CENTER FOR DRUG EVALUATION AND RESEARCH

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OFFICE DIRECTOR MEMO

FDA CENTER FOR DRUG EVALUATION AND RESEARCH

M E M O R A N D U M

DATE: September 24, 2010

TO: NDA 022532
Beyaz (drospirenone/ethinyl estradiol/levomefolate calcium tablets and levomefolate calcium tablets)

Bayer HealthCare Pharmaceuticals Inc.

FROM: Julie Beitz, M.D.
Director, Office of Drug Evaluation III

RE: Approval Action for NDA 022532

Beyaz (drospirenone/ethinyl estradiol/levomefolate calcium tablets and levomefolate calcium tablets) provides an oral contraceptive regimen consisting of 28 tablets containing the following active ingredients:

- 24 pink tablets each containing 3 mg drospirenone, 0.02 mg ethinyl estradiol, and 0.451 mg levomefolate calcium, and
- 4 light orange tablets each containing 0.451 mg levomefolate calcium

Beyaz differs from the FDA-approved oral contraceptive Yaz in that it provides daily levomefolate calcium supplementation. Levomefolate calcium is generally recognized as safe (GRAS) for use as a source of folate in dietary supplements. It is the calcium salt of L-5-methyltetrahydrofolate (L-5-MTHF), a metabolite of vitamin B_9 (folic acid), and the predominant form of folate found in foods and in the blood circulation. The dose of 0.451 levomefolate calcium is equimolar to 0.4 mg of folic acid. The bioavailability of levomefolate calcium is at least as high as that of folic acid, and equimolar doses are equally effective at increasing plasma and red blood cell folate levels.

This memorandum documents my concurrence with the Division of Reproductive and Urologic Product's (DRUP's) approval recommendation for Beyaz. I concur with the recommendation of the 2003 FDA Advisory Committee that an oral contraceptive is a reasonable delivery vehicle for the provision of additional folic acid to reproductive age women who choose to use this method for contraception. Beyaz is expected to 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 neural tube defect. Beyaz is expected to convey clinical benefit in women of reproductive age who choose to take an oral contraceptive and either conceive while on the contraceptive, or discontinue the contraceptive and conceive shortly thereafter.

Beyaz will carry the same indications that are approved for Yaz: 1) pregnancy prevention; 2) treatment of symptoms of premenstrual dysphoric disorder (PMDD) in women who choose to use an oral contraceptive as their method of contraception; and 3) treatment of moderate acne vulgaris in women at least 14 years of age who have no known contraindications to oral contraceptive therapy and have achieved menarche. These claims are supported by the demonstration of bioequivalence in the pharmacokinetics of Beyaz and Yaz with respect to the drospirenone and ethinyl estradiol components.

Unlike Yaz, Beyaz will also be 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. Discussions regarding product labeling have satisfactorily concluded and there are no inspectional issues that would preclude product approval. There are no postmarketing requirements or commitments.

Background

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 28th day of gestation. Worldwide, in 1998, approximately 300,000 births were affected by an NTD. In the US, about 4000 pregnancies were affected in 1995-1996. This number declined to 3000 pregnancies in 1999-2000 after fortification of enriched cereal grain products with folic acid was mandated.[1]

Neural tube defects are largely preventable. In 1992, the US Department of Health and Human Services Public Health Service Centers for Disease Control 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] Effective January 1, 1998, FDA required that all enriched cereal grain products sold in the US be fortified with folic acid at a level of 0.14 mg per 100 grams of product.[3] This action was taken to "help women of childbearing age to reduce their risk of having a pregnancy affected with spina bifida or other neural tube defects" and to comply with the 1992 US Public Health Service recommendations that they consume at least 0.4 mg of folic acid daily. In 2009, the US Preventive Services Task Force reviewed and concluded that "new evidence from

[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.
[3] Food and Drug Administration. Food Standards: Amendment of Standards of Identity for Enriched Grain Products to Require Addition of Folic Acid. Final Rule. *Fed Registr* 1996; 61(44):8781-8797.

observational studies provides weight to previous evidence from controlled trials that folic acid supplementation provides benefit in reduction of risk from NTD-affected pregnancies".[4]

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. Successful mandatory fortification programs have been implemented in several other countries, including Canada and South Africa.[5]

Despite mandatory fortification, certain subpopulations continue to be at greater risk of having a pregnancy affected by an 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.[6]

In 2002, Johnson & Johnson informed DRUP of its plans to develop an oral contraceptive/folic acid fixed dose combination for women who choose oral contraceptives as their method of contraception. This combination would complement public health efforts to further decrease the risk of having an NTD-affected pregnancy. Two populations of oral contraceptive users were identified: 1) women taking contraceptives who stop their medication and become pregnant shortly thereafter, and 2) women taking oral contraceptives who experience a contraceptive failure and conceive.

For oral contraceptive users who stop their contraceptive and become pregnant shortly thereafter, many of these pregnancies will remain undetected during the first few weeks when adequate folate levels are necessary to prevent NTDs. If these women were to receive a folic acid-containing oral contraceptive prior to becoming pregnant, they may have the benefit of a preconception reservoir of blood folate because serum and RBC concentrations remain elevated above pre-supplementation levels, gradually declining over a period of weeks after supplement discontinuation.

For oral contraceptive users who experience a contraceptive failure, the woman may not be consuming adequate dietary folate or taking folic acid supplements. Many of these women will not have the opportunity to see a healthcare professional or begin taking adequate vitamin supplementation until after the fetal neural tube has closed. If these women received folic acid with their oral contraceptive, their risk of having low blood folate levels (and consequently, a folic acid-preventable NTD in their fetus) may be diminished.

A Center-level briefing to discuss Johnson & Johnson's development plans was held on February 28, 2003. The case for benefit in women experiencing a contraceptive failure was thought to be solid given that many women may still be low consumers of folic acid even with current food supplementation. The case for benefit in women who decide to

[4] 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.
[5] CDC Grand Rounds 2010
[6] Ibid.

stop taking an oral contraceptive to conceive seemed less clear due to concerns about the maintenance of increased folate stores following folate discontinuation.[7] A meeting of the Reproductive Health Drugs Advisory Committee was convened on December 15, 2003 to discuss the safety and potential clinical benefit of an oral contraceptive/folic acid combination in women of reproductive age who are taking oral contraceptives and either conceive while on the contraceptive, or discontinue the contraceptive and conceive shortly thereafter.

Committee members voted unanimously (18-0) that further increases in folic acid intake, beyond what is available from fortified cereal grain products, are 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 the provision of additional folic acid; a daily dose of 0.4 mg was recommended. The majority of Committee members (14 of 18) believed that all women of reproductive age, regardless of their current folic acid intake, would be candidates for further folic acid supplementation and did not further define a subpopulation that should receive additional folic acid. In addition, most agreed that the benefits of folic acid supplementation persist if conception occurs after discontinuation of folic acid, stating that increased red cell folate levels would be maintained for up to 3 months following discontinuation.

Although Committee members indicated that chronic daily supplementation with 0.4 mg folic acid would be safe for reproductive age women, two 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 B_{12} deficiency (pernicious anemia).

Regulatory History: Beyaz

In 2005, Bayer met with DRUP to discuss the clinical development plans for oral contraceptive/folate fixed dose combinations. Bayer planned to develop products that combined an FDA-approved oral contraceptive (Yaz or Yasmin) with levomefolate calcium in an amount equivalent to 0.4 mg of folic acid.

NDA 022532, dated August 21, 2009 and received on August 24, 2009, was granted a standard review. Submissions of solicited clinical and clinical pharmacology information

[7] *See* memorandum dated February 28, 2003 from Dr. Robert Temple, Associate Director for Medical Policy, to the Director and Deputy Director of CDER, and the Director of the Office of Drug Evaluation III.

received on April 26 and May 10, 2010 were considered major amendments. The review clock was extended by three months to September 24, 2010. On August 31, 2010, the Division of Dermatology and Dental Products completed a review of available information regarding the impact, if any, of levomefolate calcium on the safety and efficacy of Beyaz for the treatment of acne vulgaris, and a labeling review.

On September 15, 2010, a meeting involving DRUP and CDER representatives from the Offices of the Center Director, New Drugs, Drug Evaluation III and IV, 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, was held to discuss Bayer's proposed indication to (b) (4) in women who choose to use an oral contraceptive as their method of contraception. The consensus view was that the indication statement include specific wording that described the purpose for which folate supplementation would be given to women using the combination, namely, to reduce the risk of a neural tube defect in a pregnancy conceived while taking the product or shortly after discontinuing the product.

Clinical Pharmacology

Orally administered levomefolate calcium is absorbed and incorporated into the body folate pool. Peak plasma folate concentrations of about 50 nmol/L above baseline are reached within 0.5-1.5 hours after a single oral dose of 0.451 mg levomefolate calcium. In contrast, mean baseline concentrations of about 15 nmol/L are reached in populations without folate food fortification under normal nutritional conditions.

An open-label, randomized, cross-over bioequivalence trial with three treatments, three study periods, and six treatment sequences was performed in 44 healthy women aged 18-38 years. The treatments administered were single doses of either Yaz, Beyaz, or 0.451 mg levomefolate calcium tablets. Bioequivalence of ethinyl estradiol (EE) and drospirenone (DRSP) was determined from the comparison of C_{max} and AUC values for these components measured in Beyaz- vs. Yaz-treated subjects. Pharmacokinetic profiles for EE and DRSP were similar for the Beyaz and Yaz formulations, and the 90% CI of the Beyaz/Yaz ratio for EE and DRSP C_{max} and AUC were within the 80-125% limits, indicating that the Beyaz and Yaz tablet formulations were bioequivalent with respect to EE and DRSP.

In this trial, bioequivalence of levomefolate calcium was also determined from the comparison of C_{max} and AUC values for L-5-MTHF measured in Beyaz- vs. levomefolate calcium-treated subjects. The pharmacokinetic profile for L-5-MTHF was similar for the Beyaz and levomefolate calcium formulations, and the 90% CI of the Beyaz/levomefolate calcium ratio for L-5-MTHF C_{max} and AUC were within the 80-125% limits, indicating that the Beyaz and levomefolate calcium tablet formulations were bioequivalent with respect to L-5-MTHF.

Efficacy: Folate Levels

The effects of an oral contraceptive/levomefolate calcium combination on plasma and RBC folate levels were evaluated in two clinical trials.

A multicenter, double-blind, randomized controlled trial was conducted in US women treated for 24 weeks with either Beyaz or Yaz. Participants consumed folate fortified food and there were no restrictions on folate supplementation. A total of 379 healthy women aged 18-40 years were randomized 3:1 to either Beyaz (n=285) or Yaz (n=94). At Week 24, the mean changes from baseline were greater for subjects treated with Beyaz as compared with subjects treated with Yaz for both plasma and RBC folate levels.

In a second trial conducted in Germany, 172 healthy women aged 18-40 years who were not consuming folate-fortified food or folate supplements were randomized 1:1 to one of two treatment groups: a related oral contraceptive product, Yasmin (3 mg drospirenone /0.03 mg ethinyl estradiol) + 0.451 mg levomefolate calcium or Yasmin + 0.4 mg folic acid. After 24 weeks, both groups received open-label treatment with Yasmin alone (elimination phase) for an additional 20 weeks to assess the duration of time during which plasma and RBC folate levels were maintained.

Treatment with Yasmin combined with either 0.451 mg levomefolate calcium or 0.4 mg folic acid produced similar maximum mean increases from baseline in plasma and RBC folate levels. Qualitatively similar folate metabolite patterns in plasma were found for both treatment groups.

Plasma and RBC folate levels gradually declined following folate discontinuation over a period of several weeks; RBC folate levels fell from a high of approximately 1300 to a low of 700 nmol/L at 20 weeks following folate discontinuation.[8]

Safety

Combined oral estrogen/progestin contraceptives (COCs) are associated with a number of well-recognized safety concerns. Product labeling for Beyaz will carry the same contraindications and warnings as other COCs including: a boxed Warning for the risk of serious cardiovascular events in women over age 35 who smoke, and warnings regarding the risks of 1) thromboembolic disorders and other vascular events, 2) carcinoma of the breast and reproductive organs, 3) liver disease, including hepatic adenomas, hepatocellular carcinoma and cholestasis, 4) hypertension, 5) gall bladder disease, 6) glucose intolerance and adverse lipid changes, 7) headaches, 8) uterine bleeding irregularities, 9) depression, and 10) interference with certain laboratory tests.

Like other COCs, labeling for Beyaz will also describe the potential for drug-drug interactions with co-administration of CYP 3A4 inducers and inhibitors. Decreased contraceptive effectiveness or, conversely, increased plasma hormone levels may result.

[8] LE Daly et al. (*JAMA* 1995, 274:1698-1702) examined early pregnancy plasma and RBC folate levels from over 55,000 women in Ireland. The risk of NTDs per 1000 births was 6.6 for women with an RBC folate level ≤ 339 nmol/L declining in a linear fashion to 0.8 for women with an RBC folate level ≥ 906 nmol/L.

Like Yaz, Beyaz labeling will include additional contraindications, involving use in individuals 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, e.g., anti-epileptics (such as phenytoin), methotrexate or pyrimethamine, thereby decreasing the pharmacological effect of the anti-folate drug. In addition, several drugs have been reported to reduce folate levels by inhibition of the dihydrofolate reductase enzyme (e.g., methotrexate and sulfasalazine), by reducing folate absorption (e.g., cholestyramine), or by unknown mechanisms (e.g., anti-epileptics such as carbamazepine, phenytoin, phenobarbital, primidone and valproic acid). Labeling for Beyaz will also mention the potential for folates to mask the anemia of vitamin B12 deficiency.

Adverse reactions commonly reported by users of Beyaz in clinical trials for contraception, acne or folate supplementation were: headache/migraine, menstrual irregularities, nausea/vomiting, and breast pain/tenderness.

Adverse reactions commonly reported by users of Beyaz in PMDD trials were: menstrual irregularities, nausea, headache, breast tenderness, fatigue, irritability, decreased libido, increased weight and affect lability.

Pediatric Considerations

Pediatric Use. The safety and efficacy of Beyaz Tablets have been established in women of reproductive age, and are expected to be the same for postpubertal adolescents under the age of 18 as for users 18 years and older.

Required Pediatric Studies. Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication in pediatric patients unless this requirement is waived, deferred, or inapplicable.

We are waiving the pediatric study requirement for pre-menarcheal patients because they are not at risk of becoming pregnant, and use of this product before menarche is not indicated. The applicant has fulfilled the pediatric study requirement for post-menarcheal pediatric patients by extrapolation of adult data.

Tradename Review

The Division of Medication Error Prevention and Analysis, in consultation with the Division of Drug Marketing, Advertising, and Communications, has concluded that the tradename “Beyaz” is acceptable.

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/s/

JULIE G BEITZ
09/24/2010