

# HT Product With Drospirenone Wins Approval

**BY ELIZABETH MEHCATIE**  
Senior Writer

A combination hormone therapy that contains drospirenone was approved in late September for treating moderate to severe vasomotor symptoms and moderate to severe symptoms of vulvar and vaginal atrophy associated with menopause, the first such product to contain this particular progestin.

ings in the label related to the potential for hyperkalemia associated with the progestin component. The product—which contains 1 mg estradiol and 0.5 mg drospirenone (DRSP), a synthetic progestin and spironolactone analog with antimineralocorticoid activity—will be marketed by Berlex as Angeliq. The approved dose is one tablet daily.

The product will not be available until mid-2006, according to Berlex, which also manufactures Yasmin, the oral contracep-

tive that contains DRSP as its progestin component.

In addition to the standard contraindications and warnings that are included in the FDA-approved labels of all hormone therapy (HT) products, the Angeliq label includes a warning about the potential for hyperkalemia in high-risk patients, because DRSP has antialdosterone activity. The warning also notes that the product should not be used in women with renal or adrenal insufficiency, hepatic dysfunc-

tion, or other conditions that predispose people to hyperkalemia.

It should be used with caution in women on other medications that can increase potassium, including NSAIDs, potassium-sparing diuretics, ACE inhibitors, or angiotensin II receptor antagonists. The label says that checking serum potassium levels during the first treatment cycle in women at high risk should be considered.

FDA approval for the indication was based on a study showing that the estradiol component of Angeliq was bioequivalent to a currently marketed estradiol product (Estrace). In another study on the endometrial effects, there were no cases of endometrial hyperplasia among almost 200 patients who had received the product for up to 12 months.

For relief of symptoms, “it’s another option that physicians can add to their armamentarium of the whole range of



**It increases treatment options for women, who react to different progestins in different ways.**

DR. UTIAN

products now available,” Wulf H. Utian, M.D., executive director of the North American Menopause Society, said.

Because of its chemistry, Angeliq is less likely to cause fluid retention “at least in theory,” and potentially might be associated with fewer of what he calls the “nuisance symptoms” that some women experience with progestin, such as a bloated feeling; tender breasts; sleepiness; or a reduced sense of well-being or slightly depressed mood, Dr. Utian noted.

But because HT products are not directly compared in clinical trials and there are no published data on this issue, he said it was difficult to comment on the effect that the DRSP component might have on mitigating these types of side effects. Nevertheless, Dr. Utian said that he welcomed the availability of a new HT product as a positive development because it increased the number of treatment options for women, who react to different progestins in different ways.

What remains are major unresolved safety questions regarding the longer term use of progestins in general, when used with estrogen, Dr. Utian noted. Those questions are whether progestin administered with continuous estrogen treatment slightly increases the risk of breast cancer beyond 5 years of use, which has been observed in the WHI and other studies, and whether the progestin component may be responsible for the slight increase in coronary heart disease observed in the WHI and the Nurses’ Health Study.

Dr. Utian, a gynecologist at the Cleveland Clinic Foundation, Cleveland, was not an investigator in Angeliq trials, but he is the director of a research institute that is currently conducting a study of this product.

not be used during pregnancy to treat threatened or habitual abortion.

- Gallbladder Disease:** Earlier studies have reported an increased lifetime relative risk of gallbladder surgery in users of oral contraceptives and estrogens. More recent studies, however, have shown that the relative risk of developing gallbladder disease among oral contraceptive users may be minimal. The recent findings of minimal risk may be related to the use of oral contraceptive formulations containing lower hormonal doses of estrogens and progestogens.
- Carbohydrate and Lipid Metabolic Effects:** Oral contraceptives have been shown to cause glucose intolerance in a significant percentage of users. Oral contraceptives containing greater than 75 micrograms of estrogens cause hyperinsulinemia, while lower doses of estrogen cause less glucose intolerance. Progestogens increase insulin secretion and create insulin resistance, this effect varying with different progestational agents. However, in the nondiabetic woman, oral contraceptives appear to have no effect on fasting blood glucose. Because of these demonstrated effects, prediabetic and diabetic women should be carefully observed while taking oral contraceptives.
- Elevated Blood Pressure:** Women with significant hypertension should not be started on hormonal contraceptive. An increase in blood pressure has been reported in women taking oral contraceptives and this increase is more likely in older oral contraceptive users and with continued use. Data from the Royal College of General Practitioners and subsequent randomized trials have shown that the incidence of hypertension increases with increasing concentrations of progestogens. Women with a history of hypertension or hypertension-related diseases, or renal disease should be encouraged to use another method of contraception. If women with hypertension elect to use oral contraceptives, they should be monitored closely, and if significant elevation of blood pressure occurs, oral contraceptives should be discontinued (see **CONTRAINDICATIONS** section). For most women, elevated blood pressure will return to normal after stopping oral contraceptives, and there is no difference in the occurrence of hypertension among ever- and never-users.
- Headache:** The onset or exacerbation of migraine or development of headache with a new pattern that is recurrent, persistent, or severe requires discontinuation of oral contraceptives and evaluation of the cause. (See **WARNINGS**, 1c.)
- Bleeding Irregularities:** When prescribing Seasonale®, the convenience of fewer planned menses (4 per year instead of 13 per year) should be weighed against the inconvenience of increased intermenstrual bleeding and/or spotting. The clinical trial (SEA 301) that compared the efficacy of Seasonale® (91-day cycles) to an equivalent dosage 28-day cycle regimen also assessed intermenstrual bleeding. The participants in the study were composed primarily of women who had used oral contraceptives previously as opposed to new users. Women with a history of breakthrough bleeding/spotting  $\geq 10$  consecutive days on oral contraceptives were excluded from the study. More Seasonale® subjects, compared to subjects on the 28-day cycle regimen, discontinued prematurely for unacceptable bleeding (7.7% [Seasonale®] vs. 1.8% [28-day cycle regimen]). Table 4 shows the percentages of women with  $\geq 7$  days and  $\geq 20$  days of intermenstrual spotting and/or bleeding in the Seasonale® and the 28-day cycle treatment groups.

Total days of bleeding and/or spotting (with/without plus intermenstrual) were similar over one year of treatment for Seasonale® subjects on the 28-day cycle regimen.

As in any case of bleeding irregularities, nonhormonal causes should always be considered and adequate diagnostic measures taken to rule out malignancy or pregnancy.

In the event of amenorrhea, pregnancy should be ruled out. Some women may encounter post-pill amenorrhea or oligomenorrhea (possibly with anovulation), especially when such a condition was preexistent.

**PRECAUTIONS**

- Sexually Transmitted Diseases:** Patients should be counseled that this product does not protect against HIV infection (AIDS) and other sexually transmitted diseases.
- Physical Examination and Follow-up:** A periodic history and physical examination are appropriate for all women, including women using oral contraceptives. The physical examination, however, may be deferred until after initiation of oral contraceptives if requested by the woman and judged appropriate by the physician. The physical examination should include special reference to blood pressure, breasts, abdomen and pelvic organs, including cervical cytology, and relevant laboratory tests. In case of undiagnosed, persistent or recurrent abnormal vaginal bleeding, appropriate diagnostic measures should be considered to rule out malignancy. Women with a strong family history of breast cancer or who have breast nodules should be monitored with particular care.
- Lipid Disorders:** Women who are being treated for hyperlipidemias should be followed closely if they elect to use oral contraceptives. Some progestogens may elevate LDL levels and may render the control of hyperlipidemias more difficult. (See **WARNINGS**, 1d.) In patients with familial defects of lipoprotein metabolism receiving estrogen-containing preparations, there have been case reports of significant elevations of plasma triglycerides leading to pancreatitis.
- Liver Function:** If jaundice develops in any woman receiving such drugs, the medication should be discontinued. Steroid hormones may be poorly metabolized in patients with impaired liver function.
- Fluid Retention:** Oral contraceptives may cause some degree of fluid retention. They should be prescribed with caution, and only with careful monitoring, in patients with conditions which might be aggravated by fluid retention.
- Emotional Disorders:** Women with a history of depression should be carefully observed and the drug discontinued if depression recurs to a serious degree. Patients becoming significantly depressed while taking oral contraceptives should stop the medication and use an alternate method of contraception in an attempt to determine whether the symptom is drug related.
- Contact Lenses:** Contact lens wearers who develop visual changes or changes in lens tolerance should be assessed by an ophthalmologist.
- Drug Interactions: Changes in contraceptive effectiveness associated with co-administration of other products.**
  - Anti-infective agents and anticonvulsants:** Contraceptive effectiveness may be reduced when hormonal contraceptives are co-administered with antibiotics, anticonvulsants, and other drugs that increase the metabolism of contraceptive steroids. This could result in unintended pregnancy or breakthrough bleeding. Examples include rifampin, barbiturates, phenylbutazone, phenytoin, carbamazepine, felbamate, oxcarbazepine, topiramate, and griseofulvin. Several cases of contraceptive failure and breakthrough bleeding have been reported in the literature with concomitant administration of antibiotics such as ampicillin and tetracyclines. However, clinical pharmacology studies investigating drug interaction between combined oral contraceptives and these antibiotics have reported inconclusive results.
  - Anti-HIV protease inhibitors:** Several of the anti-HIV protease inhibitors have been studied with co-administration of oral combination hormonal contraceptives; significant changes (increase and decrease) in the plasma levels of the estrogen and progestin have been noted in some cases. The safety and efficacy of combination oral contraceptive products may be affected with co-administration of anti-HIV protease inhibitors. Healthcare providers should refer to the label of the individual anti-HIV protease inhibitors for further drug-drug interaction information.
  - Herbal products:** Herbal products containing St. John's Wort (*hypericum perforatum*) may induce hepatic enzymes (cytochrome P450) and glycoprotein transporter and may reduce the effectiveness of contraceptive steroids. This may result in breakthrough bleeding.

**Changes in plasma levels of estradiol associated with co-administration of other products.** Co-administration of atovaquone and certain combination oral contraceptives containing ethinyl estradiol increase AUC values for ethinyl estradiol by approximately 20%. Acetaminophen may increase plasma ethinyl estradiol levels, possibly by inhibition of conjugation. CYP 3A4 inhibitors such as itraconazole or ketoconazole may increase plasma hormone levels.

- Interactions with Laboratory Tests:** Certain endocrine and liver function tests and blood components may be affected by oral contraceptives:
  - Increased prothrombin and factors VII, VIII, IX, and X; decreased antithrombin III; increased norepinephrine-induced platelet aggregability.
  - Increased thyroid-binding globulin (TBG) leading to increased circulating total thyroid hormone, as measured by protein-bound iodine (PBI), T4 by column or by radioimmunoassay. Free T3 resin uptake is decreased, reflecting the elevated TBG; free T4 concentration is unaltered.
  - Other binding proteins may be elevated in serum.
  - Sex hormone binding globulins are increased and result in elevated levels of total circulating sex steroids and corticoids; however, free or biologically active levels remain unchanged.
  - Triglycerides may be increased and levels of various other lipids and lipoproteins may be affected.
  - Glucose tolerance may be decreased.
  - Serum folate levels may be depressed by oral contraceptive therapy. This may be of clinical significance if a woman becomes pregnant shortly after discontinuing oral contraceptives.

**Carcinogenesis:** See **WARNINGS** section.

**Pregnancy:** Pregnancy Category X. See **CONTRAINDICATIONS** and **WARNINGS** sections.

- Nursing Mothers:** Small amounts of oral contraceptive steroids and/or metabolites have been identified in the milk of nursing mothers, and a few adverse effects on the child have been reported, including jaundice and breast enlargement. In addition, oral contraceptives given in the postpartum period may interfere with lactation by decreasing the quantity and quality of breast milk. If possible, the nursing mother should be advised not to use oral contraceptives but to use other forms of contraception until she has completely weaned her child.
- Pediatric Use:** Safety and efficacy of Seasonale® tablets have been established in women of reproductive age. Safety and efficacy are expected to be the same in postpubertal adolescents under the age of 16 and users 16 and older. Use of Seasonale® before menarche is not indicated.
- Geriatric Use:** Seasonale® tablets have not been studied in women having reached menopause.

**INFORMATION FOR THE PATIENT.** See Patient Labeling in the full prescribing information.  
**ADVERSE REACTIONS.** An increased risk of the following serious adverse reactions has been associated with the use of oral contraceptives (see **WARNINGS** section): • Thrombopembolism • Arterial thromboembolism • Pulmonary embolism • Myocardial infarction • Cerebral hemorrhage • Cerebral thrombosis • Hypertension • Gallbladder disease • Hepatic adenomas or benign liver tumors  
There is evidence of an association between the following conditions and the use of oral contraceptives: • Mesenteric thrombosis • Retinal thrombosis  
The following adverse reactions have been reported in patients receiving oral contraceptives and are believed to be drug-related: • Nausea • Vomiting • Gastrointestinal symptoms (such as abdominal cramps and bloating) • Breakthrough bleeding • Spotting • Change in menstrual fluid • Amenorrhea • Temporary infertility after discontinuation of treatment • Edema/fluid retention • Melasma/chloasma which may persist • Breast changes: tenderness, enlargement, and secretion • Change in weight or appetite (increase or decrease) • Change in cervical ectropion and secretion • Possible diminution in lactation when given immediately postpartum • Cholestatic jaundice • Migraine headache • Rash (allergic) • Mood changes, including depression • Vaginitis, including candidiasis • Change in corneal curvature (steepening) • Intolerance to contact lenses • Decrease in serum folate levels • Exacerbation of systemic lupus erythematosus • Exacerbation of porphyria • Exacerbation of chorea • Aggravation of varicose veins • Anaphylactoid/anaphylactoid reactions, including urticaria, angioedema, and severe reactions with respiratory and circulatory symptoms  
The following adverse reactions have been reported in users of oral contraceptives and the association has been neither confirmed nor refuted: • Premenstrual Syndrome • Dyslipidemia • Diplopia • Diplopia which may lead to partial or complete loss of vision • Dysthymia-like syndrome • Headache • Nervousness • Dizziness • Insulin resistance • Less fall hair • Erythema multiforme • Erythema nodosum • Hemorrhagic eruption • Impaired renal function • Heterolytic urticemic syndrome • Budd-Chiari syndrome • Acne • Changes in libido • Colitis • Pancreatitis • Dysmenorrhea  
**OVERDOSAGE:** Serious ill effects have not been reported following acute ingestion of large doses of oral contraceptives by young children. Overdose may cause nausea, and withdrawal bleeding may occur in females.



Brief Summary. See full package brochure for complete prescribing information.

**Patients should be counseled that this product does not protect against HIV-infection (AIDS) and other sexually transmitted diseases.**  
**CONTRAINDICATIONS.** Oral contraceptives should not be used in women who currently have the following conditions: • Thrombopembolism or thromboembolic disorders • Recent history of deep vein thrombophlebitis or thrombotic disorders • Cerebrovascular or coronary artery disease (current or history) • Valvular heart disease with thrombotic complications • Uncontrolled hypertension • Diabetes with vascular involvement • Headaches with focal neurological symptoms • Major surgery with prolonged immobilization • Known or suspected carcinoma of the breast or personal history of breast cancer • Carcinoma of the endometrium or other known or suspected estrogen-dependent neoplasia • Undiagnosed abnormal genital bleeding • Cholestatic jaundice of pregnancy or jaundice with prior pill use • Hepatic adenomas or carcinomas, or active liver disease • Known or suspected pregnancy • Hypersensitivity to any component of this product.

**WARNINGS**

**Cigarette smoking increases the risk of serious cardiovascular side effects from oral contraceptive use. This risk increases with age and with heavy smoking (15 or more cigarettes per day) and is quite marked in women over 35 years of age. Women who use oral contraceptives should be strongly advised not to smoke.**

The use of oral contraceptives is associated with increased risk of several serious conditions including venous and arterial thrombotic and thromboembolic events (such as myocardial infarction, thromboembolism, and stroke), hepatic neoplasia, gallbladder disease, and hypertension. The risk of serious morbidity or mortality is very small in healthy women without underlying risk factors. The risk of morbidity and mortality increases significantly in the presence of other underlying risk factors such as certain inherited thrombophilias, hypertension, hyperlipidemias, obesity and diabetes.

Practitioners prescribing oral contraceptives should be familiar with the following information relating to these risks. The information contained in this package insert is principally based on studies carried out in patients who used oral contraceptives with higher formulations of estrogens and progestogens than those in common use today. The effect of long-term use of the oral contraceptives with lower doses of both estrogens and progestogens remains to be determined.

- Thromboembolic Disorders and Other Vascular Problems:** Use of Seasonale® provides women with more hormonal exposure on a yearly basis than conventional monthly oral contraceptives containing similar strength synthetic estrogens and progestins (an additional 9 weeks per year). While this added exposure may pose an additional risk of thrombotic and thromboembolic disease, studies to date with Seasonale have not suggested an increased risk of these disorders.
  - Myocardial Infarction:** An increased risk of myocardial infarction has been attributed to oral contraceptive use. This risk is primarily in smokers or women with other underlying risk factors for coronary artery disease such as hypertension, hypercholesterolemia, morbid obesity, and diabetes. The relative risk of heart attack for current oral contraceptive users has been estimated to be two to six. The risk is very low under the age of 30. Smoking in combination with oral contraceptive use has been shown to contribute substantially to the incidence of myocardial infarction in women in their mid-thirties or older with smoking accounting for the majority of excess cases. Mortality rates associated with circulatory disease have been shown to increase substantially in smokers over the age of 35 and nonsmokers over the age of 40 among women who use oral contraceptives.
  - Thromboembolism:** An increased risk of thromboembolic and thrombotic disease associated with the use of oral contraceptives is well established. Case control studies have found the relative risk of users compared to non-users to be 3 for the first episode of superficial venous thrombosis, 4 to 11 for deep vein thrombosis or pulmonary embolism, and 1.5 to 6 for women with predisposing conditions for venous thromboembolic disease. Cohort studies have shown the relative risk to be somewhat lower: about 3 for new cases and about 4.5 for new cases requiring hospitalization. The approximate incidence of deep vein thrombosis and pulmonary embolism in users of low dose (<50 micrograms ethinyl estradiol) combination oral contraceptives is up to 4 per 10,000 woman-years compared to 0.5-3 per 10,000 woman-years for non-users. However, the incidence is less than that associated with pregnancy (6 per 10,000 woman-years). The risk of thromboembolic disease due to oral contraceptives is not related to length of use and disappears after pill use is stopped. A two- to four-fold increase in relative risk of postoperative thromboembolic complications has been reported with the use of oral contraceptives. The relative risk of venous thrombosis in women who have predisposing conditions is twice that of women without such medical conditions. If feasible, oral contraceptives should be discontinued at least four weeks prior to and for two weeks after elective surgery of a type associated with an increase in risk of thromboembolism and during and following prolonged immobilization. Since the immediate postpartum period is also associated with an increased risk of thromboembolism, oral contraceptives should be started no earlier than four weeks after delivery in women who elect to use oral contraceptives.

- Cerebrovascular Diseases:** Oral contraceptives 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), hypertensive women who also smoke. Hypertension was found to be a risk factor for both users and nonusers, for both types of strokes, while smoking interacted to increase the risk for hemorrhagic strokes. In a large study, the relative risk of thrombotic strokes has been shown to range from 3 for normotensive users to 14 for users with severe hypertension. The relative risk of hemorrhagic stroke is reported to be 1.2 for nonsmokers who used oral contraceptives, 2.6 for smokers who did not use oral contraceptives, and 5.1 for smokers who used oral contraceptives, 1.8 for normotensive users and 25.7 for users with severe hypertension. The attributable risk is also greater in older women. Oral contraceptives also increase the risk for stroke in women with other underlying risk factors such as certain inherited or acquired thrombophilias, hyperlipidemias, and obesity. Women with migraine (particularly migraine with aura) who take combination oral contraceptives may be at an increased risk of stroke.

- Dose-Related Risk of Vascular Disease from Oral Contraceptives:** A positive association has been observed between the amount of estrogen and progestogen in oral contraceptives and the risk of vascular disease. A decline in serum high-density lipoproteins (HDL) has been reported with many current and recent users of combined oral contraceptives (Pill-1, 2), this excess risk decreases over time after combination oral contraceptive discontinuation and by 10 years after cessation the increased risk disappears. The risk does not increase with duration of use and no consistent relationships have been found with dose or type of steroid. The patterns of risk are also similar regardless of a woman's reproductive history or her family breast cancer history. The subgroup for whom risk has been found to be significantly elevated is women who first used oral contraceptives before age 20, but because breast cancer is so rare at these young ages, the number of cases attributable to this early oral contraceptive use is extremely small. Breast cancers diagnosed in current or previous oral contraceptive users tend to be less clinically advanced than in never-users. Women who currently have or have had breast cancer should not use oral contraceptives because breast cancer is a hormone sensitive tumor. Some studies suggest that oral contraceptive use has been associated with an increase in the risk of cervical intraepithelial neoplasia or invasive cervical cancer in some populations of women. However, there continues to be controversy about the extent to which such findings may be due to differences in sexual behavior and other factors. In spite of many studies of the relationship between oral contraceptive use and breast cancer and cervical cancers, a cause-and-effect relationship has not been established.

- Hepatic Neoplasia:** Benign hepatic adenomas are associated with oral contraceptive use, although their occurrence is rare in the United States. Indirect calculations have estimated the attributable risk to be in the range of 3.3 cases/100,000 for users, a risk that increases after four or more years of use. Rupture of hepatic adenomas may cause death through intra-abdominal hemorrhage. Studies from Britain have shown an increased risk of developing hepatocellular carcinoma in long-term (>8 years) oral contraceptive users. However, these cancers are extremely rare in the U.S., and the attributable risk (the excess incidence) of liver cancers in oral contraceptive users approaches less than one per million users.

- Ocular Lesions:** There have been clinical case reports of retinal thrombosis associated with the use of oral contraceptives that may lead to partial or complete loss of vision. Oral contraceptives should be discontinued if there is unexplained partial or complete loss of vision, onset of proptosis or diplopia, papilledema, or retinal vascular lesions. Appropriate diagnostic and therapeutic measures should be undertaken immediately.

- Oral contraceptive Use Before or During Early Pregnancy:** Because women using Seasonale® will likely have withdrawal bleeding only 4 times per year, pregnancy should be ruled out at the time of any missed menstrual period. Oral contraceptive use should be discontinued if pregnancy is confirmed. 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 (see **CONTRAINDICATIONS** section).

The administration of oral contraceptives to induce withdrawal bleeding should not be used as a test for pregnancy. Oral contraceptives should

SEA0531  
May 2005



Duramed Pharmaceuticals, Inc.  
Subsidiary of Barr Laboratories, Inc.  
Pomona, New York 10970

Revised SEPTEMBER 2003