Menstruation Timing Options Abound With OCs

BY ROBERT FINN

San Francisco Bureau

SAN FRANCISCO — Seasonale and Seasonique are already on the market, and they will soon be joined by several other extended contraception options that will allow women to regulate their menstrual periods in a multiplicity of different ways, Dr. Carolyn L. Westhoff said at a conference on contraceptive technology sponsored by Contemporary Forums.

"From a medical point of view, there is no necessity to mimic regular cycling," said Dr. Westhoff of Columbia University, New York. "Lots of women are happy with the 21/7 pill, …but it's like the Model T of birth control. You don't have to do it that way anymore."

A continuous monophasic pill designed to be taken daily for 365 days is nearing Food and Drug Administration approval, she said. The pill's anticipated trade name is Lybrel.

And there are numerous other extended formulations in development. Beyond that, individual physicians and their patients are experimenting with the off-label use of options that are currently on the market.

"I would predict that we're not even going to see new pills with 21/7 [cycling] anymore," Dr. Westhoff said. "I think every variation is reasonable, whether it's 2 months or 3 months or 4 months or 6 months, [depending on] what the patient might want. Or it could be a 3-month cycle once in a while. Those sorts of regimens probably aren't going to be FDA approved, because it's hard to go to the FDA with data to cover all those different flexible possibilities."

Although a monthly cycle that repeats throughout a woman's adult life may seem normal, in fact contemporary women experience far more periods than their hunter-gatherer ancestors did. Calculations taking into account a later age of menarche, a younger age at first birth, a larger number of live births, and a longer period of breast-feeding suggest that a hunter-gatherer woman experienced approximately 160 menstrual periods in her lifetime. In contrast, contemporary women experience about 450.

Furthermore, there are many health advantages to medically regulating menstruation, including reductions in menorrhagia, uterine fibroids, adenomyosis, endometriosis, iron-deficiency anemia, and catamenial conditions such as migraine headaches and seizures.

On the other side, there's little scientific evidence that monthly menstruation is necessary for "cleansing the system," or because it's a "natural" state.

Another possible benefit of monthly menstruation is that it serves as a sign that a woman is not pregnant, and menstruation is sometimes seen as a symbol of femininity, fertility, and youth.

Among other currently available medical options for reducing menstruation are injectable progestin-only contraceptives such as depot medroxyprogesterone acetate, a progestin-releasing intrauterine device (Mirena), oral progestins such as norethindrone acetate, danazol (a gonadotropin inhibitor with progestational and androgenic properties), gonadotropin-releasing hormone analogues such as leuprolide acetate, and extended regimens of the vaginal ring and the transdermal patch.

"All of the studies of extended cycling show more unscheduled bleeding and spotting in the beginning, and then it always gets a little better with time," Dr. Westhoff said. "Very few women are amenorrheic at the beginning of continuous pill use."

Although extended regimens of the vaginal ring and the transdermal patch seem to be safe and effective in clinical trials, Dr. Westhoff cautioned that uncertainties remain. For example, pharmacokinetic profiles suggest that steady-state ethinyl estradiol levels go a little higher each week than the week before. "We don't have data telling us what will happen with circulating levels if one would use the patch for 4, 6, 8, or 12 weeks," she said.

Dr. Westhoff noted that her talk was prepared by an expert committee of the Association of Reproductive Health Professionals and was made possible by an unrestricted educational grant from Wyeth. Dr. Westhoff also disclosed receiving research support and serving as a consultant for Barr Pharmaceuticals and Organon.

Contemporary Forums and this news organization are wholly owned subsidiaries of Reed Elsevier. ■

ANGELIQ® TABLETS
(Drospirenone and Estradiol)

0.5 mg/1 mg

BRIEF SUMMARY OF PRESCRIBING INFORMATION

(for full prescribing information and patient information, please visit our website at www.angeliq-us.com)

Rx only

WARNING

Estrogens with or without progestins should not be used for the prevention of cardiovascular disease or dementia. (See **WARNINGS, Cardiovascular disorders** and **Dementia.**)

The Women's Health Initiative (WHI) study reported increased risks of myocardial infarction, stroke, invasive breast cancer, pulmonary emboli, and deep vein thrombosis in postmenopausal women (50 to 79 years of age) during 5 years of treatment with oral conjugated equine estrogens (CE 0.625mg) combined with medroxyprogesterone acetate (MPA 2.5mg) relative to placebo (see **CLINICAL PHARMACOLOGY, Clinical Studies** and **WARNINGS, Cardiovascular disorders** and **Malignant neoplasms, Breast cancer.**)

The Women's Health Initiative Memory Study (WHIMS), a substudy of WHI, reported increased risk of developing probable dementia in postmenopausal women 65 years of age or older during 5.2 years of treatment with conjugated estrogens alone and during 4 years of treatment with oral conjugated estrogens plus medroxyprogesterone acetate, relative to placebo. It is unknown whether this finding applies to younger postmenopausal women. (See **CLINICAL PHARMACOLOGY, Clinical Studies, WARNINGS, Dementia** and **PRECAUTIONS, Geriatric Use.**)

Other doses of oral conjugated estrogens with medroxyprogesterone acetate, and other combinations and dosage forms of estrogens and progestins were not studied in the WHI clinical trials, and, in the absence of comparable data, these risks should be assumed to be similar. Because of these risks, estrogens with or without progestins should be prescribed at the lowest effective doses and for the shortest duration consistent with treatment goals and risks for the individual woman.

INDICATIONS AND USAGE

ANGELIQ is indicated in women who have a uterus for the: 1. Treatment of moderate to severe vasomotor symptoms associated with the menopause. 2. Treatment of moderate to severe symptoms of vulvar and vaginal atrophy associated with the menopause. When prescribing solely for the treatment of symptoms of vulvar and vaginal atrophy, topical vaginal products should be considered.

CONTRAINDICATIONS

Progestogens/estrogens should not be used in individuals with any of the following conditions: 1. Undiagnosed abnormal genital bleeding. 2. Known, suspected, or history of cancer of the breast. 3. Known or suspected estrogen-dependent neoplasia. 4. Active deep vein thrombosis, pulmonary embolism or history of these conditions. 5. Active or recent (e.g., within the past year) arterial thromboembolic disease (e.g., stroke, myocardial infarction). 6. Renal insufficiency. 7. Liver dysfunction or disease. 8. Adrenal insufficiency. 9. **ANGELIQ** should not be used in patients with known hypersensitivity to its ingredients. 10. Known or suspected pregnancy. There is no indication for **ANGELIQ** in pregnancy. There appears to be little or no increased risk of birth defects in children born to women who have used estrogens and progestins from oral contraceptives inadvertently during early pregnancy. (See **PRECAUTIONS**).

WARNINGS

ANGELIQ contains 0.5 mg of the progestin drospirenone that has antialdosterone activity, including the potential for hyperkalemia in high-risk patients.

ANGELIQ should not be used in patients with conditions that predispose to hyperkalemia (i.e. renal insufficiency, hepatic dysfunction, and adrenal insufficiency).

Use caution when prescribing ANGELIQ to women who regularly take other medications that can increase potassium, such as NSAIDs, potassium-sparing diuretics, potassium supplements, ACE inhibitors, angiotensin-II receptor antagonists, and heparin. Consider checking serum potassium levels during the first treatment cycle in high-risk patients.

See **BOXED WARNINGS.**

1. Cardiovascular disorders Estrogen and estrogen/progestin therapy has been associated with an increased risk of cardiovascular events such as myocardial infarction and stroke, as well as venous thrombosis and pulmonary embolism (venous thromboembolism or VTE). Should any of these occur or be suspected, estrogens should be discontinued immediately.

Risk factors for cardiovascular disease (e.g., hypertension, diabetes mellitus, tobacco use, hypercholesterolemia, and obesity) and/or venous thromboembolism (e.g., personal history or family history of VTE, obesity, and systemic lupus erythematosus) should be managed appropriately.

a. Coronary heart disease and stroke In the Women's Health Initiative study (WHI), an increase in the number of myocardial infarctions and strokes has been observed in women receiving oral CE compared to placebo. (See **CLINICAL PHARMACOLOGY, Clinical Studies sections.**)

In the CE/MPA substudy of WHI an increased risk of coronary heart disease (CHD) events (defined as non-fatal myocardial infarction and CHD death) was observed in women receiving CE/MPA compared to women receiving placebo (37 vs 30 per 10,000 person years). The increase in risk was observed in year one and persisted.

In the same substudy of WHI, an increased risk of stroke was observed in women receiving CE/MPA compared to women receiving placebo (29 vs 21 per 10,000 person-years). The increase in risk was observed after the first year and persisted.

In postmenopausal women with documented heart disease (n = 2,763, average age 66.7 years) a controlled clinical trial of secondary prevention of cardiovascular disease (Heart and Estrogen/Progestin Replacement Study; HERS) treatment with CE/MPA-0.625mg/2.5mg per day demonstrated no cardiovascular benefit. During an average follow-up of 4.1 years, treatment with CE/MPA did not reduce the overall rate of CHD events in postmenopausal women with established coronary heart disease. There were more CHD events in the CE/MPA-treated group than in the placebo group in year 1, but not during the subsequent years.

Two thousand three hundred and twenty one women from the original HERS trial agreed to participate in an open label extension of HERS, HERS II. Average follow-up in HERS II was an additional 2.7 years, for a total of 6.8 years overall. Rates of CHD events were comparable among women in the CE/MPA group and the placebo group in HERS, HERS II, and overall.

Large doses of estrogen (5 mg conjugated estrogens per day), comparable to those used to treat cancer of the prostate and breast, have been shown in a large prospective clinical trial in men to increase the risks of nonfatal myocardial infarction, pulmonary embolism, and thrombophlebitis.

b. Venous thromboembolism (VTE) In the Women's Health Initiative study (WHI), an increase in VTE has been observed in women receiving CE compared to placebo. (See **CLINICAL PHARMACOLOGY** and **Clinical Studies** sections.)

In the CE/MPA substudy of WHI, a 2-fold greater rate of VTE, including deep venous thrombosis and pulmonary embolism, was observed in women receiving CE/MPA compared to women receiving placebo. The rate of VTE was 34 per 10,000 woman-years in the CE/MPA group compared to 16 per 10,000 woman-years in the placebo group. The increase in VTE risk was observed during the first year and persisted.

If feasible, estrogens should be discontinued at least 4 to 6 weeks before surgery of the type associated with an increased risk of thromboembolism, or during periods of prolonged immobilization.

2. Malignant neoplasms

a. Endometrial cancer The use of unopposed estrogens in women with intact uteri has been associated with an increased risk of endometrial cancer. The reported endometrial cancer risk among unopposed estrogen users is about 2- to 12-fold greater than in non-users, and appears dependent on duration of treatment and on estrogen dose. Most studies show no significant increased risk associated with use of estrogens for less than one year. The greatest risk appears associated with prolonged use, with increased risks of 15- to 24-fold for five to ten years or more and this risk has been shown to persist for at least 8 to 15 years after estrogen therapy is discontinued.

Clinical surveillance of all women taking estrogen/progestin combinations is important. Adequate diagnostic measures, including endometrial sampling when indicated, should be undertaken to rule out malignancy in all cases of undiagnosed persistent or recurring abnormal vaginal bleeding. There is no evidence that the use of natural estrogens results in a different endometrial risk profile than synthetic estrogens of equivalent estrogen dose. Adding a progestin to estrogen therapy has been shown to reduce the risk of endometrial hyperplasia, which may be a precursor to endometrial cancer.

b. Breast cancer The use of estrogens and progestins by postmenopausal women has been reported to increase the risk of breast cancer. The most important randomized clinical trial providing information about this issue is the Women's Health Initiative (WHI) substudy of CE/MPA (see **CLINICAL PHARMACOLOGY, Clinical Studies**). The results from observational studies are generally consistent with those of the WHI clinical trial and report no significant variation in the risk of breast cancer among different estrogens or progestins, doses, or routes of administration.

The CE/MPA substudy of WHI reported an increased risk of breast cancer in women who took CE/MPA for a mean follow-up of 5.6 years. Observational studies have also reported an increased risk for estrogen/progestin combination therapy, and a smaller increased risk for estrogen alone therapy, after several years of use. In the WHI trial and from observational studies, the excess risk increased with duration of use. From observational studies, the risk appeared to return to baseline in about five years after stopping treatment. In addition, observational studies suggest that the risk of breast cancer was greater, and became apparent earlier, with estrogen/progestin combination therapy as compared to estrogen alone therapy.

In the CE/MPA substudy, 26% of the women reported prior use of estrogen alone and/or estrogen/progestin combination hormone therapy. After a mean follow-up of 5.6 years during the clinical trial, the overall relative risk of invasive breast cancer was 1.24 (95% confidence interval 1.01-1.54), and the overall absolute risk was 41 vs. 33 cases per 10,000 women-years, for CE/MPA compared with placebo. Among women who reported prior use of hormone therapy, the relative risk of invasive breast cancer was 1.86, and the absolute risk was 46 vs. 25 cases per 10,000 women-years, for CE/MPA compared with placebo. Among women who reported no prior use of hormone therapy, the relative risk of invasive breast cancer was 1.09, and the absolute risk was 40 vs. 36 cases per 10,000 women-years for CE/MPA compared with placebo. In the same substudy, invasive breast cancers were larger and diagnosed at a more advanced stage in the CE/MPA group compared with the placebo group. Metastatic disease was rare with no apparent difference between the two groups. Other prognostic factors such as histologic subtype, grade and hormone receptor status did not differ between the groups.

The use of estrogen plus progestin has been reported to result in an increase in abnormal mammograms requiring further evaluation. All women should receive yearly breast examinations by a healthcare provider and perform monthly breast self-examinations. In addition, mammography examinations should be scheduled based on patient age, and risk factors, and prior mammogram results.

3. Dementia In the estrogen alone Women's Health Initiative Memory Study (WHIMS), a substudy of WHI, 2,947 hysterectomized women aged 65 to 79 years were randomized to CE or placebo. In the estrogen plus progestin WHIMS substudy, 4,532 postmenopausal women aged 65 to 79 years were randomized to CE/MPA or placebo.

In the estrogen alone substudy, after an average follow-up of 5.2 years, 28 women in the estrogen alone group and 19 women in the placebo group were diagnosed with probable dementia. The relative risk of probable dementia for estrogen alone versus placebo was 1.49 (95% CI 0.83-2.66). The absolute risk of probable dementia for estrogen alone versus placebo was 37 versus 25 cases per 10,000 women-years. It is unknown whether these findings apply to younger postmenopausal women. (See **CLINICAL PHARMACOLOGY, Clinical Studies** and **PRECAUTIONS, Geriatric Use.**)

After an average follow-up of 4 years, 40 women being treated with CE/MPA (1.8%, n = 2,229) and 21 women in the placebo group (0.9%, n = 2,303) received diagnoses of probable dementia. The relative risk for CE/MPA versus placebo was 2.05 (95% confidence interval 1.21 – 3.48), and was similar for women with and without histories of menopausal hormone use before WHIMS. The absolute risk of probable dementia for CE/MPA versus placebo was 45 versus 22 cases per 10,000 women-years, and the absolute excess risk for CE/MPA was 23 cases per 10,000 women-years. It is unknown whether these findings apply to younger postmenopausal women. (See **CLINICAL PHARMACOLOGY, Clinical Studies** and **PRECAUTIONS, Geriatric Use.**)

4. Gallbladder disease A 2- to 4-fold increase in the risk of gallbladder disease requiring surgery in postmenopausal women receiving estrogens has been reported.

5. Hypercalcemia Estrogen administration may lead to severe hypercalcemia in patients with breast cancer and bone metastases. If hypercalcemia occurs, use of the drug should be stopped and appropriate measures taken to reduce the serum calcium level.

6. Visual abnormalities Retinal vascular thrombosis has been reported in patients receiving estrogens. Discontinue medication pending examination if there is sudden partial or complete loss of vision, or a sudden onset of proptosis, diplopia, or migraine. If examination reveals papilledema or retinal vascular lesions, estrogens should be permanently discontinued.

PRECAUTIONS

A. GENERAL

1. Addition of a progestin when a woman has not had a hysterectomy

Studies of the addition of a progestin for 10 or more days of a cycle of estrogen administration or daily with estrogen in a continuous regimen, have reported a lowered incidence of endometrial hyperplasia than would be induced by estrogen treatment alone. Endometrial hyperplasia may be a precursor to endometrial cancer.

There are, however, possible risks that may be associated with the use of progestins with estrogens compared to estrogen-alone regimens. These include a possible increased risk of breast cancer.

2. Elevated blood pressure In a small number of case reports, substantial increases in blood pressure have been attributed to idiosyncratic reactions to estrogens. In a large, randomized, placebo-controlled clinical trial, a generalized effect of estrogen therapy on blood pressure was not seen. Blood pressure should be monitored at regular intervals with estrogen use.

3. Hypertriglyceridemia In patients with pre-existing hypertriglyceridemia, estrogen therapy may be associated with elevations of plasma triglycerides leading to pancreatitis and other complications.

4. Impaired liver function and past history of cholestatic jaundice Estrogens may be poorly metabolized in patients with impaired liver function. For patients with a history of cholestatic jaundice associated with past estrogen use or with pregnancy, caution should be exercised and in the case of recurrence, medication should be discontinued.

The clearance of drospirenone was decreased in patients with moderate hepatic impairment.

5. Hypothyroidism Estrogen administration leads to increased thyroid-binding globulin (TBG) levels. Patients with normal thyroid function can compensate for the increased TBG by making more thyroid hormone, thus maintaining free T4 and T3 serum concentrations in the normal range. Patients dependent on thyroid hormone replacement therapy who are also receiving estrogens may require increased doses of their thyroid replacement therapy. These patients should have their thyroid function monitored in order to maintain their free thyroid hormone levels in an acceptable range.

6. Fluid retention Because estrogen and estrogen/progestin therapy may cause some degree of fluid retention, patients with conditions that might be influenced by this factor, such as a cardiac or renal dysfunction, warrant careful observation when estrogens are prescribed.

7. Hypocalcemia Estrogens should be used with caution in individuals with severe hypocalcemia.

8. Hyponatremia As an aldosterone antagonist, drospirenone may increase the possibility of hyponatremia in high-risk patients.

9. Ovarian cancer The CE/MPA substudy of WHI reported that estrogen plus progestin increased the risk of ovarian cancer. After an average follow-up of 5.6 years, the relative risk for ovarian cancer for CE/MPA versus placebo was 1.58 (95% confidence interval 0.77 – 3.24) but was not statistically significant. The absolute risk for CE/MPA versus placebo was 4.2 versus 2.7 cases per 10,000 women-years. In some epidemiologic studies, the use of estrogen alone, in particular for ten or more years, has been associated with an increased risk of ovarian cancer. Other epidemiologic studies have not found these associations.

10. Exacerbation of endometriosis Endometriosis may be exacerbated with administration of estrogens.

11. Exacerbation of other conditions Estrogens may cause an exacerbation of asthma, diabetes mellitus, epilepsy, migraine, porphyria, systemic lupus erythematosus, and hepatic hemangiomas, and should be used with caution in women with these conditions.

B. PATIENT INFORMATION Physicians are advised to discuss the PATIENT INFORMATION leaflet with patients for whom they prescribe **ANGELIQ**.

C. LABORATORY TESTS Estrogen administration should be initiated at the lowest dose for the approved indication and then guided by clinical response, rather than by serum hormone levels (e.g., estradiol, FSH).

D. DRUG/LABORATORY TEST INTERACTIONS

1. Accelerated prothrombin time, partial thromboplastin time, and platelet aggregation time; increased platelet count; increased factors II, VII antigen, VIII antigen, VIII coagulant activity, IX, X, XII, VII-X complex, II-VII-X complex, and beta-thromboglobulin; decreased levels of antifactor Xa and antithrombin III, decreased antithrombin III activity; increased levels of fibrinogen and fibrinogen activity; increased plasminogen antigen and activity.

2. Increased thyroid-binding globulin (TBG) levels leading to increased circulating total thyroid hormone, as measured by protein-bound iodine (PBI), T4 levels (by column or by radioimmunoassay) or T3 levels by radioimmunoassay. T3 resin uptake is decreased, reflecting the elevated TBG. Free T4 and free T3 concentrations are unaltered. Patients on thyroid replacement therapy may require higher doses of thyroid hormone.

3. Other binding proteins may be elevated in serum (i.e., corticosteroid binding globulin (CBG), sex hormone-binding globulin (SHBG)) leading to increased circulating corticosteroids and sex steroids, respectively. Free hormone concentrations may be decreased. Other plasma proteins may be increased (angiotensinogen/renin substrate, alpha-1-antitrypsin, ceruloplasmin).

4. Increased plasma HDL and HDL-2 subfraction concentrations, reduced LDL cholesterol concentration, increased triglyceride levels.

5. Impaired glucose tolerance.

6. Reduced response to metyrapone test.

E. CARCINOGENESIS, MUTAGENESIS, AND IMPAIRMENT OF FERTILITY

Long-term continuous administration of estrogen, with and without progestin, in women with and without a uterus, has shown an increased risk of endometrial cancer, breast cancer, and ovarian cancer. (See **BOXED WARNINGS, WARNINGS** and **PRECAUTIONS.**)

Long-term continuous administration of natural and synthetic estrogens in certain animal species increases the frequency of carcinomas of the breast, uterus, cervix, vagina, testis, and liver. (See **BOXED WARNINGS, CONTRAINDICATIONS,** and **WARNINGS** sections.)

In a 24 month oral carcinogenicity study in mice dosed with 10 mg/kg/day drospirenone alone or 1 + 0.01, 3 + 0.03 and 10 + 0.1 mg/kg/day of drospirenone and ethinyl estradiol, 0.24 to 10.3 times the exposure (AUC of drospirenone) of women taking a 1 mg dose, there was an increase in carcinomas of the harderian gland in the group that received the high dose of drospirenone alone. In a similar study in rats given 10 mg/kg/day drospirenone alone or 0.3 + 0.003, 3 + 0.03 and 10 + 0.1 mg/kg/day drospirenone and ethinyl estradiol, 2.3 to 51.2 times the exposure of women taking a 1 mg dose, there was an increased incidence of benign and total (benign and malignant) adrenal gland pheochromocytomas in the group receiving the high dose of drospirenone. Drospirenone was not mutagenic in a number of *in vitro* (Ames, Chinese Hamster Lung gene mutation and chromosomal damage in human lymphocytes) and *in vivo* (mouse micronucleus) genotoxicity tests. Drospirenone increased unscheduled DNA synthesis in rat hepatocytes and formed adducts with rodent liver DNA but not with human liver DNA. (See **WARNINGS** section.)

F. PREGNANCY **ANGELIQ** should not be used during pregnancy. (See **CONTRAINDICATIONS.**)

G. NURSING MOTHERS Estrogen administration to nursing mothers has been shown to decrease the quantity and quality of the milk. Detectable amounts of estrogens have been identified in the milk of mothers receiving this drug. Caution should be exercised when **ANGELIQ** is administered to a nursing woman.

After administration of an oral contraceptive containing drospirenone about 0.02% of the drospirenone dose was excreted into the breast milk of postpartum women within 24 hours. This results in a maximal daily dose of about 3 mcg drospirenone in an infant.

H. PEDIATRIC USE **ANGELIQ** is not indicated in children.

I. GERIATRIC USE There have not been sufficient numbers of geriatric patients involved in clinical studies utilizing **ANGELIQ** to determine whether those over 65 years of age differ from younger subjects in their response to **ANGELIQ**.

In the Women's Health Initiative Memory Study, including 4,532 women 65 years of age and older, followed for an average of 4 years, 82% (n = 3,729) were 65 to 74 while 18% (n = 803) were 75 and over. Most women (80%) had no prior hormone therapy use. Women treated with conjugated estrogens plus medroxyprogesterone acetate were reported to have a two-fold increase in the risk of developing probable dementia. Alzheimer's disease was the most common classification of probable dementia in both the conjugated estrogens plus medroxyprogesterone acetate group and the placebo group. Ninety percent of the cases of probable dementia occurred in the 54% of women who were older than 70. (See **WARNINGS, Dementia.**)

ADVERSE REACTIONS

See BOXED WARNINGS, WARNINGS, AND PRECAUTIONS.

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice. The adverse reaction information from clinical trials does, however, provide a basis for identifying the adverse events that appear to be related to drug use and for approximating rates.

The following are adverse events reported with **ANGELIQ** occurring in >5% of subjects:

Table 4. Adverse Events Regardless of Drug Relationship Reported at a Frequency of >5% in a 1-year Double-blind Clinical Trial

ADVERSE EVENT	E2 1 MG (N=226) n (%)	ANGELIQ (N=227) n (%)
BODY AS A WHOLE		
Abdominal pain	29 (12.8)	25 (11)
Pain in extremity	15 (6.6)	19 (8.4)
Back pain	11 (4.9)	16 (7)
Flu syndrome	15 (6.6)	16 (7)
Accidental injury	15 (6.6)	13 (5.7)
Abdomen enlarged	17 (7.5)	16 (7)
Surgery	6 (2.7)	12 (5.3)
METABOLIC & NUTRITIONAL DISORDERS		
Peripheral edema	12 (5.3)	4 (1.8)
NERVOUS SYSTEM		
Headache	26 (11.5)	22 (9.7)
RESPIRATORY SYSTEM		
Upper respiratory infection	40 (17.7)	43 (18.9)
Sinusitis	8 (3.5)	12 (5.3)
SKIN AND APPENDAGES		
Breast pain	34 (15.0)	43 (18.9)
UROGENITAL		
Vaginal hemorrhage	43 (19.0)	21 (9.3)
Endometrial disorder	22 (9.7)	4 (1.8)
Leukorrhea	14 (6.2)	3 (1.3)

The following additional adverse reactions have been reported with estrogen and or estrogen/progestin therapy:

1. Genitourinary system Changes in vaginal bleeding pattern and abnormal withdrawal bleeding or flow; breakthrough bleeding, spotting, dysmenorrhea, increase in size of uterine leiomyomata, vaginitis, including vaginal candidiasis, change in amount of cervical secretion, changes in cervical ectropion, ovarian cancer, endometrial hyperplasia, endometrial cancer.

2. Breasts Tenderness, enlargement, pain, nipple discharge, galactorrhea, fibrocystic breast changes, breast cancer.

3. Cardiovascular Deep and superficial venous thrombosis, pulmonary embolism, thrombophlebitis, myocardial infarction, stroke, increase in blood pressure.

4. Gastrointestinal Nausea, vomiting, abdominal cramps, bloating, cholestatic jaundice, increased incidence of gall bladder disease, pancreatitis, enlargement of hepatic hemangiomas.

5. Skin Chloasma or melasma, which may persist when drug is discontinued, erythema multiforme, erythema nodosum, hemorrhagic eruption, loss of scalp hair, hirsutism, pruritus, rash.

6. Eyes Retinal vascular thrombosis, intolerance to contact lenses.

7. Central nervous system Headache, migraine, dizziness, mental depression, chorea, nervousness, mood disturbances, irritability, exacerbation of epilepsy, dementia.

8. Miscellaneous Increase or decrease in weight, reduced carbohydrate tolerance, aggravation of porphyria, edema, arthralgias, leg cramps, changes in libido, anaphylactoid/anaphylactic reactions including urticaria and angioedema, hypocalcemia, exacerbation of asthma, increased triglycerides.

OVERDOSAGE

In cases of **ANGELIQ** overdose, monitor serum concentrations of potassium and sodium since drospirenone has antimineralocorticoid properties.

Serious ill effects have not been reported following acute ingestion of large doses of progestin/estrogen-containing oral contraceptives by young children. Overdosage may cause nausea and withdrawal bleeding may occur in females.

Manufactured for: Bayer HealthCare Pharmaceuticals Inc., Wayne, NJ 07470
Manufactured in Germany
Bayer HealthCare Pharmaceuticals 6007000 3288396 September 2005

Bayer HealthCare Pharmaceuticals

Bayer HealthCare Pharmaceuticals Inc., Wayne, NJ 07470 © 2007, Bayer HealthCare Pharmaceuticals Inc. All rights reserved. 06-220-0019BH Printed in USA/February 2007