CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

022574Orig1s000

SUMMARY REVIEW

Summary Review for Regulatory Action

Date	December 16, 2010
From	Scott Monroe, MD
Subject	Division Director Summary Review
NDA	NDA 022574
Applicant Name	Bayer Healthcare Pharmaceuticals, Inc.
Date of Submission	November 16, 2009
PDUFA Goal Date	December 16, 2010 (with 3 month extension)
Proprietary Name	Safyral
Established (USAN) Name	Drospirenone (DRSP)/ethinyl estradiol (EE)/levomefolate calcium (LMF) tablets and levomefolate calcium tablets)
Dosage Forms/Strengths	Oral tablets: (3 mg DRSP/0.03 mg EE/0.451 mg LMF) tablet and 0.451 mg LMF tablet
Proposed Indications	Primary Indication: prevention of pregnancy Secondary Indication: (b) (4) in women who elect to use an oral contraceptive
Proposed Regimen	One DRSP/EE/LMF tablet daily x 21 days followed by one LMF tablet daily x 7 days
Action	***Approve (see Section 13.1)***

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	Anne Crandall PharmD/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 022574 to obtain marketing approval for Safyral (drospirenone [DRSP]/ethinyl estradiol [EE]/levomefolate calcium tablets and levomefolate calcium tablets), a new combination oral contraceptive. A similar product (Beyaz, [NDA 022532] with a lower dosage of EE and a slightly different dosing regimen) was approved in September 2010.

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 for women of childbearing potential. Safyral (also referred to as DRSP/EE/levomefolate tablets or Yasmin + levomefolate in this summary review) is identical to the Applicant's currently marketed oral contraceptive Yasmin (3 mg DRSP/0.03 mg EE tablets), with the exception that Yasmin does not contain levomefolate. Yasmin was originally approved in 2001 with the indication of "prevention of pregnancy in women who elect to use an oral contraceptive." The Applicant has added levomefolate to DRSP/EE tablets (Yasmin) to obtain the following proposed additional indication for Safyral: (b) (4)

This Application contained the necessary chemistry, manufacturing and controls (CMC) and, by cross reference to NDA 022532, the necessary clinical pharmacology and clinical information to support approval. The Applicant did not conduct any new nonclinical studies with levomefolate or any new nonclinical studies with Safyral, 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 the proposed primary indication and secondary indication.

Significant issues were identified during the review that concerned the Applicant's proposed secondary indication of (b) (4) in women. These review issues included (1) sample preparation/analytical problems regarding the measurement of red blood cell (RBC) folate concentrations and (2) the exact wording for the secondary indication. Both issues were adequately addressed and resolved. All primary reviewers, as well as the cross discipline team leader (CDTL), have recommend that Safyral be approved for the primary indication of "…*use by women to prevent pregnancy"* and the secondary indication of "…*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*." I concur with the recommendations of the primary reviewers and the CDTL that Safyral be approved for both indications.

2. BACKGROUND

2.1 Description of the Product

Safyral (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:

- 21 orange tablets each containing 3 mg drospirenone (DRSP), 0.03 mg ethinyl estradiol (EE) , and 0.451 mg levomefolate calcium
- 7 light orange tablets each containing 0.451 mg levomefolate calcium

One oral tablet is to be taken at the same time every day. Safyral will be the second 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, Yasmin, and Beyaz. 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. Levomefolate is approved as a food additive and is designated a GRAS (generally regarded as safe) compound. It is also a component of the recently approved COC Beyaz.

2.2 History and Rationale 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 recent studies and concluded

[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.

that "new 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 became 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) should 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. Johnson & Johnson, however, discontinued their development plans for an oral contraceptive/folic acid combination product in 2006.

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 levomefolate calcium with their FDA-approved oral contraceptives (Yaz and Yasmin), using a quantity of levomefolate calcium that would be equivalent to 0.4 mg of folic acid. There

[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.

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 022574 was received on November 16, 2009, and was granted a standard review. The review clock was extended by 3 months to December 16, 2010, because of clinical pharmacology submissions on August 27 and September 3, 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) in women who elect to use an oral contraceptive" for both Beyaz and Safyral. The consensus view of the meeting participants was that the secondary 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.

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

The primary Clinical Reviewer, Daniel Davis MD, stated the following in his primary Clinical Review signed on December 15, 2010:

> *"I recommend approval of Safyral (Yasmin plus Metafolin) for the two following indications:*
>
> - *Prevention of pregnancy*
> - *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*
>
> *The prevention of pregnancy indication is already approved for Yasmin and I recommend that it be approved for Safyral on the basis of demonstrated bioequivalence of pharmacokinetic parameters for the estrogen and progestin in Safyral to those in Yasmin.*
>
> *The other recommended indication is a secondary indication not labeled for Yasmin. It is that "Safyral 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." The Applicant has provided sufficient data supporting this new secondary indication.*"

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 December 16, 2010:

> *"I recommend that Safyral be approved for the secondary indication 'Safyral 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 primary indication approved for Yasmin of prevention of pregnancy*."

Dr. Soule did not recommend any postmarketing studies.

Division Director's Comment

- *I concur with the recommendations of Drs. Davis and Soule that Safyral 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 August 23, 2010:

> *"This NDA has provided sufficient information to assure identity, strength, purity and quality of the drug products. An "Acceptable" site recommendation from the Office of Compliance has been made. 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 December 15, 2010, to his primary Review, Dr. Shroff made the following recommendation on approvability:

> *"The previous CMC Review #1 noted,*
>
> > *"This NDA has provided sufficient information to assure identity, strength, purity and quality of the drug products and an "Acceptable" site recommendation from the Office of Compliance has been made. However, labeling issues are still pending as of the date of this review."*
>
> *Now, the issues on labels/labeling have been corrected and deemed adequate. Therefore, from the CMC perspective, this NDA is 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 July 8, 2010:

> ***"Approvability**: "…There were no new non-clinical safety concerns for the addition of levometafolate to Yasmin® at the proposed dose. Based on previous approval for drospirenone and ethinyl estradiol as Yasmin®, as well as previous designation of*

levometafolate as a GRAS compound and FDA approval of levometafolate as a food additive, PharmTox recommends approval of Yasmin® plus levometafolate."

***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 A27410 and Study A28575) and 2 pharmacodynamic (PD) studies. Of the 2 BE studies, only the findings from Study A27410 were necessary to support approval of Safyral. The findings from the other BE study (Study 28575) were needed primarily to support the approval of Beyaz. Findings for the 2 pharmacodynamic studies are reviewed and discussed in Section 7.

5.1 Bioequivalence of DRSP and EE in Safyral and Yasmin

The Applicant conducted a single bioequivalence (BE) study (Study A27410) to investigate the BE of DRSP and EE in Safyral tablets (test product) and Yasmin tablets (reference product) under a fasting state. This study also investigated the BE of levomefolate in Safyral tablets to levomefolate tablets.

Study A27410 was an open-label, randomized, cross-over bioequivalence trial with 3 treatments, 3 study periods, and 6 treatment sequences that was conducted in 45 healthy women, aged 18-37 years. The treatments administered were single doses of Safyral, Yasmin, 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 Safyral or Yasmin tablets. Pharmacokinetic profiles for EE and DRSP were similar for the Safyral and Yasmin formulations. The 90% confidence intervals (CIs) for the Safyral/Yasmin ratios for EE and DRSP Cmax and AUC(last) values were within the 80-125% BE limits, indicating that the Safyral and Yasmin tablet formulations were bioequivalent with respect to EE and DRSP. Results from this trial also demonstrated that levomefolate in Safyral tablets was bioequivalent to levomefolate tablets.

Division Director's Comment

- *This was a critical BE study because it provided support for bridging Safyral to the clinical trial findings from the studies that supported approval of Yasmin for the indication of prevention of pregnancy.*

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 November 4, 2010:

"The Division of Clinical Pharmacology 3/Office of Clinical Pharmacology finds NDA 022574 Acceptable from a Clinical Pharmacology perspective."

Dr. Tran did not recommend any postmarketing commitments.

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.

7. CLINICAL/STATISTICAL-EFFICACY

The Applicant conducted 2 pharmacodynamic 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. The primary objective of this study was to compare the changes in plasma folate and red blood cell folate concentrations in women treated with Beyaz (Yaz +levomefolate) compared to women treated with Yaz alone. 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.* ***There were no sample preparation issues for the plasma folate levels****.*
- *Although women were treated with Beyaz and not Safyral, the changes in plasma folate and red blood cell folate concentrations would be comparable to those resulting from treatment with Safyral. Both Beyaz and Safyral contain 0.451 mg levomefolate.*

7.1.3 Efficacy Findings for Study A43598

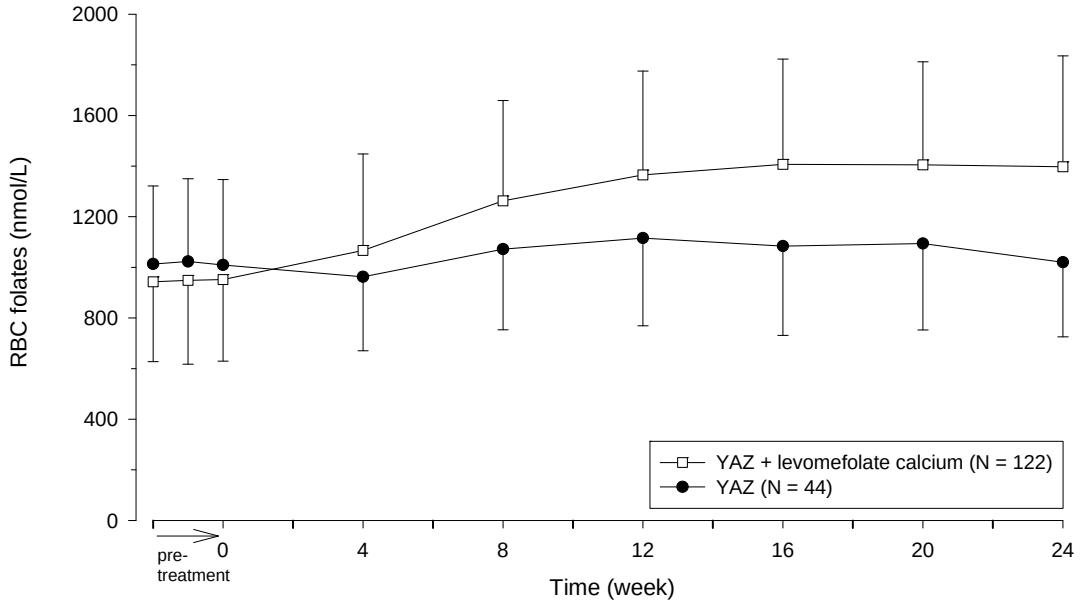
The treatment differences for change from baseline at Week 24 for RBC folate concentrations (excluding all data from Sites 104 and 108) and plasma folate concentrations (data from all sites included) for the PPS population are provided in Table 1 and Table 2, respectively. Mean concentration-time curves 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 November 10, 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 Safyral (NDA 22574).

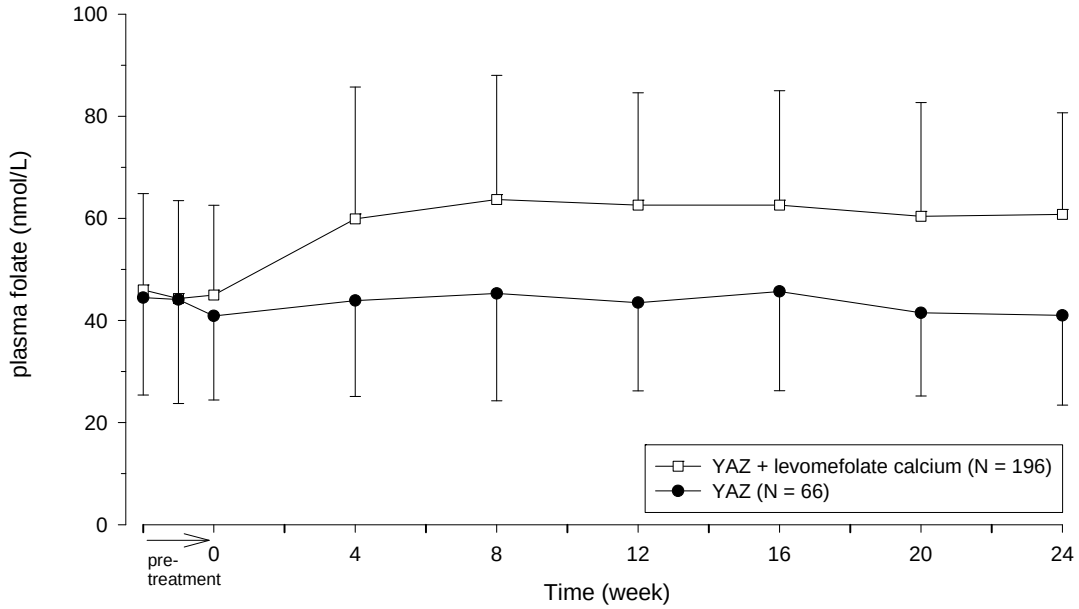
Table 2 Study A43598: Plasma Folate Concentrations (nmol/L) - Treatment Difference for Change from Baseline at Week 24 (Per Protocol Population, Using All Sites)

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 Addendum to Statistical Review, signed November 10, 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 Safyral (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 may select Safyral 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 study 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), each 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.

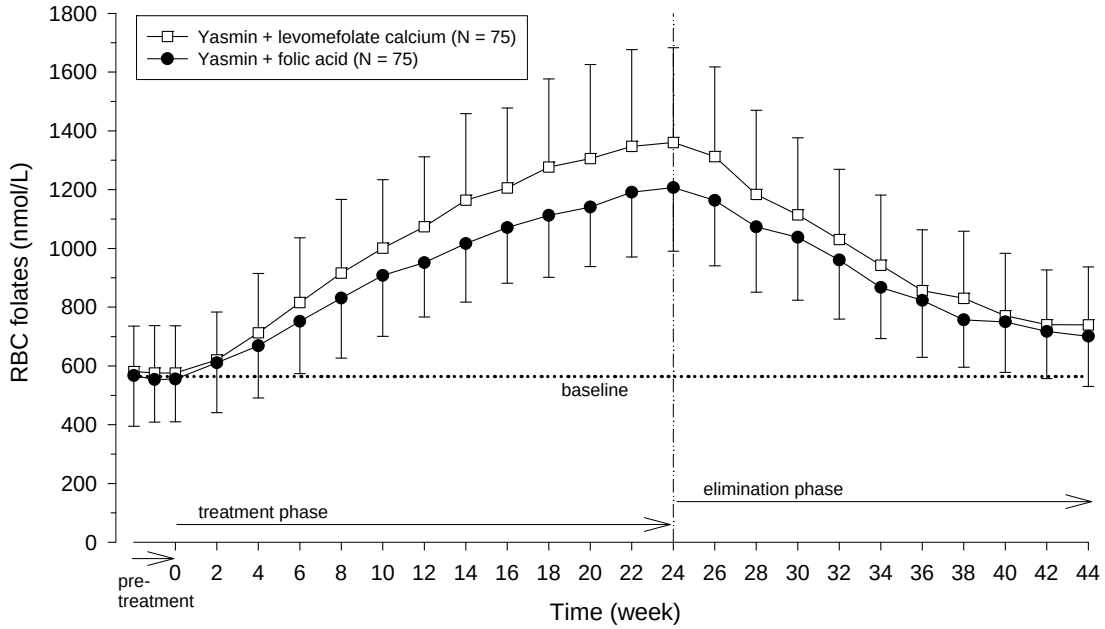
7.2.2 Efficacy Assessments for Study A39814

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

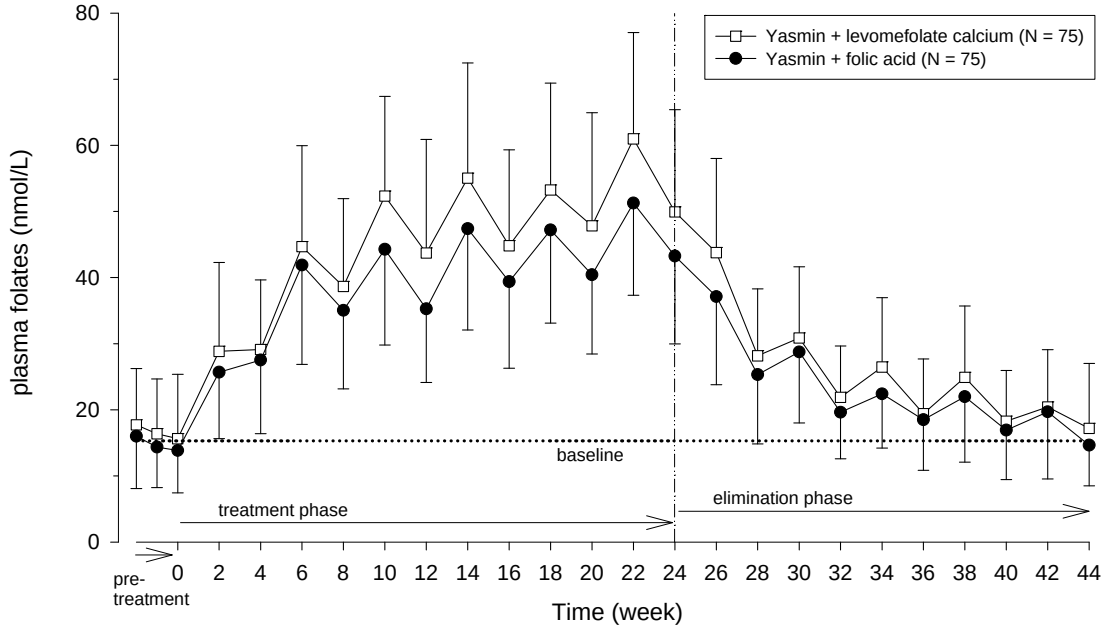
Figure 3 and Figure 4 display the results for RBC folate and plasma folate concentrations, respectively, among evaluable subjects in the levomefolate and folic acid treatment arms of Study A39814. In the treatment phase, women received Yasmin + levomefolate calcium or Yasmin + folic acid; in the elimination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

- *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 Safyral 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 Safyral 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 November 10, 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."*

Division Director's Comment

- *Although Dr. Castillo's summary statement refers to Beyaz, the findings obtained in women treated with Safyral would be comparable to those in women treated with Beyaz because (1) both products contain 0.451 mg levomefolate calcium and (2) and the bioavailability of levomefolate is comparable in Safyral and Beyaz.*

7.4 Overall Assessment of Efficacy

Prevention of Pregnancy. Based on the findings from Study A27410, Safyral and Yasmin tablet formulations were bioequivalent with respect to EE and DRSP. Therefore, the efficacy of Yasmin for prevention of pregnancy can be extended to Safyral.

Increase in folate levels to reduce the risk of a neural tube defect. Study A43598 and Study A39814 provided robust evidence that treatment with Safyral (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 Safyral would continue to provide clinical benefit, in terms of reducing the risk of a NTD, for at least several weeks (and possibly longer) after discontinuing the product.

Based on the data provided in this Application, Safyral 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 Safyral 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 Safyral. 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 and Serious Adverse Events

8.1.1 Deaths

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

8.1.2 Serious Adverse Events

Study A43598

In Study A43598 (conducted in the US), 2 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.

Study A39814

In Study A39814 (conducted in Germany), there were a total of 16 SAEs occurring in 9 women.

Treatment Period 1. In Treatment Period 1, subjects were treated with either Safyral or Yasmin + folic acid. In the Safyral treatment group, only two SAEs (both occurring in a single subject) were reported. These were an acoustic neuroma and impaired healing (following surgical treatment of the neuroma). 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 was considered related to the study medication by either the Investigator or the Applicant.

Treatment Period 2 (or elimination phase). In Treatment Period 2, all subjects received Yasmin. Six subjects (5 of whom previously were treated with Safyral) reported a total of 12 SAEs. None was considered to be related to treatment.

8.1.3 Adverse Events Leading to Discontinuation

Adverse events leading to discontinuation from treatment are listed in Table 3. In Study A43598, 11 subjects (3.9%) in the Beyaz group and 3 subjects (3.2%) in the Yaz group

discontinued the trial due to adverse events (AEs). In Study A39814 (Treatment Period 1), 1 subject (1.2%) in the Safyral group and 3 subjects in the Yasmin + folic acid group (3.5%) discontinued because of an AE. Three subjects in Treatment Period 2 (Yasmin-only treatment) discontinued because of an AE.

Table 3 Adverse Events Leading to Discontinuation in Studies A43598 and A39814

Subject	Treatment Group	Reason for Discontinuation MedDRA preferred term (AE text)
Study A43598		
1	Beyaz	Nausea Dizziness
2	Beyaz	Menstrual disorder (abnormal bleeding)
3	Beyaz	Cervical CIS*
4	Beyaz	Affect lability
5	Beyaz	Libido decreased Dysmenorrhea Menorrhagia
6	Beyaz	Hypothyroidism
7	Beyaz	Genital hemorrhage (vaginal spotting)
8	Beyaz	Libido decreased
9	Beyaz	Libido decreased
10	Beyaz	Depressed mood
11	Beyaz	Weight increased
12	YAZ	Migraine (increased)
13	YAZ	Systemic lupus erythematosus
14	YAZ	Abdominal pain Cholelithiasis
Study A39814		
1	Safyral	Acoustic neuroma
2	Yasmin alone (Period 2; previously Safyral)	Arthralgia (pain in R knee, requiring surgery)
3	Yasmin alone (Period 2; previously Safyral)	Cholelithiasis
4	Yasmin + FA *	Hyperthyroidism
5	Yasmin alone (Period 2; previously Yasmin + FA)	Pyelonephritis
6	Yasmin + FA	Ulcerative colitis
7	Yasmin + FA	Basedow's disease**

* FA = Folic Acid
** Grave's disease
Source: Table 10 of the CDTL Review, signed December 16, 2010.

Division Director's Comments

- *The small number of reported serious adverse events and the adverse events that resulted in discontinuations do not raise any safety concerns.*
- *Thromboembolic adverse events are the most serious safety concern for users of hormonal contraceptives. There were no reports of thrombotic or thromboembolic events in any of the clinical trials with levomefolate. The limited size of the safety database for Safyral, however, is not adequate to assess the risk of thromboembolic events in women who may use the*

product. Because it is not expected that the addition of levomefolate to Yasmin will alter the risk of a woman's experiencing a thrombotic or thromboembolic event, labeling for Safyral will be consistent with that for Yasmin. The label for Yasmin was revised on April 7, 2010, to report on 4 epidemiologic studies relating to thromboembolic risk in women using Yasmin.

8.2 Overall Assessment of Safety

Dr. Davis stated the following in his Clinical Review for Safyral:

"The data from the four clinical studies show a favorable safety profile for YAZ and Yasmin fortified with Metafolin [Safyral], and there are no new safety issues in comparison to YAZ and Yasmin 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 Comment

- *I concur with Dr. Davis' overall safety assessment.*

The size of the safety database in this Application, in isolation, would not be adequate to assess the overall safety profile of Safyral in terms of uncommon, but serious adverse events. Safyral, however, is bioequivalent to the approved combination oral contraceptive Yasmin in terms of DRSP and EE and differs from Yasmin only by the addition of 0.451 mg levomefolate to each daily tablet. Yasmin was approved in 2001, and its approval was supported by a large and reassuring safety database. The postmarketing safety profile for Yasmin also appears to be similar to that of other combination oral contraceptives. Addition of 0.451 mg levomefolate to Yasmin 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 either Safyral (Study A39814) or Beyaz (Study A43598), 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 combination 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 questions 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

(b) (4) The Pediatric Review Committee (PeRC) considered this application on August 18, 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 Yasmin 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 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 Safyral was found acceptable by the Division of Medication Errors Prevention and Analysis (DMEPA).

The package insert for Safyral was submitted in the format prescribed by the Physician Labeling Rule (PLR). DRUP's review of this label was based on the updated internal 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; their comments were incorporated into the label as appropriate.

Safyral labeling also will include the same Warnings/Precautions as other oral contraceptive products that contain the progestin DRSP. Like Yasmin, Safyral labeling will include two additional contraindications specific for products with DRSP that contradict its use in patients with renal or adrenal insufficiency. Labeling will also warn that Safyral should not be used in women with conditions that predispose to hyperkalemia given the known anti-mineralocorticoid activity of the DRSP component. Because of the limited size of the safety database for Safyral, labeling will include safety information obtained from clinical trials and postmarketing experience with Yasmin.

Regarding folate effects, labeling for Safyral 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 Safyral will also mention the potential for folates to mask the anemia of vitamin B_{12} deficiency.

Final product labeling (physician and patient labeling) submitted by the Applicant on December 15, 2010, is acceptable.

13. DECISION/ACTION/RISK BENEFIT ASSESSMENT

13.1 Regulatory Action

The Applicant has provided sufficient information for me to conclude that Safyral (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 Safyral that was submitted in support of NDA 022574, in conjunction with the known safety and efficacy profile for Yasmin and the agreed-to product labeling, Safyral will be approved for the primary indication of *"for use by women to prevent pregnancy."* Safyral will also be approved for the secondary indication of *"Safyral 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."*

13.2 Risk/Benefit Assessment

Safyral and Yasmin are bioequivalent in terms of EE and DRSP; therefore, the contraceptive effectiveness Safyral will be comparable to that of Yasmin. In the clinical trials that supported the approval of Yasmin, the efficacy of Yasmin was acceptable for a hormonal contraceptive product.

Study A43598 and Study A39814 provided robust evidence that treatment with Safyral (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 Safyral would continue to provide clinical benefit, in terms of reducing the risk of a NTD, for at least several weeks (possibly longer) after discontinuing the product.

Addition of 0.451 mg levomefolate to Yasmin 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 with Safyral or Beyaz, there were no safety signals of concern. In these studies, the small number of serious adverse events, the adverse events that resulted in early discontinuations, 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, Safyral 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 Safyral 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
12/16/2010