Report A25083; elevated total bilirubin); Subject 18048 (Report A25152; amenorrhea); Subject 22046 (Report A25152; amenorrhea); and Subject 23019 (Report A25152; amenorrhea), who all discontinued due to the indicated AE but the AE page of their CRF was not marked "drug withdrawn" under study drug action, and therefore they were not captured on this table.
[c] Does not include Subject 10013 (Report A25083; hyperglycemia and hyperlipidemia) and Subject 10050 (Report A25152; hypercholesterolemia) who discontinued due to the indicated AEs but the AE page of their CRF was not marked "drug withdrawn" under study drug action, and therefore they were not captured on this table. In addition, these AEs were not treatment-emergent
[d] Includes reported terms: break-through bleeding; break-through vaginal bleeding; break-through vaginal spotting; continuous/continual spotting; intracyclic bleeding; intracyclic vaginal bleeding; light vaginal spotting; menstrual spotting; metrorrhgagia (spotting); moderate spotting; spotting; spotty, vaginal bleeding; unexpected vaginal bleeding; vaginal bleeding (spotting); and vaginal spotting.

7.1.3.1 Overall profile of dropouts

The adverse events in Study 306820 and Study 306996 are commonly seen with all combination oral contraceptives, and may lead to drug discontinuation. The percentages reported are not increased above expected rates. The adverse events leading to discontinuation in the acne studies are not different than those found in other oral contraceptives.

7.1.3.3 Other significant adverse events

There is a possible risk of hyperkalemia with drospirenone based on the mechanism of action of drospirenone. Drospirenone is an analog of spironolactone and possesses antimineralocorticoid activity. Cardiovascular events that might be associated with the potential risk of hyperkalemia were identified from the HARTS dictionary, and included arrhythmia, bradycardia, tachycardia, dizziness, palpitations, and syncope.

In study 306820, all 534 subjects (266 subjects in the DRSP/EE group and 268 subjects in the placebo group) were included in the analysis of selected cardiovascular events. Of the selected cardiovascular events, dizziness was reported in 3 (1.1%) subjects in the DRSP/EE group (Subjects 10023, 20038, and 27021) and 2 (0.7%) subjects in the placebo group (Subjects 21026 and 27023). The investigator classified the relationship to study medication as none for Subject 10023 (DRSP/EE) and Subject 21026 (placebo), and unlikely for Subject 27021 (DRSP/EE) and Subject 27023 (placebo group). The

investigator classified the relationship to study medication as possible for Subject 20038 (DRSP/EE). None of the subjects in either treatment group prematurely discontinued from the study due to dizziness.

Another selected cardiovascular event, palpitation, was reported by 2 (0.7%) subjects in the placebo group (Subjects 7005 [investigator term = "heart palpitation"] and Subject 27023 [investigator term = "racing heart"]). Neither of the subjects discontinued the study due to palpitation.

None of the other selected cardiovascular events (including arrhythmia, bradycardia, syncope, and tachycardia) were reported by any subjects during the treatment phase.

None of the subjects with post-baseline serum potassium values >5.5 mEq/L experienced any of the selected cardiovascular events.

In study 306996, all 538 subjects (270 subjects in the DRSP/EE group and 268 subjects in the placebo group) were included in the analysis of selected cardiovascular events. Of the selected cardiovascular events, dizziness was reported in 2 (0.7%) subjects in the DRSP/EE group (Subjects 26020 and 26021) and 1 (0.4%) subject in the placebo group (Subject 28001). The investigator rated dizziness as unlikely related to study medication for Subjects 26020 and 26021 in the DRSP/EE group. The investigator rated dizziness as possibly related to study medication for Subjects 28001 in the placebo group. None of the subjects in either treatment group prematurely discontinued from the study due to dizziness.

None of the other selected cardiovascular events (including arrhythmia, bradycardia, palpitation, syncope, and tachycardia) were reported by any subjects during the treatment phase.

None of the subjects with post-baseline serum potassium values ≥5.5 mEq/L experienced any of the selected cardiovascular events. Further discussion of potassium values is in section 7.1.7.3.

Reviewer comment: There is no evidence in either pivotal study of significant adverse cardiovascular events being related to study medication.

7.1.5 Common Adverse Events

7.1.5.1 Eliciting adverse events data in the development program

Study 306820:
The Safety analysis set includes all randomized subjects who were dispensed study medication. There were a total of 534 subjects (266 and 268 subjects in the DRSP/EE and placebo groups, respectively).

Duration of treatment, defined as the number of days from the first dose to the last dose of study medication, was comparable between the 2 treatment groups. The mean duration of treatment was 141.7 days for the DRSP/EE group and 139.0 days for the placebo group. The range was between 0 and 196 for the DRSP/EE group, and between 0 and 231 days for the placebo group.

Study 306996:
The Safety analysis dataset includes all randomized subjects who were dispensed study medication. There were a total of 538 subjects (270 and 268 subjects in the DRSP/EE and placebo groups, respectively).

Duration of treatment, defined as the number of days from the first dose to the last dose of study medication, was comparable between the 2 treatment groups. The mean duration of treatment was 146.4 days for the DRSP/EE group and 144.1 days for the placebo group. The range was from 0 to 207 days in the DRSP/EE group and from 0 to 218 days in the placebo group.

7.1.5.2 Appropriateness of adverse event categorization and preferred terms

The HARTS Dictionary (version 2.3) was used to code adverse events for both studies.

7.1.5.3 Incidence of common adverse events

Study 306820:
There were a total of 299 (56.0%) subjects who reported at least 1 treatment-emergent AE during the study. There were a higher percentage of subjects who reported at least 1 treatment-emergent AE in the DRSP/EE group compared with the placebo group (170 [63.9%] subjects versus 129 [48.1%] subjects in the DRSP/EE and placebo groups, respectively).

The most frequently reported AEs in the DRSP/EE group were upper respiratory infection (35 [13.2%] subjects), metrorrhagia (28 [10.5%] subjects), headache (23 [8.6%] subjects), nausea (17 [6.4%] subjects), Pap smear suspicious (15 [5.6%] subjects), sinusitis (15 [5.6%] subjects), and vaginal moniliasis (15 [5.6%] subjects). The most frequently reported AEs in the placebo group were upper respiratory infection (25 [9.3%] subjects), vaginal moniliasis (12 [4.5%] subjects), Pap smear suspicious (12 [4.5%] subjects), headache (10 [3.7%] subjects), and pharyngitis (10 [3.7%] subjects).

Intensity:
The majority of the subjects reported treatment-emergent AEs that were rated by the investigator as mild (55 [20.7%] in the DRSP/EE group and 40 [14.9%] in the placebo group) or moderate (99 [37.2%] in the DRSP/EE group and 77 [28.7%] in the placebo group) in intensity. Of the 299 subjects who experienced at least 1 treatment-emergent AE, 16 (6.0%) subjects in the DRSP/EE group and 12 (4.5%) subjects in the placebo group reported AEs that were rated by the investigator as severe in intensity.

In the DRSP/EE group, the AEs that were classified as severe in intensity were accidental injury, depression, nausea, headache, dysmenorrhea, menorrhagia, hyperlipidemia, emotional lability, schizophrenic reaction, allergic reaction, thorax pain, tooth disorder, sore throat, laryngitis, bronchitis, sinusitis, and rash. The first 2 AEs were reported by at most 2 (0.8%) subjects and the remaining AEs were reported by at most 1 (0.4%) subject each.

In the placebo group, the AEs that were classified as severe in intensity were emotional lability, back pain, depression, migraine, phlebitis, dysmenorrhea, accidental injury, gastrointestinal disorder, and pharyngitis. Emotional lability was reported by at most 3 (1.1%) subjects, back pain and depression were reported by at most 2 (0.7%) subjects each, and the remaining AEs were reported by at most 1 (0.4%) subject each.

Causality:
Among the treatment groups, there were a higher percentage of subjects in the DRSP/EE group that experienced drug-related AEs as judged by the investigator compared with the placebo group (75 [28.2%] subjects in the DRSP/EE group versus 33 [12.3%] subjects in the placebo group).

In the DRSP/EE group, the following were the most frequently reported AEs that were considered by the investigator to be drug-related: metrorrhagia (28 [10.5%] subjects), nausea (14 [5.3%] subjects), headache (14 [5.3%] subjects), emotional lability (8 [3.0%] subjects), breast pain (7 [2.6%] subjects), dysmenorrhea (7 [2.6%] subjects), and menorrhagia (7 [2.6%] subjects).

In the placebo group, the following were the most frequently reported AEs that were considered by the investigator to be drug-related: headache (6 [2.2%] subjects), nausea (4 [1.5%] subjects), emotional lability (4 [1.5%] subjects), depression (3 [1.1%] subjects), and metrorrhagia (3 [1.1%] subjects).

Study 306996:
There were a total of 272 (50.6%) subjects who reported at least 1 treatment-emergent AE during the study. There were a higher percentage of subjects who reported at least 1 treatment-emergent AE in the DRSP/EE group compared with the placebo group (149 [55.2%] subjects versus 123 [45.9%] subjects in the DRSP/EE and placebo groups, respectively).

The most frequently reported AEs in the DRSP/EE group were upper respiratory infection (25 [9.3%] subjects), metrorrhagia (25 [9.3%] subjects), Pap smear suspicious (15 [5.6%] subjects), headache (14 [5.2%] subjects), and flu syndrome (10 [3.7%] subjects). The most frequently reported AEs in the placebo group were upper respiratory infection (31 [11.6%] subjects), headache (14 [5.2%] subjects), and flu syndrome (12 [4.5%] subjects).

Intensity:
The majority of the subjects reported treatment-emergent AEs that were rated by the investigator as mild (51 [18.9%] in the DRSP/EE group and 46 [17.2%] in the placebo group) or moderate (88 [32.6%] in the DRSP/EE group and 60 [22.4%] in the placebo group) in intensity. Of the 272 subjects who experienced at least 1 treatment-emergent AE, 9 (3.3%) subjects in the DRSP/EE group and 16 (6.0%) subjects in the placebo group reported AEs that were rated by the investigator as severe in intensity.

In the DRSP/EE group, the AEs that were classified as severe in intensity were malaise, SGOT increased, hot flashes, depression, headache, menorrhagia, menstrual disorder, and leukorrhea. Headache was reported by at most 2 (0.7%) subjects and the remaining AEs were reported by at most 1 (0.4%) subject each.

In the placebo group, the AEs that were classified as severe in intensity were abdominal pain, infection, neck rigidity, pelvic pain, migraine, tooth disorder, gastroenteritis, gastrointestinal disorder, vomiting, drug abuse, pneumonia, pharyngitis, sinusitis, rash, dysmenorrhea, and ectopic pregnancy. Abdominal pain was reported by at most 2 (0.7%) subjects and the remaining AEs were reported by at most 1 (0.4%) subject each.

Causality:
Among the treatment groups, there was a higher percentage of subjects in the DRSP/EE group that experienced drug-related AEs as judged by the investigator compared with the placebo group (74 [27.4%] in the DRSP/EE group and 52 [19.4%] in the placebo group).

In the DRSP/EE group, the following were the most frequently reported AEs that were considered by the investigator to be drug-related: metrorrhagia (25 [9.3%] subjects), headache (10 [3.7%] subjects), nausea (8 [3.0%] subjects), menorrhagia (7 [2.6%] subjects), and menstrual disorder (7 [2.6%] subjects).

In the placebo group, the following were the most frequently reported AEs that were considered by the investigator to be drug-related: headache (10 [3.7%] subjects) and metrorrhagia (6 [2.2%] subjects).

Reviewer comment: The adverse events are known to be associated with combination oral contraceptives and are included in the current labeling for YAZ.

7.1.5.4 Common adverse event tables

The following adverse event table is presented for both studies combined.

Clinical Review Table 15
Treatment-Emergent Adverse Events Occurring in >1% of Subjects In Any Treatment Group by Maximum Intensity-Pooled Acne studies

	Number (%) of Subjects		
Preferred Term[a]	YAZ (N=536) n (%)	Placebo (N=536) n (%)	Total (N=1072) n (%)
Subjects with at least 1 treatment-emergent AE	319 (59.5)	252 (47.0)	571 (53.3)
Upper respiratory infection	60 (11.2)	56 (10.4)	116 (10.8)
Metrorrhagia[b]	53 (9.9)	9 (1.7)	62 (5.8)
Headache	37 (6.9)	24 (4.5)	61 (5.7)
Pap smear suspicious	30 (5.6)	20 (3.7)	50 (4.7)
Nausea	26 (4.9)	14 (2.6)	40 (3.7)
Sinusitis	20 (3.7)	14 (2.6)	34 (3.2)
Vaginal moniliasis	20 (3.7)	16 (3.0)	36 (3.4)
Flu syndrome	18 (3.4)	15 (2.8)	33 (3.1)
Menorrhagia	16 (3.0)	5 (0.9)	21 (2.0)
Depression	12 (2.2)	5 (0.9)	17 (1.6)
Emotional lability	12 (2.2)	8 (1.5)	20 (1.9)
Abdominal pain	11 (2.1)	7 (1.3)	18 (1.7)
Gastroenteritis	10 (1.9)	6 (1.1)	16 (1.5)
Urinary tract infection	10 (1.9)	7 (1.3)	17 (1.6)
Tooth disorder	9 (1.7)	6 (1.1)	15 (1.4)
Infection	8 (1.5)	5 (0.9)	13 (1.2)
Vomiting	8 (1.5)	4 (0.7)	12 (1.1)
Pharyngitis	8 (1.5)	14 (2.6)	22 (2.1)
Breast pain	8 (1.5)	3 (0.6)	11 (1.0)
Dysmenorrhea	8 (1.5)	4 (0.7)	12 (1.1)
Menstrual disorder	8 (1.5)	3 (0.6)	11 (1.0)
Accidental injury	7 (1.3)	10 (1.9)	17 (1.6)
Asthenia	7 (1.3)	3 (0.6)	10 (0.9)
Sore throat	7 (1.3)	4 (0.7)	11 (1.0)
Weight gain	7 (1.3)	5 (0.9)	12 (1.1)

AE = adverse event; N = total number of subjects treated; n = number of subjects with AEs; Pap = Papanicolaou.
[a] Preferred terms are listed in the order of descending frequency of subjects in the YAZ group.
[b] Includes reported terms: break-through bleeding; break-through vaginal bleeding; break-through vaginal spotting; continuous/continual spotting; intracyclic bleeding; intracyclic vaginal bleeding; light vaginal spotting; menstrual spotting; metrorrhgagia (spotting); moderate spotting; spotting; spotty; vaginal bleeding; unexpected vaginal bleeding; vaginal bleeding (spotting); and vaginal spotting.

7.1.5.6 Additional analyses and explorations

Study 306820:
There were no subjects who had a reduction in dose of study medication.

There are no records of subjects with a significant additional concomitant therapy due to and adverse event.

Study 306996:
There were no subjects who had a reduction in dose of study medication.

There were no records of subjects with a significant additional concomitant therapy due to an adverse event.

7.1.7 Laboratory Findings

Drospirenone products have the potential to cause retention of potassium. These results will be described for the two pivotal studies in the Special Assessments section 7.1.7.5.

7.1.7.1 Overview of laboratory testing in the development program

Study 306820:
The mean absolute values for each chemistry parameter were similar at baseline between the DRSP/EE and placebo groups and changed little throughout the study. In the DRSP/EE group, total cholesterol, HDL, and triglycerides showed increases from baseline to treatment Cycle 6/Visit 5 (mean changes of 10.19 mg/dL, 7.42 mg/dL, and 37.17 mg/dL, respectively).

Study 306996:
The mean absolute values for each chemistry parameter were similar at baseline between the DRSP/EE and placebo groups and changed little throughout the study. In the DRSP/EE group, total cholesterol, HDL, LDL, and triglycerides showed increases from baseline to Treatment Cycle 6/Visit 5 (mean changes of 13.96, 6.10, 4.55, and 16.39 mg/dL, respectively).

7.1.7.2 Selection of studies and analyses for drug-control comparisons of laboratory values

Study 306820:
Overall, similar transitions were observed between the DRSP/EE and placebo groups for each parameter (except HDL). In both treatment groups, at least 85% of the subjects had normal values at baseline and at the treatment visits for all the parameters except HDL and triglycerides. In the DRSP/EE group, there was a lower percentage of subjects that had normal HDL values baseline and at each visit during the treatment phase compared with the placebo group (at least 72% of the subjects in the DRSP/EE group compared with at least 82% of the subjects in the placebo group). In addition, there was a higher percentage of DRSP/EE subjects that had transitions from normal values at baseline to high HDL values during treatment compared with placebo (17.2% of the subjects in the DRSP/EE group versus 3.2% of the subjects in the placebo group at Treatment Cycle 6/Visit 5)

Several subjects in each group experienced elevations in liver function tests, with mean values similar between DRSP/EE and placebo groups. The subjects who had clinically relevant changes as judged by the investigators are presented in the following table:

Clinical Review Table 16
Study 306820: Clinically Relevant Changes from Baseline in Chemistry Parameters:

Text Table 22: Subjects With Clinically Relevant Changes from Baseline in Chemistry Parameters

Treatment	Subject Number	Visit	Clinically Relevant Change from Baseline	Normal Range	Baseline Value	Clinically Relevant Value	Value at Last Visit	Clinically Relevant at Last Visit
DRSP/EE	2048	Treatment Cycle 1/ Visit 3	Elevated ALT	0-45 U/L	11	88	12	No
	10015	Follow-up/ Visit 6	Elevated triglycerides, not fasted	10-200 mg/dL	231	276	276	No
	10059	Follow-up/ Visit 6	Elevated AST	0-41 U/L	43	89	21	No
		Follow-up/ Visit 6	Elevated ALT	0-45 U/L	62	160	30	No
	10080	Follow-up/ Visit 6	Elevated ALT	5-20 U/L	9	57	57	Yes
	14059	Treatment Cycle 1/ Visit 3	Elevated AST	0-41 U/L	18	44	34	No
		Treatment Cycle 6/ Visit 5	Elevated AST	0-41 U/L	18	66	34	No
		Treatment Cycle 1/ Visit 3	Elevated ALT	0-45 U/L	14	72	50	No
		Treatment Cycle 6/ Visit 5	Elevated ALT	0-45 U/L	14	90	50	No
	16001	Follow-up/ Visit 6	Elevated ALT	0-45 U/L	19	163	39	No
	17013	Treatment Cycle 6/ Visit 5	Elevated inorganic phosphate	2.7-4.8 mg/dL	4	6.7	4.1	No
	19036	Treatment Cycle 1/ Visit 3	Elevated potassium	3.5-5.3 mEq/L	5.3	5.6	5	No
	20051	Unscheduled Visit	Elevated bilirubin	0.1-1.2 mg/dL	2.5	2.2	2.2	Yes
	24003	Follow-up/ Visit 6	Elevated glucose	70-125 mg/dL	92	141	95	No
	28089	Treatment Cycle 6/ Visit 5	Elevated total cholesterol	120-260 mg/dL	300	341	333	Yes
		Follow-up/ Visit 6	Elevated total cholesterol	120-260 mg/dL	300	333	333	Yes
		Treatment Cycle 6/ Visit 5	Elevated LDL	60-190 mg/dL	219	248	261	Yes
		Follow-up/ Visit 6	Elevated LDL	60-190 mg/dL	219	261	261	Yes
		Treatment Cycle 6/ Visit 5	Elevated triglycerides	10-200 mg/dL	79	207	94	No

AST = aspartate aminotransferase; ALT = alanine aminotransferase; DRSP = drospirenone 3 mg; EE = ethinyl estradiol 0.02 mg; LDL = low density lipoprotein

Clinical Review Table 16 continues:

Clinical Review Table 16, continued
Study 306820: Clinically Relevant Changes from Baseline in Chemistry Parameters:

Text Table 22: Subjects With Clinically Relevant Changes from Baseline in Chemistry Parameters (continued)

Treatment	Subject Number	Visit	Clinically Relevant Change from Baseline	Normal Range	Baseline Value	Clinically Relevant Value	Value at Last Visit	Clinically Relevant at Last Visit
DRSP/EE	29006	Treatment Cycle 6/ Visit 5	Elevated triglycerides	10-200 mg/dL	112	316	296	Yes
		Follow-up/ Visit 6	Elevated triglycerides	10-200 mg/dL	112	296	296	Yes
Placebo	1010	Follow-up/ Visit 6	Elevated triglycerides	10-200 mg/dL	163	317	317	Yes
	2033	Follow-up/ Visit 6	Elevated AST	0-41 U/L	20	79	79	Yes
		Follow-up/ Visit 6	Elevated ALT	0-45 U/L	21	70	70	Yes
	10076	Follow-up/ Visit 6	Elevated AST	0-41 U/L	18	115	115	Yes
	14016	Follow-up/ Visit 6	Elevated AST	0-41 U/L	20	46	46	Yes
		Follow-up/ Visit 6	Elevated ALT	0-45 U/L	19	76	76	Yes
	14056	Follow-up/ Visit 6	Elevated urea	6-25 mg/dL	24	29	36	Yes
		Unscheduled Visit	Elevated urea	6-25 mg/dL	24	36	36	Yes
		Unscheduled Visit	Elevated ALT	0-45 U/L	31	47	47	Yes
		Unscheduled Visit	Elevated AST	0-41 U/L	32	52	52	Yes
	19002	Treatment Cycle 1/ Visit 3	Elevated triglycerides	10-200 mg/dL	301	459	429	No
	23045	Treatment Cycle 1/ Visit 3	Elevated AST	0-41 U/L	26	72	28	No
		Treatment Cycle 1/ Visit 3	Elevated ALT	0-45 U/L	30	141	29	No
	24020	Follow-up/ Visit 6	Elevated calcium	8.6-10.5 mg/dL	10.1	11.2	10.8	No
	28058	Treatment Cycle 6/ Visit 5	Elevated triglycerides	10-200 mg/dL	174	274	212	No
	28083	Treatment Cycle 6/ Visit 5	Elevated AST	0-41 U/L	22	46	47	Yes
		Follow-up/ Visit 6	Elevated AST	0-41 U/L	22	47	47	Yes
		Treatment Cycle 6/ Visit 5	Elevated ALT	0-45 U/L	21	57	53	Yes
		Follow-up/ Visit 6	Elevated ALT	0-45 U/L	21	53	53	Yes

AST = aspartate aminotransferase; ALT = alanine aminotransferase; DRSP = drospirenone 3 mg; EE = ethinyl estradiol 0.02 mg; LDL = low density lipoprotein

Study 306996:
Overall, similar transitions were observed between the DRSP/EE and the

placebo groups for each parameter. At least 84% of the subjects in both groups had normal values at baseline and Endpoint for all parameters except HDL.

For HDL cholesterol, 73.2% and 81.1% of subjects in the DRSP/EE and placebo groups, respectively, had normal values at baseline and Endpoint, and 8.1% and 8.4% of subjects in the DRSP/EE and placebo groups, respectively, started and ended high in both treatment groups. There were a higher percentage of DRSP/EE subjects that had transitions from normal values at baseline to high HDL values at Endpoint compared with placebo (14.9% of the subjects in the DRSP/EE group versus 6.5% of the subjects in the placebo group at Treatment Cycle 6/ Visit 5).

Fewer subjects experienced clinically relevant chemistry changes from baseline in this study. As in 306820, this study had similar mean values between active and placebo groups. Subjects with clinically relevant changes from baseline in chemistry parameters are shown in the following table:

Clinical Review Table 17
Study 306996: Subjects with Clinically Relevant Changes from Baseline in Chemistry Parameters:

Text Table 22: Subjects With Clinically Relevant Changes from Baseline in Chemistry Parameters

Treatment	Subject Number	Visit	Clinically Relevant Change from Baseline	Normal Range	Baseline Value	Clinically Relevant Value	Value at Last Visit	Clinically Relevant at Last Visit
DRSP/EE	8017	Treatment Cycle 6/ Visit 5	Elevated AST	0-41 U/L	22	191	29	No
	10012	Treatment Cycle 6/ Visit 5	Low sodium	135-148 mval/L	138	131	136	No
			Low potassium	3.5-5.3 mval/L	3.5	3.4	3.6	No
			Low chloride	98-110 mval/L	101	94	97	No
	10022	Treatment Cycle 6/ Visit 5	Elevated triglycerides, fasting	10-200 mg/dL	111	301	149	No
	10043	Treatment Cycle 1/ Visit 3	Elevated ALT	0-45 U/L	20	57	24	No
	10053	Follow-up/ Visit 6	Elevated total cholesterol	120-260 mg/dL	224	279	258	No
	10075	Treatment Cycle 1/ Visit 3	Elevated glucose	70-125 mg/dL	120	157	88	No
	18024	Treatment Cycle 1/ Visit 3	Elevated HDL	25-75 mg/dL	72	77	76	No
	18044	Treatment Cycle 1/ Visit 3	Low glucose	70-125 mg/dL	101	43	85	No
	18056	Treatment Cycle 1/ Visit 3	Elevated triglycerides, fasting	10-200 mg/dL	399	302	53	No
		Treatment Cycle 6/ Visit 5	Elevated triglycerides, fasting	10-200 mg/dL	399	318	53	No
	21004	Treatment Cycle 6/ Visit 5	Low sodium	135-148 mval/L	143	129	139	No
	21010	Unscheduled Visit	Elevated triglyceride, fasting	10-200 mg/dL	275	293	228	No
	26011	Follow-up/ Visit 6	Elevated ALT	0-45 U/L	36	137	162	Yes
		Follow-up/ Visit 6	Elevated AST	0-41 U/L	27	94	94	Yes
Placebo	4003	Follow-up/ Visit 6	Elevated glucose	70-125 mg/dL	103	188	93	No
	10004	Treatment Cycle 6/ Visit 5	Decreased potassium	3.5-5.3 mEq/L	3.6	2.9	3.5	No

AST = aspartate aminotransferase; ALT = alanine aminotransferase; DRSP = drospirenone 3 mg; EE = ethinyl estradiol 0.02 mg; AP = alkaline phosphatase.

Clinical Review Table 17 continues:

Clinical Review Table 17 (continued)
Study 306996: Subjects with Clinically Relevant Changes from Baseline in Chemistry Parameters:

Text Table 22: Subjects With Clinically Relevant Changes from Baseline in Chemistry Parameters

Treatment	Subject Number	Visit	Clinically Relevant Change from Baseline	Normal Range	Baseline Value	Clinically Relevant Value	Value at Last Visit	Clinically Relevant at Last Visit
Placebo	10033	Treatment Cycle 6/ Visit 5	Decreased potassium	3.5-5.3 mEq/L	3.7	3.3	3.4	Yes
		Follow-up/ Visit 5	Decreased potassium	3.5-5.3 mEq/L	3.7	3.3	3.4	No
	10035	Treatment Cycle 1/ Visit 3	Decreased sodium	135-148 mval/L	138	130	137	No
	10047	Treatment Cycle 1/ Visit 3	Decreased sodium	135-148 mval/L	137	130	142	No
	10076	Treatment Cycle 6/ Visit 5	Elevated ALT	0-45 U/L	33	84	54	Yes
		Treatment Cycle 6/ Visit 5	Elevated AP	30-125 U/L	91	133	100	No
		Follow-up/ Visit 6	Elevated ALT	0-45 U/L	33	87	54	Yes
		Follow-up/ Visit 6	Elevated AST	0-41 U/L	21	58	21	No
		Unscheduled Visit	Elevated ALT	0-45 U/L	33	54	54	Yes
	16003	Unscheduled Visit	Elevated ALT	0-45 U/L	44	59	161	Yes
		Follow-up/Visit 6	Elevated ALT	0-45 U/L	44	161	161	Yes
		Unscheduled Visit	Elevated AP	30-125 U/L	121	176	250	Yes
		Follow-up/Visit 6	Elevated AP	30-125 U/L	121	250	250	Yes
		Unscheduled Visit	Elevated AST	0-41 U/L	45	50	101	Yes
		Follow-up/Visit 6	Elevated AST	0-41 U/L	45	101	101	Yes
		Follow-up/Visit 6	Elevated AP	30-125 U/L	121	250	250	Yes
		Follow-up/Visit 6	Elevated AST	0-41 U/L	45	101	101	Yes
	18050	Follow-up/ visit 6	Elevated triglycerides, fasting	10-200 mg/dL	129	297	124	No

AST = aspartate aminotransferase; ALT = alanine aminotransferase; DRSP = drospirenone 3 mg; EE = ethinyl estradiol 0.02 mg; AP = alkaline phosphatase.

Serum Creatinine

Study 306820:
The mean serum creatinine value at baseline for both treatment groups was the same at baseline (0.73 mg/dL in each group). At Endpoint, the mean serum creatinine values were similar between treatment groups (0.75 mEq/L versus 0.74 mEq/L, in the DRSP/EE and placebo groups, respectively). There was no statistically significant difference between the 2 treatment groups at Endpoint. In the DRSP/EE group, none of the subjects had high serum creatinine values at any timepoint during the study.

Study 306996:
The mean serum creatinine value at baseline was 0.74 mg/dL in the DRSP/EE group and 0.73 mg/dL in the placebo group. At Endpoint, the mean serum creatinine value was similar between treatment groups (0.75 mg/dL in the DRSP/EE group and 0.73 mg/dL in the placebo group). All serum creatinine levels in both treatment groups remained within normal laboratory range throughout the study.

Reviewer comment:
In the DRSP/EE groups in both studies, none of the subjects had serum creatinine values outside the normal range at any timepoint during the study.

Creatinine clearance:

Creatinine clearance was calculated using the formula:
Creatinine clearance = [0.85 x (140 – age in years) x weight in kg ÷ (72 x serum creatinine in mg/dL)

The laboratory normal range for creatinine clearance is 80 to 125 mL/min.

Study 306820:

The baseline mean creatinine clearance value was slightly lower in the DRSP/EE group compared with the placebo group (122.64 mL/min versus 130.32 mL/min, respectively), however both of these values were within the normal renal function category (>80 mL/min). During the treatment phase, the mean serum creatinine values were slightly lower in the DRSP/EE group compared with the placebo group. At Endpoint, although both were in the normal renal function category, the mean creatinine clearance values were lower in the DRSP/EE group compared with the placebo group (119.24 mL/min versus 129.03 mL/min, respectively).

The applicant presents data describing differences in the two treatment groups which may explain the differences seen in creatinine clearance. The mean baseline creatinine clearance values were lower in the DRSP/EE group compared with the placebo group (122.64 mL/min versus 130.32 mL/min, respectively). At Endpoint, the mean change from baseline in creatinine clearance values in the DRSP/EE group decreased more compared with the placebo group (-3.246 mL/min versus -1.109 mL/min). There was a statistically significant difference between the two treatment groups (p=0.0164).

This may be attributed to the fact that the baseline mean creatinine clearance value was lower in the DRSP/EE group compared with the placebo group. In addition, the creatinine clearance range at baseline was wider in the placebo group compared with the DRSP/EE group (60.3 to 217.9 mL/min in the DRSP/EE group; 58.9 to 255.4 mL/min in the placebo group).

Greater than 93% of the subjects in both treatment groups had normal renal function throughout the study. In the DRSP/EE group, a maximum of 4% of the subjects had a transition from normal renal function to mild renal impairment, and a maximum of 2% of the subjects had a transition from mild renal impairment to normal renal function during the study. None of the subjects in the DRSP/EE group had moderate or severe renal impairment during the study. In the placebo group, a maximum of 1% of the subjects had a transition from normal renal function to mild renal impairment, and a maximum of 2% of the subjects had a transition from mild renal impairment to normal renal function during the study.

Study 306996:

The baseline mean creatinine clearance value was slightly lower in the DRSP/EE group compared with the placebo group (123.35 mL/min versus 123.53 mL/min, respectively), however both of these values were within the normal renal function category (>80 mL/min). During the treatment phase, the mean serum creatinine values were slightly lower in the DRSP/EE group compared with the placebo group. At Endpoint, although both were in the normal renal function category, the mean creatinine clearance values were lower in the DRSP/EE group compared with the placebo group (120.93 mL/min versus 124.08 mL/min, respectively).

The mean baseline creatinine clearance values were essentially the same in the DRSP/EE group (123.35 mL/min) and placebo group (123.53 mL/min) compared with the placebo group (120.93 mL/min versus 124.08 mL/min, respectively). At Endpoint, the mean change from baseline in creatinine clearance values in the DRSP/EE group decreased more compared with the placebo group (–2.802 mg/dL in the DRSP/EE group and +1.273 in the placebo group). There was a statistically significant difference between the 2 treatment groups (p=0.0041).

This may be attributed to the fact that the baseline mean creatinine clearance value was slightly lower in the DRSP/EE group compared with the placebo group. In addition, the creatinine clearance range at baseline was wider in the placebo group compared with the DRSP/EE group (71.8 to 226.9 mL/min in the DRSP/EE group; 66.8 to 234.3 mL/min in the placebo group). These differences between treatment groups at baseline may result in dissimilarities at Endpoint.

Reviewer Comment: Both studies show a small, but statistically significant difference in creatinine clearance at endpoint when compared to baseline. The rationale presented by the applicant that the active and placebo groups could have been imbalanced at baseline, and had a wider variance, is not fully statistically supported.

The original NDA for YAZ, March 16, 2006, for the indication of contraception, does not report any increased risk of renal impairment with DRSP/EE use. The changes in creatinine clearance noted for DRSP/EE in those studies, which included much larger numbers of patients, were actually less than the changes for the placebo arm for measurements of creatinine clearance.

Since there was no issue with increased serum creatinine levels during the two acne trials for this NDA, and no concern for either assessment of renal function in the reviews for the primary indication, this reviewer concludes that the small decrease in creatinine clearance is not a safety issue of concern for this application. Current labeling for YAZ already includes a bolded warning and contraindication for renal insufficiency.

Hematology:

Study 306820:

Similar transitions were observed between the DRSP/EE group and the placebo group for each hematology parameter. In both treatment groups, at least 83% of the subjects had normal values at baseline and at the treatment visits. Less than 7%of the subjects in both treatment groups had transitions from normal to either high or low during the treatment phase.

The subjects with clinically relevant changes from baseline as judged by the investigator in hematology parameters are presented in the following table:

Clinical Review Table 18
Study 306820--Subjects with Clinically Relevant Hematology Changes From Baseline

Text Table 24: Subjects With Clinically Relevant Changes from Baseline in Hematology Parameters

Treatment	Subject Number	Visit	Clinically Relevant Change from Baseline	Normal Range	Baseline Value	Clinically Relevant Value	Value at Last Visit	Clinically Relevant at Last Visit
DRSP/EE	10010	Follow-up/ Visit 6	Low erythrocytes; anemia due to heavy periods	4 - 5.6 x 10^{12}/L	4.35 x 10^{12}/L	3.84 x 10^{12}/L	3.84 x 10^{12}/L	Yes
		Follow-up/ Visit 6	Low hemoglobin; anemia due to heavy periods	11.3 – 15.6 g/L	11.4	8.8	8.8	Yes
		Follow-up/ Visit 6	Low hematocrit; anemia due to heavy periods	35 – 49%	36.5	30.8	30.8	Yes
	19021	Treatment Cycle 6/ Visit 5	Elevated neutrophils	41 – 80%	59.4	84.6	67.1	No
		Treatment Cycle 6/ Visit 5	Low lymphocytes	17 – 47%	31.3	10.3	26	No
	24003	Follow-up/ Visit 6	Low erythrocytes; according to the investigator, the subject might have had anemia and an infection at the time that the samples were drawn	4 - 5.6 x 10^{12}/L	4.01 x 10^{12}/L	3.35 x 10^{12}/L	3.51 x 10^{12}/L	Yes
		Unscheduled Visit	(see reason above)	4 - 5.6 x 10^{12}/L	4.01 x 10^{12}/L	3.51 x 10^{12}/L	3.5 x 10^{12}/L	Yes
		Follow-up/ Visit 6	Low hemoglobin	11.3 – 15.6 g/L	11.9	10.7	11.2	Yes
		Unscheduled Visit	Low hemoglobin	11.3 – 15.6 g/L	11.2	11.2	11.2	Yes
		Follow-up/ Visit 6	Low hematocrit	35 – 49%	39.2	32.5	33.6	Yes
		Unscheduled Visit	Low hematocrit	35 – 49%	39.2	33.6	33.6	Yes
		Follow-up/ Visit 6	Low WBCs	3.5 – 10.5 x 10^9/L	9.04 x 10^9/L	12.04 x 10^9/L	12.3 x 10^9/L	Yes
		Unscheduled Visit	Low WBCs	3.5 – 10.5 x 10^9/L	9.04 x 10^9/L	12.3 x 10^9/L	12.3 x 10^9/L	Yes
	28089	Treatment Cycle 6/ Visit 5	Low WBCs	3.5 – 10.5 x 10^9/L	14.94 x 10^9/L	16.19 x 10^9/L	12.18 x 10^9/L	No
		Treatment Cycle 6/ Visit 5	Elevated neutrophils	41 – 80%	80.1	80.6	75.3	No
		Treatment Cycle 6/ Visit 5	Low lymphocytes	17 – 47%	15.6	15.9	20.2	No

DRSP = drospirenone 3 mg; EE = ethinyl estradiol 0.02 mg; WBCs = white blood cells.

Notes: Clinically relevant changes were determined by the investigator. Baseline is the last predose measurement.

Text Table 24: Subjects With Clinically Relevant Changes from Baseline in Hematology Parameters (continued)

Treatment	Subject Number	Visit	Clinically Relevant Change from Baseline	Normal Range	Baseline Value	Clinically Relevant Value	Value at Last Visit	Clinically Relevant at Last Visit
Placebo	27014	Treatment Cycle 1/ Visit 3	Low WBCs	3.5 – 10.5 x 10^9/L	2.4 x 10^9/L	2.49 x 10^9/L	2.49 x 10^9/L	Yes
	27040	Treatment Cycle 6/ Visit 5	Low neutrophils; subject presented with viral syndrome symptoms	41 – 80%	42.3	33.1	52.1	No
		Treatment Cycle 6/ Visit 5	Elevated lymphocytes; subject presented with viral syndrome symptoms	17 – 47%	51.5	58.8	37.5	No

DRSP = drospirenone 3 mg; EE = ethinyl estradiol 0.02 mg; WBCs = white blood cells.

Notes: Clinically relevant changes were determined by the investigator. Baseline is the last predose measurement.

Study 306996:

Similar transitions were observed between the DRSP/EE group and the placebo group for each hematology parameter. In both treatment groups, at least 80% of the subjects had

normal values at baseline and at the treatment visits. Less than 8%of the subjects in both treatment groups had transitions from normal to either high or low during the treatment phase. The number and percentage of subjects with transitions from baseline to each visit in hematology parameters with respect to laboratory reference ranges by treatment group are presented in the following table:

Clinical Review Table 19
Study 306996—Subjects with Clinically Relevant Hematology Changes From Baseline

Text Table 24: Subjects With Clinically Relevant Changes from Baseline in Hematology Parameters

Treatment	Subject Number	Visit	Clinically Relevant Change from Baseline	Normal Range	Baseline Value	Clinically Relevant Value	Value at Last Visit	Clinically Relevant at Last Visit
DRSP/EE	10030	Treatment Cycle 1/ Visit 3	Low erythrocytes	4 - 5.6 x 10^{12}/L	4.04 x 10^{12}/L	3.93 x 10^{12}/L	4.55 x 10^{12}/L	No
		Treatment Cycle 1/ Visit 3	Low hematocrit	36 - 47%	35.6	31.7	38.1	No
		Treatment Cycle 1/ Visit 3	Low hemoglobin	11.3 - 15.6 g/dL	10.5	10.6	11.7	No
	10045	Treatment Cycle 1/ Visit 3	Low hematocrit	35 - 49%	37.7	31.9	40.2	No
		Treatment Cycle 1/ Visit 3	Low hemoglobin	11.3 – 15.6 g/L	12.2	10.7	12.8	No
	10075	Treatment Cycle 1/ Visit 3	Elevated WBCs	3.5 – 10.5 x 10^{9}/L	8.03 x 10^{9}/L	14.16 x 10^{9}/L	4.58 x 10^{9}/L	No
	18024	Treatment Cycle 1/ Visit 3	Low lymphocytes	17 47%	15.4	15.6	27.6	No
	22022	Treatment Cycle 6/ Visit 5	Low erythrocytes	4 - 5.6 x 10^{12}/L	4.05 x 10^{12}/L	3.75 x 10^{12}/L	4.35 x 10^{12}/L	No
		Treatment Cycle 6/ Visit 5	Low hematocrit	35 - 49%	36.5	34.6	39.1	No
	26018	Treatment Cycle 1/ Visit 3	Elevated platelets	140-370 x 10^{9}/L	361 x 10^{9}/L	377 x 10^{9}/L	402 x 10^{9}/L	Yes
	26029	Treatment Cycle 6/ Visit 5	Low platelets	140-370 x 10^{9}/L	234 x 10^{9}/L	101 x 10^{9}/L	120 x 10^{9}/L	Yes
Placebo	18029	Treatment Cycle 1/ Visit 3	Elevated platelets	140-370 x 10^{9}/L	525 x 10^{9}/L	712 x 10^{9}/L	626 x 10^{9}/L	Yes
	26010	Treatment Cycle 6/ Visit 5	Elevated platelets	140-370 x 10^{9}/L	316 x 10^{9}/L	437 x 10^{9}/L	301 x 10^{9}/L	No

DRSP = drospirenone 3 mg; EE = ethinyl estradiol 0.02 mg; WBCs = white blood cells.
Notes: Clinically relevant changes were determined by the investigator. Baseline is the last predose measurement.

Reviewer comment: No significant hematology findings were attributable to the drug product.

Urinalysis

There were no subjects with clinically relevant changes from baseline in urinalysis parameters in either study as judged by the investigators or by this reviewer.

7.1.7.5 Special assessments

Serum Potassium Levels:
Study 306820:
The mean baseline serum potassium values for the DRSP/EE and placebo groups were similar (4.05 mEq/L versus 4.07 mEq/L, respectively). The mean serum potassium values remained at similar levels throughout the treatment phase. The range of mean serum

potassium values during the treatment phase was similar in both treatment groups (4.01 to 4.10 mEq/L in the DRSP/EE group and 4.07 to 4.11 mEq/L in the placebo group). At Endpoint, the serum potassium values were similar between treatment groups (4.10 mEq/L versus 4.11 mEq/L in the DRSP/EE and placebo groups, respectively).

The range of the mean change from baseline in serum potassium values during the treatment phase was 0.031 to 0.033 mEq/L in the DRSP/EE group and 0.017 to 0.036 mEq/L in the placebo group. At Endpoint, the mean change from baseline was similar between treatment groups (0.040 mEq/L versus 0.030 mEq/L in the DRSP/EE and placebo groups, respectively). There was no statistically significant difference between the treatment groups.

Five subjects in the YAZ treatment group and 3 in the placebo group had at least one post baseline serum potassium level ≥ 5.5 mEq/L:

Clinical Review Table 20
Study 306820—Number (%) of Subjects with Post-baseline Serum Potassium Levels ≥ 5.5 mEq/L

Text Table 23: Number (%) of Subjects With Postbaseline Serum Potassium Values ≥5.5 mEq/L (Safety Analysis Set)

	DRSP/EE (N = 266)	Placebo (N = 268)	P-value[a]
Number of subjects with at least 1 postbaseline serum potassium value	248	251	
n (%)[b]	5 (2.0%)	3 (1.2%)	0.5327

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

[a] P-value is from the StatXact.
[b] Percentage is based on the number of subjects with at least 1 postbaseline serum potassium value.

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Clinical Review Table 21
Study 306820--List of Post-baseline Serum Potassium Levels ≥ 5.5 mEq/L

Table 133: Subjects With Postbaseline Serum Potassium Values >= 5.5 (mEq/L)
(Safety Analysis Set)

Treatment Group	Subject	Visit	Potassium (K) (mval/l,mEq/l)	Creatinine (mg/dl)
DRSP/EE	9011	Screening	4.4	0.9
		Treatment Cycle 1	4	0.8
		Treatment Cycle 6	5.7	0.7
		Follow-up	5.2	0.8
	11113	Screening	4.5	0.7
		Treatment Cycle 1	5.6	0.7
		Treatment Cycle 6	5.7	0.6
		Follow-up	4	0.7
	17015	Screening	3.7	0.7
		Treatment Cycle 1	6.5 *	0.7
		Follow-up	3.9	0.7
	19036	Screening	5.3	0.7
		Treatment Cycle 1	5.6	0.8
		Treatment Cycle 6	5.2	0.8
		Follow-up	5	0.7
	23051	Screening	4.2	0.8
		Treatment Cycle 1	5.6	0.8
		Treatment Cycle 6	4.9	0.8
		Follow-up	4	0.7
placebo	11063	Screening	5.8	0.7
		Treatment Cycle 1	5.5	0.7
		Treatment Cycle 6	5.2	0.7
		Follow-up	4.6	0.8

Continued...

Note:
* Value >= 6.0 mEq/L

Clinical Review Table 21, Continued
Study 306820--List of Post-baseline Serum Potassium Levels ≥ 5.5 mEq/L

Table 133: Subjects With Postbaseline Serum Potassium Values >= 5.5 (mEq/L)
(Safety Analysis Set)

Treatment Group	Subject	Visit	Potassium (K) (mval/l,mEq/l)	Creatinine (mg/dl)
placebo	19028	Screening	5.5	0.9
		Treatment Cycle 1	5.2	0.8
		Treatment Cycle 6	5.3	0.7
		Follow-up	5.5	0.7
	23062	Screening	4.5	0.9
		Treatment Cycle 1	5.7	1
		Treatment Cycle 6	3.4	0.9
		Follow-up	4.4	0.9

Patient 17015, with a maximal potassium level of 6.5 mEq/L, had a sample which was left out overnight in a laboratory error, and the investigator did not consider the elevated potassium to be clinically relevant. At follow up, potassium returned to within the normal range (3.9 mEq/L), creatinine and creatinine clearance were unchanged. The subject did not experience any cardiovascular AEs during treatment, but prematurely discontinued study medication due to an AE (nausea). The other four active subjects all completed the study and had no cardiovascular adverse events at the time of the elevated potassium level, or at any time during the study.

The mean serum potassium values at baseline were similar between the 2 treatment groups. The mean changes from baseline in post baseline maximum serum potassium value (0.22 versus 0.21 mEq/L in the DRSP/EE and placebo groups, respectively) and post baseline average serum potassium value (0.00 versus 0.02 mEq/L in the DRSP/EE and placebo groups, respectively) were small for both treatment groups. There was statistically significant difference between the 2 treatment groups in these 2 parameters.

None of the subjects in either treatment group with post baseline serum potassium values $\geq$ 5.5 mEq/L had a corresponding high serum creatinine value. There was no correlation between elevated potassium values and changes in creatinine clearance.

Study 306996:

The mean serum potassium value at baseline was 4.12 mEq/L in both treatment groups. The mean serum potassium values remained at similar levels throughout the treatment phase. The range of mean serum potassium values during the treatment phase was similar in both treatment groups (4.05 to 4.09 mEq/L in the DRSP/EE group and 4.02 to 4.07 mEq/L in the placebo group). At Endpoint, the serum potassium values were similar between treatment groups (4.09 mEq/L versus 4.08 mEq/L in the DRSP/EE and placebo groups, respectively).

The range of the mean change from baseline in serum potassium values during the treatment phase was -0.041 to -0.049 mEq/L in the DRSP/EE group and -0.018 to -0.091 mEq/L in the placebo group. At Endpoint, the mean change from baseline was similar between treatment groups (–0.051 mEq/L in the DRSP/EE group and –0.035 mEq/L in the placebo group). There was no statistically significant difference between the treatment groups.

In the DRSP/EE group, 3 subjects that had normal levels at baseline had serum potassium values >5.3 mEq/L: 1 subject at Treatment Cycle 6 and 2 subjects at the follow-up visit. In the placebo group, 3 subjects that had normal levels at baseline had serum potassium values >5.3mEq/L: 1 subject at Treatment Cycle 1 and in 2 subjects at the follow-up visit.

This is presented in the following table:

Clinical Review Table 23
Study 306996
Number (%) of Subjects with Post-baseline Serum Potassium Levels ≥ 5.5 mEq/L

Text Table 23: Number (%) of Subjects With Postbaseline Serum Potassium Values ≥5.5 mEq/L (Safety Analysis Set)

	DRSP/EE (N = 270)	Placebo (N = 268)	P-value[a]
Number of subjects with at least 1 postbaseline serum potassium value	254	252	
n (%)	2 (0.8%)	5 (2.0%)	0.2669

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

[a] P-value is from the StatXact.

[b] Percentage is based on the number of subjects with at least 1 postbaseline serum potassium value.

Clinical Review Table 24
Study 306996--List of Post-baseline Serum Potassium Levels ≥ 5.5 mEq/L

Table 133: Subjects With Postbaseline Serum Potassium Values >= 5.5 (mEq/L)
(Safety Analysis Set)

Treatment Group	Subject	Visit	Potassium (K) (mval/l,mEq/l)	Creatinine (mg/dl)
DRSP/EE	11007	Screening	4	0.7
		Treatment Cycle 1	3.9	0.6
		Treatment Cycle 6	6.5 *	0.7
		Follow-up	4.4	0.6
	11041	Screening	5	0.9
		Treatment Cycle 1	4.7	0.9
		Treatment Cycle 6	5.2	1
		Follow-up	5.7	0.9
placebo	8018	Screening	4	0.9
		Treatment Cycle 1	5.8	0.9
		Treatment Cycle 6	4	0.8
		Follow-up	4.1	0.9
	12001	Screening	4	0.7
		Treatment Cycle 1	4.9	0.7
		Treatment Cycle 6	4.2	0.7
		Follow-up	5.5	0.6
	21047	Screening	5.5	0.9
		Treatment Cycle 1	5.5	0.9
		Treatment Cycle 6	4.1	0.7
		Follow-up	4.1	0.8
	21053	Screening	4.7	0.7
		Treatment Cycle 1	3.5	0.7
		Treatment Cycle 6	4.7	0.6
		Follow-up	5.7	0.8

Continued...

Note:
* Value >= 6.0 mEq/L

Clinical Review Table 24, continued
Study 306996--List of Post-baseline Serum Potassium Levels ≥ 5.5 mEq/L

Table 133: Subjects With Postbaseline Serum Potassium Values >= 5.5 (mEq/L)
(Safety Analysis Set)

Treatment Group	Subject	Visit	Potassium (K) (mval/l,mEq/l)	Creatinine (mg/dl)
placebo	23018	Screening	4.4	0.7
		Treatment Cycle 1	4.4	0.7
		Treatment Cycle 6	6.5 *	0.7
		Follow-up	3.5	0.7

Subject 11007, with a reported peak potassium level of 6.5 mEq/L at treatment cycle 6, was not considered clinically relevant by the investigator, and the subject did not report any of the cardiovascular adverse events. She had a history of asthma and pulmonary fibrosis, and listed albuterol and beclomethasone as concomitant medications.

None of the subjects in either treatment group with post baseline serum potassium values ≥ 5.5 mEq/L had a corresponding high serum creatinine value. There was no correlation between elevated potassium values and changes in creatinine clearance.

Reviewer comment: Although there is a possible risk of hyperkalemia with drospirenone use based on its mechanism of action, there is no evidence in either trial of significant hyperkalemia or any cardiovascular symptomatology. The slight increases in potassium appear relatively similar in the treated and placebo groups. No clinically related symptoms are reported for any of the elevated values.

In the review for the original approval for contraception, there was a small but increased percentage of DRSP/EE subjects as compared to placebo subjects who had increases in potassium levels outside the normal range over the course of treatment. These elevated potassium levels were not associated with cardiovascular sequelae in any case, and tended to resolve without discontinuation of the drug product. Currently approved labeling is adequate to inform the risks of hyperkalemia in YAZ treated patients.

7.1.8 Vital Signs

7.1.8.1 Overview of vital signs testing in the development program

There were no statistically significant differences in the change from baseline to Endpoint in blood pressure between the 2 treatment groups in either study. There were no unusual findings in vital signs, including blood pressure and heart rate.

No clinically significant body weight changes were observed during the clinical studies. No changes in other vital signs were noted during the studies.

7.1.9 Electrocardiograms (ECGs)

Electrocardiograms were not reported as part of the safety assessment in either study.

7.1.11 Human Carcinogenicity

Studies were not of sufficient duration to permit assessment of carcinogenicity.

7.1.12 Special Safety Studies

Hormone Evaluation:

Study 306820:
For a subpopulation of subjects (18 subjects in the DRSP/EE group and 18 subjects in the placebo group), the following hormones were evaluated: total testosterone, free testosterone, DHEA-S, SHBG, and androstenedione. For all the hormones tested, there were no statistically significant differences between treatment groups at baseline.
As expected, within the DRSP/EE group, there were statistically significant decreases in the mean changes from baseline to Endpoint in levels of free testosterone and androstenedione, and statistically significant increases in levels of SHBG. Within the placebo group, there were no statistically significant differences in the mean change from baseline to endpoint in any of the hormones evaluated. These hormonal changes are expected from low dose oral contraceptives. None of the other hormones evaluated showed any statistically significant differences between treatment groups.

Study 306996 had no subpopulation hormonal analysis.

7.1.13 Withdrawal Phenomena and/or Abuse Potential

YAZ does not have a known abuse potential, does not produce withdrawal phenomena, and does not belong to a class of compounds associated with these effects.

7.1.14 Human Reproduction and Pregnancy Data

Study 306820:

Positive urine pregnancy test results were observed at Treatment Cycle 1 (by 1 subject in the placebo group), and Treatment Cycle 6 (by 2 subjects in the DRSP/EE group, and 2 subjects in the placebo group). There were no positive serum pregnancy tests at screening, during the treatment phase, or at Follow-up Visit. In the DRSP/EE group, at the end of the study or at premature discontinuation, there were 4 (1.5%) ongoing pregnancies and 2 (0.8%) subjects in the "other" category (1 subject was lost to follow-up and 1 subject had a serum pregnancy test that showed an indeterminate result). In the placebo group, there were 3 (1.1%) ongoing pregnancies, 1 (0.4%) abortion, and 1 (0.4%) subject categorized as "other" (pregnancy status was unknown)

Study 306996:
There were no positive urine pregnancy test results observed at baseline. Positive urine pregnancy test results were observed by 3 subjects in the DRSP/EE group and 6 subjects in the placebo group at Treatment Cycle 6.

In the DRSP/EE group, at the end of the study or at premature discontinuation, there were 4 (1.5%) ongoing pregnancies. In the placebo group there were 8 (3.0%) ongoing pregnancies, 1 (0.4%) abortion, 1 (0.4%) ectopic pregnancy, and 1 (0.4%) subject categorized as "other" (lost to follow-up due to pregnancy).

7.1.17 Postmarketing Experience

As part of the risk management program for YAZ, the International Active Surveillance

(INAS) Study began in the USA in August 2005. The study began with recruitment of Yasmin (DRSP 3mg/EE 0.03 mg) and other OC initiators. Recruitment of YAZ initiators first began following its market introduction in late April 2006. At the end of 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.

Periodic Adverse Event Reporting
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), and was reviewed by Gerald Willett, MD of DRUP. Three initial non-serious reports were included, blue stools, pain and burning in left forearm and thigh, and severe acne.

7.2 Adequacy of Patient Exposure and Safety Assessments

The completed phase 2 and phase 3 studies comprising the safety database for DRSP 3 mg / 0.02 mg EE, were reviewed in the NDA submission 21-676, and are listed in the following table from that review:

Clinical Review Table 25
Completed Studies of 3 mg DRSP/0.02 mg EE (24 and 21 day regimens)

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

* = Derived from multiplying #subjects x mean days on drug/ 28 days
**= Based on 961 subjects completing, does not include the cycles from those prematurely discontinuing
Source: Tables of studies and individual Study reports (NDA 21-676 and NDA 21-873)

Reviewer comment:
The overall exposure in terms of numbers of subjects and duration of exposure is acceptable.

7.2.1 Description of Primary Clinical Data Sources (Populations Exposed and Extent of Exposure) Used to Evaluate Safety

The two additional studies for acne considered in this review, 302820 and 302996, add 266 and 270 patients, respectively, to the safety database. In the YAZ treated group, 75% completed six 28 day cycles of treatment.

7.2.3 Adequacy of Overall Clinical Experience

451 patients were treated with YAZ in these two trials for acne vulgaris. The age and racial makeup of the population was adequate. The dosing regimen was determined by the prior approval, March, 2006, of YAZ for oral contraception. The safety profile for the product includes patients who were studies for the indications of oral contraception and pre-menstrual dysphoric disorder in addition to the two studies reviewed here for acne.

The design of the two pivotal studies, 306820, and 306996, is acceptable to assess safety and efficacy. Exposure of YAZ now includes greater than 3300 study subjects.

7.2.4 Adequacy of Special Animal and/or In Vitro Testing

No additional animal or in-vitro testing was performed for the acne indication.

7.2.5 Adequacy of Routine Clinical Testing

The clinical testing of laboratory values was adequate for the acne studies.

7.2.6 Adequacy of Metabolic, Clearance, and Interaction Workup

No additional metabolic, clearance, or interaction studies were performed for the acne indication.

7.2.7 Adequacy of Evaluation for Potential Adverse Events for Any New Drug and Particularly for Drugs in the Class Represented by the New Drug; Recommendations for Further Study

Assessment of potential adverse events was acceptable and post marketing surveillance by DRUP for thromboembolic and other potential adverse events is now ongoing.

7.2.8 Assessment of Quality and Completeness of Data

Deficiencies in the quality or completeness of the safety data were not identified.

7.2.9 Additional Submissions, Including Safety Update

The applicant submitted a safety update with information for the reporting interval January 23, 2006- October 17, 2006. During this period, one unsubmitted foreign Phase 3 pivotal study was ongoing with DRSP 3 mg and EE 0.02 mg tablets: Protocol 308683, "A multicenter, open, randomized, parallel-group comparison to assess the safety and efficacy of the oral contraceptive SH T 00186 D (0.02 mg ethinyl estradiol as betadex clathrate and 3 mg drospirenone) in two variations of an extended regimen vs. a standard regimen (24 + 4 days) in 1122 healthy female volunteers for one year, followed by a 1-year mono-arm safety extension in one variation of the extended regimen". The primary endpoint of this study is the number of bleeding days. The secondary endpoint is the Pearl Index. In addition, metabolic and hematology parameters, biomarkers of bone turnover and bone mineral density will be investigated in subgroups. More than 1,150 women have been enrolled into the study across 38 centers [Germany-31, Canada-6, and Netherlands-1]. First patient first visit was December 2005 and last patient first visit was August 2006.

Two other foreign, phase 3 studies were previously submitted to DRUP in August, 2006, under NDA 21-873.

In the previously unsubmitted protocol 308683, one 25 year old patient presented with right leg pain and was diagnosed by Doppler ultrasound to have a deep venous thrombosis. While she was only 28 days into the study, she had a history of Yasmin use for eight months immediately prior to entering the YAZ study. The patient has not yet fully recovered. The company report judges the association with YAZ as "possible".
Reviewer comment: The association with these similar products is very likely.

An additional patient, #4397, sustained a meniscus injury 2 months into treatment and one day post operatively sustained a crural vein thrombosis. The site of the knee injury and side of the lower leg thrombosis are not specified. The applicant judged this association as "unlikely".
Reviewer comment: The association of YAZ and the post operative thrombosis seems likely.

Patients discontinued study medication for similar reasons in the two acne studies reviewed above. The ethnic distribution of patients was greater than 99% Caucasian.

The applicant states that no new safety information in the medical literature would warrant changes in labeling for safety reasons.

The safety update also includes two fatal outcomes that are submitted as Medwatch reports since the most recent update provided to DRUP. Information on both cases is limited and unverified. One patient died from a pulmonary embolus, but duration of therapy and concomitant medications and history are unknown. A 24 year old died from a cavernous sinus thrombosis after a period of treatment with four different oral contraceptives, of which one was Yasmin for a two month period five months prior to the fatal event. Attempts at obtaining follow up information were reportedly unsuccessful.

Reviewer comment:
This reviewer agrees with the applicant conclusion that there is no new safety information which would warrant a change in the currently approved labeling.

7.3 Summary of Selected Drug-Related Adverse Events, Important Limitations of Data, and Conclusions

The lower exposure to ethinyl estradiol in YAZ as compared to Yasmin, may offer a safety advantage. The lack of any thromboembolic events in the two acne studies presented in this submission is reassuring, but the total number of patients (451) is not sufficient to draw substantive conclusions regarding short or long term safety. While shortened hormone free intervals should theoretically reduce hormone withdrawal symptoms, especially withdrawal

bleeding, the assessment of whether this could increase the risk of thromboembolism awaits the results of the long term post marketing study under the auspices of DRUP which is expected to enroll 50,000 patients.

The currently available evidence is reassuring on this matter. The DRUP team leader memoranda for NDA 21-676 and 21-873 for YAZ notes an overall venous thromboembolic event rate of approximately 6.1 per 10,000 women-years for the DRSP/EE overall clinical trial experience of 42,366 28 day treatment cycles. The calculated rate for Yasmin, which has a higher EE component, has a VTE rate of 13.7-15 cases per 10,000 woman years. The cases of pulmonary embolus occurred in the 21 day dosing regimen rather than the 24 day dosing regimen that is the agent in this submission. To date there is no suggestion of higher risk for the development of serious thrombotic events for the 24 day YAZ dosing.

The theoretical risk of hyperkalemia was not demonstrated to be an issue in these acne trials. The frequency of elevated potassium levels was similar in both treatment arms, and none of the subjects experiencing elevated potassium levels reported any cardiovascular event. Post-marketing reports to date have revealed no increased risk of serious adverse events secondary to hyperkalemia. The currently approved YAZ labeling contains bolded warnings about the potential risk of hyperkalemia and the recommendation to monitor potassium when taking long term medications that may increase serum potassium.

The common adverse events are known to be associated with oral contraceptives and are similar in scope to class labeling for hormonal contraceptive products.

The safety profile for YAZ is acceptable for an effective hormonal contraceptive product, and YAZ may provide a benefit for women who choose oral hormonal contraceptives in the treatment of moderate acne.

8. ADDITIONAL CLINICAL ISSUES

8.3 Special Populations

There are no special dosing recommendations for demographics based on the clinical trial data beyond the current labeling approved by DRUP.

8.4 Pediatrics

The applicant seeks an indication for YAZ that is similar to the currently approved labeling:

The applicant has requested a full waiver of the requirement for pediatric studies for patients 0-11 years, justified by the small number of patients in this age range who would use the product for pregnancy prevention and the treatment of acne vulgaris.

Reviewer comment: This reviewer agrees that a waiver of pediatric studies is warranted for patients from 0-11 years. The current labeling is supported and recommended for this application:

8.7 Postmarketing Risk Management Plan

There are no recommendations for specific post marketing risk management plans beyond the current recommendations of DRUP.

8.8 Other Relevant Materials

See final product labeling.

9. OVERALL ASSESSMENT

9.1 Conclusions

YAZ is safe and effective for the secondary indication of acne vulgaris for post-menarchal women who desire an oral contraceptive and

9.2 Recommendation on Regulatory Action

Approval is recommended for YAZ, NDA 22-045, drospirenone 3 mg/ ethinyl estradiol 0.02 mg tablets for the secondary indication of acne vulgaris in post-menarchal women who desire an oral contraceptive. The current data submitted in this application show efficacy in two studies over all efficacy endpoints. Safety data reviewed to date indicate that the safety population exposure was adequate and that the safety profile of YAZ is acceptable.

9.3 Recommendation on Postmarketing Actions

A Phase IV Commitment surveillance study for arterial and venous thromboembolic events and a risk management plan similar to Yasmin in regard for the potential for hyperkalemia is already ongoing under the contraception NDA 21-676. The INAS surveillance study will recruit 50,000 women and follow them every 6 months for 3 years.

No additional post-marketing actions are recommended by DDDP for YAZ.

9.3.1 Risk Management Activity

Ongoing risk management includes an educational program for health care providers stressing the contraindications for use and additional risks related to its potential for hyperkalemia. The education program will continue for 3 years after the April, 2006 launch of YAZ in the United States.

Risk management for the acne vulgaris indication will be primarily addressed through labeling. Labeling stresses that acne is a secondary indication for this product, and will be a secondary benefit to women who choose to use an oral contraceptive and have been [redacted] Acne is a skin condition with a multifactorial etiology and YAZ should not be the primary therapy to address the needs of patients with moderate acne. Labeling will also clarify that YAZ [redacted]

9.3.2 Required Phase 4 Commitments

No additional phase 4 commitments are required.

9.3.3 Other Phase 4 Requests

There are no other phase 4 requests.

9.4 Labeling Review

In a letter dated November 3, 2006, the applicant submitted proposed labeling changes from the recently approved label dated October 4, 2006 which included the newly approved PMDD indication. The applicant requested the use of a new trade name specifically for the tablets indicated for oral contraception and moderate acne vulgaris. *Skyla* was the new proposed brand name.

A teleconference was held with the applicant on November 15, 2006 and included members of DMETS as well as representatives from DRUP. The various Agency divisions unanimously agreed that a separate trade name for the same product was unacceptable. The applicant was informed that the dual brand name would not be acceptable at the conclusion of that teleconference. Draft labeling was internally reviewed using only the YAZ brand name. The applicant was notified on November 21, 2006 that a labeling amendment would need to be submitted to NDA 22-045, and they could respond to the Agency's proposed draft labeling at that time.

9.5 Comments to Applicant

There are no comments to convey to the applicant.

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/s/

David Kettl
12/21/2006 11:06:34 AM
MEDICAL OFFICER

Markham Luke
12/21/2006 12:08:22 PM
MEDICAL OFFICER
I concur with Dr. Kettl's approval recommendation pending agreement on labeling with the applicant.

Stanka Kukich
12/22/2006 10:24:38 AM
MEDICAL OFFICER

Summary Memorandum
YAZ NDA Application for Acne vulgaris
NDA 22-045

January 18, 2007

YAZ is a combination of drospirenone 3 mg and ethinyl estradiol 0.02 mg, currently indicated for use as an oral contraceptive regimen. Currently, four oral contraceptives have approval for marketing that includes an indication for the treatment of acne vulgaris: Ortho Tri-Cyclen (both 21 and 28 tablet packages) and Estrostep (both Estrostep 21 and Estrostep Fe). These products allow for added treatment claims for acne vulgaris in women who desire and can use oral contraception. Thus, the acne vulgaris claim is secondary and applies only to the subset of women who would also use the product as an oral contraceptive. YAZ seeks addition to its product labeling that would allow a similar claim, i.e., "indicated for the treatment of moderate acne vulgaris in women at least 14 years of age who have no known contraindications to oral contraceptive therapy, and have achieved menarche. YAZ should be used for the treatment of acne only if the patient desires an oral contraceptive for birth control."

In keeping with the notion that the indication is secondary to contraceptive use, submitted language for labeling regarding use of the drug [redacted] This was not an exclusion criteria for the clinical study.

Efficacy

As per the FDA statistical and clinical reviews, YAZ has adequately demonstrated efficacy by being statistically superior to placebo in two studies (Study 306820 and Study 306996) in the treatment of moderate acne. Efficacy was evaluated via success rate based on the Investigator Static Global Assessment (ISGA) score and percent change from baseline for two out of three lesion-type counts (inflammatory, non-inflammatory, and total) at Day 15 of Treatment Cycle 6.

The data from these studies are summarized in the table below (Table 1) from Dr. Clara Kim's review. The information from this table provides adequate and objective information for labeling to inform the practicing physician. Prior submitted language regarding the need for [redacted] with this product may not be required as the data presented states the efficacy endpoint. Thus, a modified version of Table 1 will be presented in the Patient Package Insert for labeling.

Table 1: Efficacy Results Summary - Number (Proportion) of success on ISGA and Mean Baseline and % Reduction (SD) in Lesion Counts

	Study 306820		Study 306996	
	YAZ	Placebo	YAZ	Placebo
	N=228	N=230	N=218	N=213
ISGA				
Number of Successes	35 (15.4%)	10 (4.3%)	46 (21.1%)	19 (8.9%)
p-value*		0.0001		0.0003
Inflammatory				
Baseline count	32.61 (16.1)	32.84 (14.6)	31.73 (12.4)	31.81 (13.7)
% reduction	47.60% (35.4%)	32.34% (37.3%)	50.60% (38.3%)	34.46 (49.7%)
p-value†		<0.0001		<0.0001
Non-inflammatory				
Baseline count	47.27 (31.4)	46.99 (30.6)	43.85 (22.9)	43.85 (25.9)
% reduction	38.08% (39.0%)	18.22% (47.9%)	42.35% (38.5%)	26.02% (48.2%)
p-value†		<0.0001		<0.0001
Total				
Baseline count	79.88 (42.3)	79.83 (37.2)	75.60 (30.7)	75.67 (33.9)
% reduction	42.33% (32.7%)	25.29% (36.4%)	46.13% (33.7%)	30.64% (41.9%)
p-value†		<0.0001		<0.0001

* p-values are calculated using a logistic model with treatment and pooled centers as factors

† p-values are calculated using ANCOVA model: Baseline lesion count as covariate, and treatment, center, and treatment by center interaction (if statistically significant) as factors.

Source: Reviewer analysis

Safety

The safety of the drug was reviewed by both Dr. David Kettl, the primary clinical reviewer, and the Division of Reproductive and Urology Products (DRUP). No new signals emerged from the clinical studies conducted with YAZ for acne vulgaris. Thus, no changes are recommended to the known safety profile of the currently marketed YAZ product.

Tradename

During the review cycle, the applicant, Berlex, proposed a new name for the product (Skyla), to allow for channeled marketing. The applicant's proposed rationale for the new name to be used alongside YAZ was not supported adequately. The acne vulgaris indication is to be secondary to or a subset of patients who desire and are eligible for use of this drug as an oral contraceptive indication. Thus, the Agency proposed and the applicant accepted maintaining YAZ as the sole Tradename for this product.

Recommendation

In agreement with the primary clinical review, YAZ is recommended to be approved for use in the treatment of moderate acne vulgaris in women at least 14 years of age, who have no known contraindications to oral contraceptive therapy, and have achieved menarche. YAZ should be used for the treatment of acne only if the patient desires an oral contraceptive for birth control.

Markham C. Luke, M.D., Ph.D.
Lead Medical Officer, Dermatology

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/s/

Markham Luke
1/18/2007 11:33:43 AM
MEDICAL OFFICER
Summary Memorandum

Stanka Kukich
1/22/2007 11:44:42 AM
MEDICAL OFFICER