

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:
022532sOrig1s000

SUMMARY REVIEW

Summary Review for Regulatory Action

Date	September 24, 2010
From	Scott Monroe, MD
Subject	Division Director Summary Review
NDA	NDA 022532
Applicant Name	Bayer Healthcare Pharmaceuticals, Inc.
Date of Submission	August 24, 2009
PDUFA Goal Date	September 24, 2010 (with 3 month extension)
Proprietary Name	Beyaz
Established (USAN) Name	Drospirenone (DRSP)/ethinyl estradiol (EE)/levomefolate calcium (LMF) tablets and levomefolate calcium tablets)
Dosage Forms/Strengths	Oral tablets: (3 mg DRSP/0.02 mg EE/0.451 mg LMF) tablet and 0.451 mg LMF tablet
Proposed Indications	Primary Indication: prevention of pregnancy Secondary Indications: (1) treatment of symptoms of premenstrual dysphoric disorder; (2) treatment of moderate acne vulgaris in women at least 14 yrs of age; (b) (4)
Proposed Regimen	One DRSP/EE/LMF tablet daily x 24 days followed by one LMF tablet daily x 4 days
Action	<i>Approve (see Section 13.1)</i>

Material Reviewed/Consulted OND Action Package, including:	Names of Discipline Reviewers
Medical Officer Review	Daniel Davis MD (primary Clinical Reviewer)
Statistical Review	Sonia Castillo PhD/Mahboob Sobhan PhD
Pharmacology Toxicology Review	Leslie McKinney PhD/Alexander Jordan PhD
CMC Review	Hitesh Shroff PhD/Moo-Jhong Rhee PhD
Microbiology Review	Not required
Clinical Pharmacology Review	Doanh Tran PhD/Myong-Jin Kim PharmD
DDMAC	Janice Maniwang PharmD/Carrie Newcomer PharmD
DSI	Sean Kassim PhD/Hyojong Kwon PhD
CDTL Review	Lisa Soule MD (also Clinical Team Leader)
OSE/DMEPA	Richard Abate RPh/Melina Griffis RPh
OSE/DRISK	Not required (PPI is class labeling for an oral contraceptive)

OND=Office of New Drugs

CMC=Chemistry, Manufacturing and Controls

DDMAC=Division of Drug Marketing, Advertising, and Communication

OSE=Office of Surveillance and Epidemiology

DMEPA=Division of Medication Errors Prevention and Analysis

DSI=Division of Scientific Investigations

DRISK=Division of Risk Management

CDTL=Cross Discipline Team Leader

DIVISION DIRECTOR SUMMARY REVIEW

1. INTRODUCTION

Bayer Healthcare Pharmaceuticals, Inc. submitted NDA 022532 to obtain marketing approval for Beyaz (drospirenone [DRSP]/ethinyl estradiol [EE]/levomefolate calcium tablets and levomefolate calcium tablets), a new combination oral contraceptive. Levomefolate, a metabolite of folic acid, is a naturally occurring folate found in foods. Levomefolate calcium (also referred to as levomefolate in the review) has been added to the DRSP/EE drug product to provide daily folate supplementation in women of childbearing potential. Beyaz (also referred to as DRSP/EE/levomefolate tablets or Yaz + levomefolate in this summary review) is identical to the Applicant's currently marketed oral contraceptive Yaz (3 mg DRSP/0.02 mg EE tablets), with the exception that Yaz does not contain levomefolate. Yaz was originally approved in 2006 with the indication of "prevention of pregnancy in women who elect to use an oral contraceptive." Secondary indications for Yaz that were approved after 2006 are (1) treatment of symptoms of premenstrual dysphoric disorder (PMDD) in women who choose to use an oral contraceptive for contraception and (2) treatment of moderate acne vulgaris in women at least 14 years of age only if the patient desires an oral contraceptive for birth control. The Applicant has added levomefolate to DRSP/EE tablets (Yaz) to obtain the following proposed additional indication for Beyaz: (b) (4)

This Application contained the necessary chemistry, manufacturing and controls (CMC), clinical pharmacology, and clinical information to support approval. The Applicant did not conduct any new nonclinical studies with levomefolate or any nonclinical studies with Beyaz, in accordance with a prior agreement with the Division of Reproductive and Urologic Products (DRUP). The Applicant provided clinical data from 4 studies (2 bioequivalence studies and 2 pharmacodynamic studies) in support of their proposed additional secondary indication of (b) (4)

Significant issues identified during the review included (1) sample preparation/analytical problems regarding the measurement of red blood cell (RBC) folate concentrations and (2) the exact wording of one of the secondary indications. Both issues were adequately addressed and all primary reviewers, as well as the cross discipline team leader (CDTL), have recommend that Beyaz be approved with revised wording for one of the secondary indications: "*Beyaz is indicated for women who choose to use an oral contraceptive as their method of contraception, to raise folate levels for the purpose of reducing the risk of a neural tube defect in a pregnancy conceived while taking the product or shortly after discontinuing the product.*" I concur with the recommendations of the primary reviewers and the CDTL that Beyaz be approved. The approved indications should include the secondary indication listed immediately above as well as those indications currently approved for Yaz. These latter indications are: prevention of pregnancy (primary indication), treatment of symptoms of premenstrual dysphoric disorder (secondary indication), and treatment of moderate acne vulgaris in women at least 14 yrs of age (secondary indication).

2. BACKGROUND

2.1 Description of the Product

Beyaz (drospirenone/ethinyl estradiol/levomefolate calcium tablets and levomefolate calcium tablets) will be available in blister packs. Each blister pack will contain 28 tablets arranged in the following order:

- 24 pink tablets each containing 3 mg drospirenone (DRSP), 0.02 mg ethinyl estradiol (EE) as betadex clathrate, and 0.451 mg levomefolate calcium
- 4 light orange tablets each containing 0.451 mg levomefolate calcium

One oral tablet is to be taken at the same time every day. Beyaz will be the first approved combination oral contraceptive (COC) to contain levomefolate calcium.

Drospirenone is a spironolactone analogue with progestational, antimineralocorticoid, and antiandrogenic activity. Both DRSP and EE are available in the approved COC products Yaz and Yasmin, as well as in generic versions of these products. Ethinyl estradiol, in combination with various progestins, is the estrogen component in almost all currently marketed COCs.

Levomefolate calcium is the calcium salt of L-5-methyltetrahydrofolate (L-5-MTHF), a metabolite of vitamin B9 (folic acid) and the predominant form of folate found in foods and in the blood circulation. The dose of 0.451 mg levomefolate calcium is equimolar to 0.4 mg of folic acid. Equimolar doses of levomefolate calcium and folic acid were shown by the Applicant to produce similar increases in plasma and red blood cell folate levels (Figure 3 and Figure 4). Levomefolate is approved as a food additive and is designated a GRAS (generally regarded as safe) compound.

2.2 Rationale and History for Addition of a Folate to a Combination Oral Contraceptive

Neural tube defects (NTDs) are the second most common group of serious congenital anomalies. They result from the failure of the neural tube to close in the cranial region (anencephaly) or more caudally along the spine (spina bifida) by the end of the first month of gestation. It has been estimated that in 1998 approximately 300,000 births worldwide were affected by a NTD. In the US, about 4,000 pregnancies were affected in 1995-1996. This number declined to 3,000 pregnancies in 1999-2000 after fortification of enriched cereal grain products with folic acid was mandated.¹

Improvement in folate status prior to pregnancy is highly desirable due to the association of NTDs with low folate levels. In 1992, the US Public Health Service (USPHS) recommended that “all women of childbearing age in the United States who are capable of becoming pregnant should consume 0.4 mg of folic acid per day for the purpose of reducing their risk of having a pregnancy affected with spina bifida or other NTDs.”² Since 1998, FDA has required that all enriched cereal grain products sold in the US include 0.14 mg of folic acid per 100 grams of product. In 2009, the US Preventive Services Task Force reviewed and concluded that “new

¹ CDC Grand Rounds: Additional Opportunities to Prevent Neural Tube Defects with Folic Acid Fortification. MMWR 2010; 59:980-984.

² Centers for Disease Control. Recommendations for the Use of Folic Acid to Reduce the Number of Cases of Spina Bifida and Other Neural Tube Defects. MMWR 1992; 41 (No. RR-14):1-7.

evidence from observational studies provides weight to previous evidence from controlled trials that folic acid supplementation provides benefit in reduction of risk from NTD-affected pregnancies.”³

Since federally mandated fortification of cereal grain products began, daily folic acid intake has increased by approximately 0.2 mg/day and the incidence of neural tube defects has declined by 36% (from 10.8 per 10,000 population during 1995-1996 to 6.9 at the end of 2006). Despite mandatory fortification, certain subpopulations continue to be at greater risk of having a pregnancy affected by a NTD. In particular, Hispanic women are more likely than non-Hispanic white women to have an affected pregnancy. Although non-folate risk factors for NTDs may be contributing to this disparity, there is evidence suggesting that Hispanic women may have a need for additional folic acid.

Johnson & Johnson informed DRUP in 2002 that it planned to develop an oral contraceptive product that would also contain folic acid. The company believed that this oral contraceptive combination product would complement public health efforts to decrease further the risk of a woman having a NTD-affected pregnancy by supplementing her daily intake of folic acid. Two populations of oral contraceptive users were identified as likely to benefit: (1) women taking oral contraceptives who experienced a contraceptive failure and conceived while taking the oral contraceptive and (2) women taking oral contraceptives who stopped their medication and become pregnant shortly thereafter, before initiating folic acid supplementation. Women who experience a contraceptive failure may not recognize that they are pregnant until closure of the neural tube occurs by the end of the first month of gestation. If these women were to receive folic acid with their oral contraceptive, their risk of having low blood folate levels (and consequently, a folic acid-preventable NTD in their fetus) might be diminished.

The potential benefit of combining folic acid with an oral contraceptive was discussed in December 2003 by the Advisory Committee on Reproductive Health Drugs (ACRHD) (see Section 9). Overall, the Committee was very supportive of the concept of adding folic acid to an oral contraceptive. Committee members stated that further increases in folic acid intake, beyond that which is available from fortified cereal grain products, would be likely to result in public health advances in preventing further neural tube defects. There was also unanimous agreement that an oral contraceptive was a reasonable delivery vehicle for providing additional folic acid; a daily dose of 0.4 mg was recommended.

Following the Advisory Committee meeting, there were further discussions and meetings with Johnson & Johnson regarding their development program. (b) (4)

[REDACTED]

³ US Preventive Services Task Force. Folic Acid for the Prevention of Neural Tube Defects: US Preventive Services Task Force Recommendation Statement. *Ann Int Med* 2009; 150:626-631.

2.3 Regulatory History

In 2005, Bayer met with DRUP to discuss their clinical development plans for oral contraceptive/folate fixed dose combination products. Bayer planned to develop products that combined their FDA-approved oral contraceptive (Yaz or Yasmin) with levomefolate calcium, using a quantity of levomefolate calcium that would be equivalent to 0.4 mg of folic acid. There were several meetings/interactions between the Applicant and DRUP that resulted in agreement on an acceptable clinical development plan that would support possible marketing approval of the proposed combination drug product.

NDA 022532 was received on August 24, 2009, and was granted a standard review. The review clock was extended by 3 months to September 24, 2010, because of clinical pharmacology submissions on April 26 and May 10, 2010 that were considered major amendments.

On September 15, 2010, a meeting was held involving DRUP/Office of Drug Evaluation III (ODE III) and CDER representatives from the Center Director, Offices of Drug Evaluation IV, New Drugs, Clinical Pharmacology, New Drug Quality Assessment, Compliance, Regulatory Policy, and the Division of Drug Marketing, Advertising, and Communications, as well as representatives from CFSAN and the Office of the Chief Counsel. The purpose of the meeting was to discuss Bayer's proposed indication of (b) (4)

The consensus view was that the indication statement should include specific wording that described the purpose for which folate supplementation would be given to women using the combination product, namely, to reduce the risk of a neural tube defect in a pregnancy conceived while taking the product or shortly after discontinuing the product. Based on this meeting and subsequent interactions among various meeting participants, labeling for Beyaz, if approved, would include the following secondary indication: "Beyaz is indicated in women who choose to use an oral contraceptive as their method of contraception, to raise folate levels for the purpose of reducing the risk of a neural tube defect in a pregnancy conceived while taking the product or shortly after discontinuing the product."

2.4 Recommendations of Primary Clinical Reviewer and Cross-Discipline Team Leader regarding Approvability

The Clinical Reviewer, Daniel Davis MD, stated the following in his primary Clinical Review signed on September 24, 2010:

"I recommend approval of Beyaz for the following indications:

A secondary indication not found in labeling for YAZ: "Beyaz is indicated in women who choose to use an oral contraceptive as their method of contraception, to raise folate levels for the purpose of reducing the risk of a neural tube defect in a pregnancy conceived while taking the product or shortly after discontinuing the product."

Three indications are already approved for YAZ and I recommend that they also be approved for Beyaz on the basis of demonstrated bioequivalence of pharmacokinetic parameters for the estrogen and progestin in both Beyaz and YAZ:

- Prevention of pregnancy
- Treatment of symptoms of premenstrual dysphoric disorder (PMDD)
- Treatment of moderate acne for women of at least 14 years old"

Dr. Davis did not recommend any postmarketing studies.

The Cross Discipline Team Leader (CDTL), Lisa Soule MD (who also was the Clinical Team Leader), stated the following in her Review signed on September 24, 2010:

“I recommend that Beyaz be approved for the secondary indication “*Beyaz is indicated in women who choose to use an oral contraceptive as their method of contraception, to raise folate levels for the purpose of reducing the risk of a neural tube defect in a pregnancy conceived while taking the product or shortly after discontinuing the product*” as well as for the indications approved for YAZ of prevention of pregnancy (primary) and treatment of PMDD and acne (both secondary indications).

Dr. Soule did not recommend any postmarketing studies.

Division Director’s Comment

- *I concur with the recommendations of both Drs. Davis and Soule that Beyaz be approved for the indications listed above.*

3. CMC

The primary Chemistry Reviewer, Hitesh Shroff PhD, made the following statement in his Review signed on June 2, 2010:

“The applicant has provided sufficient information on raw material controls, manufacturing processes and process controls, and adequate specifications for assuring consistent product quality of the drug substances and drug products. The NDA also has sufficient stability information on the drug products to assure strength, purity, and quality of the drug product during the expiration dating period. All facilities have acceptable site recommendations. However, labeling issues are still pending as of the date of this review. Therefore, from the CMC perspective, this NDA is NOT recommended for approval until the labeling issues are resolved.”

In an Addendum, signed on September 20, 2010, to his primary Review, Dr. Shroff made the following recommendation on approvability:

“The previous Review #1 noted that this NDA has provided sufficient information to assure identity, strength, purity and quality of the drug products with all facilities in compliance with cGMP. However, issues on labels/labeling were pending.

Now, the labels and labeling have all the required information.

Therefore, from the CMC perspective, this NDA is now recommended for ‘Approval.’”

Dr. Shroff did not request any postmarketing commitments.

Division Director’s Comment

- *I concur with the assessments and recommendation by Dr. Shroff, that from a CMC perspective this NDA can be approved.*

4. NONCLINICAL PHARMACOLOGY/TOXICOLOGY

The primary Toxicology Reviewer, Leslie McKinney PhD, made the following recommendations in her review signed March 24, 2010:

“Approvability: NDA 22-532 ... drospirenone 3 mg, ethinyl estradiol 0.02 mg, and levometafolate 0.451 mg has been submitted by Bayer Healthcare Pharmaceuticals, Inc. for improvement in folate status in women using oral contraceptives. YAZ® (drospirenone 3 mg, ethinyl estradiol 0.02 mg) is an FDA approved contraceptive, and levometafolate is both a naturally occurring human metabolite and an FDA approved food additive. There were no new non-clinical safety concerns for the addition of levometafolate to YAZ® at the proposed dose. Based on previous approval for drospirenone and ethinyl estradiol as YAZ®, as well as previous designation of levometafolate as a GRAS compound and FDA approval of levometafolate as a food additive, Pharm/Tox recommends approval of YAZ Plus®.

Additional Non Clinical Recommendations: There are no nonclinical recommendations.”

Division Director’s Comment

- *I concur with the conclusions and recommendations of Dr. McKinney.*

5. CLINICAL PHARMACOLOGY/BIOPHARMACEUTICS

This Application included final Reports from 2 bioequivalence (BE) studies (Study 309664 and Study 309662) and 2 pharmacodynamic (PD) studies. Of the 2 BE studies, only the findings from Study 309664 were necessary to support approval of Beyaz. Findings for the 2 pharmacodynamic studies are reviewed and discussed in Section 7.

5.1 Bioequivalence of DRSP and EE in Beyaz and Yaz

The Applicant conducted a single BE study (Study 309664) to compare the bioavailability of DRSP/EE in Beyaz tablets (test product) to that in Yaz tablets (reference product) under a fasting state.

Study 309664 was an open-label, randomized, cross-over bioequivalence trial with 3 treatments, 3 study periods, and 6 treatment sequences that was conducted in 44 healthy women, aged 18-38 years. The treatments administered were single doses of Yaz, Beyaz, or 0.451 mg levomefolate calcium tablets. Bioequivalence of EE and DRSP was determined from the comparison of Cmax and AUC values for these components following administration of Beyaz or Yaz tablets. Pharmacokinetic profiles for EE and DRSP were similar for the Beyaz and Yaz formulations. The 90% confidence intervals (CIs) for the Beyaz/Yaz ratios for EE and DRSP Cmax and AUC(last) values were within the 80-125% BE limits, indicating that the Beyaz and Yaz tablet formulations were bioequivalent with respect to EE and DRSP.

Division Director’s Comments

- *This was a critical BE study because it provided support for bridging to Beyaz the clinical trial findings from the studies that supported approval of Yaz for the indications of (1) prevention of pregnancy, (2) treatment of symptoms of premenstrual dysphoric disorder (PMDD), and (3) treatment of moderate acne.*
- *Because of the bioequivalence of Beyaz to Yaz, it is appropriate to approve Beyaz for all of the indications presently approved for Yaz, assuming that levomefolate, per se, does not reduce the effectiveness of DRSP and EE for the treatment of these conditions. A review of*

the literature by the Applicant did not identify any information that the addition of levomefolate would mitigate the effectiveness of DRSP and EE for the prevention of pregnancy or the treatment of PMDD or moderate acne.

5.2 Overall Assessment by Clinical Pharmacology Reviewer

The primary Clinical Pharmacology Reviewer, Doanh Tran PhD, stated the following in his primary Review signed on July 29, 2010:

“The Division of Clinical Pharmacology 3/Office of Clinical Pharmacology finds NDA 022532 Acceptable from a Clinical Pharmacology perspective, pending agreement on labeling changes.”

Dr. Tran did not recommend any postmarketing commitments.

In an Addendum, signed on September 24, 2010, to his original review, Dr. Tran stated after reviewing final agreed-to labeling:

“The Division of Clinical Pharmacology 3/Office of Clinical Pharmacology finds NDA 022532 acceptable from a Clinical Pharmacology perspective.”

Division Director’s Comment

- *I concur with Dr. Tran’s assessment and recommendation.*

6. CLINICAL MICROBIOLOGY

A microbiology consult was not needed nor requested for this oral tablet product. The Applicant tested microbial purity of the validation batches manufactured at the production facility in Germany. These batches met USP microbial specifications.

7. CLINICAL/STATISTICAL-EFFICACY

The Applicant conducted 2 clinical trials to assess the effect of treatment with DRSP/EE/levomefolate tablets on plasma and RBC concentrations of folates.

7.1 Study A43598

7.1.1 Overview of Study A43598

This was a multicenter (8 US sites), randomized, double-blind, active-controlled, parallel-group study to investigate plasma folate and red blood cell folate concentrations in 385 healthy women of reproductive age, between 18 to 40 years of age, during a 24-week treatment period. Subjects were randomized 3:1 to Beyaz (n=291) or Yaz (n=94). Six subjects randomized to Beyaz treatment never received study drug. Subjects were permitted to consume their normal diets, and there was no restriction on their use of folate supplementation. Plasma and RBC folate concentrations at Week 24 were the co-primary endpoints.

7.1.2 Efficacy Assessments for Study A43598

Before starting treatment, 3 blood samples used for calculation of RBC and plasma folate concentrations were taken and their medians were used as the baseline values. Blood samples were then drawn every 4 weeks during the treatment period (Weeks 4 through 24) for determination of RBC and plasma folate concentrations. These blood samples were prepared for

laboratory analysis at the study sites and were then sent to centralized laboratories for measurement of folate concentrations. Plasma and RBC folate concentrations at Week 24 were the co-primary endpoints. The primary efficacy analyses of RBC folate and plasma folate levels at Week 24 used an analysis of covariance (ANCOVA) with treatment as factor and respective baseline folate concentrations as covariate. The primary efficacy population per the Applicant's amended protocol was the Per Protocol Set (PPS), which consisted only of subjects who had both baseline and Week 24 folate values.

Division Director's Comments

- *Blood sample preparation problems were discovered at 2 of the 8 study sites during an interim analysis of blinded baseline plasma and red blood cell (RBC) folate data for all pre-treatment samples in Study A43598. One of the sites was the largest study site, which enrolled 31.2% of all subjects (120 of 385) and the other site enrolled 3.4% of all subjects (13 of 385). Samples from both sites **were not processed correctly for RBC folate determinations** due to incorrect dilution during sample preparation and/or a failure to protect blood samples from excessive light exposure. Both the primary Clinical Reviewer and the Division of Scientific Investigations Report recommended that these RBC folate samples be removed from the RBC folate primary efficacy analysis. **There were no sample preparation issues for the plasma folate levels.***
- *I concur with the recommendation that all data for RBC folate concentrations from these 2 sites not be used in the primary analyses. Data for plasma samples from these sites, however, should be included in the final analyses.*

7.1.3 Efficacy Findings for Study A43598

The treatment differences for change from baseline at Week 24 for RBC folate concentrations (excluding all data from Sites 104 and 108) and plasma folate concentrations (data from all sites included) for the PPS population are provided in Table 1 and Table 2, respectively. Mean concentration-time curves for RBC folate concentrations (excluding all data from Sites 104 and 108) and plasma folate concentrations (data from all sites included) for the PPS population are provided in Figure 1 and Figure 2, respectively.

Table 1 Study A43598: Red Blood Cell (RBC) Folate Concentrations (nmol/L) - Treatment Difference for Change from Baseline at Week 24 (Per Protocol Population, Excluding Sites 104 and 108)

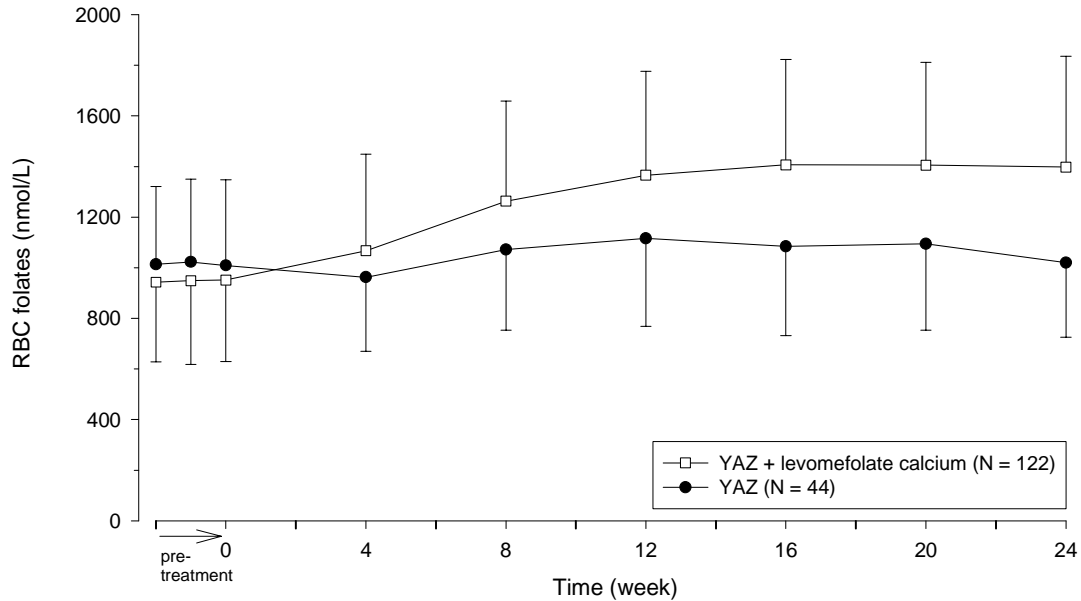
Treatment	n	Baseline	LS Mean Change from Baseline	LS Mean Difference ¹ (95% C.I.)	p-value*
Beyaz	122	961.4	436.1	403.4 (311.4, 495.4)	< 0.0001
YAZ	44	987.6	32.7		

¹ Least Squares mean estimates, confidence intervals, and p-values based on an ANCOVA model with treatment as factor and baseline value as covariate.

* P-value should be used with caution because of the large amount of data that were excluded.

Source: Modified from Table A.1 of FDA Statistical Review, signed September 2, 2010.

Figure 1 Study A43598: Mean (SD) Concentration-time Curves for RBC Folates after Daily Oral Administration of Beyaz (YAZ + Levomefolate Calcium) or YAZ (Per Protocol Population, Excluding Sites 104 and 108)



Source: Figure 2 from the to-be-approved Package Insert for Beyaz (NDA 22532).

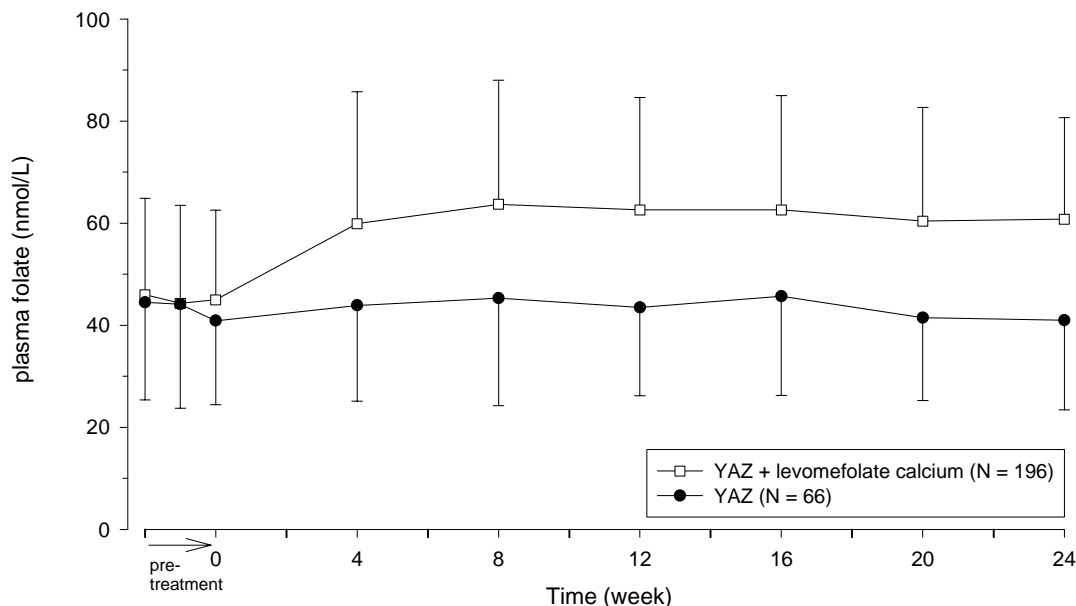
Table 2 Study A43598: Plasma Folate Concentrations (nmol/L) - Treatment Difference for Change from Baseline at Week 24 (Per Protocol Population, Using All Sites)

Treatment	n	Baseline	LS Mean Change from Baseline	LS Mean Difference ¹ (95% C.I.)	p-value
Beyaz	196	45.0	16.0	18.9 (14.0, 23.7)	< 0.0001
YAZ	66	43.1	-2.9		

¹ Least Squares mean estimates, confidence intervals, and p-values based on an ANCOVA model with treatment as factor and baseline value as covariate.

Source: Modified from Table A.4 of FDA Statistical Addendum, signed September 22, 2010.

Figure 2 Study A43598: Mean (SD) Concentration-Time Curves for Plasma Folate after Daily Oral Administration of Beyaz (Yaz + Levomefolate Calcium) or Yaz (Per Protocol Population, Using All Sites)



Source: Figure 1 from to-be-approved Package Insert for Beyaz (NDA 22532).

Division Director's Comments

- *Based on mean change from baseline values, the changes in RBC and plasma folate concentrations at Week 24 in subjects treated with Beyaz were significantly greater than those in subjects treated with Yaz, which does not contain levomefolate.*
- *Although a large quantity of potential data for RBC folate concentrations was lost because of sample processing errors at Study Sites 104 and 108, the results of Study A43598 remain compelling. The Applicant conducted several different analyses that ranged from excluding all samples from these 2 sites to using correction factors, where possible, for samples that were likely to have been misprocessed. Regardless of the analysis, the conclusion remained the same, namely, that treatment with 0.451 mg levomefolate significantly increased RBC folate concentrations.*
- *It was decided that the most conservative approach for analyzing change from baseline in RBC folate concentrations was to discard all RBC folate data from Sites 104 and 108. I concur with this decision and labeling will present this analysis.*
- *Sample processing errors at Study Sites 104 and 108 did not impact of the validity of the plasma folate measurement. For plasma folate, data from all sites were included in the analyses.*
- *Information obtained for changes in RBC and plasma folate concentrations in Study A43598 are reflective of those changes that are likely to be observed in women in the US who select Beyaz for contraception. Enrollment criteria for Study A43598 did not include any dietary restrictions nor did they exclude the use of other forms of folate supplementation.*

7.2 Study A39814

7.2.1 Overview of Study A39814

This was a single center (Germany), randomized, double-blind, double-dummy, parallel group Phase 1 clinical trial to assess the pharmacodynamic effect on plasma folate and red blood cell folate during 24 weeks of treatment with 0.451 mg levomefolate calcium or with 0.4 mg folic acid (equimolar dose to 0.451 mg levomefolate calcium), both in combination with 3 mg DRSP/0.03 mg EE (Yasmin) followed by 20 weeks of open-label treatment with Yasmin only (elimination phase). One-hundred seventy-two (172) healthy women, 18 to 40 years of age, from a German population without folate food fortification and without concomitant intake of folate supplements were randomized to one of 2 treatments.

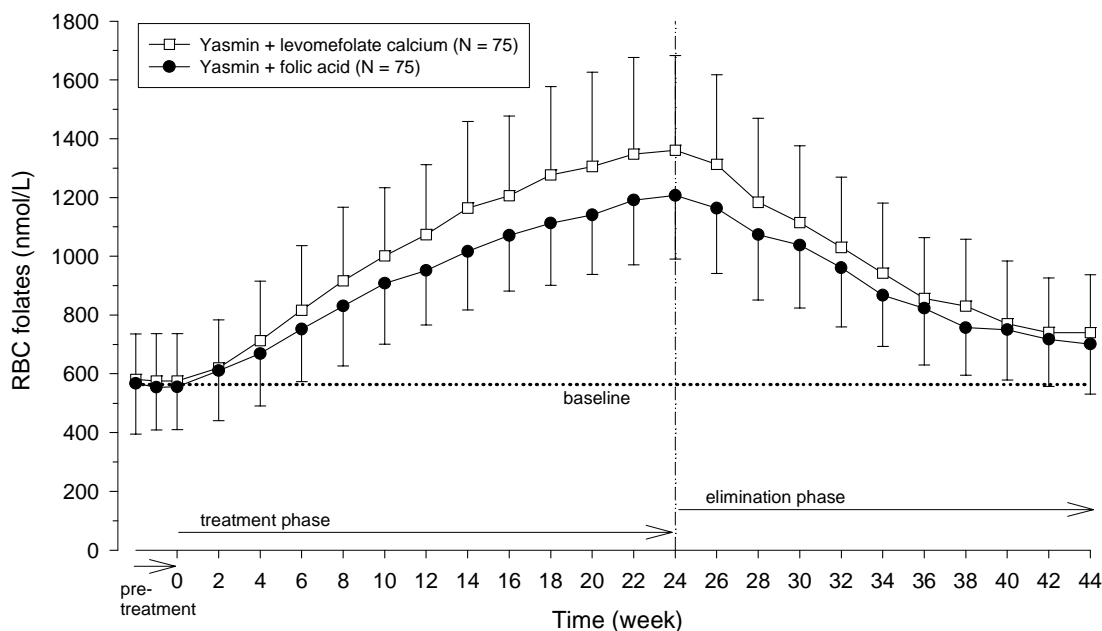
7.2.2 Efficacy Assessments for Study A39814

Before starting treatment, 3 blood samples for RBC and plasma folate concentrations were drawn and used to calculate the baseline values. Blood samples were then drawn every 14 days during the treatment period (Weeks 2 through 44) for determination of plasma folate and RBC folate concentrations.

7.2.3 Efficacy Findings for Study A39814

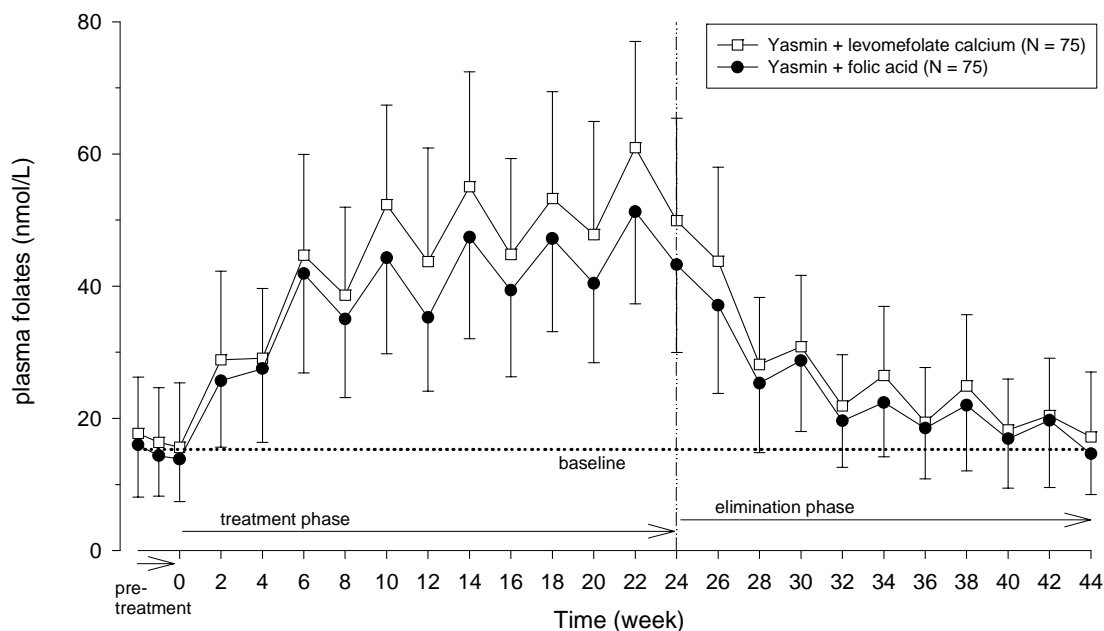
Figure 3 and Figure 4 display the results for RBC folate and plasma folate concentrations, respectively, among evaluable subjects in the levomefolate and folic acid treatment arms of Study A39814. In the treatment phase, women received Yasmin + levomefolate calcium or Yasmin + folic acid; in the elimination phase, all women received only Yasmin.

Figure 3 Study A39814: Mean (SD) Concentration-Time Curves for RBC Folate Concentrations after Daily Oral Administration of (Yasmin + Levomefolate Calcium) or (Yasmin + Folic Acid) for 24 Weeks (Per Protocol Population)



Source: Figure 4a from Applicant's e-mail communication of September 23, 2010.

Figure 4 Study A39814: Mean (SD) Concentration-Time Curves for Plasma Folate Concentrations after Daily Oral Administration of (Yasmin + Levomefolate Calcium) or (Yasmin + Folic Acid) for 24 Weeks (Per Protocol Population)



Source: Figure 3a from Applicant's e-mail communication of September 23, 2010.

Division Director's Comments

- *Although Study A39814 was conducted with Yasmin (which contains 3 mg DRSP/0.03 mg EE per hormone tablet), the findings from this study are applicable to women who would use Beyaz, which contains 3 mg DRSP/0.02 mg EE per hormone tablet. The Applicant demonstrated in one of the bioequivalence studies that DRSP/EE did not alter the bioavailability of levomefolate.*
- *Mean RBC folate and plasma concentrations in those subjects who received 0.451 mg levomefolate were numerically slightly higher than those who received 0.4 mg folic acid. This observation provides support for the expectation that treatment with Beyaz will be as effective as treatment with 0.4 mg folic acid in terms of reducing the risk of a NTD defect.*
- *Following discontinuation of treatment, there was a gradual decrease in plasma and RBC folate concentrations. Based on the rate of decline of folate concentrations, it is likely that treatment with Beyaz would continue to provide benefit for at least several weeks (possibly longer) in reducing the risk of a folate-dependent NTD in a pregnancy that was conceived after discontinuing the product.*

7.3 FDA Statistician's Assessment of Efficacy

The primary Biostatistical Reviewer, Sonia Castillo PhD, stated the following in her Statistical Review, signed on September 2, 2010:

“A large amount of data submitted in support of this application was invalid due to poor blood sample preparation. ... Both the clinical reviewer and the Division of Scientific Investigations report recommended that these RBC folate samples be removed from the RBC

folate primary efficacy analysis. There were no sample preparation issues with plasma folate levels.”

“Despite dropping this substantial amount of data, the two submitted studies provide supportive evidence demonstrating the efficacy of the oral contraceptive Beyaz (0.020 mg ethinyl estradiol + 3.0 mg drospirenone + 0.451 mg levomefolate calcium) to improve the folate status in women who elect to use an oral contraceptive. There was an increase in RBC folate and plasma folate levels with Beyaz use compared to YAZ.”

7.4 Overall Assessment of Efficacy

Study 43598 and Study A39814 provided robust evidence that treatment with Beyaz (which contains 0.451 mg levomefolate) will significantly increase RBC and plasma folate concentrations. Data from Study A39814 also demonstrated that following discontinuation of treatment, there was a gradual decline in folate concentrations. Based on the rate of decline of folate concentrations, it is likely that treatment with Beyaz would continue to provide clinical benefit for at least several weeks (possibly longer) after discontinuing the product.

Based on the data provided in this Application, Beyaz will deliver a daily folate dose equivalent to that of 0.4 mg folic acid, the dose that the US Public Health Service has recommended that women of reproductive age consume to reduce the risk of having a pregnancy affected by a NTD. The Applicant did not conduct a randomized trial designed to demonstrate a reduction in NTD incidence with levomefolate treatment, as such a trial would not be feasible. It is expected, however, based on prior clinical trial data with folic acid and a substantial quantity of epidemiologic data, that Beyaz will convey clinical benefit by raising folate levels in women who choose to use an oral contraceptive and either conceive while using the product, or discontinue the product and conceive shortly thereafter.

8. SAFETY

The primary Clinical Reviewer (Dr. Davis) has provided a thorough discussion and review of the safety findings from Studies A43598 and A39814, which both included 24 weeks of treatment with Beyaz or Yasmin + levomefolate. Dr. Soule (the Clinical Team Leader and CDTL for this application) also has conducted a separate safety review of the Application. Neither Reviewer identified any safety issues other than those that are well known to be associated with the use of combination oral contraceptives. Neither Reviewer identified any safety issues that would negatively affect the approvability of this Application.

8.1 Deaths, Discontinuations due to Adverse Events, and Non-fatal Serious Adverse Events

No deaths were reported in the clinical development program for Beyaz.

In US Study A43598, 12 subjects (4.2%) in the Beyaz group and 3 subjects (3.2%) in the Yaz group discontinued prematurely because of an adverse event. Two subjects in the Beyaz group each experienced a single serious adverse event (SAE) of moderate intensity. One subject was diagnosed with cervical carcinoma in situ and was withdrawn from the trial. This SAE was considered by the investigator as possibly related to the study medication. The other subject was diagnosed with a pneumonia, which was assessed by the investigator as being unrelated to the study medication.

In German Study A39814, one subject in the Yasmin + levomefolate group (1.2%) and 3 subjects in the Yasmin + folic acid treatment group (3.5%) discontinued prematurely because of an adverse event in the levomefolate/folic acid treatment period. One woman in the Yasmin + levomefolate treatment group experienced 2 SAEs in the levomefolate treatment period: an acoustic neuroma and impaired healing. In the Yasmin + folic acid treatment group, 2 women each experienced one SAE: pyelonephritis and ulcerative colitis, respectively. None of the SAEs in either treatment group were considered related to the study medication by either the Investigator or the Applicant.

Dr. Davis stated the following in his primary Clinical Review:

“The data from the four clinical studies show a favorable safety profile for YAZ fortified with Metafolin, and there are no new safety issues in comparison to YAZ only. The adverse event profile compares with those for other COCs. Based on the two long-term studies, AEs which occurred in at least 3% of the study population were nausea, breast pain, dysmenorrhea, headache, metrorrhagia, and increased low density lipoprotein values, all of which are well-established side effects of COCs. There were no safety-relevant effects observed with regard to laboratory variables, vital signs, and the other measured safety parameters. The limited new safety data show no signal of an increased risk of venous thromboembolism, other cardiovascular events, or events of cancer, compared to other marketed COCs.”

Division Director's Comments

- *I concur with Dr. Davis' overall safety assessment.*
- *Thromboembolic adverse events are the most serious safety concern for users of hormonal contraceptives. As noted earlier, there were no reports of thrombotic or thromboembolic adverse events in any of the clinical trials with levomefolate. The label for Yaz was revised on April 7, 2010, to report on 4 epidemiologic studies relating to thromboembolic risk. Labeling for thromboembolic risk for Beyaz will be consistent with that for Yaz.*
- *The small number of serious adverse events and the adverse events that resulted in early terminations do not raise any safety concerns.*

8.2 Overall Assessment of Safety

The size of the safety database in this Application, in isolation, would not be adequate to assess the overall safety profile of Beyaz in terms of uncommon but serious adverse events. Beyaz, however, is bioequivalent to the approved combination oral contraceptive Yaz in terms of DRSP and EE and differs from Yaz only by the addition of 0.451 mg levomefolate to each daily tablet. Yaz was approved in 2006, and its approval was supported by a large and reassuring safety database. The postmarketing safety profile for Yaz also appears to be similar to that of other combination oral contraceptives. Addition of 0.451 mg levomefolate to Yaz for the purpose of folate supplementation, based on the data provided in this NDA, did not raise any new safety concerns. In the 2 pharmacodynamic studies in which subjects were treated for up to 24 weeks with Beyaz (Study A43598) or Yasmin (3 mg DRSP/0.03 mg EE) + levomefolate (Study A39814), there were no safety signs of concern. In these studies, the small number of serious adverse events, the adverse events that resulted in early terminations, and the most commonly reported adverse events do not raise any safety concerns beyond those known to be associated with hormonal contraceptives.

9. ADVISORY COMMITTEE MEETING

This Application was not presented to an Advisory Committee (AC) because the potential benefit and potential safety concerns of combining folic acid with an oral contraceptive was previously discussed in December 2003 by the Advisory Committee on Reproductive Health Drugs (ACRHD). Among the question presented and discussed at the meeting were the following:

1. Are further increases in folic acid intake, beyond what is available in fortified cereals, likely to result in public health advances in preventing further neural tube defects?

Yes - 18 No - 0 Abstain - 0

2. Is it necessary to define a subpopulation among women of reproductive-age that needs additional folic acid?

Yes - 4 No - 14 Abstain - 0

3. Are there any safety issues associated with folic acid supplementation targeted at reproductive-age women?

Yes - 7 N - 11 Abstain - 0

Although Committee members indicated that chronic daily supplementation with 0.4 mg folic acid would be safe for reproductive-age women, 2 concerns were raised: (1) the potential for folates to modify the pharmacokinetics or pharmacodynamics of certain anti-folate drugs (e.g., valproic acid, phenytoin, methotrexate, and pyrimethamine) thereby reducing the pharmacologic effects of these drugs, and (2) the potential for folic acid at high doses (i.e., greater than 1.0 mg/day) to mask the anemia of vitamin B12 deficiency (pernicious anemia).

4. Is an oral contraceptive pill a reasonable delivery vehicle if additional folic acid supplementation is likely to provide public health advances in preventing further neural tube defects? If so, would 400 micrograms (mcg) be a reasonable dose?

Yes - 18 N - 0 Abstain - 0

10. PEDIATRICS

The Applicant requested a full waiver of pediatric studies. The Pediatric Review Committee (PeRC) considered this application on April 14, 2010, and granted a partial waiver for ages 0 to 11 years (i.e., premenarcheal patients), because the risk of pregnancy does not exist in this population. The remainder of the PREA requirement has been fulfilled by extrapolation from studies on adult women. DRUP's long experience with a variety of hormonal contraceptives and with Yaz specifically has supported the expectation that efficacy and safety results in postmenarcheal adolescents do not differ from those in adult women. There is not expected to be any difference in the impact of folate supplementation in adolescent users.

11. OTHER RELEVANT REGULATORY ISSUES

Division of Scientific Investigation Inspections

Site inspections by the Division of Scientific Investigation (DSI) were requested for various clinical and analytic sites associated with the 2 PK and 2 PD studies. Because the endpoints in all studies were based on laboratory analyses, the inspections were requested to be performed by

the GCP branch of DSI. There were numerous findings of concern, particularly at 2 clinical sites for Study A43598 (see Section 7.1.2) that (1) resulted in Voluntary Action Indicated (VAI) classifications at all inspected sites and (2) necessitated elimination of a number of samples, reanalyses of several of the studies, and revision of study reports. DSI findings from the various sites and DSI recommendations are summarized in Table 12 of the CDTL review.

12. LABELING

The proprietary name Beyaz was found acceptable by DMEPA.

Package labeling for Beyaz was submitted in the format prescribed by the Physician Labeling Rule (PLR). DRUP's review of this label was informed by the internal updated draft Guidance for oral contraceptive (OC) labeling, as well as by several other approved OC labels in PLR format. Consultative reviews were provided by the Division of Drug Marketing, Advertising and Communication (DDMAC), and the Study Endpoints and Label Development (SEALD) group, and their comments were incorporated into the label as appropriate.

Among the major issues addressed in labeling negotiations with the Applicant were:

- Clarification of the specifics of the folate supplementation indication
- Addition of detailed information on bleeding irregularities, which had not previously been included in the Yaz label.
- Description of Adverse Drug Reactions in PLR format, with reporting separately for the contraception/acne/folate supplementation trials (pooled) and the PMDD clinical trials. The current, non-PLR, Yaz label is primarily class labeling, with minimal detailed information about adverse reactions seen in the clinical trials and postmarketing reports for Yaz.
- Revision of the Clinical Pharmacology section.

Beyaz labeling also will contain the same Warnings/Precautions as other contraceptive products that have drospirenone as the progestin. Like Yaz, Beyaz labeling will include two additional contraindications, involving use in patients with renal or adrenal insufficiency, and will warn that the product should not be used in women with conditions that predispose to hyperkalemia given the known anti-mineralocorticoid activity of the drospirenone component.

Regarding folate effects, labeling for Beyaz will describe the potential for folates to modify the pharmacokinetics or pharmacodynamics of certain anti-folate drugs, thereby decreasing the pharmacological effect of the anti-folate drug. Labeling for Beyaz will also mention the potential for folates to mask the anemia of vitamin B₁₂ deficiency.

Final labeling submitted by the Applicant on September 23, 2010, is acceptable

13. DECISION/ACTION/RISK BENEFIT ASSESSMENT

13.1 Regulatory Action

The Applicant has provided sufficient information for me to conclude that Beyaz (drospirenone/ethinyl estradiol/levomefolate calcium tablets and levomefolate calcium tablets) will be a safe and effective combination oral contraceptive when used in accordance with to-be-approved product labeling. Based on the safety and efficacy data for Beyaz that was

submitted in support of NDA 022532, in conjunction with the known safety and efficacy profile for Yaz, and the agreed-to product labeling, I recommend that Beyaz be approved. I further recommend that Beyaz be approved for the secondary indication “*Beyaz is indicated in women who choose to use an oral contraceptive as their method of contraception, to raise folate levels for the purpose of reducing the risk of a neural tube defect in a pregnancy conceived while taking the product or shortly after discontinuing the product*” as well as for the indications currently approved for Yaz. These latter indications are: (1) use by women to prevent pregnancy, (2) treatment of symptoms of premenstrual dysphoric disorder (PMDD) for women who choose to use an oral contraceptive for contraception, and (3) treatment of moderate acne for women at least 14 years old only if the patient desires an oral contraceptive for birth control.

13.2 Risk/Benefit Assessment

Study 43598 and Study A39814 provided robust evidence that treatment with Beyaz (which contains 0.451 mg levomefolate) will significantly increase RBC and plasma folate concentrations. Data from Study A39814 also demonstrated that following discontinuation of treatment, there was a gradual decline in folate concentrations. Based on the rate of decline of folate concentrations, it is likely that treatment with Beyaz would continue to provide clinical benefit for at least several weeks (possibly longer) after discontinuing the product.

Addition of 0.451 mg levomefolate to Yaz for the purpose of folate supplementation, based on the data provided in this NDA, did not raise any new safety concerns. In the 2 clinical studies in which subjects were treated for up to 24 weeks, there were no safety signals of concern. In these studies, the small number of serious adverse events, the adverse events that resulted in early terminations, and the most commonly reported adverse events do not raise any safety concerns beyond those known to be associated with hormonal contraceptives.

I concur with the 2003 recommendation of the Advisory Committee for Reproductive Health Products that an oral contraceptive is a reasonable delivery vehicle for the provision of additional folate supplementation to reproductive age women who choose to use this method for contraception. Based on the data in this Application, Beyaz will deliver a daily folate dose similar to that of 0.4 mg folic acid, the dose that the US Public Health Service has recommended that women of reproductive age consume to reduce the risk of having a pregnancy affected by a neural tube defect. It is expected that Beyaz will convey clinical benefit by raising folate levels in women who choose to use an oral contraceptive and either conceive while using the product, or discontinue the product and conceive shortly thereafter.

13.3 Recommendation for Postmarketing Risk Evaluation and Mitigation Strategies (REMS)

None.

13.4 Recommendations for other Postmarketing Requirements and Commitments

None.

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/s/

SCOTT E MONROE
09/24/2010