POLICY & PRACTICE

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Women Face Chronic Pain

Millions of American women are living with disorders that cause chronic pain but are being neglected by many researchers and practitioners, according to a report from the Campaign to End Chronic Pain in Women, which includes the Endometriosis Association and the National Vulvodynia Association. Failure to adequately diagnose and treat just six conditions affecting women – chronic fatigue syndrome, endometriosis, fibromyalgia, interstitial cystitis, temporomandibular disorders, and vulvodynia – adds as much as $80 billion in direct and indirect costs to the health care system each year, according to the report. The group recommended that the National Institutes of Health fund at least four women's chronic pain centers of excellence at leading academic health centers. The report also called on the Centers for Disease Control and Prevention to launch a program studying and comparing the six chronic conditions cited.

Heart Disease Also at Issue

Health care providers and policymakers are also neglecting cardiovascular diseases in women, according to a report from the Society for Women's Health Research and WomenHeart. The "call to action" document listed the top 10 unanswered questions in the prevention, diagnosis, and treatment of women with heart disease, including how to explain cardiovascular disease disparities between men and women, what role a woman's reproductive history plays in heart disease, and how psychosocial factors affect cardiovascular disease in women. The report also called on Congress to pass the HEART for Women Act (S. 438), which would step up government efforts to address the topic.

AMA Adopts BPA Policy

At its recent annual meeting, the American Medical Association recognized bisphenol A (BPA) as an endocrine-disrupting agent, supported existing bans on BPA in baby bottles and infant-feeding cups, and called on manufacturers to clearly label products that contain the substance. The AMA policy resolution noted that the chemical can be found in the lining of canned food containers, cigarette filters, certain medical devices, cash register receipts, and dental sealants. "Both the FDA and Canadian officials have recently expressed concern about potential harmful effects of BPA and taken interim actions to protect sensitive populations such as infants and toddlers by banning the sale of baby bottles, food containers, and cups containing BPA," Dr. Edward Langston, an AMA board member, said in a statement.

New York Abortion Fight Goes On

A federal judge has temporarily blocked enforcement of a new New York City ordinance regulating pregnancy centers that counsel women against abortion. The ordinance would have required the centers, also known as crisis-pregnancy centers, to post signs and make clear on their websites whether they provide prenatal care by a licensed medical provider, emergency contraception, or abortion. Abortion-rights supporters say the centers advertise in a deceptive way that leads women to believe they offer comprehensive reproductive health services. Judge William H. Pauley III granted a temporary injunction to stop the ordinance from taking effect. He wrote that the law infringes on free speech rights. City officials said they plan to appeal the ruling.

Progress vs. Cancer Is Uneven

Nearly 900,000 cancer deaths have been avoided in the past 17 years thanks to bet-

INDEX OF ADVERTISERS

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

Beyaz is indicated for use by women to prevent pregnancy.

1.2 Premenstrual Dysphoric Disorder (PMDD)

Beyaz 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 Beyaz for PMDD when used for more than three menstrual cycles has not been evaluated.

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

1.3 Acne

Beyaz 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. Beyaz should be used for the treatment of acne only if the patient desires an oral contraceptive for birth control.

1.4 Folate Supplementation

Beyaz is indicated in women who choose to use an oral contraceptive as their method of contraception, to raise folate levels for the purpose of reducing the risk of a neural tube defect in a pregnancy conceived while taking the product or shortly after discontinuing the product.

4 CONTRAINDICATIONS

Do not prescribe Beyaz 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 Beyaz 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 Beyaz 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 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 Beyaz 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.[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

Beyaz 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. Beyaz 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 Beyaz 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 Beyaz 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 Beyaz 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 Beyaz. 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 Beyaz develops new headaches that are recurrent, persistent, or severe, evaluate the cause and discontinue Beyaz 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 Beyaz 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 Beyaz was 15.1 days. The intensity of bleeding for Beyaz 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 Beyaz 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 Beyaz 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 Beyaz 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
- 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

ter cancer prevention, detection, and treatment, but those advances have disproportionately eluded the least-educated people in the United States, the American Cancer Society said. Cancer death rates for individuals with the least education are 2.6 times those for the most-educated segment of the population, a society report said. The disparity is highest for lung cancer: The death rate for the least-educated segment was five times that of the most-educated population. The report pointed out that 31% of men with 12 or fewer years of education are smokers, compared with 12% of college graduates and 5% of men with graduate degrees. Closing the cancer gap between demographic groups could have prevented 60,370 deaths in 2007, or more than one-third of the premature cancer deaths that occurred in people aged 25-64 years, the report said.

'Bad Ad' Reports Triple

Reports to the FDA of potentially misleading or untruthful drug ads tripled after the FDA launched a "Bad Ad" outreach program to urge health care professionals to report offenders. During its first year, ending in May, the program received 328 reports of problem ads, 188 of which were submitted by health care professionals. Prior to the outreach program's launch, the FDA received only about 104 reports per year. Of the reports submitted by professionals, the agency identified 87 for a comprehensive review, "demonstrating a relatively strong level of knowledge in the medical community about what constitutes misleading promotion," an FDA announcement said. The agency said it will continue to promote the program to the medical community.

–Mary Ellen Schneider

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from the pooled dataset. The most common treatment-emergent adverse reactions (≥ 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 (≥ 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 (≥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 ≥ 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 CLcr, 50-80 mL/min) were comparable to those in subjects with normal renal function (CLcr, >80 mL/min). The serum DRSP levels were on average 37 % higher in subjects with moderate renal impairment (CLcr, 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 antimineralocorticoid 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 harderian 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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6704100BS Revised: 09/2010