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In 2001, 49% of pregnancies in the United States were unplanned.¹ One in 20 women overall, and more than 1 in 10 women between the ages of 18 and 24 experienced an unintended pregnancy.¹

Neural tube defects (NTDs), which are rare birth defects caused by a malformation in the embryo's central nervous system, are largely preventable but continue to affect approximately 1 in every 1000 pregnancies.² NTDs occur when the neural tube fails to close, usually within 4 weeks of conception and often at least 1 month before a woman is even aware she is pregnant.^{3,4}

Folate is a B vitamin that the human body cannot synthesize on its own. Folate can be found either naturally in some foods (eg, green leafy vegetables) or synthetically in fortified foods and/or supplements.²⁻⁵ It is recommended by the Centers for Disease Control (CDC) and the US Preventive Services Task Force (USPSTF) that all women of childbearing age supplement their diet with at least 400 mcg of folic acid daily to reduce the risk of NTDs should pregnancy occur.^{3,6,7} Because NTDs mainly occur in the first 4 weeks after conception, daily folic acid supplementation is recommended at least 1 month before conception and through the first trimester.²⁻⁴

OC Options Containing Folate

BeyazTM and SAFYRALTM are two FDA-approved estrogen/progestin combination oral contraceptives (OCs), each of which contain 451 mcg of levomefolate calcium. Levomefolate calcium is a synthetic form of folate that is structurally identical to L-5-methyltetrahydrofolate, which is a metabolite of vitamin B9. The Beyaz regimen consists of 24 days of drospirenone 3 mg/ethinyl estradiol 20 mcg plus 451

mcg levomefolate calcium, followed by 4 days of 451 mcg levomefolate calcium only. SAFYRAL, containing drospirenone 3 mg/ethinyl estradiol 30 mcg plus 451 mcg levomefolate calcium, is taken for 21 days, followed by 7 days of 451 mcg levomefolate calcium only.^{8,9} Both Beyaz and SAFYRAL are indicated for prevention of pregnancy and to raise folate levels in women who choose to use an OC for contraception.^{8,9} In these women, Beyaz and SAFYRAL raise folate levels for the purpose of reducing the risk of an NTD in a pregnancy conceived while taking the product or shortly after discontinuing the product. Beyaz is also indicated in women who choose to use an OC for contraception for the treatment of the symptoms of premenstrual dysphoric disorder (PMDD) or the treatment of moderate acne in women at least 14 years of age who have had a first menstrual period.⁸ The effectiveness of Beyaz for PMDD when used for more than 3 menstrual cycles has not been evaluated. Beyaz has not been evaluated for the treatment of premenstrual syndrome. Both OCs are 99% effective at preventing pregnancy when used as directed, and neither are indicated for use during pregnancy. Results of the contraceptive efficacy clinical trial for Beyaz showed a pregnancy rate (Pearl Index) of 1.41 per 100 woman-years of use based on 12 pregnancies that occurred after treatment began and within 14 days of the last dose in women 35 years of age or younger during cycles in which no other form of contraception was used.⁸ For SAFYRAL, the pregnancy rates in the contraceptive efficacy clinical trials were less than 1 per 100 woman-years of use.⁹

FDA approval of both OCs is supported by a development program consisting of two folate supplementation clinical trials. One study was a 24-week multicenter, randomized, double-blind, parallel group clinical trial of 379 healthy women between the ages of 18 and 40 years conducted in the United States. Mean red blood cell (RBC)

and plasma folate levels were significantly increased from baseline to week 24 among women who took Beyaz (Figure) compared with women who took 3 mg drospirenone/20 mcg ethinyl estradiol alone without levomefolate calcium. Another study evaluated 24 weeks of blinded treatment with 451 mcg levomefolate calcium or with 400 mcg folic acid, both in combination with 3 mg drospirenone/30 mcg ethinyl estradiol, followed by 20 weeks of open-label treatment with 3 mg drospirenone/30 mcg ethinyl estradiol alone (folate elimination phase). Among 172 healthy German women, 18 to 40 years old, from a population without folate fortified food or concomitant intake of folate supplements, the study showed maximum mean increases from baseline in RBC and plasma folate levels were similar between groups, respectively, after 24 weeks of blinded treatment. Upon discontinuation of folate intake, RBC and plasma folate levels are likely to decrease to baseline over 20 weeks, with plasma folate levels dropping more rapidly.

Beyaz and SAFYRAL may be able to help women elevate their folate levels to reduce the risk of having an NTD should an unplanned pregnancy occur during use or if pregnancy occurs shortly after OC discontinuation.

Contraception and Folate in 1 Step

Women who discontinue their OC or take OCs incorrectly may become pregnant. Combining folate with an OC may help women who choose an OC for contraception establish a daily routine that includes taking the recommended amount of folate.

Pharmacists should counsel patients on such points as the correct way to take OCs (one tablet daily in the order directed on the blister pack), and also advise patients to report whether they are taking folate supplements and to continue folate supplementation if they discontinue taking Beyaz or SAFYRAL.

Reviewed by:

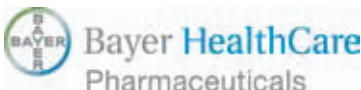
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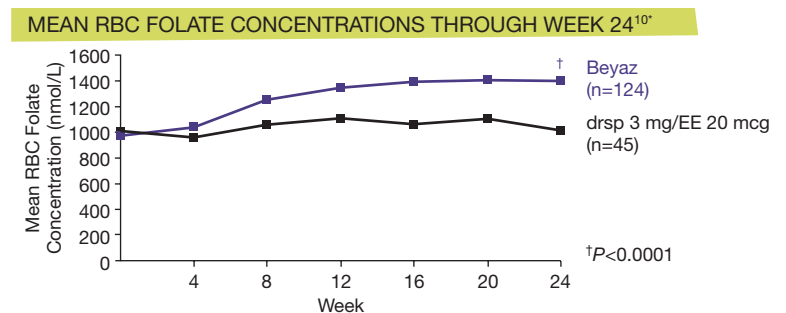
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This article was written by Mary Mihalovic, Elsevier and Bayer HealthCare Pharmaceuticals Inc. This space was made available for a fee to Bayer.

Figure.



Important Safety Information about Beyaz™ and SAFYRAL™

Patients who should not take Beyaz or SAFYRAL

Women over 35 years old who smoke should not use Beyaz or SAFYRAL. Smoking increases the risk of serious cardiovascular side effects from Beyaz or SAFYRAL use. This risk increases with age and the number of cigarettes smoked.

Beyaz and SAFYRAL are contraindicated in women with a high risk of arterial or venous thrombotic diseases, undiagnosed abnormal uterine bleeding, breast cancer or other hormone-sensitive cancer, liver tumors (benign or malignant) or liver disease, conditions that predispose to hyperkalemia (ie, renal impairment, hepatic dysfunction, and adrenal insufficiency), or who are pregnant.

Know serious risks with Beyaz and SAFYRAL

Thromboembolic and Other Vascular Events: Stop Beyaz or SAFYRAL if an arterial or deep venous thrombotic event occurs. The risk of venous thromboembolism is highest during the first year of use of combination oral contraceptives (COCs). COC use also increases risk of arterial thromboses (eg, stroke and myocardial infarction), especially in women with risk factors for these events.

Use COCs with caution in women with cardiovascular disease risk factors. If feasible, stop Beyaz or SAFYRAL at least 4 weeks before and through 2 weeks after major surgery or other surgeries known to have an elevated risk of thromboembolism. Start Beyaz or SAFYRAL no earlier than 4 weeks after delivery in women not breastfeeding.

Hyperkalemia: Beyaz and SAFYRAL contain drospirenone that has the potential for hyperkalemia in high-risk patients and is contraindicated in patients with conditions that predispose to hyperkalemia. Check serum potassium level during the first treatment cycle in women who receive long-term treatment with medications that may increase serum potassium (eg, ACE inhibitors, angiotensin-II receptor antagonists, potassium-sparing diuretics, potassium supplementation, heparin, aldosterone antagonists, and NSAIDs).

Liver Disease: Discontinue Beyaz or SAFYRAL if jaundice develops.

High Blood Pressure (BP): Women with uncontrolled hypertension or hypertension with vascular disease should not use COCs. Monitor BP in women with well-controlled hypertension and stop Beyaz or SAFYRAL if BP rises significantly. BP may increase in COC users, more likely occurring in older women and with extended use.

Gallbladder Disease: Studies suggest a small increased relative risk of developing gallbladder disease among COC users.

Carbohydrate and Lipid Metabolic Effects: Monitor prediabetic and diabetic COC users. Consider alternative contraception for women with uncontrolled dyslipidemia.

Headache: If a Beyaz or SAFYRAL user develops new headaches that are recurrent, persistent, or severe, evaluate the cause and discontinue Beyaz or SAFYRAL if indicated.

Bleeding Irregularities: Evaluate irregular bleeding or amenorrhea; check for causes such as pregnancy or malignancy.

Folates may mask vitamin B12 deficiency.

Counsel patients that Beyaz and SAFYRAL do not protect against HIV infection and other sexually transmitted diseases.

Serious adverse reactions in Beyaz clinical trials:

Cervix carcinoma stage 0, cervical dysplasia, and migraine

Serious adverse reactions in SAFYRAL clinical trials: Depression, pulmonary embolism, toxic skin eruption, and uterine leiomyoma

Most common adverse reactions in Beyaz clinical trials:

Frequent ($\geq 2\%$) adverse reactions in contraception, moderate acne and folate clinical trials were: headache/migraine (5.9%), menstrual irregularities (4.1%), nausea/vomiting (3.5%), and breast pain/tenderness (3.2%).

Frequent ($\geq 2\%$) adverse reactions in PMDD clinical trials were: menstrual irregularities (24.9%), nausea (15.8%), headache (13.0%), breast tenderness (10.5%), fatigue (4.2%), irritability (2.8%), decreased libido (2.8%), increased weight (2.5%), and affect lability (2.1%).

Most common adverse reactions in SAFYRAL clinical trials: Frequent ($\geq 2\%$) adverse reactions in contraception and folate clinical trials were: premenstrual syndrome (12.4%), headache/migraine (10.3%), breast pain/tenderness/discomfort (8.1%), nausea/vomiting (4.4%), and abdominal pain/discomfort/tenderness (2.2%).

Drug interactions (see Prescribing Information of concomitant drugs)

Effects of Other Drugs on COCs: Drugs or herbal products that induce certain enzymes (eg, CYP3A4) may decrease the effectiveness of COCs or increase breakthrough bleeding. Counsel patients to use a back-up or alternate method of contraception during use and for 28 days following discontinuation of concomitant use. Certain drugs (eg, atorvastatin, CYP3A4 inhibitors) may increase plasma levels of COCs. HIV protease inhibitors and non-nucleoside reverse transcriptase inhibitors may increase or decrease plasma levels of COCs. There have been reports of pregnancy while taking hormonal contraceptives and antibiotics concomitantly.

Effects of COCs on Other Drugs: COCs may inhibit or induce metabolism

of other drugs (eg, lamotrigine).

Effects on Serum Potassium: See hyperkalemia information in the left column.

Effects of Folates on Other Drugs: Folates may decrease the pharmacological effect of certain antifolate drugs.

Effects of Other Drugs on Folates: Several drugs (eg, methotrexate and sulfasalazine, cholestyramine, certain anti-epileptics) may reduce folate levels via various mechanisms.

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Please see www.beyaz.com and www.SAFYRAL.com for full Prescribing Information.

Please see brief summaries of full Prescribing Information about Beyaz and SAFYRAL, including boxed warning, on adjacent pages.



Trim along this line

BEYAZ (drospirenone/ethinyl estradiol/ levomefolate calcium tablets and levomefolate calcium tablets)

Initial U.S. Approval: 2010

**BRIEF SUMMARY OF PRESCRIBING INFORMATION
CONSULT PACKAGE INSERT FOR FULL PRESCRIBING INFORMATION**

WARNING: CIGARETTE SMOKING AND SERIOUS CARDIOVASCULAR EVENTS

Cigarette smoking increases the risk of serious cardiovascular events from combination oral contraceptives (COC) use. This risk increases with age, particularly in women over 35 years of age, and with the number of cigarettes smoked. For this reason, COCs should not be used by women who are over 35 years of age and smoke. [See Contraindications (4)].

1 INDICATIONS AND USAGE

1.1 Oral Contraceptive

Be Yaz is indicated for use by women to prevent pregnancy.

1.2 Premenstrual Dysphoric Disorder (PMDD)

Be Yaz is also indicated for the treatment of symptoms of premenstrual dysphoric disorder (PMDD) in women who choose to use an oral contraceptive as their method of contraception. The effectiveness of Be Yaz for PMDD when used for more than three menstrual cycles has not been evaluated.

Be Yaz has not been evaluated for the treatment of premenstrual syndrome (PMS).

1.3 Acne

Be Yaz is indicated for the treatment of moderate acne vulgaris in women at least 14 years of age, who have no known contraindications to oral contraceptive therapy and have achieved menarche. Be Yaz should be used for the treatment of acne only if the patient desires an oral contraceptive for birth control.

1.4 Folate Supplementation

Be Yaz 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.

4 CONTRAINDICATIONS

Do not prescribe Be Yaz to women who are known to have the following:

- Renal impairment
- Adrenal insufficiency
- A high risk of arterial or venous thrombotic diseases. Examples include women who are known to:
 - Smoke, if over age 35 [see *Boxed Warning and Warnings and Precautions (5.1)*]
 - Have deep vein thrombosis or pulmonary embolism, now or in the past [see *Warnings and Precautions (5.1)*]
 - Have cerebrovascular disease [see *Warnings and Precautions (5.1)*]
 - Have coronary artery disease [see *Warnings and Precautions (5.1)*]
 - Have thrombogenic valvular or thrombogenic rhythm diseases of the heart (for example, subacute bacterial endocarditis with valvular disease, or atrial fibrillation) [see *Warnings and Precautions (5.1)*]
 - Have inherited or acquired hypercoagulopathies [see *Warnings and Precautions (5.1)*]
 - Have uncontrolled hypertension [see *Warnings and Precautions (5.5)*]
 - Have diabetes mellitus with vascular disease [see *Warnings and Precautions (5.7)*]
 - Have headaches with focal neurological symptoms or have migraine headaches with or without aura if over age 35 [see *Warnings and Precautions (5.8)*]
- Undiagnosed abnormal uterine bleeding [see *Warnings and Precautions (5.9)*]
- Breast cancer or other estrogen- or progestin-sensitive cancer, now or in the past [see *Warnings and Precautions (5.3)*]
- Liver tumors, benign or malignant, or liver disease [see *Warnings and Precautions (5.4)* and *Use in Specific Populations (8.7)*]
- Pregnancy, because there is no reason to use COCs during pregnancy [see *Warnings and Precautions (5.10)* and *Use in Specific Populations (8.1)*]

5 WARNINGS AND PRECAUTIONS

5.1 Thromboembolic Disorders and Other Vascular Problems

Stop Be Yaz if an arterial or deep venous thrombotic (VTE) event occurs. Although the use of COCs increases the risk of venous thromboembolism, pregnancy increases the risk of venous thromboembolism as much or more than the use of COCs. The risk of venous thromboembolism in women using COCs is 3 to 9 per 10,000 woman-years. The risk is highest during the first year of use of a COC. Use of COCs also increases the risk of arterial thromboses such as strokes and myocardial infarctions, especially in women with other risk factors for these events. The risk of thromboembolic disease due to oral contraceptives gradually disappears after COC use is discontinued.

If feasible, stop Be Yaz at least 4 weeks before and through 2 weeks after major surgery or other surgeries known to have an elevated risk of thromboembolism.

Start Be Yaz no earlier than 4 weeks after delivery, in women who are not breastfeeding. The risk of postpartum thromboembolism decreases after the third postpartum week, whereas the risk of ovulation increases after the third postpartum week.

COCs have been shown to increase both the relative and attributable risks of cerebrovascular events (thrombotic and hemorrhagic strokes), although, in general, the risk is greatest among older (>35 years of age), hypertensive women who also smoke. COCs also increase the risk for stroke in women with other underlying risk factors.

Oral contraceptives must be used with caution in women with cardiovascular disease risk factors.

Stop Be Yaz if there is unexplained loss of vision, proptosis, diplopia, papilledema, or retinal vascular lesions. Evaluate for retinal vein thrombosis immediately. [See *Adverse Reactions (6)*.]

Epidemiologic studies including a DRSP-containing COC

Several studies have investigated the relative risks of thromboembolism in women using a different DRSP-containing COC (Yasmin, which contains 0.03 mg of EE and 3 mg of DRSP) compared to those in women using COCs containing other progestins. Two prospective cohort studies, both evaluating the risk of venous and arterial thromboembolism and death, were initiated at the time of Yasmin approval.²³ The first (EURAS) showed the risk of thromboembolism (particularly venous thromboembolism) and death in Yasmin users to be comparable to that of other oral contraceptive preparations, including those containing levonorgestrel (a so-called second generation COC). The second prospective cohort study (Ingenix) also showed a comparable risk of thromboembolism in Yasmin users compared to users of other COCs, including those containing levonorgestrel. In the second study, COC comparator groups were selected based on their having similar characteristics to those being prescribed Yasmin.

Two additional epidemiological studies, one case-control study (van Hylckama Vlieg et al.⁴) and one retrospective cohort study (Lidegaard et al.⁵) suggested that the risk of venous thromboembolism occurring in Yasmin users was higher than that for users of levonorgestrel-containing COCs and lower than that for users of desogestrel/gestodene-containing COCs (so-called third generation COCs). In the case-control study, however, the number of Yasmin cases was very small (1.2% of all cases) making the risk estimates unreliable. The relative risk for Yasmin users in the retrospective cohort study was greater than that for users of other COC products when considering women who used the products for less than one year. However, these one-year estimates may not be reliable because the analysis may include women of varying risk levels. Among women who used the product for 1 to 4 years, the relative risk was similar for users of Yasmin to that for users of other COC products.

5.2 Hyperkalemia

Be Yaz contains 3 mg of the progestin DRSP which has antiminerlocorticoid activity, including the potential for hyperkalemia in high-risk patients, comparable to a 25 mg dose of spironolactone. Be Yaz should not be used in patients with conditions that predispose to hyperkalemia (i.e., renal insufficiency, hepatic dysfunction and adrenal insufficiency). Women receiving daily, long-term treatment for chronic conditions or diseases with medications that may increase serum potassium should have their serum potassium level checked during the first treatment cycle. Medications that may increase serum potassium include ACE inhibitors, angiotensin-II receptor antagonists, potassium-sparing diuretics, potassium supplementation, heparin, aldosterone antagonists, and NSAIDs.

5.3 Carcinoma of the Breasts and Reproductive Organs

Women who currently have or have had breast cancer should not use Be Yaz because breast cancer is a hormonally-sensitive tumor.

There is substantial evidence that COCs do not increase the incidence of breast cancer. Although some past studies have suggested that COCs might increase the incidence of breast cancer, more recent studies have not confirmed such findings.

Some studies suggest that COCs are associated with an increase in the risk of cervical cancer or intraepithelial neoplasia. However, there is controversy about the extent to which these findings may be due to differences in sexual behavior and other factors.

5.4 Liver Disease

Discontinue Be Yaz if jaundice develops. Steroid hormones may be poorly metabolized in patients with impaired liver function. Acute or chronic disturbances of liver function may necessitate the discontinuation of COC use until markers of liver function return to normal and COC causation has been excluded.

Hepatic adenomas are associated with COC use. An estimate of the attributable risk is 3.3 cases/100,000 COC users. Rupture of hepatic adenomas may cause death through intra-abdominal hemorrhage.

Studies have shown an increased risk of developing hepatocellular carcinoma in long-term (>8 years) COC users. However, the attributable risk of liver cancers in COC users is less than one case per million users.

Oral contraceptive-related cholestasis may occur in women with a history of pregnancy-related cholestasis. Women with a history of COC-related cholestasis may have the condition recur with subsequent COC use.

5.5 High Blood Pressure

For women with well-controlled hypertension, monitor blood pressure and stop Be Yaz if blood pressure rises significantly. Women with uncontrolled hypertension or hypertension with vascular disease should not use COCs.

An increase in blood pressure has been reported in women taking COCs, and this increase is more likely in older women and with extended duration of use. The incidence of hypertension increases with increasing concentration of progestin.

5.6 Gallbladder Disease

Studies suggest a small increased relative risk of developing gallbladder disease among COC users.

5.7 Carbohydrate and Lipid Metabolic Effects

Carefully monitor prediabetic and diabetic women who are taking Be Yaz. COCs may decrease glucose tolerance in a dose-related fashion.

Consider alternative contraception for women with uncontrolled dyslipidemia. A small proportion of women will have adverse lipid changes while on COCs.

Women with hypertriglyceridemia, or a family history thereof, may be at an increased risk of pancreatitis when using COCs.

5.8 Headache

If a woman taking Be Yaz develops new headaches that are recurrent, persistent, or severe, evaluate the cause and discontinue Be Yaz if indicated.

An increase in frequency or severity of migraine during COC use (which may be prodromal of a cerebrovascular event) may be a reason for immediate discontinuation of the COC.

5.9 Bleeding Irregularities

Unscheduled (breakthrough or intracyclic) bleeding and spotting sometimes occur in patients on COCs, especially during the first three months of use. If bleeding persists or occurs after previously regular cycles, check for causes such as pregnancy or malignancy. If pathology and pregnancy are excluded, bleeding irregularities may resolve over time or with a change to a different COC.

Data for Be Yaz show the average number of episodes of bleeding per reference period (90 days) was 3.2 in Cycles 4-6. The average number of bleeding and/or spotting days with Be Yaz was 15.1 days. The intensity of bleeding for Be Yaz based on the ratio of spotting-only days versus total bleeding and/or spotting days was 5.2/15.1 days.

Based on patient diaries from two contraceptive clinical trials of YAZ, 8 to 25% of women experienced unscheduled bleeding per 28-day cycle. A total of 12 subjects out of 1,056 (1.1%) discontinued YAZ due to menstrual disorders including intermenstrual bleeding, menorrhagia, and metrorrhagia.

Women who use Be Yaz may experience absence of withdrawal bleeding, even if they are not pregnant. Based on subject diaries from YAZ contraception trials for up to 13 cycles, 6 to 10% of women experienced cycles with no withdrawal bleeding. Some women may encounter post-pill amenorrhea or oligomenorrhea, especially when such a condition was pre-existent.

If withdrawal bleeding does not occur, consider the possibility of pregnancy. If the patient has not adhered to the prescribed dosing schedule (missed one or more active tablets or started taking them on a day later than she should have), consider the possibility of pregnancy at the time of the first missed period and take appropriate diagnostic measures. If the patient has adhered to the prescribed regimen and misses two consecutive periods, rule out pregnancy.

5.10 COC Use Before or During Early Pregnancy

Extensive epidemiological studies have revealed no increased risk of birth defects in women who have used oral contraceptives prior to pregnancy. Studies also do not suggest a teratogenic effect, particularly in so far as cardiac anomalies and limb-reduction defects are concerned, when taken inadvertently during early pregnancy. Discontinue Be Yaz if pregnancy is confirmed and initiate a prenatal vitamin containing folate supplementation.

The administration of oral contraceptives to induce withdrawal bleeding should not be used as a test for pregnancy [see *Use in Specific Populations (8.1)*].

5.11 Depression

Women with a history of depression should be carefully observed and Be Yaz discontinued if depression recurs to a serious degree.

5.12 Interference with Laboratory Tests

The use of COCs may change the results of some laboratory tests, such as coagulation factors, lipids, glucose tolerance, and binding proteins. Women on thyroid hormone replacement therapy may need increased doses of thyroid hormone because serum concentrations of thyroid-binding globulin increased by use of COCs. DRSP causes an increase in plasma renin activity and plasma aldosterone induced by its mild antiminerlocorticoid activity.

Folates may mask vitamin B12 deficiency.

5.13 Monitoring

A woman who is taking COCs should have a yearly visit with her healthcare provider for a blood pressure check and for other indicated healthcare.

5.14 Other Conditions

In women with hereditary angioedema, exogenous estrogens may induce or exacerbate symptoms of angioedema. Chloasma may occasionally occur, especially in women with a history of chloasma gravidarum. Women with a tendency to chloasma should avoid exposure to the sun or ultraviolet radiation while taking COCs.

6 ADVERSE REACTIONS

The following serious adverse reactions with the use of COCs are discussed elsewhere in the labeling:

- Serious cardiovascular events and smoking [see *Boxed Warning and Warnings and Precautions (5.1)*]
- Vascular events [see *Warnings and Precautions (5.1)*]
- Liver disease [see *Warnings and Precautions (5.4)*]

Adverse reactions commonly reported by COC users are:

- Irregular uterine bleeding
- Breast tenderness
- Nausea
- Headache

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, the adverse reaction rates observed cannot be directly compared to rates in other clinical trials and may not reflect the rates observed in clinical practice.

Contraception, Acne and Folate Supplementation Clinical Trials

The data provided reflect the experience with the use of YAZ (3 mg DRSP/0.02 mg EE), in the adequate and well-controlled studies for contraception (N=1,056), for moderate acne vulgaris (N=536) and folate supplementation (N=379).

The adverse reactions seen across the 3 indications overlapped, and are reported using the frequencies from the pooled dataset. The most common treatment-emergent adverse reactions ($\geq 2\%$ of users) were: headache/migraine (5.9%), menstrual irregularities (including vaginal hemorrhage [primarily spotting], metrorrhagia and menorrhagia) (4.1%), nausea/vomiting (3.5%), and breast pain/tenderness (3.2%).

PMDD Clinical Trials

Safety data from trials for the indication of PMDD are reported separately due to differences in study design and setting in the OC, Acne and Folate Supplementation studies as compared to the PMDD clinical program.

Common treatment-emergent adverse reactions ($\geq 2\%$ of users) were: menstrual irregularities (including vaginal hemorrhage [primarily spotting] and metrorrhagia) (24.9%), nausea (15.8%), headache (13.0%), breast tenderness (10.5%), fatigue (4.2%), irritability (2.8%), decreased libido (2.8%), increased weight (2.5%), and affect lability (2.1%).

Adverse Reactions ($\geq 1\%$) Leading to Study Discontinuation:

Contraception Clinical Trials

Of 1,056 women, 6.6% discontinued from the clinical trials due to an adverse reaction; the most frequent adverse reactions leading to discontinuation were headache/migraine (1.6%) and nausea/vomiting (1.0%).

Acne Clinical Trials

Of 536 women, 5.4% discontinued from the clinical trials due to an adverse reaction; the most frequent adverse reaction leading to discontinuation was menstrual irregularities (including menometrorrhagia, menorrhagia, metrorrhagia and vaginal hemorrhage) (2.2%).

Folate Clinical Trial

Of 285 women, 4.6% who used Beyaz or YAZ discontinued from the clinical trials due to an adverse reaction; no reaction leading to discontinuation occurred in $\geq 1\%$ of women.

PMDD Clinical Trials

Of 285 women, 11.6% discontinued from the clinical trials due to an adverse reaction; the most frequent adverse reactions leading to discontinuation were: nausea/vomiting (4.6%), menstrual irregularity (including vaginal hemorrhage, menorrhagia, menstrual disorder, menstruation irregular and metrorrhagia) (4.2%), fatigue (1.8%), breast tenderness (1.4%), depression (1.4%), headache (1.1%), and irritability (1.1%).

Serious Adverse Reactions (Definitely, Probably, or Possibly Related to Study Drug):

Contraception Clinical Trials: migraine and cervical dysplasia

Acne Clinical Trials: none reported in the clinical trials

Folate Supplementation Clinical Trial: cervix carcinoma stage 0

PMDD Clinical Trials: cervical dysplasia

6.2 Postmarketing Experience

The following adverse reactions have been identified during post approval use of YAZ. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Adverse reactions are grouped into System Organ Classes, and ordered by frequency.

Vascular disorders: Venous and arterial thromboembolic events (including pulmonary emboli, deep vein thrombosis, cerebral thrombosis, retinal thrombosis, myocardial infarction and stroke), hypertension (including hypertensive crisis)

Hepatobiliary disorders: Gallbladder disease, liver function disturbances, liver tumors

Immune system disorders: Hypersensitivity (including anaphylactic reaction)

Metabolism and nutrition disorders: Hyperkalemia, hypertriglyceridemia, changes in glucose tolerance or effect on peripheral insulin resistance (including diabetes mellitus)

Skin and subcutaneous tissue disorders: Chloasma, angioedema, erythema nodosum, erythema multiforme

Gastrointestinal disorders: Inflammatory bowel disease

Musculoskeletal and connective tissue disorders: Systemic lupus erythematosus

7 DRUG INTERACTIONS

Consult the labeling of all concurrently-used drugs to obtain further information about interactions with hormonal contraceptives or the potential for enzyme alterations.

7.1 Effects of Other Drugs on Combined Hormonal Contraceptives

Substances diminishing the efficacy of COCs: Drugs or herbal products that induce certain enzymes, including CYP3A4, may decrease the effectiveness of COCs or increase breakthrough bleeding. Some drugs or herbal products that may decrease the effectiveness of hormonal contraceptives include phenytoin, barbiturates, carbamazepine, bosentan, felbamate, griseofulvin, oxcarbazepine, rifampicin, topiramate and products containing St. John's wort. Interactions between oral contraceptives and other drugs may lead to breakthrough bleeding and/or contraceptive failure. Counsel women to use an alternative method of contraception or a back-up method when enzyme inducers are used with COCs, and to continue back-up contraception for 28 days after discontinuing the enzyme inducer to ensure contraceptive reliability.

Substances increasing the plasma levels of COCs: Co-administration of atorvastatin and certain COCs containing EE increase AUC values for EE by approximately 20%. Ascorbic acid and acetaminophen may increase plasma EE levels, possibly by inhibition of conjugation. CYP3A4 inhibitors such as itraconazole or ketoconazole may increase plasma hormone levels.

HIV Protease Inhibitors and non-nucleoside reverse transcriptase inhibitors: Significant changes (increase or decrease) in the plasma levels of estrogen and progestin have been noted in some cases of co-administration with HIV protease inhibitors or with non-nucleoside reverse transcriptase inhibitors.

Antibiotics: There have been reports of pregnancy while taking hormonal contraceptives and antibiotics, but clinical pharmacokinetic studies have not shown consistent effects of antibiotics on plasma concentrations of synthetic steroids.

Effect on DRSP: The main metabolites of DRSP in human plasma are generated without involvement of the cytochrome P450 system. Inhibitors of this enzyme system are therefore unlikely to influence the metabolism of DRSP.

7.2 Effects of Combined Oral Contraceptives on Other Drugs

COCs containing EE may inhibit the metabolism of other compounds. COCs have been shown to significantly decrease plasma concentrations of lamotrigine, likely due to induction of lamotrigine glucuronidation. This may reduce seizure control; therefore, dosage adjustments of lamotrigine may be necessary. Consult the labeling of the concurrently-used drug to obtain further information about interactions with COCs or the potential for enzyme alterations.

In vitro and clinical studies did not indicate an inhibitory potential of DRSP towards human CYP450 enzymes at clinically relevant concentrations [see *Clinical Pharmacology* (12.3)].

7.3 Interactions that Have the Potential to Increase Serum Potassium

There is a potential for an increase in serum potassium in women taking Beyaz with other drugs that may increase serum potassium [see *Warnings and Precautions* (5.2) and *Clinical Pharmacology* (12.3)].

7.4 Effects of Folates on Other Drugs

Folates may modify the pharmacokinetics or pharmacodynamics of certain antifolate drugs, e.g., antiepileptics (such as phenytoin), methotrexate or pyrimethamine, and may result in a decreased pharmacological effect of the antifolate drug.

7.5 Effects of Other Drugs on Folates

Several drugs have been reported to reduce folate levels by inhibition of the dihydrofolate reductase enzyme (e.g., methotrexate and sulfasalazine) or by reducing folate absorption (e.g., cholestyramine), or via unknown mechanisms (e.g., antiepileptics such as carbamazepine, phenytoin, phenobarbital, primidone and valproic acid).

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

There is little or no increased risk of birth defects in women who inadvertently use COCs during early pregnancy. Epidemiologic studies and meta-analyses have not found an increased risk of genital or non-genital birth defects (including cardiac anomalies and limb-reduction defects) following exposure to low dose COCs prior to conception or during early pregnancy.

The administration of COCs to induce withdrawal bleeding should not be used as a test for pregnancy. COCs should not be used during pregnancy to treat threatened or habitual abortion.

Women who do not breastfeed may start COCs no earlier than four weeks postpartum.

8.3 Nursing Mothers

When possible, advise the nursing mother to use other forms of contraception until she has weaned her child. Estrogen-containing OCs can reduce milk production in breastfeeding mothers. This is less likely to occur once breastfeeding is well-established; however, it can occur at any time in some women. Small amounts of oral contraceptive steroids and/or metabolites are present in breast milk.

After oral administration of 3 mg DRSP/0.03 mg EE tablets (Yasmin), about 0.02% of the DRSP dose was excreted into the breast milk of postpartum women within 24 hours. This results in a maximal daily dose of about 0.003 mg DRSP in an infant.

Studies to date indicate there is no adverse effect of folate on nursing infants.

8.4 Pediatric Use

Safety and efficacy of Beyaz has been established in women of reproductive age. Safety and efficacy are expected to be the same for postpubertal adolescents under the age of 18 and for users 18 years and older. Use of this product before menarche is not indicated.

8.5 Geriatric Use

Beyaz has not been studied in postmenopausal women and is not indicated in this population.

8.6 Patients with Renal Impairment

Beyaz is contraindicated in patients with renal impairment [see *Contraindications* (4) and *Warnings and Precautions* (5.2)].

Following administration of DRSP 3 mg daily for 14 days, serum DRSP levels in subjects with mild renal impairment (creatinine clearance CL_{cr}, 50-80 mL/min) were comparable to those in subjects with normal renal function (CL_{cr}, >80 mL/min). The serum DRSP levels were on average 37 % higher in subjects with moderate renal impairment (CL_{cr}, 30 - 50 mL/min) compared to those with normal renal function. DRSP treatment did not show any clinically significant effect on serum potassium concentration. Although hyperkalemia was not observed in the study, in five of the seven subjects who continued use of potassium sparing drugs during the study, mean serum potassium levels increased by up to 0.33 mEq/L. Therefore, potential exists for hyperkalemia to occur in subjects with renal impairment whose serum potassium is in the upper reference range, and who are concomitantly using potassium sparing drugs [see *Clinical Pharmacology* (12.3)].

8.7 Patients with Hepatic Impairment

Beyaz is contraindicated in patients with hepatic disease [see *Contraindications* (4) and *Warnings and Precautions* (5.4)]. The mean exposure to DRSP in women with moderate liver impairment is approximately three times higher than the exposure in women with normal liver function. Beyaz has not been studied in women with severe hepatic impairment.

10 OVERDOSAGE

There have been no reports of serious ill effects from overdose, including ingestion by children. Overdosage may cause withdrawal bleeding in females and nausea.

DRSP however, is a spironolactone analogue which has antiminerocorticoid properties. Serum concentration of potassium and sodium, and evidence of metabolic acidosis, should be monitored in cases of overdose.

Levomefolate calcium doses of 17 mg/day (37-fold higher than the levomefolate calcium dose of Beyaz) were well tolerated after long-term treatment up to 12 weeks.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

In a 24 month oral carcinogenicity study in mice dosed with 10 mg/kg/day DRSP alone or 1 + 0.01, 3 + 0.03 and 10 + 0.1 mg/kg/day of DRSP and EE, 0.1 to 2 times the exposure (AUC of DRSP) of women taking a contraceptive dose, there was an increase in carcinomas of the hardener gland in the group that received the high dose of DRSP alone. In a similar study in rats given 10 mg/kg/day DRSP alone or 0.3 + 0.003, 3 + 0.03 and 10 + 0.1 mg/kg/day DRSP and EE, 0.8 to 10 times the exposure of women taking a contraceptive dose, there was an increased incidence of benign and malignant adrenal gland pheochromocytomas in the group receiving the high dose of DRSP. Mutagenesis studies for DRSP were conducted *in vivo* and *in vitro* and no evidence of mutagenic activity was observed.

Long-term animal studies have not been conducted to evaluate the carcinogenic potential of levomefolate. Mutagenesis studies for levomefolate were conducted *in vitro* and *in vivo* and no evidence of mutagenic activity was observed.

17 PATIENT COUNSELING INFORMATION

[See *FDA-approved Patient Labeling*.]

- Counsel patients that cigarette smoking increases the risk of serious cardiovascular events from COC use, and that women who are over 35 years old and smoke should not use COCs.
- Counsel patients that Beyaz does not protect against HIV-infection (AIDS) and other sexually transmitted diseases.
- Counsel patients on Warnings and Precautions associated with COCs.
- Counsel patients that Beyaz contains DRSP. Drospirenone may increase potassium. Patients should be advised to inform their healthcare provider if they have kidney, liver or adrenal disease because the use of Beyaz in the presence of these conditions could cause serious heart and health problems. They should also inform their healthcare provider if they are currently on daily, long-term treatment (NSAIDs, potassium-sparing diuretics, potassium supplementation, ACE inhibitors, angiotensin-II receptor antagonists, heparin or aldosterone antagonists) for a chronic condition.
- Beyaz is not indicated during pregnancy. If pregnancy is planned or occurs during treatment with Beyaz, further intake must be stopped. However, women should be advised on the continued need of sufficient folate intake.
- Counsel patients to take one tablet daily by mouth at the same time every day. Instruct patients what to do in the event pills are missed. See "What to Do if You Miss Pills" section in *FDA-Approved Patient Labeling*.
- Counsel patients to use a back-up or alternative method of contraception when enzyme inducers are used with COCs.
- Counsel patients who are breastfeeding or who desire to breastfeed that COCs may reduce breast milk production. This is less likely to occur if breastfeeding is well established.
- Counsel any patient who starts COCs postpartum and who have not yet had a period, to use an additional method of contraception until she has taken a pink tablet for 7 consecutive days.
- Counsel patients that amenorrhea may occur. Rule out pregnancy in the event of amenorrhea in two or more consecutive cycles.
- Counsel patients to report whether they are taking folate supplements. Beyaz contains the equivalent of 0.4 mg (400 mcg) of folic acid.
- Counsel patients to maintain folate supplementation if they discontinue Beyaz due to pregnancy.

Manufactured for:



**Bayer HealthCare
Pharmaceuticals**

Bayer HealthCare Pharmaceuticals Inc.

Wayne, NJ 07470

Manufactured in Germany

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Bayer HealthCare Pharmaceuticals Inc.

6704100BS

Revised: 09/2010

SAFYRAL (drospirenone/ethinyl estradiol/levomefolate calcium tablets and levomefolate calcium tablets)

Initial U.S. Approval: 2010

**BRIEF SUMMARY OF PRESCRIBING INFORMATION
CONSULT PACKAGE INSERT FOR FULL PRESCRIBING INFORMATION**

WARNING: CIGARETTE SMOKING AND SERIOUS CARDIOVASCULAR EVENTS

Cigarette smoking increases the risk of serious cardiovascular events from combination oral contraceptives (COC) use. This risk increases with age, particularly in women over 35 years of age, and with the number of cigarettes smoked. For this reason, COCs should not be used by women who are over 35 years of age and smoke. [See Contraindications (4)].

1 INDICATIONS AND USAGE

1.1 Oral Contraceptive

Safyral is indicated for use by women to prevent pregnancy.

1.2 Folate Supplementation

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.

4 CONTRAINDICATIONS

Do not prescribe Safyral to women who are known to have the following:

- Renal impairment
- Adrenal insufficiency
- A high risk of arterial or venous thrombotic diseases. Examples include women who are known to:
 - Smoke, if over age 35 [see Boxed Warning and Warnings and Precautions (5.1)]
 - Have deep vein thrombosis or pulmonary embolism, now or in the past [see Warnings and Precautions (5.1)]
 - Have cerebrovascular disease [see Warnings and Precautions (5.1)]
 - Have coronary artery disease [see Warnings and Precautions (5.1)]
 - Have thrombotic valvular or thrombotic rhythm diseases of the heart (for example, subacute bacterial endocarditis with valvular disease, or atrial fibrillation) [see Warnings and Precautions (5.1)]
 - Have inherited or acquired hypercoagulopathies [see Warnings and Precautions (5.1)]
 - Have uncontrolled hypertension [see Warnings and Precautions (5.5)]
 - Have diabetes mellitus with vascular disease [see Warnings and Precautions (5.7)]
 - Have headaches with focal neurological symptoms or have migraine headaches with or without aura if over age 35 [see Warnings and Precautions (5.8)]
- Undiagnosed abnormal uterine bleeding [see Warnings and Precautions (5.9)]
- Breast cancer or other estrogen- or progestin-sensitive cancer, now or in the past [see Warnings and Precautions (5.3)]
- Liver tumor (benign or malignant) or liver disease [see Warnings and Precautions (5.4) and Use in Specific Populations (8.7)]
- Pregnancy, because there is no reason to use COCs during pregnancy [see Warnings and Precautions (5.10) and Use in Specific Populations (8.1)]

5 WARNINGS AND PRECAUTIONS

5.1 Thromboembolic Disorders and Other Vascular Problems

Stop Safyral if an arterial or deep venous thrombotic (VTE) event occurs. Although the use of COCs increases the risk of venous thromboembolism, pregnancy increases the risk of venous thromboembolism as much or more than the use of COCs. The risk of venous thromboembolism in women using COCs is 3 to 9 per 10,000 woman-years. The risk is highest during the first year of use of a COC. Use of COCs also increases the risk of arterial thromboses such as strokes and myocardial infarctions, especially in women with other risk factors for these events. The risk of thromboembolic disease due to oral contraceptives gradually disappears after COC use is discontinued.

If feasible, stop Safyral at least 4 weeks before and through 2 weeks after major surgery or other surgeries known to have an elevated risk of thromboembolism.

Start Safyral no earlier than 4 weeks after delivery, in women who are not breastfeeding. The risk of postpartum thromboembolism decreases after the third postpartum week, whereas the risk of ovulation increases after the third postpartum week.

COCs have been shown to increase both the relative and attributable risks of cerebrovascular events (thrombotic and hemorrhagic strokes), although, in general, the risk is greatest among older (>35 years of age), hypertensive women who also smoke. COCs also increase the risk for stroke in women with other underlying risk factors.

Oral contraceptives must be used with caution in women with cardiovascular disease risk factors.

Stop Safyral if there is unexplained loss of vision, proptosis, diplopia, papilledema, or retinal vascular lesions. Evaluate for retinal vein thrombosis immediately.

Epidemiologic studies including a DRSP-containing COC

Several studies have investigated the relative risks of thromboembolism in women using a different DRSP-containing COC (Yasmin, which contains 0.03 mg of EE and 3 mg of DRSP) compared to those in women using COCs containing other progestins. Two prospective cohort studies, both evaluating the risk of venous and arterial thromboembolism and death, were initiated at the time of Yasmin approval.^{2,3} The first (EURAS) showed the risk of thromboembolism (particularly venous thromboembolism) and death in Yasmin users to be comparable to that of other oral contraceptive preparations, including those containing levonorgestrel (a so-called second generation COC). The second prospective cohort study (Ingenix) also showed a comparable risk of thromboembolism in Yasmin users compared to users of other COCs, including those containing levonorgestrel. In the second study, COC comparator groups were selected based on their having similar characteristics to those being prescribed Yasmin.

Two additional epidemiological studies, one case-control study (van Hylckama Vlieg et al.⁴) and one retrospective cohort study (Lidegaard et al.⁵) suggested that the risk of venous thromboembolism occurring in Yasmin users was higher than that for users of levonorgestrel-containing COCs and lower than that for users of desogestrel/gestodene-containing COCs (so-called third generation COCs). In the case-control study, however, the number of Yasmin cases was very small (1.2% of all cases) making the risk estimates unreliable. The relative risk for Yasmin users in the retrospective cohort study was greater than that for users of other COC products when considering women who used the products for less than one year. However, these one-year estimates may not be reliable because the analysis may include women of varying risk levels. Among women who used the product for 1 to 4 years, the relative risk was similar for users of Yasmin to that for users of other COC products.

5.2 Hyperkalemia

Safyral contains 3 mg of the progestin DRSP, which has antimineralocorticoid activity, including the potential for hyperkalemia in high-risk patients, comparable to a 25 mg dose of spironolactone. Safyral should not be used in patients with conditions that predispose to hyperkalemia (i.e., renal impairment, hepatic dysfunction and adrenal insufficiency). Women receiving daily, long-term treatment for chronic conditions or diseases with medications that may increase serum potassium should have their serum potassium level checked during the first treatment cycle. Medications that may increase serum potassium include ACE inhibitors, angiotensin-II receptor antagonists, potassium-sparing diuretics, potassium supplementation, heparin, aldosterone antagonists, and NSAIDs.

5.3 Carcinoma of the Breasts and Reproductive Organs

Women who currently have or have had breast cancer should not use Safyral because breast cancer is a hormonally-sensitive tumor.

There is substantial evidence that COCs do not increase the incidence of breast cancer. Although some past studies have suggested that COCs might increase the incidence of breast cancer, more recent studies have not confirmed such findings.

Some studies suggest that COCs are associated with an increase in the risk of cervical cancer or intraepithelial neoplasia. However, there is controversy about the extent to which these findings may be due to differences in sexual behavior and other factors.

5.4 Liver Disease

Discontinue Safyral if jaundice develops. Steroid hormones may be poorly metabolized in patients with impaired liver function. Acute or chronic disturbances of liver function may necessitate the discontinuation of COC use until markers of liver function return to normal and COC causation has been excluded.

Hepatic adenomas are associated with COC use. An estimate of the attributable risk is 3.3 cases/100,000 COC users. Rupture of hepatic adenomas may cause death through intra-abdominal hemorrhage.

Studies have shown an increased risk of developing hepatocellular carcinoma in long-term (> 8 years) COC users. However, the attributable risk of liver cancers in COC users is less than one case per million users.

Oral contraceptive-related cholestasis may occur in women with a history of pregnancy-related cholestasis. Women with a history of COC-related cholestasis may have the condition recur with subsequent COC use.

5.5 High Blood Pressure

For women with well-controlled hypertension, monitor blood pressure and stop Safyral if blood pressure rises significantly. Women with uncontrolled hypertension or hypertension with vascular disease should not use COCs.

An increase in blood pressure has been reported in women taking COCs, and this increase is more likely in older women and with extended duration of use. The incidence of hypertension increases with increasing concentration of progestin.

5.6 Gallbladder Disease

Studies suggest a small increased relative risk of developing gallbladder disease among COC users.

5.7 Carbohydrate and Lipid Metabolic Effects

Carefully monitor prediabetic and diabetic women who are taking Safyral. COCs may decrease glucose tolerance in a dose-related fashion.

Consider alternative contraception for women with uncontrolled dyslipidemia. A small proportion of women will have adverse lipid changes while on COCs.

Women with hypertriglyceridemia, or a family history thereof, may be at an increased risk of pancreatitis when using COCs.

5.8 Headache

If a woman taking Safyral develops new headaches that are recurrent, persistent, or severe, evaluate the cause and discontinue Safyral if indicated.

An increase in frequency or severity of migraine during COC use (which may be prodromal of a cerebrovascular event) may be a reason for immediate discontinuation of the COC.

5.9 Bleeding Irregularities

Unscheduled (breakthrough or intracyclic) bleeding and spotting sometimes occur in patients on COCs, especially during the first three months of use. If bleeding persists or occurs after previously regular cycles, check for causes such as pregnancy or malignancy. If pathology and pregnancy are excluded, bleeding irregularities may resolve over time or with a change to a different COC.

Data from ten Yasmin contraceptive efficacy clinical trials (N=2,467) show that the percent of women who took Yasmin and experienced unscheduled bleeding decreased over time from 12% at cycle 2 to 6% (cycle 13). A total of 25 subjects out of 3,009 in the Yasmin and Safyral trials (<1% discontinued due to bleeding complaints. These are described as metrorrhagia, vaginal hemorrhage, menorrhagia, abnormal withdrawal bleeding, and menometrorrhagia.

The average duration of scheduled bleeding episodes in the majority of subjects (86%-88%) was 4-7 days. Women who use Safyral may experience absence of withdrawal bleeding, even if they are not pregnant. Based on subject diaries from Yasmin contraceptive efficacy trials, during cycles 2 - 13, 1 - 11% of women per cycle experienced no withdrawal bleeding. Some women may encounter post-pill amenorrhea or oligomenorrhea, especially when such a condition was pre-existent.

If withdrawal bleeding does not occur, consider the possibility of pregnancy. If the patient has not adhered to the prescribed dosing schedule (missed one or more active tablets or started taking on a day later than she should have), consider the possibility of pregnancy at the time of the first missed period and take appropriate diagnostic measures. If the patient has adhered to the prescribed regimen and misses two consecutive periods, rule out pregnancy.

5.10 COC Use Before or During Early Pregnancy

Extensive epidemiological studies have revealed no increased risk of birth defects in women who have used oral contraceptives prior to pregnancy. Studies also do not suggest a teratogenic effect when COCs are taken inadvertently during early pregnancy, particularly in so far as cardiac anomalies and limb-reduction defects are concerned. Discontinue Safyral if pregnancy is confirmed and initiate a prenatal vitamin containing folate supplementation.

The administration of oral contraceptives to induce withdrawal bleeding should not be used as a test for pregnancy [see Use in Specific Populations (8.1)].

5.11 Depression

Women with a history of depression should be carefully observed and Safyral discontinued if depression recurs to a serious degree.

5.12 Interference with Laboratory Tests

The use of COCs may change the results of some laboratory tests, such as coagulation factors, lipids, glucose tolerance, and binding proteins. Women on thyroid hormone replacement therapy may need increased doses of thyroid hormone because serum concentrations of thyroid-binding globulin increase with use of COCs. DRSP causes an increase in plasma renin activity and plasma aldosterone induced by its mild antimineralocorticoid activity.

Folates may mask vitamin B12 deficiency.

5.13 Monitoring

A woman who is taking COCs should have a yearly visit with her healthcare provider for a blood pressure check and for other indicated healthcare.

5.14 Other Conditions

In women with hereditary angioedema, exogenous estrogens may induce or exacerbate symptoms of angioedema. Chloasma may occasionally occur, especially in women with a history of chloasma gravidarum. Women with a tendency to chloasma should avoid exposure to the sun or ultraviolet radiation while taking COCs.

6 ADVERSE REACTIONS

The following serious adverse reactions with the use of COCs are discussed elsewhere in the labeling:

- Serious cardiovascular events and smoking [see Boxed Warning and Warnings and Precautions (5.1)]
- Vascular events [see Warnings and Precautions (5.1)]
- Liver disease [see Warnings and Precautions (5.4)]

Adverse reactions commonly reported by COC users are:

- Irregular uterine bleeding
- Nausea
- Breast tenderness
- Headache

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, the adverse reaction rates observed cannot be directly compared to rates in other clinical trials and may not reflect the rates observed in clinical practice.

Contraception and Folate Supplementation Clinical Trials

The data provided reflect the experience with the use of Yasmin (3 mg DRSP/0.03 mg EE) in the adequate and well-controlled studies for contraception (N=2,837) and folate supplementation (N=172). For contraception, the US pivotal clinical study (N=326) for the oral contraception indication for Yasmin was a multicenter, open-label trial in healthy women aged 18-35 who were treated with Yasmin for up to 13 cycles. The second contraceptive pivotal study was a multicenter, randomized, open-label comparative European study of Yasmin vs. 0.150 mg desogestrel/0.03 mg EE conducted in healthy women aged 17-40 who were treated for up to 26 cycles. The primary efficacy study using Safyral for folate supplementation was a randomized, single-center European trial in 172 healthy, female subjects aged 18-40 years comparing the pharmacodynamic effects of Yasmin + 0.451 mg levomefolate calcium to Yasmin co-administered with folic acid during 24 weeks of treatment followed by 20 weeks of open-label Yasmin.

The adverse reactions seen across the 2 indications overlapped and are reported using the frequencies from the pooled dataset. The most common treatment-emergent adverse reactions ($\geq 2\%$ of users) were: premenstrual syndrome (12.4%), headache/migraine (10.3%), breast pain/tenderness/discomfort (8.1%), nausea/vomiting (4.4%) and abdominal pain/discomfort/tenderness (2.2%).

Adverse Reactions ($\geq 1\%$) Leading to Study Discontinuation:

Contraception Clinical Trials

Of 2,837 women, 6.7% discontinued from the clinical trials due to an adverse reaction; the most frequent adverse reaction leading to discontinuation was headache/migraine (1.5%).

Folate Clinical Trial

There were no subjects who discontinued due to an adverse reaction.

Serious Adverse Reactions (Definitely, Probably, or Possibly Related to Study Drug):

Contraception Clinical Trials: depression, pulmonary embolism, toxic skin eruption, and uterine leiomyoma.

Folate Supplementation Clinical Trial: none reported in the clinical trial

6.2 Postmarketing Experience

The following adverse reactions have been identified during post-approval use of Yasmin. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Adverse reactions, including fatalities, are grouped into System Organ Classes and ordered by frequency.

Vascular disorders: Venous and arterial thromboembolic events (including pulmonary emboli, deep vein thrombosis, intracardiac thrombosis, intracranial venous sinus thrombosis, sagittal sinus thrombosis, retinal vein occlusion, myocardial infarction and stroke), hypertension

Hepatobiliary disorders: Gallbladder disease

Immune system disorders: Hypersensitivity

Metabolism and nutrition disorders: Hyperkalemia

Skin and subcutaneous tissue disorders: Chloasma

7 DRUG INTERACTIONS

Consult the labeling of all concurrently-used drugs to obtain further information about interactions with hormonal contraceptives or the potential for enzyme alterations.

7.1 Effects of Other Drugs on Combined Hormonal Contraceptives

Substances diminishing the efficacy of COCs: Drugs or herbal products that induce certain enzymes, including CYP3A4, may decrease the effectiveness of COCs or increase breakthrough bleeding. Some drugs or herbal products that may decrease the effectiveness of hormonal contraceptives include phenytoin, barbiturates, carbamazepine, bosentan, felbamate, griseofulvin, oxcarbazepine, rifampicin, topiramate and products containing St. John's wort. Interactions between oral contraceptives and other drugs may lead to breakthrough bleeding and/or contraceptive failure. Counsel women to use an alternative method of contraception or a back-up method when enzyme inducers are used with COCs, and to continue back-up contraception for 28 days after discontinuing the enzyme inducer to ensure contraceptive reliability.

Substances increasing the plasma levels of COCs: Co-administration of atorvastatin with certain COCs containing EE increase AUC values for EE by approximately 20%. Ascorbic acid and acetaminophen may increase plasma EE levels, possibly by inhibition of conjugation. CYP3A4 inhibitors such as itraconazole or ketoconazole may increase plasma hormone levels.

HIV protease inhibitors and non-nucleoside reverse transcriptase inhibitors: Significant changes (increase or decrease) in the plasma levels of estrogen and progesterone have been noted in some cases of co-administration with HIV protease inhibitors or with non-nucleoside reverse transcriptase inhibitors.

Antibiotics: There have been reports of pregnancy while taking hormonal contraceptives and antibiotics, but clinical pharmacokinetic studies have not shown consistent effects of antibiotics on plasma concentrations of synthetic steroids.

Effect on DRSP: The main metabolites of DRSP in human plasma are generated without involvement of the cytochrome P450 system. Inhibitors of this enzyme system are therefore unlikely to influence the metabolism of DRSP.

7.2 Effects of Combined Oral Contraceptives on Other Drugs

COCs containing EE may inhibit the metabolism of other compounds. COCs have been shown to significantly decrease plasma concentrations of lamotrigine, likely due to induction of lamotrigine glucuronidation. This may reduce seizure control; therefore, dosage adjustments of lamotrigine may be necessary. Consult the labeling of the concurrently-used drug to obtain further information about interactions with COCs or the potential for enzyme alterations.

In vitro and clinical studies did not indicate an inhibitory potential of DRSP towards human CYP450 enzymes at clinically relevant concentrations [see *Clinical Pharmacology* (12.3)].

7.3 Interactions that Have the Potential to Increase Serum Potassium

There is a potential for an increase in serum potassium in women taking Safyral with other drugs that may increase serum potassium [see *Warnings and Precautions* (5.2) and *Clinical Pharmacology* (12.3)].

7.4 Effects of Folates on Other Drugs

Folates may modify the pharmacokinetics or pharmacodynamics of certain antifolate drugs, e.g., antiepileptics (such as phenytoin), methotrexate or pyrimethamine, and may result in a decreased pharmacological effect of the antifolate drug.

7.5 Effects of Other Drugs on Folates

Several drugs have been reported to reduce folate levels by inhibition of the dihydrofolate reductase enzyme (e.g., methotrexate and sulfasalazine) or by reducing folate absorption (e.g., cholestyramine), or via unknown mechanisms (e.g., antiepileptics such as carbamazepine, phenytoin, phenobarbital, primidone and valproic acid).

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

There is little or no increased risk of birth defects in women who inadvertently use COCs during early pregnancy. Epidemiologic studies and meta-analyses have not found an increased risk of genital or non-genital birth defects (including cardiac anomalies and limb-reduction defects) following exposure to low dose COCs prior to conception or during early pregnancy.

The administration of COCs to induce withdrawal bleeding should not be used as a test for pregnancy. COCs should not be used during pregnancy to treat threatened or habitual abortion. Women who do not breastfeed may start COCs no earlier than four weeks postpartum.

8.3 Nursing Mothers

When possible, advise the nursing mother to use other forms of contraception until she has weaned her child. Estrogen-containing OCs can reduce milk production in breastfeeding mothers. This is less likely to occur once breastfeeding is well-established; however, it can occur at any time in some women. Small amounts of oral contraceptive steroids and/or metabolites are present in breast milk.

After oral administration of 3 mg DRSP/0.03 mg EE tablets (Yasmin), about 0.02% of the DRSP dose was excreted into the breast milk of postpartum women within 24 hours. This results in a maximal daily dose of about 0.003 mg DRSP in an infant.

Studies to date indicate there is no adverse effect of folate on nursing infants.

8.4 Pediatric Use

Safety and efficacy of Safyral has been established in women of reproductive age. Safety and efficacy are expected to be the same for postpubertal adolescents under the age of 18 and for users 18 years and older. Use of this product before menarche is not indicated.

8.5 Geriatric Use

Safyral has not been studied in postmenopausal women and is not indicated in this population.

8.6 Patients with Renal Impairment

Safyral is contraindicated in patients with renal impairment [see *Contraindications* (4) and *Warnings and Precautions* (5.2)].

Following administration of DRSP 3 mg daily for 14 days, the serum DRSP levels in subjects with mild renal impairment (creatinine clearance CL_{cr}, 50-80 mL/min) were comparable to those in subjects with normal renal function (CL_{cr}, >80 mL/min). The serum DRSP levels were on average 37% higher in the group with moderate renal impairment (CL_{cr}, 30-50 mL/min) compared to those in the group with normal renal function. DRSP treatment did not show any clinically significant effect on serum potassium concentration. Although hyperkalemia was not observed in the study, in five of the seven subjects who continued use of potassium sparing drugs during the study, mean serum potassium levels increased by up to 0.33 mEq/L. Therefore, potential exists for hyperkalemia to occur in subjects with renal impairment whose serum potassium is in the upper reference range, and who are concomitantly using potassium sparing drugs [see *Clinical Pharmacology* (12.3)].

8.7 Patients with Hepatic Impairment

Safyral is contraindicated in patients with hepatic disease [see *Contraindications* (4) and *Warnings and Precautions* (5.4)]. The mean exposure to DRSP in women with moderate liver impairment is approximately three times higher than the exposure in women with normal liver function. Safyral has not been studied in women with severe hepatic impairment.

10 OVERDOSAGE

There have been no reports of serious ill effects from overdose, including ingestion by children. Overdose may cause withdrawal bleeding in females and nausea.

DRSP however, is a spironolactone analogue which has antiminerlocorticoid properties. Serum concentration of potassium and sodium, and evidence of metabolic acidosis, should be monitored in cases of overdose.

Levomefolate calcium doses of 17 mg/day (37-fold higher than the levomefolate calcium dose of Safyral) were well tolerated after long-term treatment up to 12 weeks.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

In a 24 month oral carcinogenicity study in mice dosed with 10 mg/kg/day DRSP alone or 1 + 0.01, 3 + 0.03 and 10 + 0.1 mg/kg/day of DRSP and EE, 0.1 to 2 times the exposure (AUC of DRSP) of women taking a contraceptive dose, there was an increase in carcinomas of the hardener gland in the group that received the high dose of DRSP alone. In a similar study in rats given 10 mg/kg/day DRSP alone or 0.3 + 0.003, 3 + 0.03 and 10 + 0.1 mg/kg/day DRSP and EE, 0.8 to 10 times the exposure of women taking a contraceptive dose, there was an increased incidence of benign and total (benign and malignant) adrenal gland pheochromocytomas in the group receiving the high dose of DRSP. Mutagenesis studies for DRSP were conducted *in vivo* and *in vitro* and no evidence of mutagenic activity was observed.

Long-term animal studies have not been conducted to evaluate the carcinogenic potential of levomefolate. Mutagenesis studies for levomefolate were conducted *in vitro* and *in vivo* and no evidence of mutagenic activity was observed.

17 PATIENT COUNSELING INFORMATION

[See FDA-approved Patient Labeling]

- Counsel patients that cigarette smoking increases the risk of serious cardiovascular events from COC use, and that women who are over 35 years old and smoke should not use COCs.
- Counsel patients that Safyral does not protect against HIV-infection (AIDS) and other sexually transmitted diseases.
- Counsel patients on Warnings and Precautions associated with COCs.
- Counsel patients that Safyral contains DRSP. Drospirenone may increase potassium. Patients should be advised to inform their healthcare provider if they have kidney, liver or adrenal disease because the use of Safyral in the presence of these conditions could cause serious heart and health problems. They should also inform their healthcare provider if they are currently on daily, long-term treatment (NSAIDs, potassium-sparing diuretics, potassium supplementation, ACE inhibitors, angiotensin-II receptor antagonists, Heparin or aldosterone antagonists) for a chronic condition.
- Safyral is not indicated during pregnancy. If pregnancy is planned or occurs during treatment with Safyral, further intake must be stopped. However, women should be advised on the continued need of sufficient folate intake.
- Counsel patients to take one tablet daily by mouth at the same time every day. Instruct patients what to do in the event pills are missed. See "What to Do if You Miss Pills" section in **FDA-Approved Patient Labeling**.
- Counsel patients to use a back-up or alternative method of contraception when enzyme inducers are used with COCs.
- Counsel patients who are breastfeeding or who desire to breastfeed that COCs may reduce breast milk production. This is less likely to occur if breastfeeding is well established.
- Counsel any patient who starts COCs postpartum, and who have not yet had a period, to use an additional method of contraception until she has taken an orange tablet for 7 consecutive days.
- Counsel patients that amenorrhea may occur. Rule out pregnancy in the event of amenorrhea in two or more consecutive cycles.
- Counsel patients to report whether they are taking folate supplements. Safyral contains the equivalent of 0.4 mg (400 mcg) of folic acid.
- Counsel patients to maintain folate supplementation if they discontinue Safyral due to pregnancy.

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