POLICY æ PRACTICE

Women Bear HIV/AIDS Burden

Women and girls are being infected with HIV/AIDS at an alarming rate, according to Dr. Anthony S. Fauci, director of the National Institute of Allergy and Infectious Diseases, part of the National Institutes of Health. In the United States, the proportion of AIDS cases among women aged 13 years and older has increased from 7% in 1985 to 27% in 2005, Dr. Fauci said in a statement last month to highlight National Women and Girls HIV/AIDS Awareness Day. Worldwide, women and girls now make up nearly half

of the 39.5 million people who are living with HIV/AIDS. "The imperative to bolster our collective commitment to fighting HIV/AIDS among women and girls has never been stronger," Dr. Fauci said. Researchers have found that women are affected by HIV/AIDS differently from the way men are and have a higher incidence of drug toxicity when taking antiretroviral therapy. In an effort to better understand and address these differences, NIH is supporting the Women's Interagency HIV Study, which aims to shed light on the course of HIV/AIDS in women.

Women Face Sleep Problems

About two-thirds of women report experiencing some type of sleep problem a few nights a week, according to a survey released by the National Sleep Foundation. The sleep problems include waking up unrefreshed, waking frequently during the night, difficulty falling asleep, and waking too early and being unable to return to sleep. About 42% of women surveyed reported signs of snoring, restless legs syndrome, or sleep apnea at least a few nights a week, with 28% saying they experienced one of these problems every night or almost every night. Older women reported more signs of sleep problems. For example, 36% of women aged 25-34 years reported signs of a sleep problem at least a few nights a week, compared with 44% of women aged 35-44 years and 48% of women aged 55-64 years. The random telephone survey included more than 1,000 women aged 18-64 years.

Pregnancy Discrimination Case

A federal judge has upped the stakes for an Illinois-based HMO that was found guilty of health care fraud for discriminating against pregnant women. The judge raised the \$144 million verdict to \$334 million, calling the company's conduct "egregious and calculated." The lawsuit against Amerigroup Illinois and its parent company, Amerigroup Corporation, alleged that the insurer was paid \$243 million to establish a Medicaid managed care health plan in Illinois aimed at providing insurance coverage, including prenatal care, to low-income residents. The jury concluded that Amerigroup avoided enrolling pregnant women and others with expensive health conditions while at the same time accepting state and federal money. The company plans to appeal the ruling.

FDA Women's Health Office Funded

Officials at the Food and Drug Administration plan to provide the full \$4 million allocated by Congress to fund the Office of Women's Health in fiscal year 2007. In February, news reports circulated that the FDA commissioner intended to cut funding for the office by about 25% and use the money for other projects at the agency. That idea was met with swift criticism by members of Congress and women's health advocates, who said such a slash in funding would essentially shut down the Office of Women's Health for the rest of the year. With the announcement that FDA will retain full funding for the office, many of those critics applauded the agency's change in course. "The FDA has done the right thing for women's health,' Sen. Patty Murray (D-Wash.), Sen. Hillary Rodham Clinton (D-N.Y.), Sen. Barbara Mikulski (D-Md.), and Sen. Olympia Snowe (R-Maine) said in a statement. "By responding to our call and heeding Congress' clear intentions, the Office of Women's Health will have the funding needed to continue the leadership role it has served for 16 years in improving the health and well-being of women across the United States.'

New Imaging-Cut Moratorium

Several members of Congress have introduced legislation to put a 2-year moratorium on cuts to Medicare payments for medical imaging that started this year. The bill also requires a Government Accountability Office study of patient access to imaging. The bill—H.R. 1293—was introduced by Rep. Carolyn McCarthy (D-N.Y.), Rep. Gene Green (D-Tex.), and Rep. Joseph Pitts (R-Pa.) and had 49 cosponsors at press time. Rep. Pitts sponsored similar legislation in the last Congress; the cuts were mandated as part of the Deficit Reduction Act (DRA) of 2005. A Senate companion bill is expected soon. Under the DRA, payments for the technical component of an imaging service are to be set at the hospital outpatient department rate, if the payment under the Medicare physician fee schedule is higher.

ANGELIQ® TABLETS
(Drospirenone and Estradiol)

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

WARNING

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 infaction, stroke, invasive breast cancer, pulmonary embloi, and deep vein thrombosis in post-menopausal women (50 to 79 years of age) during 5 years of treatment with oral conjugate equine estrogens (CE 0.65 reging) combined with medroxyprogesteron acetate (MPA 2.5mg), relative to placebo (see CLINICAL PHARMACOLORY, Clinical Studies and WARN-INGS, Cardiovascular disorders and Malignant neoplasms, Breast caneer.)

The Women's Health Initiative Memory Study (WHIMS), a substudy of WHI, reported increased risk of developing profable dementia in postmeropausal women 65 years of read or older during 4 years of readment with conjugated estrogens alone and during 4 years of treatment with conjugated estrogens alone and during 4 years of treatment with conjugated estrogens is observed and during 4 years of treatment with or value of the confusion of the confusion

ed estrogens plus medroxyprogesterone acetate, relative to placebo. It is this finding applies to younger postmenopausal women. (See CLINICAL PHAR vical 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 Will 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

INDICATIONS AND USAGE
MARGEU is indicated in women who have a uterus for the: 1. Treatment of moderate to severe var motor symptoms associated with the menopause. 2. Treatment of moderate to severe symptoms volvar and vaginal artophy associated with the menopause. When prescribing solely for the treatm of symptoms of vulvar and vaginal atrophy, topical vaginal products should be considered.

vulkar allo vagines and vaginal atrophy, topical vaginal process.

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 neoptasia. 4. Active deep vien thrombosis, journous yer books 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 diseases. 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 oith directions 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.

ANGELIO should not be used in patients with conditions that precisionse 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-sparring diuretics, potassium supplements, ACE inhibitors, angiotensi-ril receptor ratagonists, and heparin. Consider checking serum potassium levels during the first treatment cycle in high-risk patients.

inhibitors, angioretism: The continuation of t

I WILL OURSIN, and Systemic upus erymematosus snound de managed appropriately, an 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.)

and increase in the funding of in the compared to placebo. (See CLINICA PHARMACOLOGY, Clinical Studies sections.)

In the CEMPA 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 Deckology. (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 Deckology. (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 Deckology. (37 vs. 30 per 10,000 person-years). The increase in risk was observed after the first year and persisted.

In postmenopasal women with documented heart disease (n = 2763, average age 66.7 years) a controlled clinical trial of secondary prevention of cardiovascular disease (heart and Estrogen-Progestin Replacement Study, HERS) treatment with CEMPA-0.65cmg/2 Grap per day demonstrated no cardiovascular benefit. During an average follow-up of 4.1 years, treatment with CEMPA did not reduce the overall rate of CHD events in postmenopausal women with established coronary heart disease. There were more CHD events in the CEMPA-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 CEMPA group and the placebo group in HERS, HERS II, and overall.

Large doses of estrogen (6 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 nonlitaal myocardial infarction, pulmonary embolism, and

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 PHAR-MACOLORY and Clinical Studies sections.)

In the CEAMPA substudy of WHI, a 2-fold greater rate of VTE, including deep venous thrombosis and pulmonary embolism, was observed in women receiving DEAMPA compared to women receiving placebo. The rate of VTE was 34 per 10,000 woman-years in the CEAMPA 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 pleaseobogroup of the proposed state of the person of

gen 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, the endometrial size of the progress results in a different endometrial risk profile than synthetic estrogens of equivalent estrogens results in a different endometrial risk profile than synthetic estrogens of equivalent estrogen dose, Adolfora progestin to estrogen therapy thas 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 WH1 clinical trial and report no significant variation in the risk of breast cancer among different estrogens or propesties, doses, or routes of administration. The CEMPA substudy of WH1 reported an increased risk of breast cancer in women who took CEMPA for a mean follow-up of 5.6 years. Observational studies have also reported an increased risk for estrogen propestin combination therapy, and a smaller increased risk for estrogen alone therapy, after several years of use. In the WH1 trial and from observational studies, the excess risk increased with outdardon of use. From observational studies, the risk august to the studies of breast cancer was greater, and became apparent earlier, with estrogen/propestin combination therapy as compared to estrogen alone therapy.

In the CEMPA 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 (69% confidence interval 1.01-1.54), and the overall absolute risk was 41 vs. 33 cases per 10,000 women-years, for CEMPA 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 CEMPA compared with placebo. Among women who reported prior use of hormone therapy, the relative risk of invasive breast cancer was 1.03, and the absolute risk was 40 vs. 25 cases per 10,000 women-years, for CEMPA compared with placebo. In the same substudy, invasive breast cancer was 1.68, and the absolute risk was 40 vs. 25 cases per 10,000 women-years, for CEMPA compared with placebo. In the same substudy, invasive breast cancers were larger and diagnosed at a more advanced stage in the CEMPA group compared with the placebo group. Metastatic disease was ra

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 (MHIMS), a substudy of WHI. 294 Typistercolined women aged 65 to 79 years were randomized to 65 or place-bo. In the estrogen plus progestin WHIMS substudy, 4,532 postmenopausal women aged 65 to 79 years were randomized to ECMPA 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 74 yersys 5.2 cases per 10,000 women-years. It is unknown whether these findings apply to younger postmenopausal women. (See CLINICAL PHARIMACOLOGY, Clinical Studies and PRE-CAUTIONS, Geriatric Use.)

After an average follow-up of 4 years, 40 women being treated with CEMPA (1.8%, n = 2.29) and 21 women in the placebo group (0.9%, n = 2,303) received diagnoses of probable dementia. The relative risk for CEMPA versus placebo was 2.05 (95% confidence interval 1.21 – 3.48), and was similar for women with and without histories of menopausal hormon use before WHIMS. The absolute risk of probable dementia for CEMPA versus placebo was 45 versus similar for women with and without histories of menopausal hormon use before WHIMS. The absolute risk of probable dementia for CEMPA wersus placebo was 45 versus cases per 10,000 women-years. It is unknown whether these findings apply to younger postmenopausal women. (See CLINICAL PHARIMACOLLOGY, Clinical Studies and PRECAUTIONS, Geriatric Use.)

4. Gallbladder disease A.2-to 4-fold increase in the risk of gallbladder disease requiring sur-

women. (See CLINICAL PHARIMACOLOSY, Clinical Studies and PRECAUTIONS, Geriatric Use.)

4. Galibladder disease A 2: to 4-fold increase in the six of galibladder disease requiring surgery in postmenopausal women receiving estrogens has been reported.

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

6. Visual abnormalities Refinal 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 proprioss, dipolopic, or migraine. If examination reveals papilledema
or retinal vascular lesions, estrogens should be permanently discontinued.

1. Addition of a progestin when a woman has not had a hysterectomy 1. Addition to a progessin when a woman has not indea dysterectionly 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 endome-trial hyperplassi than would be induced by estrogen treatment alone. Endometrial hyperplassi 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

estrogens compatieu or estrogensions. Services de proposa 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.

other complications.

4. Impaired liver function and past history of cholestatic jaundice
Estrogens may be poor
y 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 drospierone was decreased in patients with moderate hepatic impairment.

5. Hypothyroidism
Estrogen administration leads to increased thyroid-binding globulin (TBG)

S. 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 T and T3 serum concentrations in the normal range. Patients dependent on thyroid hormone 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. Hypocateemia Estrogens should be used with caution in individuals with severe hypocatemia 8. Hyponatremia As an aldosterone antagonist, drospirenone may increase the possibility of hyponatremia in high-risk patients.

ty of flyponatremia in high-risk patients.

9. Ovarian cancer The CEMPA substudy of WHI reported that estrogen plus progestin increased the risk of ovarian cancer. After an average follow-up of 5.5 years, the relative risk for ovarian cancer for CEMPA versus placebo was 1.58 (95% confidence interval 0.77 - 3.24) but was not statistically significant. The absolute risk for CEMPA versus placebo was 2.4 versus 2.7 osage 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 estrogen.

tion of estrogens.

11. Exacerbation of other conditions
Estrogens may cause an exacerbation of asthma, diabetes mellitus, spilepsy, migraine, porphyria, systemic lugus 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 AMRELIO.

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).

mone levels (e.g., estradiol, FSH). D. DRUG/LABORATORY TEST INTERACTIONS

D. DRUGLABORATORY TEST INTERACTIONS

1. Accelerated prothrombin time, partial thromboplastin time, and platelet aggregation time; increased platelet count; increased factors II, VII artigen, VIII artigen, VIII cagulant activity, IX, X, XII, VII-X complex, II-VII-X complex, and beta-thromboglobulin; decreased elvels of anti-actor X and antitrombin III, decreased antitrombin III activity, increased elvels of fibrinogen and fibrinogen activity, increased plasminogen antigen and activity.

2. Increased throid-binding globulin (TBG) levels estaing to increased circulating total thyroid hormone, as measured by protein-bound iodine (PBI), T4 levels (by column or by radioim-nunoassay) or T3 levels by radioimmussassay in T3 levels by radioimmussassay. To resin uptake is decreased, reflecting the elevated TBG. The T4 and fire T3 concentrations are unafleted. Patients on thyroid replacement therapy may require higher doses of thyroid hormone.

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. Fre hormone concentrations may be decreased. Other plasma proteins may be increased (angiotensinogen/reini substrate, alpha-1-antitrypsin, ceruloplasmin).

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

I presided queep televisore.

5. Impaired glucose tolerance.

ced response to metyrapone test.

Cinogenesis, mutagenesis, and impairment of fertility

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, CONTRANDICATIONS, 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 (ALIC 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
smilar study in rats given 10 mg/kg/day drospirenone alone or 0.3 + 0.03, 3 + 0.03, and
10 + 0.1 mg/kg/day drospirenone and ethinyl estradiol, 2.3 to 5.12 times the exposure of women taking a 1 mg dose, there was an increased incidence of benign and total (benign and malignart) adrenal gland phecotromocytomas in the group receiving the high dose of drospirenone. Prospirenone
was not mutagenic in a number of *in vitro* (Arnes, Chinese Harnster Lung gene mutation and chromosomal damage in human lymphocytes) and *in vivo* (mouse micronucleus) gendoxicity 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 ANGELIO should not be used during pregnancy. (See CONTRANDICATIONS.)

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 ANGELIO is administered to a nursing woman.

titled 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 amaximal daily dose of about 3 mag 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 dementa. Alzheimer's disease was the most common classification of probable dementa in both the conjugated estrogens plus medroxyprogesterone acetate group and the placebog orup. Ninety person to the cases of probable dementa occurred in the 54% of women who were older than 70. (See WARNINGS, Dementia.)

ADVERSE REACTIONS

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the finited trials of a func areas of the developing of the prior to the support of the prior to t

See Ouze Wanning, Manufacture with the property of the 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 DISO	RDERS	
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)

ollowing additional adverse reactions have been reported with estrogen and or estro-rogestin therapy:

en/progestin therapy:

1. Geniflourinary system Changes in vaginal bleeding pattern and abnormal withdrawal bleeding of offwor breakthrough bleeding, spotting, dysmenorrhea, increase in size of uterine leiomy-omata, vaginitis, including vaginal candidiasis, change in amount of cervical secretion, changes in cervical ectropion, ovarian cancer, endometrial byrepstiasi, endometria cancer.

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

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

6. Sastninisetrial. Mausea, overpriling, addominal cramps, bloating, cholestatic isundice.

popniebitis, myocardial infarction, stroke, increase in blood pressure.

4. Gastrointestinal Nuesa, vormiting, adbornial cramps, bloating, cholestatic jaundice, increased incidence of gall bladder disease, pancreatis, enlargement of hepatic hemangiomas.

5. Skin Chloasma or melasma, which may persist when drug is discontinued, erythema motion, which may persist when drug is discontinued, erythema multiforme, erythema nodosum, hemorrhagic eruption, rices of scalar bloade.

6. Fuer Religial vascular thromphasic intolerance to control bloade.

torme, erythema nodosum, hemorrhagic eruption, loss of scalp hair, hirsultism, pruntus, 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 portphyria, edema, arthralgias, leg cramps, changes in libido, anaphylactioractions 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 III effects have not been reported following acute ingestion of large doses of progestin/destopen-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