

New Initiatives Aim to Encourage ACOs

BY FRANCES CORREA

FROM THE CENTERS FOR MEDICARE AND MEDICAID SERVICES

Three new initiatives aim to help physicians make the jump to becoming part of an accountable care organization, officials from the Centers for Medicare and Medicaid services announced May 17.

The Pioneer ACO Model would accelerate the process for ACOs that already have the infrastructure in place to coordinate care for patients. Under this model, private payers would offer provider incentives and would function on a separate contract from the Medicare Shared Savings

Use of the pioneer model could result in \$430 million in Medicare savings over 3 years, according to the CMS Office of the Actuary.

Program. About 30 integrated health systems are expected to participate in the Pioneer ACO Model project this summer, making a full transition to ACO by September or October, according to Jonathan Blum, director of the Center for Medicare Management, a part of the CMS.

Use of the pioneer model could result in \$430 million in Medicare savings over 3 years, according to the CMS Office of the Actuary. The pioneer model will follow the same 65 quality measurements and regulations already assigned to ACOs.

The second initiative is a series of free accelerated development learning sessions to educate providers on becoming an ACO and implementing a coordinated care model. The first of the four learning sessions offered in 2011 will be available June 20-22 in Minneapolis. All materials from the sessions, including webcast sessions, will be publicly available.

Finally, the CMS is requesting public comment on the proposal for providing upfront payments to providers who are

interested in becoming ACOs but lack the resources. The accelerated payment program would allow providers who lack the capital to invest in the necessary infrastructure and staffing, Mr. Blum said, adding that the CMS plans to determine how much funding might be provided after evaluating public comments.

These initiatives came as a result of feedback from medical associations during

the comment period of the ACO regulations, according to Dr. Donald Berwick, CMS administrator, who added that the challenge to implementing the best model is striking a balance between patient and provider needs. This includes balancing an ACO's need for data with patient privacy, the need for better coordinated care without overburdening providers with regulations, and the need for creating provider incentives without allowing them to avoid

methods of care that might threaten those incentives.

Regardless, Mr. Blum said the CMS is devising a model that will greatly improve care. "We think that the ACO model, both the base model but also the Pioneer [model], is one of the best ways for us to improve care and so we're very conscious of the fact that we have to create payment policies and other requirements that provide an attractive model." ■

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 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 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.^{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

Be Yaz 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. 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 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

INDEX OF ADVERTISERS

Abbott Laboratories Inc.	
Similac	3
Amerifit, Inc.	
Brainstrong	12
Bayer HealthCare LLC	
One A Day	5
Citracal	17
Bayer HealthCare Pharmaceuticals Inc.	
Mirena	9-10
Be Yaz	34-36
CooperSurgical, Inc.	
Filshie	8
Ferring Pharmaceuticals Inc.	
Lysteda	13-14
Hologic, Inc.	
Cervista	15
Merz Pharmaceuticals	
Mederma	19
Union-Swiss	
Bio-Oil	7